INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 290 **SEPTEMBER 2018** **27th YEAR**

In the past few years we have discussed many important aspects of chronic disease; diet, lifestyle (exercising, smoking, socializing, family interactions, psychosocial stress, etc.) and the hazards out there which include foods that have a negative impact, food contaminants, food additives of unproven but strongly suspected risk, and toxins in air, water and food. The picture that has been painted is not pretty for good reason. However, the good news is that there are signs that some are waking up to reality. Prevalence of smoking, in for example the US, continues to decline. There are reports of growing interest in healthier and safer foods and diets. Some major grocery store chains are increasing the number of organic items and interest in organic foods appears to be accelerating, although it appears to still represent a small portion of total consumption, mostly being controlled by availability, skepticism and lack of appreciation. While I have no data, it seems that I am seeing a significant increase of joggers, walkers, and dog walkers going past my living room window morning and evening, although the observations are haphazard.

This increasing interest in healthy food has motivated fraudulent and misleading marketing such as the increased use of terms such as natural, healthy, heart healthy, wild, free-range and other promotional tricks. One wonders how far one can trust organic certification and of course this varies from country to country. Repeated inspections, monitoring and laboratory testing are probably not feasible nor the cost acceptable to the general public. While it is natural to wish to remain healthy over the years and die old and swiftly, an enthusiastic quest for this goal is difficult, requires knowledge the general public lacks, and almost everyone is forced to compromise. Many obviously fail. We will be forced to continue to help pay the ever-increasing price for the vast number of citizens who will never give up ultra-processed food or junk food, sitting endless hours, or ignoring poor sleep habits. Working in a psychological toxic environment or enduring discrimination and bullying are unhealthy but for many offer a challenging problem. Furthermore, the modern hectic lifestyle characterized by "eat and run" and the stress of excessive commitments both domestic and work-related is something many have no choice but to live with. The ideal lifestyle is frequently not possible or simply unattractive.

The idealistic goal can be partly achieved by recognizing that cures or reversal protocols for dramatically decreasing risk exist for some major chronic diseases. They are holistic, alternative and even simple, but it seems that most are not widely known, unrecognized by health authorities, or ridiculed as not being evidence based. These chronic diseases include cancer, type 2 diabetes, Alzheimer's disease, and multiple sclerosis and have been featured in IHN (see index). Some cynics espouse the hypothesis that powerful financial interests do not want cures for chronic diseases, will fight to preserve the status quo and want only slow changes in attitudes and policy. Pills that cure chronic diseases like antibiotics cure infections are still mostly in the distant future. Moreover, critics can make a strong case that special interests have great power over regulatory agencies, research grant support, academic research and medical continuing education, and even the media and employ a proven game plan developed by the tobacco industry ages ago and perfected by Big Pharma, Big Food, Big Agriculture and Big Chemical.

*IHN will continue to provide readers whenever possible with the tools, perspective, and up-to-date information to assist all those who out of choice or necessity are dissatisfied with having only symptoms treated or are searching for help when nothing is working. An important component of getting help when nothing is working involves finding a practitioner who attempts to see the whole picture presented by the patient when conventional approaches have failed, and uses a multifactorial, personalized view in search of a solution. A highly recommended starting point is the recent book "**The Other Side of Impossible**. **Ordinary people who faced daunting medical challenges and refused to give up"** by Susannah Meadows.*

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

WHY DON'T ALL OBESE INDIVIDUALS GET TYPE 2 DIABETES?

This question has puzzled medical scientists for decades. A simplistic answer would be to just wait. The risk of diabetes increases rapidly (exponentially) with how fat one is. This strongly suggests that it should happen.[1] Nevertheless, almost three-quarters of individuals who are obese (BMI> 40) not only do not have diabetes but are unlikely to get it.[2] However, the issue is probably more complicated than it first appears. To think about the relationship between obesity and type 2 diabetes (T2DM), it is necessary first to have a model of how diabetes develops and progresses. One model is that proposed by Professor Roy Taylor, Newcastle Magnetic Resonance Centre, Institute for Cellular Medicine, Campus for Aging and Vitality.[3] This is the so-called twin cycle theory of the etiology of diabetes. It was first described in 2011, supported by a small clinical study and then presented in a high profile way by Taylor in the Banting Memorial Lecture in 2012 which was published.[4]

The key feature is the accumulation of fat (triacylglycerol or triglycerides) in the liver due to consuming more calories than are required, leading to liver fat storage. This increases the liver insulin resistance. Some of these accumulating fatty acids move from the liver to the pancreas and accumulate there, rendering the beta cells dysfunctional and increasing hyperglycemia which in turn increases fat accumulation in the liver.[5] This hypothesis has been extensively confirmed by experimental studies involving MRI imaging of liver and pancreatic fat and clinical studies where the liver and pancreatic fat levels were observed to be reduced by severe calorie reduction over 2 months causing restoration of normal beta-cell function and putting diabetes into remission.[6-8] Furthermore, work in other laboratories demonstrated that the toxicity of fat toward pancreatic beta cells is due to an epigenetic effect which causes the cells to de-differentiate; that is, ceasing to be beta cells and thus becoming unable to secrete insulin. This work is summarized in a review published in 2018.[3]

