INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 273 DECEMBER 2016/JANUARY 2017 25th YEAR

At the recent annual meeting of the Society for Neuroscience in San Diego, research reported by Dr. Changiz Geula from Northwestern University Feinberg School of Medicine attracted quite a lot of attention. The researchers reported on the autopsy results of eight individuals over 90 who had what was described as excellent recall, presumably indicating the absence of Alzheimer's disease. Three of the eight had pathological evidence of full-blown Alzheimer's but showed no evidence of cognitive abnormality. They appeared to be immune to the expected effects of extensive beta-amyloid plaque and tau tangles, the hallmarks of the disease. One neuroscientist commenting on the results pointed out that this was not the first time this phenomenon had been seen, but these findings were clearer because the individuals were older and the plaques and tangles should have "wreaked their terrible havoc." The results call into question the primary paradigm of Alzheimer's research and drug development, the culprits beta-amyloid and tau.

Beta-amyloid came on the scene in 1991 and there have been over two thousand papers published concerning it. Beta amyloid has been the focus of drug development and clinical trials, mostly directed at beta-amyloid. These trials are characterized by spectacular failure rate of almost 100%. Most studies were terminated because of side effects or ineffectuality. The pharmaceutical company Eli Lilly recently reported another failure in a large trial. This trial involved individuals with mild disease since one of the reasons for failure so far has been partly attributed to disease too advanced to benefit from targeting amyloid plaques.

So far no drug has been able to demonstrate that removing or preventing the accumulation of amyloid translated in a benefit to treated patients, i.e. stalling, blocking or reversing some of the symptoms of dementia. However, there are still a large number of trials in progress indicating the hope for at least as statistically significant benefit. One is reminded of Einstein's famous statement that insanity is repeating over and over again an experiment in the hope that different result will emerge. Throughout the history of the amyloid hypothesis there have be critics, some even calling it the "Holy Mother of Amyloid Church." The critics had a good point. If researchers are barking up the wrong tree then time and money is being wasted which might be better spent finding a new paradigm that showed more promise. Rather than

concentrate on this, some drug companies have given up their dementia research programs altogether to seek greener pastures.

While it is too early to cite the results of a quite different ongoing clinical trial, there seems to be a very good chance that medium chain triglycerides such as found in coconut oil may if fact produce vastly more benefit that any drug has so far (IHN Dec 2014). Real success requires a vast improvement such as has been seen in anecdotal reports that finally became so compelling that a trial not sponsored by a drug company is actually ongoing at the University of South Florida Byrd Alzheimer's Institute. A commercial drink called "Fuel for Thought" containing a mixture of coconut oil and other medium chain triglycerides is being used. Subjects have documented mild to moderate Alzheimer's disease.

Wishing you and your family a Happy Holiday Season and continuing good health in the New Year,

William R. Ware, PhD, Editor

Highlights

AUTISM – AN EPIDEMIC THAT IS TREATABLE

"An understanding of autism and the development and provision of appropriate care for affected individuals and their families is, in our view, one of the central challenges of contemporary medicine."
S. M. Edelson, PhD. Executive Director, Autism Research Institute

Strictly speaking, autism should now be called the A*utism Spectrum Disorder* and includes Asperger's syndrome. Since 1975 the prevalence of autism in the US first increased super exponentially and then from 2004 presents a simple exponential increase, ending up in 2015 with 1 in 66 children (1 in 42 boys). It is tempting to extrapolate—one gets 1/28 in 2024. Special schools for 1/28 might be a problem. Perhaps 1/66 already is. We have reached the point where the incidence is so large that it does not even matter if the real numbers are a bit higher or lower. It is a disaster for the child, the parents, the extended family, and the health care and support systems. And while theories abound, no one has satisfactorily explained what is responsible for going from 1/5000 in 1975 to 1/66 in 2015, probably because there are a number of interacting causes. Some autism victims are now working on or obtaining college degrees. The November 20, 2016 *New York Times* has an article by Jan Hoffman describing the support they need and the variable success. The impact of autism on

intellect covers a wide range and some autistic children and adults are exceptionally gifted.

