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The feature piece in this month's IHN involves autism and its continuing dramatic increase. Your editor's interest in autism is prompted by such factors as the existence of a therapeutic protocol which offers the potential for improvements well beyond what is currently being achieved by mainstream medicine which almost entirely deals with treating symptoms and improving coping. Also treatment with antipsychotic drugs never tested on children throughout their years of development is increasing. But an important reason is that this disorder seems like the classical canary in the mine. The incredibly rapid growth in incidence in the past 10 years, as discussed in this issue, and the latest prevalence of 1 in 42 boys points strongly to the notion, if this data is indeed correct, that there is something seriously wrong with our current environment, lifestyle and attitude toward the safety of medications. The dramatic increase in the use of powerful psychiatric drugs among all ages including children, even toddlers, merely reinforces this fear of something terribly amiss out there. One even sees this in our closest animal friends. About 50% of cats and dogs now die of cancer. It is easy to imagine their long-term exposure to a large variety of toxic substances, an exposure, aside from contaminated pet food, that we share with them. Many other examples could be given to strengthen the notion of a crisis associated with toxins. There are many canaries showing signs of distress.

But there appear to be scant indications for optimism. Big agriculture, Big Pharma, the gigantic food industry, and government regulatory bodies which exist to protect us have remarkably successful strategies long perfected to convince us that the air we breathe inside and outside the home, the water we drink, and the food we eat are all safe and the medications we consume in incredible amounts provide benefits that in most cases vastly exceed the risks the manufactures have allegedly quantified. While effective methods are used to muzzle what are viewed as alarmist academics, today the internet and the social media offer critics a great platform, but they have little hope of overcoming the classical approach perfected long ago by the tobacco companies—there is no scientific proof. The very nature of the problems we face fit nicely with this strategy. One cannot do the ideal experiments to gather acceptable data when humans are involved. Furthermore, as adverse data accumulates on some chemical or drug, new ones are there to fill the void with safety testing that is mostly the same as created the existing problems. Thus we are entirely on our own in attempting to devise a safer home environment, safer lifestyle, and a detoxification program that is multifactorial, easy to implement, and addresses the hopelessness of totally avoiding becoming loaded with the multitude of toxic substances we are exposed to each day, even from some organic foods.

This issue also contains discussion of testosterone therapy, the issue of chemotherapy for breast cancer in the presence of a favourable prognosis, and the shocking waste of billions of dollars of public funds stockpiling virtually useless antiviral drugs that received regulatory approval and enthusiastic support from the medical community based on incomplete and apparently selected data. Also, the disease creation machine is very seriously proposing a new mental disorder afflicting mankind, Sluggish Cognitive Tempo.

Finally, if you need to restock your supplements, please remember that by ordering through the on-line vitamin store you will be helping to maintain the web site and publication of IHN. You can find the store at http://www.yourhealthbase.com/vitamins.htm.

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

AUTISM RATES SKYROCKET

The U.S. Centers for Disease Control has just published on their internet site the latest numbers for the prevalence of autism spectrum disorder (ASD). The data apply to 8-year old children and the numbers are derived from surveillance data gathered in 2010 from 11 communities. An overall prevalence of 1/68 was found. The CDC breaks down the data to show that for boys the 2010 prevalence was 1/42, girls 1/189, white children 1/63, black children 1/81 and Hispanic 1/93. Almost half of the children had average or above average IQs. About 80% received special educational services. The reason for the difference between boys and girls is not clear.[1] The above approach of looking at single birth-year cohorts is justified by the finding that children diagnosed with this disorder are likely to retain the diagnosis, something that it is important to realize in the context of this disorder.[2] One result of this study points to critical need for additional research. Why in this latest set of data, is the overall prevalence in New Jersey 1/45 whereas in Alabama it is 1/175 with other states well above or below the average?

In 1990 the prevalence was 1/500 and 10 years earlier 1/2500. The CDC data for 2000-2010 are show in the table below. If one graphs the data using a logarithmic scale, it is evident that the rate of increase from 2002 to 2010 is slightly faster than simple exponential growth.

