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William R. Ware, PhD - Editor

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This month we discuss several important issues. The first involves the growing threat to children due to the ever-increasing toxic environment created by Big Chemical, Big Agriculture and Big Pharma and modern civilization in general. Children are exquisitely vulnerable due to the simple fact that they are constantly undergoing extremely complex developmental processes. They are a *priori* dependent on their parents to look after their safety and the risks out there start even before conception and last until the late teens. The toxic environment is also a risk to the parents themselves, and in spite of official pronouncements, everyone is on their own and it is naïve to believe that any government agency or even some professional organization is sincerely concerned about this growing and very serious problem.

The second topic involves actions one can take, not involving prescription drugs, to keep the risk of stroke low and potentially lower it. This comes from the INTERSTROKE study and follows a similar study called INTERHEART, which has already been discussed in IHN. Again, the results provide a convincing example of how important it is to modify or eliminate or avoid as many risk factors as possible since the cumulative effect is impressive and may be even greater than estimated due to unknown synergistic effects.

The third subject concerns our old friend blood cholesterol and is prompted by a sensational paper just published which suggests the estimation of cardiovascular events, both fatal and non-fatal, is being greatly overestimated and that the true risks are so small that they call into question attaching any importance whatsoever to serum cholesterol unless it is very high, as seen in the genetic disease. Two critical components in all risk estimations are the levels of total and HDL cholesterol and lowering the perceived risk with drugs has become a multibillion-dollar industry. This latest study suggests that this represents almost unimaginable over-treatment which is far from free of side effects.

Finally, a Research Review is included in this issue which deals with the subject of cancer and the role of Salvestrols in both treatment and prevention and will bring the reader up-to-date on many important issues. The focus on an inexpensive and natural product like Salvestrols for both cancer therapy and prevention is becoming more appropriate as the new immunotherapeutic drugs come onto the market. Consider incurable malignant melanoma which

Salvestrols appear to effectively treat even if it is metastatic. The current standard of care with an immunotherapy drug is ipilimumab which costs about $160,000 for a median progression free survival (PFS) of 2.9 months. Better results are obtained by combining this with nivolumab at about a total of $300,000 for a PFS of 11.4 months (numbers from a talk by Dr. Leonard Saltz at the America Society of Clinical Oncology annual meeting). Patients on Medicare with a 20% copayment would be out of pocket $60,000 to gain a year on average. The latest melanoma drug to be approved and now being used at high dose in clinical trials is pembrolizumab which comes in for low doses at $83,000 per month but if used at a dose appropriate for a 75 kg patient, would be about $1 million per year. These costs go from be mostly unaffordable to being unsustainable.

In Brian Schaefer's book *Salvestrols. Journeys to Wellness,* he describes the case history of a 94 year old woman with rapidly progressing metastatic melanoma who had refused conventional therapy and was about to be put on palliative care. After 12 months of Salvestrol therapy the cancer was in total remission and still was at 18 months when she died of a non-cancer related cause. If she had taken 4000 points per day of Salvestrols rather than 3000 for 12 months, the cost today would have been about $1000.

Wishing you and your family continuing good health,

William R. Ware, PhD, Editor

Highlights

OUR TOXIC WORLD, CHILDREN AND NEURODEVELOPMENT

In 2015 a project called *Targeting Environmental Neuro-Developmental Risks* (TENDR) was formed by leading American scientific and medical experts along with children's health advocates. The goal was to increase awareness of the urgent need for action in order to protect the current and future generations from neurological damage having the end result of limiting them from reaching their full potential or even condemning them to a life of dysfunction and disability. In the July 2016 issue of *Environmental Health Perspectives,*[1] they present a consensus statement which appears to describe a crisis which is being largely ignored. Another recent review also addresses neurotoxicants and neurodevelopmental risks.[2] At issue is the widespread exposure to toxic chemicals implicated in neurodevelopment from conception to the time when neurodevelopment is more or less complete, which is in the late teens. Toxic chemical exposure can cause

lasting harm to the brain starting with the embryonic and fetal stage of development followed by infancy, early childhood and adolescence. The crisis appears to be escalating. For example the latest estimate finds that 1 in 45 US children have autism, up from 1 in 68 a few years ago. Yet there appears to be no meaningful or significant progress is identifying precisely what is going on and there seems to be a state of denial that the driving force could be a man-made toxic environment. Furthermore, progress in significant treatment protocols continue to be ignored because they involve departing from the status-quo and adopting approaches foreign to modern practice. See for example the recent book by Harvard professor and pediatric neurologist Martha Herbert, MD, PhD, titled *The Autism Revolution. Whole Body Strategies For Making Life All It Can Be.* Dr. Herbert promotes a whole body approach, as did the late Jaquelyn McCandless, MD[3] and the neurologist and nutrition expert Natasha Campbell-McBride, MD.[4] Autism is only one problem. Parents report that 1 in 6 children have development disability including not only autism but ADHD and other developmental delays, a 17% increase over a decade.

Consider the prenatal problem. A 2011 analysis from the US Centers for Disease Control and Prevention (CDC) found that 90% of pregnant women in the US have detectable levels of 62 chemicals out of the 163 screened for. Included were the commonly encountered toxins polybrominated flame retardants, phthalates, perfluorinated compounds, polychlorinated biphenyls (PCBs), perchlorate, lead and mercury. Many of these can cross the placenta, are routinely found in cord blood and fetal tissue and are neurodevelopmentally toxic. Little changes after birth since the child is then exposed to the huge spectrum of environmental toxins as well as toxins potentially in breast milk. The following are prime examples, all of which have documented neurodevelopmental toxicity. It is a fantasy to believe that these can be avoided. A recent comprehensive review suggests that all of these have also been found in prenatal exposure to increase the risk of autism.[5]

- Organophosphate pesticides.[6]
- Polybrominated flame retardants.[5]
- Combustion related air pollutants such as polynuclear aromatic hydrocarbons, particulate matter and nitrogen dioxide to name only a few.[7]
- Heavy metals such as lead and mercury.[5]
- PCBs.[8]
- Phthalates.[9]

A first step to reducing the risks of learning and developmental disorders is obviously reducing exposure which translates into reducing the prevalence of these chemicals in air, food, water, household furnishings, personal care items, indoor and outdoor use of pesticides, etc. This amounts to an ambitious project considering the commercial interests involved and the false claims of product safety and the absence of established toxic thresholds, the latter being impossible due to the complexity of the issue, human variability, the reluctance of regulatory agencies to admit negligence and denial, and the obvious ethical prohibition of experimenting on fetuses, young children, and adolescents and pregnant women. The statement that some chemical has been scientifically proven

safe at some level is generally merely self-serving for the various industries involved which would like everyone to believe irrelevant animal studies and hand-waving. The tobacco industry wrote the playbook decades ago and a very good one it is indeed. The consensus statement cited above states it very well: “Our system for evaluating scientific evidence and making decisions about environmental chemicals is broken.” While they call for fixing this problem, it is not that simple and it can be argued that it is in fact nearly impossible through government action.

There is one disturbing problem highlighted by the consensus statement. When enough data exists to trigger concern, a new chemical claimed safer is substituted and the product labeled free of the old toxin. A good example is the chemical BPH leached from some plastics such as food can liners and plastic bottles. Two new similar compounds are being substituted even though initial evidence suggests they are even worse. Here we are talking about endocrine disrupters which can raise havoc with hormone regulated biochemical processes resulting in sickness and disability.

Prevention of the disaster of adverse neurodevelopmental would, at least for the foreseeable future, appear to be a problem that parents are left to solve. The actions are numerous and not very simple. While there are individuals who specialize in going through homes from basement to attic and identifying everything that must be thrown out, such experts are not that commonly available. This is unfortunate because a certain level of expertise is necessary to overcome the deceptive labeling and other practices of the industry and their expertise in hiding toxins.

It is sometimes convenient to divide exposure into two periods, prenatal and postnatal. Postnatal is complicated by exposure from breastfeeding as well as all the potential exposures from the day of birth onward. Prenatal involves some unique exposures due to maternal medication, smoking, alcohol use, or transfer of toxins to the fetus already accumulated or acquired by the mother, sometimes on a daily basis. This raises complex issues. A further complication arises with unplanned pregnancy where dangerous exposures can occur during the first month or so after conception. Alcohol is a prime example. Always keep in mind the tiny number of fetal cells subject to toxin invasion compared even to a one-year old. During pregnancy, here is a short list of hazardous substances.

- **Alcohol**. Abstinence is the only safe action since there is insufficient evidence concerning intake thresholds for the adverse fetal effects.[10]
- **Tobacco smoking**. The evidence is compelling.[11] Tobacco smoke contains a large number of toxins and nicotine is also implicated. Do not smoke. Avoid secondhand smoke.
- **Marijuana**. Fetal development may be influenced as well as infant cognitive behavior.[12]
- **Prescription medications**. Evidence is of necessity limited because it is well known that adverse effects can appear at any time, even after the child has become an adult and the number of medications in common use is huge. Safety during pregnancy or after birth is not generally required to be demonstrated for

regulatory approval and is probably impossible. The obvious candidates have been sufficiently studied so the risks are clear.[11, 13] Included are antidepressants,[14, 15] antiepileptic drugs,[16] stimulants including cocaine, heroin and opiates, [11] and glucocorticoids.[17] If the broad definition of opiates is used, it includes common painkillers such as morphine and OxyContin-based formulations. The issue of abuse vs. chronic use vs. occasional use is difficult to assess. Since this only scratches the surface of prescription drugs in use, it is of vital importance that this issue is discussed with the health care providers involved in managing the pregnancy since they should have access to extensive databases of relevance. They should also be able to add perspective in cases where the medication is regarded as essential but may not be when one considers the risk to the fetus. Never forget the shockingly narrow time window during gestation when Thalidomide caused a major and permanent development disaster and relate this to the problem of testing for safety.

- **Over-the-counter drugs**. The US FDA has developed a classification system for the safety of these drugs during pregnancy. The presentation of this online system makes it clear that there is considerable uncertainty and the necessary reliance on animal studies some of which are considered unreliable, especially if negative. At issue are mostly neurodevelopmental problems. This requires studies of use over all three trimesters with follow-up for as long as possible since delayed adverse effects are well recognized. Given the large number of over-the-counter drugs which are widely used, it is not surprising that human studies are few and mostly uninformative. Thus of the categories A, B, C, D and X, only A (no evidence of risk in humans) or X (demonstrated risk in humans), provide significant guidance, and category A can hardly be viewed as definitive. Drugs falling in the remaining categories should be viewed with great caution. One exception where there have been a number of studies is prenatal use of acetaminophen (Tylenol) which is implicated in various disorders in children including ADHD and autism.[18-21] Acetaminophen is also implicated in increased postnatal risk of autism and asthma.[22-26] It is important when looking at lists of safe and unsafe drugs in this context to realize that the information can be seriously out of date and incomplete. Acetaminophen is a good example where the risks meriting an X classification are very recent. The lack of human and especially recent human studies makes the selection of safe over-the-counter drugs almost impossible and might inspire one to avoid them altogether unless the reason is compelling.