An answer to the question posed involves the postulated personal fat threshold for the start of the cycle proposed by Taylor and Holman.[9] The physiological factors in Taylor's proposed mechanism are observed to be independent of the body mass index (BMI which is weight in kg divided by height in meters squared). Individuals vary considerably with regard to the pathological aspects of these factors such as liver fat accumulation, pancreatic triglyceride accumulation, and liver insulin resistance. Here are the essential features of an answer to the question posed above.[9]

- People with T2DM have modestly greater insulin resistance at any level of BMI.
- The critical stage in glucose metabolism is the first phase insulin response which comes quickly after increased serum glucose, i.e. post meal. It is absent in T2DM whatever the BMI.
- The total reversal of T2DM is equally achievable independent of BMI.
- Plots of number (prevalence) of a given BMI vs. BMI with and without T2DM are very similar, look like normal distributions, but are simply right-shifted by about 2.5 units for diabetes, and independent of BMI.

- Individuals vary greatly in the threshold weight beyond which T2DM develops and being lean is no guarantee of not becoming pre-diabetic and then progressing to diabetes.
- Liver fat and its relation to body fat or BMI vary from individual to individual as does the tendency to develop liver insulin resistance. Excess liver fat is required in the T2DM mechanism. These two qualifications also apply to pancreatic triglyceride accumulation.
- When T2DM is put into remission by severe calorie restrictions and concomitant weight loss, this reversal is found to be equally possible with obese people or those of lower initial BMI. However, it was unnecessary for the obese to become normal weight to achieve reversal.

Thus four variable characteristics of an individual independent of BMI come into the play in the generation of a threshold. However, there may also be a genetic component. These determine the individual variation in personal fat threshold (BMI threshold) for diabetes which may not be exceeded even in obesity. However, the probability of crossing the threshold increases with increasing BMI.

The personal fat threshold is hypothesized by Taylor and Holman to be determined both by the extent of intra-liver and intra-pancreatic fat accumulation in addition the individual susceptibility to the biochemical impact of this lipid excess. Furthermore, T2DM has a pathophysiology largely independent of BMI. At any BMI, some individuals are above and some below this personal threshold for developing T2DM. The obese individual free of T2DM simply has not crossed their personal threshold. Weight gain at some point pushes one over the threshold. Weight loss can bring one back below it and restore beta cell function provided the damage to the pancreatic beta cells is not such that it cannot be reversed. Permanent damage occurs after a long duration of the disease but how long is also variable. As mentioned above, the beta cell damage is an epigenetic effect called cellular de-differentiation.[10] The beta cells change in their nature and cease to produce insulin even though they may still be alive. Reversing the de-differentiation cures the diabetes. Severe weight loss accomplished this, as is demonstrated in three clinical trials[6,7,11] and in a number of experimental studies.

This body of work is the first ever demonstration that T2DM is curable and it appears to be largely ignored. Perhaps there is a strong resistance to the notion that T2DM can be put into durable remission, i.e. completely normal glucose metabolism, in 8 weeks with a simple dietary intervention. In fact the simplicity was such that in England, many read about it in the newspapers, obtained the protocol, and successfully tried it themselves and many reported their results to Taylor.[12] They even introduced variations such as different reduced calorie diets that were more appealing than the liquid plus vegetables

diet used in the clinical studies. This did not appear to matter. Weight loss and reversal were the same, evidentially approximately independent of the macro nutrient distribution in the diet. The clinical diet that worked incidentally was not even low-carbohydrate or ketogenic. All the more reason to ignore this new protocol. After all huge amounts of money being earned by selling or prescribing rather ineffective drugs that only appear effective because of impressive relative risk reductions. No one mentions the trivial absolute benefit (1-2%). The drugs slow progression a bit, have very modest impacts on the adverse effects of hyperglycemia, and do not cure the disease. In fact almost all those treated fail to clinically benefit. The disease progresses such that there is need for additional drugs and finally insulin. Insulin-dependent T2DM becomes the symbol of failure.

A good example of ignoring the work of Taylor can be seen in two articles published in 2018. One concerned novel approaches to restore beta cell function in diabetics.[13] The other was long discussion on mechanisms of weight loss and improved metabolism following bariatric surgery.[14] Bariatric surgery is known to cure diabetes in many patients, but the intervention is generally restricted by guidelines to the morbidly obese and reimbursement regulations. Neither of these recent papers made reference to the work of Taylor in spite of his group having published two papers pointing out that the principal mechanism for curing diabetes is the same for both bariatric surgery and the Newcastle diet, namely determined by the degree of weight loss.[15,16] Furthermore, the same effect of long term vs. short turn duration of diabetes was seen in the efficacy of both the Newcastle diet and bariatric surgery in putting diabetes into remission. This is in addition to the extensive work strongly related to beta cell function restoration that Taylors's group published over 8 years which was not cited.