PREVALENCE OF AUTISM SPECTRUM DISORDER						
SURVEY YEAR	2000	2002	2004	2006	2008	2010
PREVALENCE	1/150	1/150	1/125	1/110	1/88	1/68

Allen Frances in his 2013 book *Saving Normal. An insider's revolt against out-of-control psychiatric diagnosis, DSM-5, Big Pharma, and the medicalization of ordinary life,*[3] took the position that the rapid increase in the prevalence of autism is caused to a significant extent by overdiagnosis due to the expanded definition in the 1994 DSM-IV diagnostic manual. He directed the writing of this manual. He suspects that physicians were also looking harder for symptoms, and acting on earlier signs. Also, the definition of ASD after 1994 contained additional disorders aside from classical autism such as Asperger syndrome, pervasive development disorder not otherwise specified and childhood disintegrative disorder. The CDC counts all of these but unfortunately does not provided a breakdown since data on classical autism would be most informative. Data from the CDC based on a uniform data collection protocol did not begin until the 2000 assessment date of an 8-year old 1992 birth cohort. If overdiagnosis was occurring arising from DSM-IV it would have impacted the result of this assessment, but the effect should have then reached a plateau in subsequent assessments. However, the use of an 8-year cohort evaluated every 2 years would tend to

smooth out the effect and thus the observed almost exponential increase in prevalence from the 2000 to the 2010 assessment cannot be used to judge the validity of the overdiagnosis hypothesis. Instead, a levelling off of overdiagnosis would probably simply reduce the rate of increase.

US data based on autistic children obtaining service under the *Individuals with Disability Educational Act* (IDEA) provide relevant data. A graph covering 12 years from 1996 to 2007 showed an exponential increase in prevalence in 6-17 year olds evaluated annually with a doubling time of about 4 years, which is similar to a data from 1994 to 2005 from a difference source cited by the CDC which had a crude doubling time of about 3.5 years. This can be compared with the data in the above table which, ignoring the departure from a pure exponential increase between 2008 and 2010, had a doubling time of about 6 years. Thus there is no evidence of levelling off, but again the wide age range used could mask it. There do not appear to be any useful data covering 1990 to 2000 which might show this effect. If one uses the commonly cited figure of a prevalence of 1/500 in 1990, then the semi-log graph of the CDC data in the above table extends downward to exactly intersect this point, but the difference in assessment methods in 1990 makes this extrapolation highly suspect and simply an interesting observation. If the 1/500 number is close to being valid, then again there is no evidence of the impact of DSM-IV starting in 1994. However, the range of doubling times described is curious.

The UK provides an interesting contrast. Following a 5-fold increase in the annual prevalence rates of autism during the 1990s, the rates in 8-year old children reached a plateau in the early 2000s and has remained steady through to 2010.[4] Note they are using the same protocol as the CDC. One explanation is that these data indeed show the impact of DSM-IV but that the UK differs from the US in significant causes of autism which continue to increase in importance.

Independent of the extent of overdiagnosis, the prevalence numbers represent a crisis. The CDC claims 80% are in special education programs. However, there is the ADS label, and both this and the disorder represent a disaster for both patients and their parents.

The approach of mainstream medicine when confronted with the problem of autism is to address symptoms. Assistance in the form of therapy is available to aid autistic children in coping with their disorder and achieving as much as possible under the circumstances. Psychiatric medications may be prescribed to treat autism-related symptoms such as anxiety, depression or obsessive-compulsive disorder and antipsychotic drugs are used to treat behavioral problem. The use of these drugs to deal with symptoms in autistic children may do them vastly more harm than good in the long run.

Alternatives exist. As discussed in the November 2012 issue of IHN and in the book *Children with Starving Brains. A medical treatment guide for Autism Spectrum Disorder* (4th Edition*)* by Jaquelyn McCandless, MD (certified as a diplomat of the American Board of Psychiatry and Neurology, now deceased), doctors practicing integrative medicine have achieved good results in returning many autistic children to at least near normal using a so-called biomedical, whole person approach which addresses causes including diet, environmental toxins and gut dysfunction.

In her book, Dr. McCandless outlined the suspected causes of autism. The list is consistent with the current view concerning the multifactor nature of the disorder.