When a woman is contemplating pregnancy or finds she is pregnant, the mother and child during gestation must be protected from the multiple threats that our modern way of life has created. Consider first the diet and attempt to eliminate all unnatural substances such as antibiotics, hormones, industrial fats, excess sugar, and of course toxins. However, the identity of all the toxins in the environment, food and water is unknown, and thus one should eat organic food and rid the home of as many chemicals as possible. They even collect in house dust, a particular threat to children who spend a

lot of time on the floor. Vegetarians should obtain reliable advice concerning potential dietary deficiencies that might jeopardize the prenatal and postnatal period. Only pure water should be used for drinking and cooking and this generally means reverse osmosis water since almost all other filter systems are either ineffective or selective in what they more or less remove. Attempt to imitate the diet of the modern primitive groups as described by the work of Weston Price (the Weston T Price foundation has an informative website and as well Price wrote an excellent book[27]).

Planning for a pregnancy should involve the same actions and should involve a significant detoxification program and reduction of the body load of toxins. Detoxification is greatly accelerated simply by total avoidance of toxins. Detoxification, especially during pregnancy with supplements such as milk thistle, n-acetyl cysteine and alpha lipoic acid should be done only through consultation with a knowledgeable physician. Attention should be paid to personal care items since they represent a significant source of undesirable chemicals, many of which are readily absorbed through the skin. All of this is challenging since we have reached the point where it impossible to justify trust in labels or claims of safety. Look with skepticism at the conventional wisdom concerning diet and lifestyle during pregnancy. Postnatal development problems can be subtle and difficult to associate with toxin intake either during or after pregnancy and are frequently incorrectly attributed to irrelevant causes.

BOTTOM LINE

One must never forget that we live in a world that is significantly foreign and hostile when viewed from the perspective of our evolution and even our adaptations prior to the industrialization of almost all aspect of our lives and the creation of our toxic environment. Along with these revolutionary changes came a new commercial business philosophy involving deception and manipulation in all its various forms and concern for only profits even at the expense of huge damage to almost everyone. The above discussion concerns the most vulnerable and defenseless, our children.

MODIFIABLE RISK FACTORS FOR STROKE. THE INTERSTROKE STUDY

In the June 2016 issue of IHN in the piece on the HOPE study the INTERHEART[28] study was also discussed since is allowed the calculation of the cumulative risk reduction associated with non-drug potentially modifiable risk factors for fatal heart attacks. Even the absence of just a few factors resulted in very large cumulative risk reductions. Similar research results by the same group have just been published for a large multinational study of potentially modifiable risk factors on stroke, both due to clot formation and intracranial bleeding.[29] This study was also of the case control design where cases were matched with controls to obtain the enhanced or decreased risk associated with various factors. Data was acquired on 26,919 participants recruited from 32 countries and the following risk factors were examined: hypertension, current smoking, waist to hip ratio (belly fat), diet, regular physical activity, alcohol intake, a blood lipid related ratio called APO (B/A1), history of diabetes, psychosocial factors,

cardiac causes and atrial fibrillation. Some might correctly not regard these as all equally modifiable and question the implication that reduction or elimination of a factor would produce changes in the actual future event rates. Research is sadly lacking. Nevertheless, these 10 factors were collectively associated with about 90% of the population attributable risk for stroke in each of the major regions of the world.

In an attempt to make this study more relevant to the majority of readers, only data from Western Europe, North America and Australia was examined. Furthermore only five factors will be discussed, hypertension, presence or absence of current smoking, abdominal obesity, healthy diet and exercise. These risk factors offer the opportunity to easily intervene, or act at the first signs appear of adverse changes in lifestyle.

The same approach to cumulative risk reduction as was used in INTERHEART will be used. Odds ratios will be used and when they reflect risk, the reciprocal (1/OR) will be taken to reflect a measure benefit. The effect of starting out with the absence of hypertension risk and then adding other factors is shown in the table below.

As an example, not having hypertension and not smoking would give cumulative benefit odds of 0.48 X 0.34 = 0.16. Similarly, not having hypertension, not smoking, and not having a high waist/hip ratio would give cumulative benefit odds of 0.48 X 0.34 X 0.47 = 0.08.

***Table*. Cumulative risk reductions associated with modified multiple risk factors for all stroke events. Data for Western Europe, North America and Australia**

Modifiable Risk Factor	Risk Odds	Benefit Odds	Cumulative Odds
Hypertension	2.08	0.48	0.48
Current smoking	2.97	0.34	0.16
Waist/hip ratio	2.14	0.47	0.08
Healthy diet	0.44	0.44	0.03
Physical activity	0.74	0.74	0.02

The small cumulative odds obtained even by adding one additional factor to avoiding hypertension or not smoking seem impressive. The same large effects were seen in INTERHEART as discussed in the June 2016 IHN. Four of the five factors in the above table also were modifiable risks found associated with heart attack in the INTERHEART heart attack study discussed connection with the HOPE trial. Taken together, these two studies provide guidance for non-drug prevention of heart disease and stroke.

In assessing hypertension the study used either self-declared hypertension or blood pressure ≥ 140/90. Presence of antihypertension therapy was not considered. The impact on strokes due to bleeding is strongly influenced by blood pressure levels but clot-based strokes were much more common in this study. For heart attacks due to clot formation, reducing blood pressure with drugs does not decrease the risk and all risk algorithms in fact find enhanced risk due to treatment, a phenomenon attributed to the

residual damage caused while the hypertension was untreated. In the INTERSTROKE study, for the factors in the above table, when only intracranial hemorrhage was considered did a healthy diet yield a statistically significant results making further analysis of this subgroup questionable. History of diabetes has also been omitted. Drug Treatments of hyperglycemia have modest if any impact on cardiovascular risk and it is unknown whether or not eliminating type 2 diabetes with either bariatric surgery or the Newcastle 8-week very low calorie diet results in reduced events since the first approach is new and the second at present ignored by mainstream medicine in spite of accumulating studies supporting the dramatic cures.[30-34] For atrial fibrillation (AFIB) it is well known that successful surgical procedure (ablation) can strongly reduce or eliminate episodes and presumably reduce clot-based stroke risk. The OR for the risk of AFIB is 4.05, highly significant, and eliminating it has the potential of a benefit represented by an OR of 0.25. If this were added to the above table, the results would be dramatic. But modification of risk of AFIB involves a highly invasive procedure which is not always successful.

When average population attributed risks were calculated, an approach which provides meaningful and comparative individual values for each factor, the average obtained was 61%, i.e. these 5 factors accounted for over 50% of the events observed. Note, however that this is for the entire international set of participants whereas the odds given in the table apply to a restricted population relevant to the readers of IHN.

Finally, the cumulative risk reductions in the table must be viewed in the context of the other risk six factors which are not being addressed. Nevertheless, it seems clear that the four in the table merit consideration due to the relative ease of implementation.

CHOLESTEROL: THE MYTH ON STEROIDS. DOES IT MATTER ANYMORE?

In the last issue of IHN the results of the latest validation test of the new (2013) and now widely used calculator for the 5- or 10-year risk of an acute event associated with atherosclerosis (acute heart attack, mortality from coronary heart disease, fatal or non-fatal stroke due to an clot) was discussed.[35] The new research found that for a very large and contemporary US cohort, the American Heart Association/American College of Cardiology (AHA/ACC) calculator grossly overestimated risk by about a factor of about 5 (factor, not %). This factor is so large that it suggests there may be a problem in even associating cholesterol levels, the major input parameter, and this type of risk. Thus just how relevant are blood cholesterol levels?

Let's take an example of a 60-year-old man free of heart disease, blood pressure 140/85 mmHg, HDL cholesterol 55 mg/dL, no family history of heart disease, non-African American, no lipid or blood pressure medication, and a non-smoker. Using values of total cholesterol (TC) ranging from 150 to 300 mg/dL, the AHA/ACC risk can be calculated online for each value. The AHA/ACC risk was then adjusted according to the results of the latest study using overestimation of risk with the AHA/ACC calculator

for non-diabetic men, which was a factor of 4.2 averaged over the four risk categories based on the AHA/ACC calculator (<2% to ≥ 10%) with little variation over this risk range. In the table below risk change in percentage points is for a 50 mg/dL change in total cholesterol. The units for cholesterol are in mg/dL and can be converted to mmol/L by dividing by 38.6.

NON-DIABETICS

Total Cholesterol	10-Year % AHA/ACC Risk	Adjusted % Risk	Risk Change %*
150	7.2	1.7	-
200	9.4	2.3	0.6
250	11.4	2.7	0.4
300	14.4	3.4	0.7

**** for a 50 mg/dL change in total cholesterol***

The investigators also examined a diabetic subgroup containing a much smaller number of subjects with associated increased uncertainty in the results. The group with ≥ 10% 10-year risk provided the lowest uncertainty and found an over-estimation factor of about 2.5. Using the same test individual, but this time with diabetes, the adjusted risks found are presented in the table below.

DIABETICS

Total Cholesterol	10-Year % AHA/ACC Risk	Adjusted % Risk	Risk Change %
150	13.5	5.6	-
200	17.3	7.2	1.6
250	20.9	8.2	1.0
300	24.3	10.0	1.8

Both tables illustrate the very dramatic effect of overestimation of risk evident in the adjusted values. Repeating this calculation for a 60-year-old non-diabetic female yields adjusted 10-year risks from 0.6% to 1.0% over this range of TC levels. These numbers are so small they speak for themselves. The study also examined the same question for non-diabetic African-Americans and Hispanics and found for men over-estimation factors of 6 and 4 respectively. Subgroup analysis of individuals taking statins found that for non-diabetics the average over the four risk groups gave an over-estimation factor of 6.5, whereas for diabetics the over-estimation factor was 4.7. It is important to recognize that a reduction factor of 6.5 means 6.5 times less risk.