The issue of causes is confused by political issues and conflicts of interest involving strong commercial and regulatory issues related to the possibility of pollutants and toxins in food, air and water being partly responsible as well as maternal prescription drugs, type of delivery of the child (C-section vs. normal), excessive antibiotic use, and vaccinations. Some are hot button issues, areas of research dangerous to an investigator's career, and carry almost insurmountable barriers to the truth. The issue of the role of vaccination in the incidence of autism, the centerpiece of the hot buttons, will not be resolved until examined by a group of experts totally free of conflicts of interest and bias and willing to risk their careers even to participate.

The classical view of autism is that it is a genetic brain disorder and that the underlying problem is generally permanent. Behavioral problems can be moderated with therapy but the essential deficits are lifelong. A devastating view when presented to parents. An alternative view is that it is a whole body problem. In this view autism is a very complex disorder involving dysfunction in many interconnected aspects of a child's biochemistry and physiology. Autistic children appear to each have a set of dysfunctional systems rather than all plausible ones, rarely just one, and this set varies from child to child, complicating the issues tremendously. Thus it can be argued that each child is different and requires a different therapeutic approach. There appears to be no *one size fits all* approach. The essential point is that the dysfunctions can be treated successfully.

First we look to the mainstream experts and in particular what appear to be the latest guidelines put forward on the internet by the American Academy of Child and Adolescent Psychiatry. Their recommendations are simple. Use evidence-based educational and behavioral interventions including cognitive behavior therapy. Then with the aid of four large tables summarizing trials, they suggest drug therapy to target specific symptoms. Finally they deal with the use of alternative/complementary treatments and present a very negative view discussing a limited number of studies as support for saying that they have not been demonstrated to "work." The guideline writers regard parents looking for alternatives as needing advice to keep them from going astray and wasting money on unproven therapies. While recommended approaches may indeed produce improvements, parents naturally want a cure, partial or complete, not symptom management. Furthermore, as pointed out in a recent review in Pediatrics[1], the standard of care involving behavioral therapies lack controlled studies and by most definitions, are in fact not really evidence based. The authors also point out the high rate of adverse side effects in the other mainstream approach, symptomatic therapy with antipsychotic drugs. In addition, this review presents a favorable view of the so-called biomedical approach which some would say represents a highly developed form of personalized medicine.[2]

Giving children psychiatric drugs is controversial. At one extreme they are prescribed with little hesitation whereas at the other extreme giving them to children is considered outright child abuse and has been called this in the peer-reviewed literature.[3] At issue is

the fact that these drugs have never been studied or approved for children, there are no significant safety data, and for older children, the only approved drugs are for ADHD. The central argument against them is that they may temporarily or permanently result in brain damage and interfere with brain development, and the child's developing brain is particularly susceptible to this type of insult. Informative studies are of course impossible for two reasons. Parental approval for using a child in a safety or efficacy trial is hard to come by and detecting long-term interference with brain development or brain damage requires studies continuing into early adulthood which is near impossible. However, the industry sees a big market here which has to be "off label" meaning unapproved use.

In sharp contrast, those favoring the biomedical approach attempt to deal with fundamental biological and physiological causes. They recognize that there is a large collection of these causes and the ones involved in any given autistic child are difficult to establish, and may in fact require simple elimination. Thus they favor an organized approach to find what intervention is targeting the dysfunctional system effective and slowly combine all the effective therapies to take advantage of synergism. Contrary to the official view, it turns out that there is a large body of research involving these alternative approaches. In addition, the proponents are not just a fringe group pushing untested and risky approaches. One of the recent high profile proponents of the biomedical approach is a pediatric neurologist at Massachusetts General Hospital who is also on the faculty of Harvard Medical School. She also directs a research program on autism. We will get to her book shortly.

Some may decide that the psychotherapy approach has merits and is worth a try for serious behavioral problems, but may still decide to also make a major commitment to the biomedical approach. However, how to accomplish this is another matter. Finding a knowledgeable practitioner experienced in this approach may be difficult if not impossible. It depends on where the family lives. See the advice given on the Autism Research institute website (www.autism.com) under "Finding a Practitioner." In general, parents are on their own and must fall back on the resources available. Some doctors will ridicule the decision but some may provide valuable tests and support. Parents need resources and providing a guide to these resources seems much more valuable than attempting to deal with this highly complex subject in a research review.
For an introduction to the biomedical approach, there are three highly recommended books.