- Genetics
- The toxic chemical model
- The heavy metal contamination model
- Vaccinations
- The auto-immunity/allergy model

- The viral model
- The gluten/casein, enzyme deficiency and yeast overgrowth model
- The metallothionein theory (dysfunction or deficiency of an important regulatory and detoxification protein)

Dr. McCandless discussed how these models of causation lead to treatments that result in significant improvements and even the discarding of the diagnosis entirely. A working hypothesis she advanced was that impaired immunity, gut inflammation, elevated infection rate, increase use of antibiotics, maldigestion and malabsorption, and decreased ability to handle toxins such as heavy metals or pathogens, including viruses and fungi, is a description that fits most autistic children. Her book describes how this hypothesis has successfully guided the design of a whole-person biomedical approach to therapy.

The approach described and used by McCandless in her practice and by physicians who believed in it is in sharp contrast to the recommendations recently provided in an article in *Autism Research and Treatment*,[5] where three complementary and alternative treatments were recommended: melatonin, vitamin/mineral supplement at the official recommended daily intake or allowance and massage therapy. Everything else is more or less dismissed with the comment "without rigorous scientific research, we don't actually know whether these so-called treatments are effective for treating autistic symptoms." Parents who seek out complementary and alternative therapy were viewed by the authors as concerned about the adverse effects of psychiatric drugs and were probably desperate. Can one blame them? The fact that many are willing to try anything does not reflect well on the conventional therapeutic approach. For them, helping the autistic child to cope is not enough.

It is time for medical science to give high priority to the question, why are the rates of ASD both so high and increasing so rapidly? These children are like the classical canary in the mine. There is something terribly wrong out there associated with factors such as lifestyle, environment and probably medication practices, and while genetic effects are no doubt in play, so are environmental effects on genetic expression. Scientists have to open their minds to unpleasant and unpopular theories and governments need to act with vastly increased research support. The answer is probably not in single drugs aimed at single targets.

RECENT STUDIES CONTINUE TO IMPLICATE ENVIRONMENTAL TOXINS AND PRESCRIPTION DRUGS AND RISK OF AUTISM

- Gestational exposure to environmental endocrine-disrupting chemicals was identified with the risk of autism. Included were PCBs and flame retardants. Flame retardants are common household pollutants and are found in fabrics, carpets, mattresses, insulation and electronic devices.[6]
- Living in highly polluted areas in the US, as judged by the prevalence of reproductive abnormalities in newborn boys (the classical canary in the mine), strongly increases the risk of autism. The incidence of autism increased by 238% for every percent increase in reproductive malformation incidence. Heavy metals and pesticides are implicated.[7]
- Prenatal antidepressant use was found to increase the risk of autism in offspring. Among boys, prenatal SSRI exposure was nearly 3 times as likely in children with autism relative to those with typical development.[8]
- Prenatal use of the psychiatric drug Valproate has been associated with autism. Valproate is used to treat or prevent seizures, manic or mixed episodes in bipolar patients, and to prevent migraine headaches.[9]

This is just a sample. The reader is referred to the discussion in IHN (April 2014 issue) regarding toxins and neuronatal development.

SLUGGISH COGNITIVE TEMPO. THE POTENTIAL NEW ADDITION TO MENTAL DISEASE MENAGERIE

The January 2014 issue of the *Journal of Abnormal Psychology* devotes 136 pages to papers describing this proposed mental illness which would open new markets for drugs now used to treat ADHD. Your editor examined the full text versions of the papers in both ordinary and pdf format. This journal apparently does not require explicit declaration of conflicts of interest or the absence thereof. However, in an article in the April 11 *New York Times* Alan Schwarz pointed out that one of the co-authors of three of the papers had conducted a clinical trial for a major pharmaceutical whose flagship drug is used to treat ADHD. Other prominent authors involved with this set of papers refused Schwarz's request to comment on their work.

The issue here is the same as with ADHD, i.e. how many of those diagnosed are in fact normal and do not need therapy, especially drug therapy which is the typical response. It is well known that one of the achievements of the pharmaceutical industry is its incredibly successful business plan which includes the creation of diseases for which companies either have or can develop drugs. This has worked especially well in the field of psychopharmacy. Currently we are told there are over 300 mental disorders afflicting mankind.