All but one of the AHA/ACC 10-year risks in these tables derived from the online calculator included a boxed warning to the user that "***On the basis of your age and risk of heart disease or stroke, the ACC/AHA guidelines suggest you should be on a moderate to high intensity statin***". These calculated risks did not take into

account LDL cholesterol and did not require the input of a triglyceride level, so they are independent of LDL, although if one looks at the details of the guidelines, LDL is involved. However, users of this online calculator are told in a footnote only that LDL may be considered to inform treatment decisions. All they will probably notice is the recommendation of statin therapy. Note that in the study finding these large overestimates, the cohort included LDL levels from 70 to 190 mg/dL.

The study on which these adjustments are based needs to be taken very seriously. It involved over 300,000 individuals drawn from the US Kaiser Permanente health care organization database who were free of heart disease, diabetes and prior lipid-lowering. As indicated above, a much smaller group of diabetics was also studied as well as a group using statins. Participants were 40-75 years of age, and included stratification for African Americans and Hispanics. Participants were identified in 2008 and followed to 2013. The investigators were from Kaiser Permanente, University of California at San Francisco, Baylor, Stanford and the Houston Methodist DeBakey Heart and Vascular Center. Kaiser and the National Heart, Lung and Blood Institute financed the study. The authors reported no conflicts of interest related to the content of the paper, although some had received research support from a number of pharmaceutical companies which in this case strengthens rather than weakens the paper, given the results are highly unfavorable if not disastrous to the industry.

Traditionally, most physicians seeing a 10-year risk in the range of 1.7% to 3.4% (5-year risks would be half of this) for a nondiabetic man would presumably tell the patient not to worry, "Y*our numbers are really great if not remarkable*". If our test individual had diabetes the overestimate is about a factor of 2.5. As seen in the second table, even at a total cholesterol of 300, our test individual is below the threshold for intermediate risk ($\geq 10\%$), i.e. low risk whereas diabetes has always been considered to automatically put the individual in the highest 10-year risk of > 20% and statins recommended. While true that the risk increases with this disease, most diabetics will remain in the low risk category, still below the traditional 10% threshold for concern. The study does not give overestimation data for diabetic women, but for non-diabetic women the overestimation is similar to that for men. The AHA/ACC risks for diabetes would be scary for most diabetics since above a TC level between 200 and 250 mg/dL, they are at > 20% risk, whereas after adjustment, a conservative approach because of the low to modest actual risk would be to suggest dietary intervention. Furthermore, a study from the same group involving 1.5 million participants has demonstrated that for diabetics the 10-year risk is far below the risk found for individuals with prior coronary heart disease (10-year event free survival of 10% vs. 35%), invalidating the automatic and time honored automatic classification as high risk.[36] However for diabetics having the disease for > 10 years, the enhanced risk approaches the enhanced risk for prior heart disease. Obviously, it is important to deal with type 2 diabetes early, preferably at the prediabetes stage.

The range of TC in our example is large with higher values that ring conventional alarm bells. However, if one accepts the latest analysis of the validity of the AHA/ACC calculator, then this large range of TC after adjustment actually involved a range of 10-year risks of 1.7 to 3.4% for men and 0.6% to 1.0% for women. These would normally

be interpreted as negligible and no cause at all for any concern. Yet here we have a now very popular calculator promoted by two major and highly respected associations (cynics call them guilds) for five different cholesterol levels in a 60-year male individual with no other risk factors who, if willing, would be put on statins. In addition, the event risk changes by only about 0.5% per 50 mg/dL change in TC for men and are negligible for women.

WHAT DOES THIS ALL IMPLY? A HUGE DISASTER FOR CONVENTIONAL WISDOM!

TC is an excellent surrogate for LDL (LDL = TC – HDL + 0.2 X triglycerides; this is the way it is calculated from blood tests). The typical range of HDL is small and the triglyceride level effect is attenuated by one fifth. If high risk can be inferred from LDL levels, why is this not reflected also in adjusted the risk calculation associated with TC? In addition, all the adjusted numbers apply to individuals with LDL anywhere between 70 and 190 mg/dL, and the upper end of this range is quite high.

This simple example provided above with its low risks as well as the study from which the data was derived suggests that it is time to seriously consider the hypothesis that blood levels of cholesterol do not matter unless they are considerably higher than 300 mg/dL (7.8 mmol/L), reflecting a genetic disorder, and that the advocates of the term "the cholesterol myth" are much closer to the truth than is mainstream medicine with its almost pathological fixation on cholesterol. It also is consistent with a study that found half of all those presenting in the ER with a heart attack had low cholesterol and with the statin lipid lowering studies that over more than 2 decades have consistently found that in the context of primary prevention, the typical absolute benefit for men for lipid-lowering therapy was about 1.0 to 1.3% with 99 to 98.7% having no benefit with only slightly more favorable results for diabetics. These small benefits may not even have anything to do with lipid lowering but rather some other effect of the statin such as an anti-inflammatory action. The analysis is also consistent with the fact that, contrary to the conventional wisdom, according to 17 studies neither TC nor LDL blood levels are factors in the prevalence or progression of coronary calcification, a reliable marker of coronary plaque and atherosclerosis and thus the risk of the events we are talking about. Three autopsy studies found the same result.[37, 38] Furthermore there is now the officially adopted view that dietary cholesterol is irrelevant and its presence in guidelines with a limit on intake was nonsense. The adjusted risks cited above for a 60-year-old woman are also consistent with the absence of any benefit of lipid-lowering for women of any age. See the supplementary material in this reference[39] where a recent and large meta-analysis for major cardiovascular events in women yielded a null result, but the main paper does not mention this, using a composite endpoint including soft endpoints which shifted the risk to slightly positive, a standard statistical trick. In fact it is almost as common for women to be on statins as men.

Some will challenge the assertion that cholesterol no longer is an issue by pointing out that the paper under discussion involves risks calculated only with TC and HDL cholesterol and that one cannot ignore the so-called bad LDL. However, as pointed out

above TC is a very good surrogate for LDL and the subjects included individuals with high LDL.

If one compares the *adjusted* AHA/ACC risk estimates, the very low risk results also differ significantly from those calculated by the MESA calculator discussed and used several times in IHN. The MESA study has been used as a standard of reference in the context of the question of overestimation, is only about 7 years less contemporary, and was also based on a US population, but involved only about 6000 participants rather than 300,000 and did not use a single database or an ideal data source such as a homogeneous healthcare organization. One attractive explanation is that the study we are discussing used only acute heart attack, CHD related death or fatal or non-fatal stroke attributable to a clot. This was identical to the endpoints used in the AHA/ACC creation of their calculator. The online MESA calculator expanded the endpoint to include resuscitated cardiac arrest, and revascularization (bypass or angioplasty) in response to angina. Expansions of endpoints almost always results in increase in events.

The above study applies directly to North Americans and millions of individuals living here are being prescribed statins for high cholesterol, but most cases will have at levels within the large range used in our example with 10-year risks that do not indicate the need for any therapy.

BOTTOM LINE

The attempt to quantify the risk of CVD using commonly measured factors has been going on for several decades starting with the Framingham Study. The obvious conclusion to be derived from the above discussion is that blood cholesterol is not an important biomarker and it is time for a new paradigm. When told your cholesterol is too high, ask for your 10-year risk of fatal or non-fatal heart attack or stroke. Then if it is done with the new AHA/ACC calculator, divide by 5, a good approximation and you have a basis for a discussion (and perhaps severe conflict). The chances are that your risk will come out at less than 3%. If you are diabetic with high cholesterol with a 10-year AHA/ACC risk near 10%, a discussion can be initiated regarding numbers around 10% being merely the top of the traditional low risk category and diet might be prudent approach.

The risk calculator is available at http://www.cvriskcalculator.com/ Try it on your own values to get the AHA/ACC 10-year risk and then adjust by dividing by 5 (2.5 if diabetic). The interned has unit conversions calculators for TC and HDL from mmol/L to mg/dL. If the lab and blood pressure numbers are not unavailable, it would be surprising if a single phone call would not provide TC, HDL and blood pressure numbers. The paper on which the above discussion is based[35] is open access—just type in the title on Google and the links to the full-text pdf will be found. A copy might be useful in arguments with one's primary health provider.

There will no doubt be attempts to discredit the study we are discussing. It leads to profound heresy and conflicts with mainstream thinking. However, challenges will be

difficult given the participant size, diversification, and the quality of the data and the study design. At this writing, none have appeared—no letters to the editor, nothing. Perhaps the response will be to ignore it and hope that life with statins goes on as usual. This is the traditional approach when entrenched dogma strongly influenced by the pharmaceutical industry and an essential part of the usual medical practice is involved.

REFERENCES

(1) Bennett D. Project TENDR: Targeting Environmental neuro-developmental Risks. *Environmental Health Perspectives* 2016;124(7).
(2) Antonelli MC, Pallares ME, Ceccatelli S, Spulber S. Long-term consequences of prenatal stress and neurotoxicants exposure on neurodevelopment. *Prog Neurobiol* 2016 May 25.
(3) McCandless J. *Children with Starving Brains. A medical treatment guide for autism spectrum disorder. Fourth Edition*. Bramble Books; 2009.
(4) Campbell-McBride N. *Gut and psychology syndrome*. 2nd ed. Cambridge, UK: Medinform Publishing; 2010.
(5) Wong CT, Wais J, Crawford DA. Prenatal exposure to common environmental factors affects brain lipids and increases risk of developing autism spectrum disorders. *Eur J Neurosci* 2015 November;42(10):2742-60.
(6) Gonzalez-Alzaga B, Lacasana M, Aguilar-Garduno C et al. A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure. *Toxicol Lett* 2014 October 15;230(2):104-21.
(7) Vieira SE. The health burden of pollution: the impact of prenatal exposure to air pollutants. *Int J Chron Obstruct Pulmon Dis* 2015;10:1111-21.
(8) El MN, Bouchard M, Carrier G. Systematic analysis of the relationship between standardized prenatal exposure to polychlorinated biphenyls and mental and motor development during follow-up of nine children cohorts. *Regul Toxicol Pharmacol* 2013 June;66(1):130-46.
(9) Martinez-Arguelles DB, Papadopoulos V. Prenatal phthalate exposure: epigenetic changes leading to lifelong impact on steroid formation. *Andrology* 2016 April 4.
(10) Carson G, Cox LV, Crane J et al. Alcohol use and pregnancy consensus clinical guidelines. *J Obstet Gynaecol Can* 2010 August;32(8 Suppl 3):S1-31.
(11) Minnes S, Lang A, Singer L. Prenatal tobacco, marijuana, stimulant, and opiate exposure: outcomes and practice implications. *Addict Sci Clin Pract* 2011 July;6(1):57-70.
(12) Huizink AC. Prenatal cannabis exposure and infant outcomes: overview of studies. *Prog Neuropsychopharmacol Biol Psychiatry* 2014 July 3;52:45-52.
(13) van Gelder MM, van Rooij IA, de Jong-van den Berg LT, Roeleveld N. Teratogenic mechanisms associated with prenatal medication exposure. *Therapie* 2014 January;69(1):13-24.
(14) Pedersen LH. Prenatal Antidepressant Exposure and Childhood Autism Spectrum Disorders: Cause for Concern? *Paediatr Drugs* 2015 December;17(6):443-8.
(15) Grigoriadis S, Vonderporten EH, Mamisashvili L et al. Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. *BMJ* 2014;348:f6932.
(16) Nadebaum C, Anderson V, Vajda F, Reutens D, Wood A. Neurobehavioral consequences of prenatal antiepileptic drug exposure. *Dev Neuropsychol* 2012;37(1):1-29.
(17) Wyrwoll CS, Holmes MC. Prenatal excess glucocorticoid exposure and adult affective disorders: a role for serotonergic and catecholamine pathways. *Neuroendocrinology* 2012;95(1):47-55.
(18) Hoover RM, Hayes VA, Erramouspe J. Association Between Prenatal Acetaminophen Exposure and Future Risk of Attention Deficit/Hyperactivity Disorder in Children. *Ann Pharmacother* 2015 December;49(12):1357-61.
(19) Andrade C. Use of acetaminophen (paracetamol) during pregnancy and the risk of autism spectrum disorder in the offspring. *J Clin Psychiatry* 2016 February;77(2):e152-e154.