- ***The Autism Revolution****. Whole-body strategies for making life all its can be.* Martha Herbert, MD, PhD with Karen Weintraub*.* Harvard Health Publications and Ballantine Books, New York, 2012*.* Dr. Herbert is the physician from Harvard Medical School mentioned above. Every parent with an autistic child needs to read this book. It will dramatically change the way you view the child's problem and will probably strongly motivate adopting it.
- ***Children with Starving Brains****. A medical treatment guide for autism spectrum disorder.* Fourth Edition, 2009, by the late Jaquelyn McCandless, MD. An excellent companion to the above book which deals with the same subject. .

- ***Gut and Psychology Syndrome****,* Revised and expanded edition, 2012. Medinform Publishing, Cambridge, UK, by Natasha Campbell-McBride, MD. A definitive treatment of the interaction between gut disorders and the brain, including autism.

Together these provide a comprehensive introduction to the biomedical approach based on years of clinical experience.

What is needed next is a handbook to serve as a guide in navigating the implementation of the decision to go biomedical. An excellent and well-documented guide is available online from the Autism Research Institute, which incidentally is a reliable resource for information. On their home page under "Research" there is a link to "*Summary of Dietary, Nutritional and Medical Treatments for Autism*" by James B. Adams, PhD, director of the Arizona State University Autism /Asperger's Research Program. Or use this link http://ariconference.com/enews/treatment.pdf

This 52-page document covers ideal diets, identifying food sensitivities, gut disorder treatments, use of amino acids, carnitine, melatonin, thyroid supplements, decreasing oxidative stress, immune system boosting and hyperbaric oxygen therapy. This document is just what parents need and the general simplicity of most of what is required will provide huge encouragement. In the complete set, some interventions will work, some won't and the only way to find out is to try them. Diagnostic tests require professional interpretation, some involving the stomach and gut would be very frightening to children and they are not 100% reliable. Interventions such as antifungals may require a prescription but could be very important. Very few clinics offer hyperbaric therapy but this appears to be a minor issue. A very interesting feature of this document is that for many of the interventions, it gives the results of parent rating of the treatment as % worse, % no change, % better, and number of respondents. The large number of reports for each intervention (frequently several thousand) and the frequency of 50% to 65% "better" speak for itself, especially since it refers to a single area of intervention.
Many parents will conclude "we can do this" and realize that no one else will. Ideally, working with an experienced practitioner is desirable and the possibility should be seriously investigated. The Autism Research Institute website has a great deal of information, but it takes some searching around and trying links. For example, there is an excellent guide to special diets and their implementation at
https://www.autism.com/treating_diets#sthash.HeRF0vm3.dpbs

The sections on each intervention in Dr. Adam's guide also contain discussions of safety and research backing up the intervention. This guide also includes dose information when required. This guide appears authoritative and each section has been reviewed by someone viewed by the author as an expert. Many of these interventions are discussed in the two books listed above. It is important to realize that parent-organized biomedical treatment appears widespread and in fact a growing movement. McCandless also comments that while most benefit from the biomedical approach, it is not uncommon for a child to eventually be declared as no longer diagnosable with

autism. Even if this does not happen, the residual symptoms may frequently be of little consequence in terms of leading a normal life.

Dr. Campbell-McBride's book makes a special plea for recognition of the role of proper gut function and a proper gut microbiome (the collection of friendly gut bacteria—over a trillion in adults!). For example, she develops the view that abnormal gut flora are a very serious matter from birth on and correction in the first month of life plays a crucial role in the maturation of the child's immune system, a vital aspect of overall health and related to autism. It is well known that the C-section delivery generally deprives the baby of normal gut flora. This can be avoided by post-delivery inoculation with the proper mix of bacteria, but interest is just now developing regarding oral inoculation of C-section babies at birth with vaginal bacteria, the normal source of the infant's starter "culture." Prior to birth, the infant gut is essentially sterile. Since the gut does not appear to be very high on the mainstream list of autism issues, given that behavioral therapy and powerful drugs are all they view as useful, it may be a long time before such interventions become recognized as important, and yet elective C-sections are very common. Repeated insults on the gut microbiome by antibiotic treatment is obviously also a big problem in the context of autism. It can be progressive over the early years, and the pediatric overuse of antibiotics is widespread if not notorious.