The lead paper claims that the question of the existence of this new disease "seems to be laid to rest as of this issue." It is touted as the new attention disorder. Sluggish Cognitive Tempo is characterized by lethargy, daydreaming, mind wandering and slow mental processing. In his *New York Times* article, Schwarz quotes Allen Frances, emeritus professor of psychiatry at Duke, who was head of the DSM-IV program, "We're seeing a fad in evolution: Just as ADHD has been the diagnosis du jour for 15 years or so, this is the beginning of another [fad]…..This is a public health experiment on millions of kids." Readers are referred to the new book by Frances, *Saving Normal. An insider's revolt against out-of-control psychiatric diagnosis, DSM-5, Big Pharma, and the medicalization of ordinary life.*[3]

The magnitude of the problem is clear from the latest US Centers for Disease Control survey of the use of medications prescribed for emotional or behavioral difficulties among children 6-17 years of age.[10] The results: 7.5% of children, 5.2% of girls, 9.7 % of boys are taking psychiatric drugs for what they, their parents and the prescribing physician view as mental disorders. The prevalence is highest among Medicaid/Children's Health Insurance Program participants and among children where the family income is less than 100% of the poverty threshold. It may surprise some readers that the highly addictive street drug crystal meth (methamphetamine), target of swat team raids on illegal labs, is also a prescription drug (Desoxyn) for ADHD.

If almost one in ten US boys have a mental disorder, its seems time to ask why. Either there is a huge unaddressed health problem in the US or overdiagnosis and thus overtreatment is rampant. The latter view has many supporters. Readers are also referred to an article by Alan Schwarz in the *New York Times*, December 14, 2013 titled *The Selling of Attention Deficit Disorder*, which is available on the internet. See also *No Child Left Undiagnosed* by Allen Frances (*Psychiatric Times*, April 18, 2014. Free online, registration required).

According to the high profile psychiatrist and critic Peter Breggin, psychiatric drugs do not correct chemical imbalances in the brain since there is no evidence that they exist. Instead, they alter the brain providing for some the impression of benefit but in fact this involves, for a significant number of treated individuals, changes and damage to the brain which can become permanent.[11,12] In his view, based on 40 years of experience in private and forensic

practice, psychiatric drugs do not cure mental disease for a significant number of disorders, but rather in many cases they cause them or convert a mild disturbance into a major and perhaps life–altering disorder. When their condition worsens, patients are told a new disorder has been "unmasked."

It must be pointed out that there are mental disorders which require aggressive drug therapy. However, some of the greatest successes in modern psychiatry appear to be associated with successful drug withdrawal returning the patient to normal, giving them back their lives.[12,13]

DOWNSIDE OF AGGRESSIVE BREAST CANCER TREATMENT IN INDIVIDUALS WITH FAVORABLE PROGNOSIS

In a recent viewpoint article in the *Journal of the American Medical Association,* Stephen Katz (University of Michigan Medical School) and Monica Morrow (Weil Medical College and Memorial Sloan Kettering Cancer Center), discuss the importance of focusing on individualized treatment for patients with breast cancer.[14] The issue is the overtreatment of patients with favorable prognosis increasing identified through population screening which results in unnecessary morbidity and treatment burden. Many factors drive aggressive treatment. These include payment structures (physician and hospital revenue), and uncertainty about the extent of the disease which may be avoidable. Clinicians are concerned about being faulted for not using all possible therapies if a bad result occurs. In addition, they are praised for favorable outcomes, although in most cases the more aggressive treatment was unlikely to have made a difference if the prognosis was favorable. Katz and Morrow cite data indicating that 87 out of 100 patients with invasive breast cancer with favorable prognosis treated with locoregional and endocrine therapy alone will be disease free and alive at 10 years compared to 89 of 100 who were also given chemotherapy. But most of the women who underwent chemotherapy will attribute their disease-free survival in part to the more aggressive therapy and praise their physicians for the achievement.

The authors also discuss the impact of patient views such as strong aversion to risk, desire for peace of mind, and the fear of regret over omitting some aspect of the standard therapy if recurrence were to occur. They also point out that advances in the use of tumor markers have the potential to reduce the morbidity and burden of treatment by increasing the accuracy of predicting individual net benefit. These tests are less prone to error than current commonly used methods to determine the extent of the disease (imaging and lymph node histology--biopsy). It is important to realize that the recent trends in screening have resulted in a high rate of diagnosis of very early and possibly insignificant cancers, some of which perhaps should not be called cancer at all. The common although certainly not universal practice is to aggressively treat all.