(20) Sordillo JE, Scirica CV, Rifas-Shiman SL et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. *J Allergy Clin Immunol* 2015 February;135(2):441-8.
(21) Liu X, Liew Z, Olsen J et al. Association of prenatal exposure to acetaminophen and coffee with childhood asthma. *Pharmacoepidemiol Drug Saf* 2016 February;25(2):188-95.
(22) Torres AR. Is fever suppression involved in the etiology of autism and neurodevelopmental disorders? *BMC Pediatr* 2003 September 2;3:9.
(23) Bauer AZ, Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. *Environ Health* 2013;12:41.
(24) Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* 2013 December;42(6):1702-13.
(25) Schultz ST. Can autism be triggered by acetaminophen activation of the endocannabinoid system? *Acta Neurobiol Exp (Wars)* 2010;70(2):227-31.
(26) Becker KG, Schultz ST. Similarities in features of autism and asthma and a possible link to acetaminophen use. *Med Hypotheses* 2010 January;74(1):7-11.
(27) Price WT. *Nutrition and Physical Degeneration.* Oxford: Benediction Classics; 2010.
(28) Yusuf S, Bosch J, Dagenais G et al. Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease. *N Engl J Med* 2016 April 2.
(29) O'Donnell MJ, Chin SL, Rangarajan S et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016 July 15.
(30) Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011 October;54(10):2506-14.
(31) Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med* 2013 March;30(3):267-75.
(32) Taylor R. Type 2 diabetes: etiology and reversibility. *Diabetes Care* 2013 April;36(4):1047-55.
(33) Steven S, Taylor R. Restoring normoglycaemia by use of a very low calorie diet in long- and short-duration Type 2 diabetes. *Diabet Med* 2015 February 12.
(34) Steven S, Hollingsworth KG, Al-Mrabeh A et al. Very-Low-Calorie Diet and 6 Months of Weight Stability in Type 2 Diabetes: Pathophysiologic Changes in Responders and Nonresponders. *Diabetes Care* 2016 March 21.
(35) Rana JS, Tabada GH, Solomon MD et al. Accuracy of the Atherosclerotic Cardiovascular Risk Equation in a Large Contemporary, Multiethnic Population. *J Am Coll Cardiol* 2016 May 10;67(18):2118-30.
(36) Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and Prior Coronary Heart Disease are Not Necessarily Risk Equivalent for Future Coronary Heart Disease Events. *J Gen Intern Med* 2016 April;31(4):387-93.
(37) Ware WR. The mainstream hypothesis that LDL cholesterol drives atherosclerosis may have been falsified by non-invasive imaging of coronary artery plaque burden and progression. *Med Hypotheses* 2009 October;73(4):596-600.
(38) Ware W. Does cholesterol drive atherosclerosis? in Atherosclerosis: risk factors, prevention and treatment, edited by Murakami,E; Sakamoto,H. Nova Publishers; 2012.
(39) Fulcher J, O'Connell R, Voysey M et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015 April 11;385(9976):1397-405.

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RESEARCH REVIEW

Cancer and the Role of Salvestrols

by William R. Ware, PhD

INTRODUCTION

Professor Dan Burke and his team of associates at the University of Aberdeen discovered in the early 1990s that cancer cells associated with soft tissue sarcomas had an enzyme of the P450 family, CYP1B1, present as the enzyme (protein) in the cytoplasm which was absent in normal cells. His group went on to find the same results in cancer cells of the colon, lung, esophagus, skin, lymph nodes, brain, and testis and always no detectable presence in surrounding tissue. Since then, a number of laboratories have confirmed and extended this work until practically all cancer tissues have been studied and found to have cancer cells with CYP1B1 expressed in the cytoplasm as the enzyme (in this case a protein which enables cellular chemical reactions).[1]

Burke later left Aberdeen to become head of the School of Pharmacy at the University of Leicester where he recruited Gerry Potter, an expert in drug development. Professor Potter developed what is called a prodrug which CYP1B1 converted in cancer cells into a compound that killed the cell. It was during the development of this drug that the two professors thought a great deal about CYP1B1, and why it existed and behaved as it did. They hypothesized that CYP1B1 must be involved in a rescue function for ridding the body of aberrant cancer cells and if this was true, there must be substances in the diet that served the same function as the drug Potter had developed and that this enzyme would facilitate the conversion of some dietary substances into chemicals that induced cancer cell death. When they found naturally occurring substances that indeed did this, an entirely new vista in the field of cancer therapy was opened up. Burke described the discovery of the remarkable properties of CYP1B1 as the most significant breakthrough in nutrition since the discovery of vitamins. This was somewhat of an understatement. They had in fact found the holy grail of cancer prevention and therapy

which qualified by any definition as the long sought after magic bullet. The rescue function prompted the name Salvestrol (from Latin—*salvia*, to save) and with the help of an expert on extraction methods from plants, Anthony Daniels, a product was developed with high potency for cancer prevention and therapy which could be used by humans. More details of the history of this discovery can be found in the book *Salvestrols, Nature's Defense Against Cancer*.[1]

One would have thought that these discoveries would ignite a flurry of research activity, clinical trials, and completely change the landscape of cancer therapy. While there was a lot of research which made clear that all cancer cells contained this enzyme and normal cells did not, a flurry of clinical research did not happen. Instead, most research on CYP1B1 involves its ability to convert certain compounds like estrogen and hydrocarbons found in tobacco smoke into carcinogens, something which is irrelevant if one already has cancer, as implied by the presence of this enzyme. There has been considerable interest in inhibiting this enzyme simply because of this because it is viewed as "bad." Given its properties of being principally an anti-cancer agent, this appears to be counterintuitive.

The lack of interest in the therapeutic aspects of CYP1B1 is a sad commentary on how medical research functions and how strong the bias is against a simple approach using natural products without first modifying them to make them patentable. Instead, vast sums have been spent on a reductionist approach in cancer research focused mainly on specific types of cancer, searching for weaknesses in the cancer cell defenses, and attempting to find new chemotherapeutic agents and to engage the immune system in the fight and kill cancer cells. Huge efforts have go into refining and fine-tuning chemotherapy and no one questions that for a very few cancers, mostly hematologic, chemotherapy can affect a durable remission which in some cases can be called a cure. However, the principal challenge has always remained the solid adult tumors and metastasis, the process that turns cancers deadly. Frequently surgical removal of a tumor followed by radiation and chemotherapy does not prevent subsequent relapse with metastasis resulting in new tumors commonly found too late.

Life extensions achieved by current therapies are highly variable but the nature of the underlying problem is illustrated by the enthusiasm if not joy of researchers when heat-to-head comparisons of two therapeutic protocols results in merely a month or two life extension, frequently with side effects reducing the quality of life dramatically. Unbridled enthusiasm even leads to treating patients with very limited life expectancy and making their remaining time more miserable. Treating pre-cancer with aggressive therapy normally used for cancer that has progressed beyond this stage is widely used as a conservative "play it safe" approach, while critics point to this as overtreatment. This practice also distorts the statistics used to measure efficacy because frequently indolent pre-cancer or even indolent cancer is being treated with almost guaranteed success. Furthermore, watchful waiting does not appear to be an option actively promoted, although in prostate cancer it has been studied as an option and for some patients, encouraged.

CANCER IN PERSPECTIVE

A recent book by a well-known cancer researcher is titled *The Death of Cancer.*[2] Readers were advised to be optimistic, some cancers were now being cured, and targeted therapy was developing rapidly. Unfortunately, one is reminded of the famous statement of Mark Twain pointing out that the reports of his death were an exaggeration. In Canada, for example, in the past 10 years new cancer cases have increased by 29% and from 2015 to 2030 the projection is 41%. Five-year survival rates for all cancers have only increased from 55% to 63% and among the major cancers such as prostate, breast, colorectal and melanoma, only prostate cancer has shown a large survival increase (68% to 96%). In addition, statistics such as these are confounded by successes with tumors treated in some cases before they presented any risk, and the 5-year survival ignores the sharp rise in detecting recurrence after this period.

Projections of cancer mortality predict an increase for adult solid tumors. Intensive chemotherapy is now thought to leave treatment resistant cancer cells to proliferate and metastasize, a so-called evolutionary or Darwinian effect[3] and new treatment protocols are being suggested.[4, 5] This view seriously challenges one of the pillars of chemotherapy theory and provides an explanation for failure that turns up 5-10 years after treatment. The theory that all cancer cells can be killed by intensive conventional chemotherapy appears flawed but the simple solution, long-term chemotherapy for life surely must have its problems. In some, remission may mean the burden of cancer cells has been reduced to the point where renewed proliferation will not yield symptomatic disease, metastatic or localized, during the remaining lifetime of the patient. But with cancers that occur in younger adults this may not be the case.

Many individuals also harbor dormant cancer cells. The true extent of dormant cancer is unknown but its presence cannot be denied. Many autopsy studies have documented the presence of cancer in asymptomatic individuals who have died from other causes such as trauma. Thyroid, breast, and prostate are common sites. These cancers may be dormant and pose no immediate threat, although given the right circumstances, may begin to proliferate rapidly and eventually lead to diagnosis. Small tumors made up of these dormant cancer cells present a problem for screening, trigger biopsies which may be positive and initiate unnecessary treatment when in fact they present no risk whatsoever at the time of discovery. Thyroid nodules, most of which are benign, are a prime example and are seen frequently in routine carotid artery ultrasound scans and called incidentalomas.