Underlying the biomedical approach is the fact that there are limited diagnostic tools that can reliably indicate which dysfunctional systems are involved in an autistic child. Furthermore if professional help is unavailable, even the laboratory tests that McCandless discusses in Chapter 4 are out of reach without an understanding pediatrician or family doctor. Trial and error becomes the only approach. This is where the Autism Research Institute guide mentioned above can help.

It is possible the pediatrician may be helpful. Pediatric gastroenterologists now have a consensus statement indicating they are open to the hypothesis that gut problems are important in autism and can be treated.[4] In addition, the family physician may be able to provide support with some laboratory tests and even heavy metal hair analysis. There are lots of books on implementing gluten-free, casein-free, soy-free diets which provide recipes. In autistic children eating problems are common and may present a significant challenge.

Psychiatrists treating autistic children may view their problem as only a brain dysfunction and tend to be uninterested in parents comments about bowel dysfunction or strange skin rashes or allergies presenting just before the initial autism symptoms. They treat the brain and leave the parents with only the option of taking these problems to specialists. Neither an allergist nor a gastroenterologist will generally adopt a whole body view.

The goal of treatment is for children to retain their unique and wonderful personalities, be better able to manage life and feel physically well, eventually live independently, be fully employed, develop personal relationships and have a fulfilling life. Nevertheless, it is realistic to anticipate some residual autistic traits.

Resources. The only resource that can be recommended without reservation appears to be the Autism Research Institute www.austism.com. Autism Speaks, www.autismspeaks.org has a high profile but their website makes it clear that they concentrate on behavioral therapy and discourage the approach we have been discussing, claiming that it is unproven. Unfortunately, the suspected underlying biological and physiological causes are not modified by behavioral therapy, which, for example cannot restore a dysfunctional gut microbiome or deal with food sensitivities.

BOTTOM LINE
It appears that autism is essentially curable using the biomedical approach. However, for many parents it will be necessary to orchestrate and accomplish this therapeutic approach themselves with the aid of books and a guide from the Autism Research Institute. Those who are lucky will locate a professional experienced in this approach or at least willing and hopefully interested in helping.

DOES METFORMIN REALLY WORK?
AMERICAN DIABETES ASSOCIATION
DIABETES MANAGEMENT GUIDELINES FOR 2016

It is common to find in the introductions to reviews on the treatment of type 2 diabetes a statement that this disease is progressive and not significantly impacted by medication. However, the usual result of diabetes diagnosis is first diet and exercise, which is generally ineffective, then a single drug, usually metformin, then the addition of a second drug and then perhaps a third and finally insulin, at which point the patient is described as an insulin-dependent type 2 diabetic. Thus there appears to be a consensus that drug therapy is beneficial and of course it does impact the magnitude of the hyperglycemic providing “management” of the diabetes. When metformin fails to provide satisfactory management, there are currently 5 different potential drug additions plus insulin. There are also 5 candidates for a third drug, again plus insulin to deal with the inevitable progression of diabetes.

Since the ultimate objective of therapy is the prevention of the adverse effects of the disease such as death from cardiovascular causes, all-cause mortality, heart attack, stroke, heart failure, peripheral vascular events, amputation or microvascular complications, one might ask regarding these 10 additional drugs if there is evidence that they affect the risk or rate of these complications over for example 10 years. If they indeed significantly impact progression, then this becomes the main rationale for treatment aside from the psychological effect of having the disease managed and the relevant glucose metabolism biomarkers decline but rarely normalize. However, such studies appear absent which is not surprising since randomized controlled trials over a number of years would be necessary but unrealistic from the industry point of view, and regulatory approval of new diabetes drugs therefore must be based on simply a positive effect on hyperglycemia and the evidence of safety. Positive in this context is simply a superiority over mono or dual therapy. With this in mind, let’s examine some aspects of

the latest American Diabetes Association (ADA) guidelines concerning the management of type 2 diabetes.[5] (Note the complete report is available on the internet under AHA guidelines 2016 published in the journal *Diabetes Care,* a 109-page supplement).