A study has just appeared that is highly relevant to the above viewpoint. It examined the impact of including chemotherapy in the treatment of early-stage breast cancer on return to work and long-term employment.[15] The researchers used a questionnaire approach to ascertain employment information four years after treatment for non-metastatic breast cancer at hospitals in both Los Angeles and Detroit. Subjects were free of recurrence. It was found that the loss of paid employment after a diagnosis of breast cancer may be common, often undesired, not restricted to the treatment period but potentially related to the type of treatment given. The important aspect of treatment that they found associated with the failure to return to work, even though there was no recurrence, was chemotherapy which has the potential for both neurocognitive and neuropathologic long-term adverse effects. Those who had chemotherapy had a 38.4% 4-year unemployment rate whereas for those who did not, the number was 26.7%. This is in spite of a range of stages with 42% having stage III. They point to these results as supporting initiatives now being actively evaluated including

improved strategies to identify patients who might omit chemotherapy because the marginal benefit in their particular early stage cancer is very small.

TAMIFLU SAGA

There are two antiviral drugs approved for the treatment of influenza, Tamiflu and Relenza. Both belong to the same class of drug called neuraminidase inhibitors. The medical establishments worldwide embraced these drugs. According to the US Centers for Disease Control, "For people with a high risk medical condition, treatment with an antiviral drug can mean the difference between having a milder illness instead of a very serious illness that could results in a hospital stay." The National Instituted for Health and Care Excellence in the UK (NICE) stated that these two antivirals are indicated for patients who have a high risk of complications. The American Academy of Pediatrics states: "Investigators have consistently found that timely oseltamivir (Tamiflu) treatment can reduce the risk of complications, including those resulting in hospitalization and death." The World Health Organization lists Tamiflu as an essential medicine for adults and children. Billions were spent by countries, including the US, stockpiling these drugs in preparation for serious influenza epidemics.

There was, however, a problem. The data on which these beliefs and actions were based were significantly incomplete. The company which makes Tamiflu had made available only a portion of the clinical study reports. Cochrane reviews, considered the most reliable available, highlighted this weakness and several British medical scientists commenced a campaign several years ago to apply pressure on the drug company to release all the data. This request, while well publicized, produced no results until recently when the pressure from articles in the *British Medical Journal* and very unfavorable publicity in the media forced an unconditional release.[16]

The analysis of all the data showed that Tamiflu reduced symptom duration by roughly 17 hours but made no difference in hospital admissions rates or carefully defined pneumonia, the only endpoints of real concern for this intervention and the only reason for national stockpiles.[17] Relenza, produced by another company, was also found upon reanalysis with a total data set to reduce symptom duration by 14 hours with no effect on pneumonia.[18] The reported and published studies based on company selected data clearly and seriously overestimated the benefits. It also was found that harms such as nausea and vomiting and the risk of headaches, kidney problems and psychiatric syndromes were under-reported. Published studies were in some cases ghost written and the investigators found that even from the company clinical study reports that it was sometimes impossible to ascertain who carried out the research, raising serious questions about academic accountability and independence. The published studies were found to represent only a highly selective portion of the complete clinical trial data, that which could be used for regulatory approval! In the latest analysis, the published Cochrane reviews relied only on the complete set of clinical study reports.

Editorialists observed that the latest analysis showed with great clarity that the current system for drug regulation is broken.[16,19] This story is consistent with the common finding that when industry sponsored clinical trials are compared with independent trials, it is sometimes found that the former support the intervention whereas the latter do not. One is left wondering how many drugs that are centerpieces of official guidelines or in widespread use have been approved by this broken system and in fact don't offer significant benefit. Furthermore, the practice of underestimating and downplaying adverse side effects presents a risk to the patient over and above their placing faith and hope in a worthless drug.

For a detailed picture of how the magnificently successful business plan used by most pharmaceutical companies really works, the reader is directed to the recent book by Peter C,

Gostzsch, MD, a specialist in internal medicine. He co-founded the famous Cochrane Collaboration (which attempts to answer important health questions by unbiased systematic reviews and meta-analyses) in 1993 and established the Nordic Cochrane center the same year. He is a professor at the University of Copenhagen. The book published in 2013 is titled *Deadly Medicine and Organized Crime. How Big Pharma has Corrupted Healthcare.* A companion volume is *Bad Pharma* by Ben Goldacre, a British physician, academic and science writer, which tells a similar story in a somewhat different style.