However, it is important to realize that the natural history of a tumor starts with one cell but in general is detectable only when somewhere around a billion cells are present. This is the silent period where diagnosis is for many cancers impossible and the time period can cover many years. Metastasis can also occur in the latter stages of this silent growth, giving rise to what is called cancer of unknown primary origin. One can conclude that while not everybody gets cancer, more have it than is generally recognized.

WHAT CAUSES CANCER?

For five decades the conventional and widely held belief is that cancer is genetically ordained, but the genetic picture that has emerged in the last few years suggests this view is burdened by impossible complexity. When individuals are studied, the presence of 250 oncogenes and 700 tumor suppressors are found. Cancer in this view represents about 1 million different genotypes. Nearly 1 million tumor samples have been genetically studied. Great enlightenment was expected. Instead millions of mutations have been discovered as well as 10,000 to 50,000 single nucleotide variants. When tumors cells are compared to adjacent normal tissue, tumor cells are like a huge train wreck. With rare exceptions, using genetic fingerprints to design drugs appears to be a daunting challenge or worse.

An alternative view which has only become a serious contender during the last decade is that cancer is a metabolic disease. This theory is supported by the fact that most oncogenes and tumors suppressors appear to be associated with cancer cell metabolism. There appear to be only three major metabolic pathways affected. Thus the metabolic disease model seems to be remarkably simple. The metabolic theory of carcinogenesis focuses on the mitochondria which reside in the cellular cytoplasm but are complex structures with cells containing DNA, incidentally only of maternal origin. As we age, not only do our cells loose mitochondria, but those that remain can become damaged and dysfunctional. Cellular energy generation involves the mitochondria, normally with glucose as the fuel. The instability in tumor genetics is considered in this theory as a downstream effect of the initial disturbance of cellular energy production.

In this theory, an unspecified condition damages and impairs cellular mitochondrial energy production capacity (respiration) and initiates the path to malignant cancer. One result is that the cytoplasmic environment changes from suppressing to promoting cancer. These events can be triggered by inflammation, carcinogens, radiation, low oxygen levels, new mutations, viral infections, and age. The details are the subject of ongoing research. Add to this a poor diet in general, dietary lack of micronutrients essential as cofactors for enzyme-mediated reactions and other biochemical and microbiological processes, and a diet that is at odds with what we evolved to thrive on. One result is a large increase in glucose needs to satisfy energy demands, a hallmark of cancer cells first pointed out by Warburg years ago. This change in mitochondrial function offers important therapeutic interventions like ketogenic diets since cancer cells cannot use ketones as an alternative fuel.

The metabolic theory of cancer is consistent with a therapeutic approach which combines a ketogenic diet which severely deprives the cancer cells of the required sugar for metabolism coupled with hyperbaric oxygen treatments which eliminate the low oxygen environment that encourages cancer cell proliferation.[6-8] Evidence so far appears restricted to studies with mice.

The diagnosis of cancer should come as no surprise. We are immersed in risk factors which are implicated in both the genetic and metabolic theories of carcinogenesis.

- smoking
- radiation
- viruses
- cancer-causing chemicals
- obesity
- hormones
- chronic inflammation
- lack of exercise

It is noteworthy that four of the above factors are modifiable. It is perhaps surprising that we do not all get cancer and the high burden of redolent cancer seen in autopsy in the elderly suggests that may be close to the truth. If one chooses to be guided by the observations on modern day isolated societies generally free of cancer, then the way most live today is both all wrong and potentially carcinogenic.[9]

However, we have defense systems. These include the following:

- the immune system
- DNA repair
- programmed cell death (apoptosis)
- proper nutrition so all these systems function optimally
- phytochemicals in the diet, for example from fruits, beverages, vegetables, herbs and spices. ***One class of phytochemicals is called Salvestrols.***
- exercise indirectly improves defense
- avoidance of toxic chemicals.

Cancer partly (perhaps principally) results from the failure or dysfunction of these defense systems due to defects in lifestyle, diet and living in a toxic environment (air, water, food).

There seems to be general agreement that when cancer is caught early, the chances of success for standard therapy are enhanced. However, we have a big problem. Screening does not work very well, is plagued by false positive and false negative results and overtreatment. The result is that the PSA test and mammography are controversial.[10-13] Colonoscopy, the Pap test and x-rays for lung cancer are exceptions. But for most cancers, screening is not possible. One waits until cancers become symptomatic when it is too late to successfully intervene. The effectiveness of conventional therapy is highly variable, frequently ineffective in preventing metastasis and carries a high level of side effects. While lifestyle and dietary changes can have an impact, for many individuals the risk reduction or benefit is not large. The ideal approach to prevention is to identify the presence of cancer while the number of cells is well below that required for any diagnostic technique. The ideal therapy is to target and kill cancer cells with a method that is not toxic to normal cells and does not product systemic side effects. Both of these approaches are the subject of considerable research effort. However, as will be discussed below, from what we know about Salvestrols and with blood tests now developed for the cancer-positive enzyme, both of these approaches already exist, are successful, have compelling biological plausibility and Salvestrols appear to be vastly better than anything conventional medical research has come up with except for a very few exceptional therapies for specific cancers and even for these,

Salvestrols may be equivalent. Nevertheless, Salvestrols as an unapproved alternative are ignored by most in keeping with modern attitudes of evidence based medicine.

The real danger of cancer and associated mortality involves metastasis. If cancer cells have not escaped the tumor and are either very slow growing or can be removed without spreading the cancer, then chances of a cure are high. It is frequently routine to examine nearby lymph nodes for evidence of spreading, and the results can influence decisions regarding radiation and chemotherapy to kill any remaining cells when the tumor removal was suspected of not being perfect, or simply to play it safe. However, once the cancer is spreading, even though radiation might kill some or most of the cells, it is not possible to irradiate the whole body. Low dose chemotherapy is sometimes employed, but as pointed out above, the metastasizing cells may have already been selected for treatment resistance by the initial chemotherapy making this approach futile. Metastasis involves the silent (asymptomatic) spread to other organs and locations such as liver, lung, brain, and bone. Remission merely means that there is no evidence of cancer, but this is exactly the situation with a primary cancer developing but not detectable by current methods. It is quite common for someone to be in remission or pronounced probably cured but after 5-10 years to have a secondary cancer develop which is identified as originating from the primary cancer. It is also quite common for the patient to be told “we got all the cancer” but obviously in most cases this is really a guess. Even when surgical margins are examined and pronounced cancer cell free, this is not necessarily definitive. Positron Emission Tomography (PET scans) can be very informative, but are in many jurisdictions reserved for those who can pay for it. The PET scan is just emerging from being almost entirely a research tool.

AFTER DIAGNOSIS, DECISIONS, DECISIONS, DECISIONS

This is a situation faced by thousands of individuals every day. Diagnosis will lead to a recommendation for treatment according to guidelines and in keeping with the usual practices. Unless the patient is a minor, in which case treatment can be forced against the parent’s wishes in some jurisdictions, the newly diagnosed patient will probably be given the option of making an informed decision regarding the proposed plan. This immediately raises a number of issues (caution, list incomplete):

- Are the decisions really informed decisions and consent really informed?
- Are those providing the information biased?
- Is the clinical data biased or even any good?
- What is the variation in survival times with treatment from individual to individual?
- Do the survival times seen in practice correspond to those reported in trials?
- Am I being deceived by the spin put on clinical results (dismal absolute benefits, sensational relative benefits based on the same data)?
- How often is the pathologist wrong?
- How many second, third or… opinions do I need?
- Have my tests been mixed up and actually apply to someone else?

- What is the track record where I am being sent for fatal or life altering mistakes in therapy which are well known to occur with both chemotherapy and radiation therapy?
- Is the oncologist selling chemotherapy drugs for personal profit?

These questions may strike some readers as a bit odd since they suggest that some of their perceptions concerning the diagnosis and treatment of cancer may not be correct. I know of one case where a friend's doctor commented while examining the report of a bone scan that he had a hip replacement which really shook up my friend since this was not true. In addition, we are seeing reports in the literature where the survival times of some very expensive new cancer drugs found in trials to obtain approval are not being seen in practice.

The decision regarding therapy and its aggressiveness, e.g. surgery vs. radiation, and chemotherapy, is obviously a personal decision involving many factors. Even cost has become an issue with some of the new therapies costing $50,000 to well over 100,000 per year and some are not covered by insurance or government plans. Patients are being offered the hope of, for example, an extra six months to a year, but this may include bankruptcy or great family financial hardship. The decision to accept some or all of the conventional recommendations for therapy should involve a risk-benefit analysis, but this is extremely difficult given the frequently imprecise knowledge of the extent of the cancer, the actual effectiveness of therapy for the individual when predicted from population studies, the potential for permanent damage from therapy even if administered correctly, something that does not always happen, the risk of mortality associated with the therapy, and in the final analysis, the reaction to what amounts to gambling on a game only partially understood.

It is important to realize that the evidence so far suggests that whatever choice is made, the door has not been closed to alternative treatments such as Salvestrols. Many of the successful case histories involve individuals who had undergone various conventional therapies first, sometimes electing only one of a set proposed. Some turn to Salvestrols with good results after failed conventional therapy. Patients may reject conventional therapy altogether and turn to alternative medicine, some which may be ineffective, some of which may work quite well. So much depends on the type of cancer, stage and grade, overall health and lifestyle of the individual, comorbidities, genetics, and much more.

In the discussion of Salvestrols that follows, emphasis will be on how these unique natural products solve the problems outlined above that exist for treatment, prevention, dealing with metastasis and the success of conventional therapy. Some readers are already familiar with various aspects of this subject, but this will serve to update the subject in the context of the above issues. Furthermore, the development of a blood test for Salvestrol substrates and metabolites should be of interest.

SALVESTROLS FOR CANCER THERAPY

Many IHN readers are familiar with how Salvestrols work. The active molecule circulating in the blood, a fruit derived polyphenol, enters the cancer cell and is metabolized in a reaction made possible by the enzyme CYP1B1. The Salvestrol is termed a substrate for the enzyme reaction that produces a product called a metabolite which acts to initiate cell death. When the Salvestrol molecule enters a normal cell, there is no enzyme and thus the reaction to produce a cell-toxic metabolite cannot happen. This is why there are no systemic side effects common in chemotherapy.