We will focus on the drug metformin. When diet and exercise and weight loss fail, we are told that metformin "has a long standing evidence-base for efficacy and safety, is inexpensive, and may reduce the risk of cardiovascular events and death." Only one reference[6] is given which concerns a post-trial follow-up of the famous (or infamous) 10-year trial called the UK Prospective Diabetes Study (UKPDS).[7] In this follow-up little was known about diabetes medications, lifestyle changes or dietary modifications. The post-trial follow-up included annual assessment for five years and then every three years, but if subjects were unable to attend clinics, a questionnaire was used. The UKPDS metformin trial[7] randomized a total of 753 individuals and thus the treated and control groups were rather small and the event numbers even smaller. The second UKPDS trial which was called the sulfonylurea-insulin group was included in the follow-up but the results were listed separately for this group and the metformin group. By the final year of the post-trial follow-up there were only 588 individuals in the metformin group (as compared to 753 at the start). This then is the long-standing evidence on which the guideline recommendations concerning metformin are based. But there is more to the story.

UKPDS started in 1983 and reported finally in 1998. Over this period, the primary and main endpoints were changed a number of times and the announced termination date repeatedly extended. Furthermore, the study was not blinded for the investigators and the results of interim analysis were available to the investigators. This study protocol is obviously open to bias. To quote one citric, "It seems that the authors continued the study until they obtained a result that was significant without adjusting for repeatedly looking at the data."[8] An investigator involved in the trial commented in 2008 that "UKPDS-34 broke almost all the rules of trial design. We are taught to believe that a study protocol should be predetermined and set in stone, but this study went to the other extreme, elevating the ad hoc into an art form."[9] Thus the key study in the in 2016 guidelines concerning metformin appears flawed.

The UKPDS metformin study found an approximate 7.1% absolute risk reduction for all-cause mortality, a 5.1% effect for cardiovascular mortality, a 6.4% effect for fatal and non-fatal heart attacks, and no significant benefits for stroke, heart failure, peripheral vascular events, amputation or micro vascular events. Thus even when there was a benefit, in absolute terms, most did not benefit from the therapy (subtract the percentages from 100%).

In 2009 it was pointed out by Reaven,[10] based on the 6-year report from UKPDS,[11] that following enrolment there was a progressive deterioration of glycemic control in all groups including those assigned to intensive control which included metformin. In addition, beta cell function was estimated and the investigators concluded that increasing hyperglycemia and decreasing beta cell function were significant features irrespective of the drug protocol used. Reaven also points out that the loss of secretory

function does not appear to be inexorable and cites two studies where weight loss improved glycemic control. This view is supported by the study of Lim *et al,* based on the Newcastle diet study.[12]

In 2012 a meta-analysis was published where the efficacy of metformin was re-examined since there were now more trials.[13] They were either metformin vs. diet or non-drug care or a placebo, metformin plus a sulphonylurea vs. the sulphonylurea alone, or metformin plus insulin vs. insulin plus a placebo or metformin vs. total withdrawal from the drug. For all of the above comparisons, no significant benefit was found for the endpoints listed above for the UKPDS trial. In other words, the results from the UKPSD metformin study were not confirmed and rather serious questions raised concerning their validity. The 2016 ADA guidelines fail to mention or address the implications of this meta-analysis. It is not just farmers who are cherry pickers. After all, metformin has been the recommended drug therapy for newly diagnosed type 2 diabetics for a long time. Writers of guidelines love meta-analyses. Thus it would appear that the evidence for the first-line recommended drug therapy for type 2 diabetes is questionable, not confirmed by other randomized trials and fails to impact the relentless progression of the disease or the macro and micro vascular effects of the disease.

The 2016 guidelines do not mention the 2011 study by Professor Roy Taylor and colleagues which introduced the Newcastle Diet,[12] an intervention that actually offered a cure for type 2 diabetes, further discussed in the published Banting Memorial Lecture by Professor Taylor in 2012[14] nor was there any mention of subsequent trials of this dietary breakthrough (IHN DEC 12, JUL 15). Bariatric surgery got only passing mention that in many cases it also cures diabetes. Instead, mainstream diabetololgy appears to be playing around with 10 drugs to add a huge number of combinations and permutations to metformin prior the total failure of drug therapy and thus insulin dependence. The Mediterranean diet was promoted as the recommended dietary approach, replacing the low-fat dietary recommendations popular for decades, and the guidelines even gave up demonizing saturated fat. But it is doubtful that those managed according the 2016 guidelines will see light at the end of the tunnel.