TESTOSTERONE THERAPY AND CARDIOVASCULAR EVENTS

Testosterone therapy (TT) has made it to prime time and the US main network nightly news programs. The underarm gel advertized is available only by prescription in the US. Advertizing campaigns of the magnitude we are seeing suggests robust sales. It is noteworthy that only the US and New Zealand allow direct to consumer advertising of prescription drugs. It is of interest to examine recent studies which suggest that TT increases the risk of cardiovascular events, and in particular heart attacks.

In 2013 the *JAMA* published a paper by Vigen *et al*[20] which found for a cohort of men in the VA health care system who underwent coronary angiography and had low serum testosterone levels, that the use of TT was associated with significant adverse outcomes such as heart attack, mortality and stroke. This paper received wide publicity in the media due in part to the high profile of the journal, but its publication was soon followed by heavy criticism. A significant problem was that the raw data reported that the percentages of individuals who suffered an event was half as great in the group treated with testosterone compared to the control group (10.1% vs. 21.2%), in direct contradiction to the conclusions of the paper. Statistical analysis reversed this to yield percentages of 25.7 % vs. 19.1% when the treated and untreated groups were compared. This was viewed by the critics as an unacceptable difference and merely reflected the "highly statistical nature of the final results."[21] There were many other problems identified including the finding that of the 1132 individuals in the original study group, 100 were actually women. This was a study where even the title indicated it involved men. Yet one out of eleven were women. Critics requested on March 25, 2014 that the editor of the *JAMA* retract this paper but this does not appear to happen as yet.

At about the same time, a paper by Finkle *et al* appeared in *Plos One*, an open access journal, which was based entirely on insurance claims and also found that TT increased the risk of non-fatal heart attacks.[22] Critics deemed the control, a group receiving medication for erectile dysfunction, to be unsatisfactory. The authors compared non-fatal MI rates in the 12 months prior to receiving a testosterone prescription but looked for MIs for only 90 days following the prescription (until the first refill). Critics deemed the study design prone to error and bias and for a number of other reasons dismissed it as "data-mining exercise with the express goal of obtaining statistical significant result worthy of publication."[21].

In an invited commentary in the *Journal of Sex Medicine*[23] titled *Death by Testosterone? We Think Not!"* the authors present a detailed critique of the paper by Vigen *et al* with the same conclusions as discussed above. The three authors, which included one of the world's foremost experts on testosterone, Harvard's Abraham Morgentaler, were joined by 15 clinicians/scientists who had reviewed the commentary and were in full agreement. This paper also included an interesting table summarizing published results of prospective (follow-up) studies on the association of low testosterone with mortality. The mean follow-up was 6.4 years and most of the results show a large enhanced risk of mortality associated with low testosterone and all were statistically significant. The studies involved all-cause mortality, cardiovascular-related mortality, or both. The authors comment that while the use of TT has

always been controversial, “It is curious that as the spectre of prostate cancer risk appears to be receding in the light of new evidence, we are now confronted with new fears regarding CV risk and mortality……we believe that the evidence to date strongly suggests that TT improves CV risk.”[23]

WHO SHOULD BE TREATED FOR LOW TESTOSTERONE?

The belief that androgens such as testosterone are a risk factor for the development of prostate cancer and that testosterone accelerates its growth has been called the *androgen hypothesis*. It had its origin the 1940s. It became dogma that the administration of testosterone to men with existing prostate cancer was like pouring gasoline on fire. As late as 2012, the most common concern about TT among physicians was the risk of prostate cancer.

In an article in *European Urology* a number of individuals with extensive experience in this area, including Abraham Morgentaler, published a review describing in detail how the androgen hypothesis has been seriously challenged with overwhelming evidence contradicting its basic principles.[24] The viewpoint they presented is as follows:

- Men with high serum testosterone are not at increased risk of developing prostate cancer.
- Low serum testosterone provides no protection against the development of prostate cancer. There is evidence that reduced testosterone increases the risk of prostate cancer at any given PSA level.
- A study found reduced risk of recurrence after radical prostatectomy for men with levels above 317 ng/dL.
- Multiple studies have reported an association of lower serum testosterone concentrations with high-grade prostate cancer and higher stage at diagnosis.
- Men with untreated prostate cancer have received TT without of evidence of prostate cancer progression.
- The current view is encompassed by a saturation model. Prostate cancer is exquisitely sensitive to variations of androgens at low serum concentrations, but indifferent to variations at normal or high concentrations.