As mentioned above, the remarkable property of CYP1B1 prompted two researchers, Professors Gerald Potter and Dan Burke in Leicester, U.K. to search for both synthetic and natural substrates using cancer cell culture techniques [14-16] A synthetic prodrug was developed and as well, natural substrates for CYP1B1 yielding potent cytotoxic metabolites in cell culture studies were identified. Their research focused on the latter and Salvestrols were found in a number of fruits. A very interesting observation was that in comparison with organically grown fruit, that grown with insecticides and from highly inbred varieties or hybridized to decrease bitterness had remarkably low levels of these substrates. The name *Salvestrol* was given to these active compounds or extracts.[17] This name reflected their belief that Salvestrols are nature's defense mechanism against cancer. Salvestrols are vastly more selective than conventional chemotherapy because they target a single enzyme which is only in the cytoplasm of cancer cells, CYP1B1. The commercial product contains extracts from four fruits and thus provides a number of different substrate molecules for CYP1B1. The fruits were selected to provide maximum cancer cell death at the lowest concentration in cell culture experiments involving a number of different cancer cell lines.

The fruits used in the current Salvestrol formulation to make extracts are strawberries, blueberries, black berries and tangerine rind, all organic and older varieties where hybridization has not lowered the Salvestrol content. One might ask, why not just eat fruit? The answer is that one would have to eat an impossible amount of fruit to get the amount of Salvestrols available in a few capsules of the extracts. The cost would also be prohibitive and obtaining appropriate fruit nearly impossible for most individuals. However, Salvestrols are not a replacement for fruit consumption universally recommended for optimum health.

After ingestion, it takes about four hours for Salvestrols to reach peak blood levels. In the presence of cancer, after an additional 2 hours the metabolite will peak in the blood, reflecting release from dead cells into the circulation. As will be discussed below, this influences the ideal dosing protocol.

The evidence for human therapeutic efficacy derives from a number of case studies. In all cases listed in the table below, the cancer was considered to have gone into remission (after Salvestrol therapy) by the oncologists involved. Detailed case histories are available.[18-21] See in particular, *Salvestrols, Journeys to Wellness.*[21]

Table 1. **Summary of case histories by site collected by Dr. Brian Schaefer.**[21]

PRIMARY SITE	STAGE	CASES
Lung. Squamous-cell carcinoma	2-3	1
Melanoma	4	1
Prostate	3	3
Breast	3	2
Bladder	-	1
Liver	2	1
Colon	-	1
Hodgkin's lymphoma	3B	1
Anus. Squamous-cell carcinoma	-	1
Lymphocytic leukemia	-	1
Primary peritoneal carcinoma	-	1
Pancreas	-	1
Benign prostatic hyperplasia	-	1

The age range was 36-94, 59% male. Regarding conventional treatment prior to starting Salvestrols, 35% had surgery, 35% chemotherapy, 6% radiation and 18% had two different treatments and 23% had no conventional treatment. The results can be summarized as follows:

- For these 16 cases, average time to observed remission from start of Salvestrol treatment was 6 months (range 1-18). However, 15 reached remission within a year with a prostate cancer case taking 18 months. Average time in remission and still in remission, 41 months (range 8-82), 12 cases.
- Average time in remission followed by recurrence, 45 months (range19-60), 5 cases.
- Average time to remission for rapid responders, 2.1 months (range 1-3), 6 cases. Mortality. Two deaths, one from Alzheimer's disease, one of unknown cause. Both were in remission.
- All who had recurrences abandoned Salvestrols and did not change diet or lifestyle.
- For those still in remission 10 out of 12 continued to take maintenance doses of Salvestrols.

In the cases where the attending oncologist estimated life expectancy associated with conventional treatment, most cases reflected a large, unexpected survival due to Salvestrol therapy. It will be noted that the above table includes benign prostatic hyperplasia (BPH), normally not considered cancer and thus called benign. However, BPH tissue contains cells that express CYP1B1 as the enzyme,[22] and thus it is not surprising that the disease appears to respond to Salvestrols. Also, a recent study rather strongly links BPH to increasing the risk of both prostate and bladder cancer.[23] This is important since conventional treatments for BPH have unpleasant side effects and Salvestrols would probably prevent progression to prostate cancer and as well prevent bladder cancer. There is urgent need to examine the same question in benign

pre-cancer in the breast and as well, investigation of the question of Salvestrols preventing BPH from progressing to prostate cancer.

OTHER SETS OF CASE HISTORIES

Very exciting results are being reported by the distributor of Salvestrols in New Zealand. He is sponsoring a study of pediatric brain cancer in 20 children and with the assistance of an oncologist has assembled complete documentation of the cancers. The study is now in the follow-up stage and is obtaining excellent results as measured by remission or tumor shrinkage. It is the intention to publish the results in a book and hopefully in a journal article. Pediatric brain tumours are frequently fatal and conventional treatment debilitating. Two common types (glioblastoma and anaplastic astrocytoma) have 5–year survival rates of 20-30% according to NIH statistics.

FAILURES, INTERFERENCE AND INHIBITION OF SALVESTROL ACTION[24]

Treatment failures were also observed and appeared to arise from the following factors: poor diet and toxin intake, inhibition of CYP1B1 activity by drugs or diet, cancer too advanced, low dietary cofactors or micronutrients required for the enzyme mediated chemistry, and failure to continue taking a maintenance dose after remission. No evidence has been found for the development of treatment resistance.

As is common with enzyme-mediated chemical reactions, CYP1B1 does not operate in isolation but rather with the aid of cofactors.[25, 26] These include:

- biotin
- magnesium
- niacin (vitamin B3)
- riboflavin (vitamin B6
- iron
- vitamin C
- Fish oils and evening primrose oil (equazen and efalex) as health food store supplements

For the vitamins and minerals—a good multivitamin-mineral formulation offering at least the recommended daily allowance is a good start. Extra magnesium and vitamin C are advisable.

A number of chemicals found in food and supplements act as inhibitors of CYP1B1. This means that they bind to a site on the enzyme and may actually be a substrate generating a nontoxic metabolite or even a toxic metabolite but at too low a concentration to be important. However, in doing this they block or decrease the action of the Salvestrol. Resveratrol found in red wine and also sold as a supplement is an example of this latter effect, but the amount in red wine is insufficient to interfere with Salvestrol therapy. The following are contraindicated:

- fungicides: present in dandruff shampoos and antifungal creams and cleaning agents used in cleaning ductwork and as a prescription drug.

- resveratrol: not from red wine but only in high doses as found in supplements
- B17: laetrile, amygdalin, cyanogenic compounds
- fruit and vegetable juices: excessive consumption
- grapefruit
- cannabis
- gingko biloba
- ginseng: Asian or North American
- metformin: the popular type 2 diabetes drug.

In addition, it is important to avoid the supplement calcium D-glucarate, artificial sweeteners, and smoking.

The diet which gives the Salvestrols the best chance of being effective should be organic, high in fruit and vegetables, and the sources of protein should be grass-fed with poultry and eggs free range.

CYP1B1 requires oxygen for metabolism. Therefor modest exercise is important and oxygen levels can be enhanced by deep breathing exercises which should be done about 4 hours after taking a dose to have the advantage of high blood and cellular levels. This appears to be very important for optimum results.[24]

DIAGNOSIS BY DETECTING CYP1B1 IN SERUM

The original observation that CYP1B1 is not expressed in normal cells was found not to be universally true when highly sensitive methods of detection were used, although the levels were still vastly lower than found in tumor tissue.[27] Eventually the researchers developed a highly sensitive serum assay specific for human CYP1B1 protein.[27] It was possible to establish a baseline CYP1B1 level in individuals believed to be free of cancer which was minute but not zero. This background of CYP1B1 may reflect adventitious cancer cells constantly being generated. Another explanation is that some individuals judged free of cancer may have very low levels of circulating cancer cells from dormant cancer or small cancers which while proliferating, will take years to become symptomatic or detectable. In fact, one can hypothesize that everyone is constantly acquiring cancer cells and many simply overcome them via natural defense mechanisms. But a sensitive test picks it up. Based on thresholds derived from this background level, it is estimated that the present level of sensitivity allows cancer detection about 6 years prior to clinical manifestation. For example, CYP1B1 at between 100 and 6000 times normal background was measured in lung cancer patients with levels providing a good correlation with the extent of disease.[27]

MONITORING SUCCESS OF THERAPY WITH SERUM CYP1B1 METABOLITES

In the journal article dealing with the blood tests, Schaefer describes a second blood test termed the metabolic approach.[27] A sensitive analytical method was developed for testing blood and urine for both the Salvestrol (substrate) and its CYP1B1 metabolite, and provided the opportunity to detect the action of the enzyme and measure the extent

of the cancer by the change in substrate concentration and the appearance of metabolite. A Salvestrol was used that produced large amounts of metabolite with no confounding from dietary sources, and upon testing a group of healthy individuals it was found the Salvestrol was recovered unmetabolized in the blood and urine. When cancer patients were given the Salvestrol, the metabolite was found and the amount of substrate decreased with the magnitude of the effect dependent on the severity of the disease as estimated from the clinical presentation. For severe disease, the researchers were unable to detect any substrate, only the metabolite. These observations were made on individuals with breast, stomach, kidney, and prostate cancer with an array of stages but skewed towards more advanced cases.

The metabolic approach obviously offers the opportunity to measure the effectiveness of any given Salvestrol mixture, and as well to examine and adjust for individual dose dependence and response using the commercial extract. Finally a non-invasive judgment is possible regarding when a “cure” or significant regression has been achieved by this alternative approach. This can then be confirmed by conventional methods.

The proteomic approach is exquisitely sensitive and close to the state of the art for detection of a chemical in the circulation. Thus if screening is done and a positive result is obtained, where is the cancer? A serious problem since it may be small enough as to escape all modern attempts to locate it. Also, there is no *non-specific* anticancer treatment in so-called evidence-based or officially sanctioned cancer therapy that could be used in the absence of knowledge of the identity of the tumor site. But the metabolic approach allows testing the most modern and powerful Salvestrol on patients with cancer, even if not clinically evident, to determine if the metabolic markers change, thus potentially justifying and encouraging an alternative therapeutic program, independent of the lack of knowledge of the actual site. This represents a huge advance in the field of cancer detection and treatment. Unfortunately, few seem to be even aware of its existence.