BOTTOM LINE
Metformin appears to be an excellent example of a drug that is only very modestly effective in treating a very common chronic disease and most taking it do not realize this, nor do they realize that a dietary alternative, the Newcastle diet, might very well solve all the inevitable problems in their future.

KNOW YOUR NUMBERS

Most readers know a set off important numbers, their age, weight, height, frequently used phone numbers, the birthdays of their children, perhaps license plate numbers of their cars, etc., but they might consider whether or not they know or have a record of the following that relate to their health or for that matter, if they have even been measured:

- **25-hydroxyvitamin D.** The measure of vitamin D status.
- **Blood pressure.** Measured in the last 6 months to a year.
- **Fasting blood glucose** (FBG). Really fasting plasma glucose measured in the last year if not more frequently if indicated.
- **HbA1c.** Measured in the past year. This measure of blood glucose more or less averaged over 3 months, and combined with the FBG provides an alert for prediabetes or diabetes. A substantial fraction of diabetes cases go undiagnosed.
- **Ferritin.** The measure of body stores of iron. See the Research Review in the 2016 JUL-Aug issue of IHN which will provide a guide to the numbers, the risks and how to modify them favorably. Reference ranges appear to be out of touch with reality.
- **C-reactive protein** (hsCRP). A measure of temporary or chronic inflammation. Your physician should be able to provide guidance if it is chronically elevated.
- **Liver enzymes** ALT and AST. Can provide a number of indications of impending or existing problems.
- **TSH.** The thyroid hormone indicator which can point to hypothyroidism or hyperthyroidism and in some practices, lead to the measurement of individual free thyroid hormones.
- **Triglycerides.** When elevated can contribute to cardiovascular risk.
- **PSA**. For men a baseline for future reference. Threshold for concern is complex since it is dependent on prostate size and age and offers the opportunity for excessive further investigation with potential side effects and overtreatment. Thus discussions are in order to decide on the merits of even getting a baseline value.
- **Vitamin B12** level. If low, could herald among other things, cognitive problems in the future. Especially important in older individuals. The majority of nursing home patients have been fond deficient and the cognitive consequences can be severe.
- **Urate,** equivalent to uric acid. Elevated levels indicate increased risk of gout and heart problems.

There are other biomarkers that could be added, but these appear to be the most important. There is a urine based kidney function screening test, the eGFR, which could be included, and there are certainly individuals out there who know their coronary calcium score, mainly because of the importance their doctor places on this in evaluating CVD risk. By putting your total cholesterol and HDL cholesterol numbers available from blood lab printouts, copies of which your physician can supply, into the online American College of Cardiology/American Heart Association (ACC/AHA) risk calculator, along with other numbers and information, a 10-year risk of hard CVD events (fatal and nonfatal heart attack and stroke) will result. Current evidence as discussed in IHN suggests then dividing the number by 5 to yield an adjusted number for non-diabetics, 2.4 for diabetics, to yield a number one should know, but it is not possible to

lower this number significantly due to its strong dependence on gender and age and the fact that treated hypertension elevates rather than decreases the number. Chances are it will be very low (< 4%) and this may provide relief from concern and provide a basis for discussion when statins are being recommended. Given the need to divide by 5 should lead one to ignore the clinical evaluation statement that is included with the results of this calculation. Mainstream medicine would react strongly and adversely to this approach and view, even though the factor of 5 comes from what appears to be a very good validation study on a huge contemporary cohort. Blood lab reports come with reference ranges and alerts, but it is a mistake to blindly rely on this information, with ferritin, total and LDL cholesterol, and TSH as prime examples.

There is one school of thought that recommends against physical exams except very infrequently or in response to symptoms. A physical would include blood and urine tests which are potentially comprehensive although this is very much physician-dependent. The highly debatable argument is that such exams lead to over treatment and false positive results, i.e. risk exceeds benefit. There are many physicians who do indeed measure all or most of the above numbers, but there are also jurisdictions with universal health care or insurance plans that force one to pay for some of the tests, regarding them as not important enough to cover. Also in some cases the reimbursement or health care coverage system penalizes physicians for ordering too many tests.

BOTTOM LINE

The basic philosophy here is that in many cases it is in general better to respond to early warning signs than to symptomatic presentations of a disorder. This is why one should consider regular physical examinations. The above provides a checklist to use when examining the checked blood and urine tests.

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

ISSN 1203-1933

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