The review provides extensive documentation for the above and the authors suggest the revised paradigm creates opportunities for new clinical uses of TT. Since this shift is at odds with longstanding beliefs, considerable controversy has resulted.

However, the authors state that the challenging question is how to address the issue of the large number of men with treated and cured prostate cancer. Some have long life expectancies and reduced quality of life because of a testosterone deficiency and desire therapy. While there is a new understanding of androgens and prostate cancer, there is extremely limited clinical experience and no controlled studies. There is also a medico-legal issue since some men with a history of prostate cancer will experience recurrence and if this occurs, physicians and patients may well believe that TT was the cause even if the events were unrelated. Thus the authors advise great care in proceeding. The guidelines they present for considering initiating TT in men with a history of treated prostate cancer are as follows.

- There is a clinical diagnosis of testosterone deficiency.
- The patient must be made aware that safety data are limited and the degree of risk associated with PC progression or recurrence is unknown.
- Informed consent is necessary.
- No medical contraindications for the therapy exist.
- The PSA level is either undetectable or stable.

- TT should be used with extreme caution in the presence of high risk for PC recurrence or progression.
- Clinicians must be prepared for the possibility of prostate cancer recurrence or progression, which will occur in some men regardless of TT but may be attributed to the therapy.
- TT is not recommended for men currently receiving any form of androgen deprivation therapy.

To this list should probably be added concern of TT therapy for individuals with very low testosterone levels due very low levels of testosterone after androgen deprivation therapy and/or radiation therapy. The levels are in many cases well below the threshold where prostate cancer is indifferent to TT and there may be a significant risk of a flare-up with increasing PSA under these circumstances. This does not appear to be discussed in any detail.

For men free of prostate cancer, low testosterone is a significant issue. Not only is there frequently a decline in quality of life, but low testosterone is associated with a number of disorders and replacement therapy has been found to offer benefits.

Two approaches are generally combined to determine deficiency.[25] One is based on symptoms, the other on various blood tests. Symptoms include low libido and erectile dysfunction, fatigue, lack of energy and reduced motivation, depressed mood, reduced bone density, and changes in body composition such reduced muscle mass and increased body fat. Some of these are vague or do not prompt complaints to physicians, and the strongest indicators of deficiency are associated with sexual dysfunction. However, most of the above symptoms impact the quality of life to a greater or lesser extent and as will be discussed below, the range of disorders where benefit is associated with TT is much larger than the above symptom list suggests. Depression or depressed mood is a perfect example where the knee-jerk response is with an antidepressant without seriously considering causes such as dietary or vitamin deficiency, thyroid problems or testosterone deficiency, to name just a few, and is tantamount to malpractice, but nevertheless, considering the significant percentage of the population worldwide on antidepressants, must be common.

Blood tests involve total and calculated free testosterone, and frequently one or more of the following: hematocrit, luteinizing hormone, follicle stimulating hormone, sex hormone binding globulin, estradiol and prolactin.[25] Obviously, the interpretation of blood tests requires expert knowledge and clinical experience. Some physicians will treat based on symptoms when the blood tests are normal, and vice versa, and the ideal situation exists when one confirms the other. Reference values provided by laboratories are not clinically based and of little value but can cause misdiagnosis among the inexperienced. No detailed sets of numbers will be given since diagnosis and treatment recommendations must be left up to physicians experienced in this area.

The widespread advertising on prime time TV no doubt results in innumerable requests for a prescription based on a variety of patient motivations, and will probably prompt at least a total testosterone blood test. Laboratory report reference ranges for the lower limit of normal have been reported to range from 130 to 450 ng/dL, but total testosterone below 350 ng/dL is frequently seen in the literature an indication for considering the possibility of deficiency.[25] However, this should precipitate a much more detailed examination of the issue, perhaps through a referral, not a prescription.

The benefits of treating testosterone deficiency go well beyond the problems suggested by the traditional symptoms and in fact, multiple benefits are common. Benefits have been seen from TT in studies involving mortally, cardiovascular disease, atherosclerosis, insulin resistance, glycemic control, visceral adiposity, angina, metabolic syndrome, heart failure, muscle function, and type 2 diabetes.[26] A discussion of this complex issue will be presented

in a future research review. The reader is referred to the book *Testosterone for Life* by Dr. Morgentaler mentioned above.

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