SALVESTROLS FOR PRIMARY PREVENTION OF CANCER

A key question, the answer to which provides profound insight into cancer prevention, is cancer simply a disease of civilization or, put another way, is it caused by civilization? However, civilization is too broad a term. The beginnings of agriculture were about 10,000 years ago but fundamental changes only occurred in the late 1880s when food started to become industrialized with refined grain and sugar. This was followed by commercial vegetable oils, the introduction of trans-fats into the human diet, and the toxification of food due to the advent of Big Chemical entering the food business in so many ways with the ever increasing use of chemical additives in prepared foods. Pesticides and herbicides contaminate food, soil and water, and lately there is the rapid increase in GMO foods. Chemicals leach out of food and water containers. Highly toxic chemicals are even sprayed on some crops just before harvesting. Even the final product such as cereals and chips are sprayed with preservatives before packaging. The air we breathe contains toxins and even dangerous particular matter. Organic farmers can’t grow crops on ground contaminated by herbicides and pesticides. Their

crops are also contaminated by wind-born pollen from GMO fields. For a long time, affluent neighborhoods tended to be upwind in terms of the prevailing winds and wind-born toxins from industrial operations. The west end of town was the best place to live. This is still true in a number of towns today. One could go on and on about this.

A good example of the change that took place in the 20th century and the assault on human metabolic processes that had evolved over eons with the hunter-gatherer diets is the rise in production of refined omega-6 vegetable oils which are often described as pro-inflammatory fats. Virtually unknown in the early part of the century, production by the year 2000 had already reached 12 kg per person per year in the US,[28] and the ratio of omega-6 to omega-3 intake the US has now reached 15-20 whereas we evolved on a ratio near 1. Over this period, refined sugar consumption went from near negligible to over 170 pounds or 77 kg per person per year. White bleached flour went from a speciality item for the rich to a dietary staple. Today Big Food, Big Agriculture and the media dominate our dietary culture. There is compelling evidence that this has not been beneficial and not just in the context of cancer.

A recent study reviewed knowledge concerning cancer in ancient populations. For example a large amount of mummy and skeleton evidence revealed almost a total absence of cancer and no bone cancer.[29] But the implied question is complex and difficult to answer with data. There is a huge gap between the data on ancient populations and much more recent times when incidence of cancer appears to be rapidly increasing. An epidemiologist working for The World Health Organization once asked a Chinese doctor how he explained the low incidence of breast cancer there. He replied that it is a disease of rich women. "You will see it in Hong Kong but not here."[28]

Considerable insight can be gained by examining modern isolated populations viewed as representative of people untouched by civilization which also reveals little or no evidence of cancer. Dr. Albert Schweitzer examined over 10,000 natives in Africa in 1931 and found no cancer,[30] and Dr. Alexander Berglas searched for cancer in isolated populations in Brazil and Ecuador and found none.[31] Sir Robert McCarrison conducted a 7-year medical survey of the Hunza people living in isolation in northern India and could not find a single case of cancer (www.globaldialoguefoundation.org/files/41.pdf). Weston T. Price reported the same in his studies of 13 isolated populations and generalized his observations by saying that populations who had perfect teeth and dental arches were almost completely free of cancer or other diseases of civilization.[9] These observations suggest that cancer prevention might be successfully achieved by adopting the diet common to isolated tribes, i.e. limit or avoid all refined foods and eat only truly organically grown foods and meat from animals raised according to the practices used before the industrialization of meat production. Furthermore, drink and cook with only pure water, which today means reverse osmosis water. Tap water and even well water can no longer be assumed potable. It is also well known that when individuals move from countries or areas where cancer rates are low to where they are high, their risk levels tend to approach those associated with their new environment.[28,32]

A recent very large study examined the impact of a healthy lifestyle pattern on the incidence of cancer.[33-36] The healthy pattern involved never smoking or only past smoking, moderate alcohol consumption, not being overweight, weekly aerobic physical activity for 75 minutes or moderate activity like walking for 150 minutes. Participants who made up this group were defined as low risk and used as a reference group. All others were high risk. A third comparison group was the general US population, data being derived from a national database. It was found that when just the low and high risk groups were compared, 20 to 40%% of cancer cases can be prevented through lifestyle changes. The high risk group appeared to still be a lower risk than the general US population, where the comparable numbers using the low risk group as a control were 40% and 80% of cancer cases prevented. This study coupled with the studies of modern primitive populations leaves little doubt as to the importance of lifestyle and diet in preventing cancer. It seems clear that many years ago humans changed how they live in keeping with modern advances that provided convenience, rewarding taste and integrated well into the hectic lives of people constantly on the go. But adaptation was necessary since what was happening was contrary to human physiology and evolution. The adaptation does not appear to have been neither extensive enough nor very successful. Today chronic disease is rampant and cancer incidence is increasing for most cancers.

There are now vaccines either approved or being developed that may provide prevention, although the heavily promoted Gardasil has turned out to be controversial and may have an unacceptable benefit vs. risk. Removal of precancerous tissue also qualifies as prevention. Examples are excisions prompted by positive Pap smears and the removal of polyps found in colonoscopy. But this barely scratches the surface of the overall problem. Even though screening such as with mammography or the PSA test has the potential to detect early cancer which can be prevented from becoming invasive or metastatic, these screening tests remain controversial due again to problems with benefits vs. risks, in this case of over diagnosis and overtreatment. Current guidelines restrict the eligible population for mammography and discourage the PSA test.[10-13] The US Preventive Tasks Force's latest positon on PSA testing based on no effect on mortality has been challenged on the basis of a re-evaluation of a key study and may be softened.[37] Some critics view the recommendation to discourage PSA screening as bad advice. It is hard to argue against having a baseline value at middle age. However, the colonoscopy and occult fecal blood tests get qualified approval as does the Pap test and screening for lung cancer in high risk individuals. Given the large number of different cancer types for which there is no recommended screening protocol, screening cannot solve the larger problem of early detection in general. In fact, what really happens is that most simply sit and wait until they have symptoms. The symptoms may even be from metastatic cancer where the primary cancer has remained asymptomatic. Clearly, the challenge is to prevent all cancers, and targeted prevention or specific screening fail to solve this key problem.

It can be argued that Salvestrols are the ideal preventive agent. They target all cancer cells, should kill cancer cells very early in the natural history of the disease, have compelling biological plausibility supported by a large peer-reviewed literature, and may

also target benign hyperplasic tissue and benign tumors. They also solve the problem of theoretically being able to kill individual cells or small clumps of cells that are years away from proliferating to yield diagnosable cancer. Cancer cells caused by mutations from cosmic rays and natural radioactivity, replication errors, and epigenetic factors related to environmental interactions, all yield cancer cells which would be expected to be destroyed sooner or later by circulating Salvestrols. The same would apply to tumors too small to detect by any present conventional procedures. Furthermore, the blood tests discussed above can be used to detect subclinical cancer and even determine the success of Salvestrols in eradicating it. All that is required is for the cancer cell to encounter a Salvestrol molecule which enters the cell cytoplasm. The identity of the cancer appears irrelevant as does the location unless the location has a high level of inhibitors which may be the case with prostate cancer. What more would one ask for? Not only is this approach highly biologically plausible, it is simple and apparently totally safe. The active chemicals have been in the human diet for eons. Furthermore, one is not trying to zero in on one cancer but all cancers. One can seemingly ignore the huge literature on preventing this or that cancer, generally with only modest effects, and there are too many cancers to make this a reasonable approach. Salvestrols have the potential for being 100% effective and independent of the cancer type with rare exceptions. A large cohort follow-up prevention study would be wonderful, but it will probably never happen. But the benefit/risk ratio of using Salvestrols for prevention would appear to have a zero denominator and most readers know what division by zero yields.

While follow-up studies using low doses of Salvestrols for prevention would be very informative and desirable, they require large cohorts and long follow-up, and would need to be financed by non-industry sources, which is unlikely because of the bias against natural approaches to solve problems in mainstream medicine.

DOSES

The supplier of Salvestrols does not provide dose information for cancer therapy or prevention, but only for serious health challenges in general. There are no published clinical trials that provide dose guidance, only case histories which Evidence Based Medicine regards as unreliable and unsatisfactory. The dose information given below is not approved by any government regulator. Salvestrol strength is given in an unusual unit termed “points” which relates to results in cell culture studies of cancer cell toxicity. A low dose is 2000 points. The most common capsule contains 2000 points.

***For primary prevention*:** First complete a cleansing program using 4000 points per day for at least two months. Then drop to 2000 per day for another two months. Then use this dietary supplement at 2000 per day for continued prevention.

***Therapeutic dosing guide**:* This is complicated because of dependence on the severity of the disorder and individual weight or body mass index. The company provides the following guidelines (as approved by Health Canada). Consult your health care provider for guidance. A dose regime to be considered might include 6000 points per day with

4000 at breakfast and the balance at lunch. Individuals overweight or obese may want to consider higher doses.

***When in remission*:** Take 2000 points daily with a meal and once a year return to the therapeutic dose for one month.
Author's comment: Once the blood tests are available, the obvious solution to the dosing is to monitor the effectiveness of the initial choice. As the tumor or cancer regresses there should be a decrease in the metabolite for a given dose. Increasing the dose should increase the metabolite levels and indicate that the therapy is working in a dose dependent manner. If remission is hoped to be achieved in a year or less, the rate of decrease of metabolite production can be extrapolated to get some idea of an adequate dose. Tumor size change from imaging would provide additional information. If the therapy does not appear to be working or working poorly, look for reasons among those given above.

THE FUTURE

One fascinating question in this field concerns the expression of CYP1B1 in tumor progenitor cells also called tumor stem cells. While this does not appear to have been studied, indirect evidence comes from studies where resveratrol, a polyphenol in red wine and the first Salvestrol discovered, was found to kill cancer cultured cancer stem cells derived from a number of different cancers, implying a single mechanism which is likely to involve CYP1B1.[38-40] It is well established that metabolism of this polyphenol produces a metabolite which is cytotoxic.[1] If it turns out that cancer stem cells all express CYP1B1 as the enzyme just like regular cancer cells, this would be sensational and of great importance. For example, cancer stem cells may be directly involved in metastasis. Interestingly, this appears to have never occurred to the authors of the cited resveratrol papers.

Salvestrols are a natural product which cannot be patented. The company that sells this product makes no specific health claims whatsoever which concern cancer prevention or treatment, and only in the resources section of their website is the word "cancer" to be found in titles of papers or talks. Regulatory agencies, especially the US FDA take great pride in protecting the general public from ineffective products, false claims regarding benefits, and quacks in general, and companies that sell products such as Salvestrols must operate with extreme care or face brutal treatment. Claims regarding efficacy must be based on clinical evidence approved by regulatory bodies, and generally this involves randomized, blinded, placebo-controlled trials as the final step in proof of efficacy. Such requirements erect a huge barrier for natural products when health benefits are seen outside the strict rules and context of evidence based medicine and cost hundreds of millions of dollars. Regulatory agencies severely limit claims that can be made on websites and advertising. Thus so-called alternative medicine and its approaches to disease and treatments only become known by word of mouth and in writing by individuals who are either not connected with commercial enterprises involved or are merely presenting facts that are public knowledge.

Given the above, it can be predicted that the potential benefits of Salvestrols will continue to become known by word of mouth, social media, and from articles and books that do not come under the control of regulatory bodies defending the public from harm and quackery. It is irrelevant that what really goes on as the pharmaceutical industry interacts with regulators and the medical profession may suggest a certain level of hypocrisy and inconsistency and fraud in the system. It is certainly of interest to Big Pharma to suppress alternative medicine that would compete directly with drugs and therapies each generating billions per year.

There is obviously a great need for private or government money to finance appropriate clinical trials concerning promising natural and alternative therapies. This does happen and is happening today, but this is exceptional. The sad thing is that only the pharmaceutical industry has the money to finance the testing of new drugs and devices. This of course has inherent conflicts of interest which frequently become known with concomitant scandal and even criminal charges and fines, the magnitude of which boggle the mind of the uninitiated.

Readers of the above review and perspective are merely being given what is public knowledge, information they can use as they see fit with full recognition of the absence of proof of efficacy or safety that would satisfy regulators.

CONCLUSIONS

Since the discovery by Dr. Burke, great progress has been made. The attempt to formulate an optimum and effective mixture of Salvestrols providing both water and fat solubility and passage through the blood-brain barrier appears to have been very successful. Physicians and clinics around the world are trying Salvestrol therapy.

DISCLAIMER

This review must not in any way be regarded as providing medical advice but rather information that individuals can use in discussions with their doctor. INTERNATIONAL HEALTH NEWS does not provide medical advice. Do not attempt self-diagnosis or self-medication based on reports in INTERNATIONAL HEALTH NEWS. Please consult your healthcare provider if you are interested in following up on the information presented herein.

RECOMMENDED ADDITIONAL READING *

- **THE DEATH OF CANCER: AFTER FIFTY YEARS ON THE FRONT LINES OF MEDICINE, A PIONEERING ONCOLOGIST REVEALS WHY THE WAR ON CANCER IS WINNABLE—AND HOW TO GET THERE.** Vincent T. DeVita, MD and Elizabeth DeVita-Raeburn. Macmillan, 2015.

- **SALVESTROLS. NATURE'S DEFENSE AGAINST CANCER.** Brian A. Schaefer, D. Phil (Oxon), Clinical Intelligence Corp, 2012. Available in English, Spanish, German, Dutch, French, Hungarian and Romanian. And soon in Greek, Turkish and Japanese.

- **SALVESTROLS. JOURNEY TO WELLNESS.** Brian A. Schaefer, D. Phil (Oxon) Clinical Intelligence Corp. 2013. Available in English and soon to be available in Spanish, Dutch and Greek.

- **ANTICANCER. A NEW WAY OF LIFE**. David Servan-Schreiber, MD, PhD. HarperCollins, 2009, recently updated.

- **THE EMPEROR OF ALL MALADIES. A BIOGRAPHY OF CANCER.** Siddhartha Mukherjee, MD. Scribner (Simon & Schuster), 2010.

- **RADICAL REMISSION. SURVIVING CANCER AGAINST ALL ODDS.** Kelly A. Turner, PhD. HarperCollins, 2014. Currently translated into 18 languages.

- **TRIPPING OVER THE TRUTH. THE RETURN OF THE METABOLIC THEORY OF CANCER ILLUMINATES A NEW AND HOPEFUL PATH TO A CURE.** Travis Christofferson, 2014.

* In the opinion of the author of this review, these are among the most significant and authoritative books on this subject published in recent years.

REFERENCES

(1) Schaefer B. *Salvestrols. Nature's Defence Against Cancer. Linking diet and cancer.* Clinical Intelligence Corp; 2012.
(2) DeVista V, DeVita-Raeburn E. *The Death of Cancer*. New York: Macmillan; 2015.
(3) Friedman R. Drug resistance in cancer: molecular evolution and compensatory proliferation. *Oncotarget* 2016 March 15;7(11):11746-55.
(4) Day T, Read AF. Does High-Dose Antimicrobial Chemotherapy Prevent the Evolution of Resistance? *PLoS Comput Biol* 2016 January;12(1):e1004689.
(5) Klement GL. Eco-evolution of cancer resistance. *Sci Transl Med* 2016 February 24;8(327):327fs5.
(6) Poff AM, Ari C, Seyfried TN, D'Agostino DP. The ketogenic diet and hyperbaric oxygen therapy prolong survival in mice with systemic metastatic cancer. *PLoS One* 2013;8(6):e65522.
(7) Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. *Carcinogenesis* 2014 March;35(3):515-27.
(8) Poff AM, Ward N, Seyfried TN, Arnold P, D'Agostino DP. Non-Toxic Metabolic Management of Metastatic Cancer in VM Mice: Novel Combination of Ketogenic Diet, Ketone Supplementation, and Hyperbaric Oxygen Therapy. *PLoS One* 2015;10(6):e0127407.
(9) Price WT. *Nutrition and Physical Degeneration.* Oxford: Benediction Classics; 2010.
(10) Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012 July 17;157(2):120-34.
(11) Penson DF. The Pendulum of Prostate Cancer Screening. *JAMA* 2015 November 17;314(19):2031-3.

(12) Mandelblatt JS, Stout NK, Schechter CB et al. Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies. *Ann Intern Med* 2016 February 16;164(4):215-25.
(13) Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. *JAMA* 2014 April 2;311(13):1327-35.
(14) Potter GA, Burke MD. Salvestrols--Natural products with tumour selective activity. *Journal of Orthomolecular Medicine* 2006;21(1):34-6.
(15) Potter GA, Patterson LH, Wanogho E et al. The cancer preventative agent resveratrol is converted to the anticancer agent piceatannol by the cytochrome P450 enzyme CYP1B1. *Br J Cancer* 2002 March 4;86(5):774-8.
(16) Androutsopoulos V, Arroo RR, Hall JF, Surichan S, Potter GA. Antiproliferative and cytostatic effects of the natural product eupatorin on MDA-MB-468 human breast cancer cells due to CYP1-mediated metabolism. *Breast Cancer Res* 2008;10(3):R39.
(17) Tan HL, Butler PC, Burke MD, Potter GA. Salvestrols: A New Perspective in Nutritional Research. *Journal of Orthomolecular Medicine* 2007;22(1):39-47.
(18) Schaefer BA, Hoon.L.T., Burke MD, Potter GA. Nutrition and Cancer: Salvestrol Case Studies. *Journal of Orthomolecular Medicine* 2007;22(4):177.
(19) Schaefer B, Dooner C, Burke D, Potter G. Nutrition and Cancer: Further case studies involving salvestrol. *Journal of Orthomolecular Medicine* 2010;25(1):17-23.
(20) Schaefer B, Potter G, Wood R, Burke D. Cancer and related case studies involving salvestrol and CYP1B1. *Journal of Orthomolecular Medicine* 2012;27(3):131-8.
(21) Schaefer BA. *Salvestrols. Journey to Wellness*. Clinical Intelligence Corp.; 2013.
(22) Carnell DM, Smith RE, Daley FM et al. Target validation of cytochrome P450 CYP1B1 in prostate carcinoma with protein expression in associated hyperplastic and premalignant tissue. *International Journal of Radiation Oncology*Biology*Physics* 2004 February 1;58(2):500-9.
(23) Dai X, Fang X, Ma Y, Xianyu J. Benign Prostatic Hyperplasia and the Risk of Prostate Cancer and Bladder Cancer: A Meta-Analysis of Observational Studies. *Medicine (Baltimore)* 2016 May;95(18):e3493.
(24) Schaefer B. Personal communication. 2012.
(25) Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K(m)): relevance to genetic disease and polymorphisms. *Am J Clin Nutr* 2002 April;75(4):616-58.
(26) Ames BN. A role for supplements in optimizing health: the metabolic tune-up. *Arch Biochem Biophys* 2004 March 1;423(1):227-34.
(27) Schaefer B. Development of Blood Tests for Early Cancer Detection. *The International Journal of Phytotherapy* 2013;1(2):6-12.
(28) Servan-Schreiber D. Anticancer. A New Way of Life.New York: HarperCollins; 2009.
(29) David AR, Zimmerman MR. Cancer: an old disease, a new disease or something in between? *Nat Rev Cancer* 2010 October;10(10):728-33.
(30) Stefansson W. *Cancer, Diseases of Civilization*. 1980.
(31) Berglas A. *Cancer: Nature, Cause and Cure*. Institute Pasteur, 1957.
(32) Sasco AJ. [Migration and cancer]. *Rev Med Interne* 1989 July;10(4):341-8.
(33) Song M, Giovannucci E. Preventable Incidence and Mortality of Carcinoma Associated With Lifestyle Factors Among White Adults in the United States. *JAMA Oncol* 2016 May 19.
(34) Colditz GA, Wolin KY, Gehlert S. Applying what we know to accelerate cancer prevention. *Sci Transl Med* 2012 March 28;4(127):127rv4.
(35) Colditz GA, Sutcliffe S. The Preventability of Cancer: Stacking the Deck. *JAMA Oncol* 2016 May 19.
(36) Dart H, Wolin KY, Colditz GA. Commentary: eight ways to prevent cancer: a framework for effective prevention messages for the public. *Cancer Causes Control* 2012 April;23(4):601-8.
(37) Shoag JE, Mittal S, Hu JC. Reevaluating PSA Testing Rates in the PLCO Trial. *N Engl J Med* 2016 May 5;374(18):1795-6.
(38) Filippi-Chiela EC, Villodre ES, Zamin LL, Lenz G. Autophagy interplay with apoptosis and cell cycle regulation in the growth inhibiting effect of resveratrol in glioma cells. *PLoS One* 2011;6(6):e20849.

(39) Seino M, Okada M, Shibuya K et al. Differential contribution of ROS to resveratrol-induced cell death and loss of self-renewal capacity of ovarian cancer stem cells. *Anticancer Res* 2015 January;35(1):85-96.
(40) Fu Y, Chang H, Peng X et al. Resveratrol inhibits breast cancer stem-like cells and induces autophagy via suppressing Wnt/beta-catenin signaling pathway. *PLoS One* 2014;9(7):e102535.

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