Another example is a paper just published.[17] The study randomizing a group of type 2 diabetics to two interventions for 12 months. One was intermittent fasting at 500-600 calories for two days a week, the other continuous calorie restriction to 1200-1500 calories per day, both running 12 months. The mean duration of diabetes was around 8 years with around 6 years at one standard deviation lower. At the end weight loss difference between the two groups (–2.2 kg) was not significant, nor was the small HbA1c difference (0.2%). In the discussion of this failure, there was no mention of the work from Taylor's group which could be held up in sharp contrast to the two interventions.

When obese individuals become diabetic, they must at some time pass through a prediabetic stage. Diabetic responders to the Newcastle protocol who achieve remission must do the reverse on the way to total remission, diabetes to prediabetes to normal glucose metabolism, to achieve fasting blood glucose at or below the values for

diagnosis of prediabetes, (≤ 6.2 mmol/L) and HbA1c levels (≤ 5.8%). Incidentally, responders had a duration of diabetes of < 4 years, non-responders > 8 years in the relevant study.[7]

The personal fat threshold is based on diabetes, not prediabetes. Thus according to this view, independent of weight or BMI, if one does not have diabetes, one is below the threshold. This is a very useful hypothesis for explaining much data about the incidence of diabetes, but there is a risk of associated complacency. While one may feel comfortable with a current BMI, they should feel much more comfortable if they are also not prediabetic. The development of diabetes is a continuum and is different from suddenly catching an infectious disease. If prediabetes is present then there should be cause for concern. If it progresses, then it is necessary to consider where one is with respect to this threshold and in fact how fuzzy the threshold is. The threshold may have been crossed. In addition, there appears to be no information on how stable this threshold is or to what extent prediabetes at some stage implies having already crossed it.

Prediabetes is a very important risk factor for developing full-blown diabetes as well as a prerequisite. The same intervention that now appears eminently sensible if diabetes is diagnosed should be considered by prediabetics to play it safe. However, the required duration of the diet is not clear since to be sure requires complete restoration of the beta cell response to glucose which is measured only in studies. The diet time necessary also appears variable since there is anecdotal evidence of individuals curing diabetes in one week with this diet, and the cure was durable and verified by a physician. If one week appears to be enough to cure prediabetes based on home measurements of fasting glucose, then the normalization of this marker should be checked frequently to detect evidence of a false signal. Ideally, a before and after 2-hour glucose tolerance test would be informative. Some would say a confirmatory normal HbA1c is enough.

BOTTOM LINE

Being lean or normal weight is no guarantee of avoiding diabetes, nor does obesity mean that one is condemned to this fate, although the probability is vastly higher. Diabetes can be cured if it is treated early enough by an 8-week severe calorie restricted diet. The time limit for success is somewhere around 6 years disease duration. Weight gain is an indication of, among other things, consuming more calories than needed which for many leads to the fat accumulation and for some the appearance of prediabetes. This waves a big red flag. Diabetes is much easier to cure when it is treated early, and prediabetes is probably even easier. This seems like an excellent reason for screening for prediabetes. The diet can cure diabetes without the patient leaving the obese category and the same must be true for prediabetes. All that matters is weight loss.

THINK TWICE BEFORE AGREEING TO TAKE A NEW BREAKTHROUGH DRUG

In 2012, the US Congress established a so-called *Breakthrough* drug category to expedite development and review of new medicines deemed high priority. To qualify the medicine must be intended to treat serious or life-threatening disorders and, on the basis of preliminary evidence, have the potential to provide substantial improvements over existing options. The US Food and Drug Administration's move was to facilitate shorter drug development and a faster approval process. The general public had for some time been led to believe that they were being deprived of quick access to more effective drugs, targeted drugs, and miracle drugs. The approval protocol was modified in the interest of speed. After a drug was deemed a potential breakthrough, the hoops through which industry had to jump to obtain approval were changed. This included significant changes in the amounts and nature of clinical trial data necessary, changes some regarded as leading to higher risks that dangerous and only modestly more effective drugs would be quickly approved. The FDA statements of course suggested this was not true.[18]

Since then several hundred drugs became eligible for 'breakthrough' designation, and a much smaller number have been approved. There has been considerable discussion in the literature as to whether or not the breakthrough drugs are significantly more effective, adequately tested and safe. One commentary pointed out that many approved drugs lacked trials that included randomization, double blinding, control groups, and used surrogate markers rather than events as primary endpoints, and enrolled small numbers of subjects. In addition more than half of the approved drugs were based on a single pivotal trial.[19] In addition a study examining physician attitudes toward breakthrough drugs found their confidence inconsistent with the facts surrounding the approval process, thus expressing unjustified confidence.[20]

Since many of the approved breakthrough drugs are for cancer therapy, we will concentrate on this class. In 2017 a paper appeared in the *Journal of Clinical Oncology* concerning the efficacy and safety of these drugs which between 2012 and 2017 numbered 25 out of a total of 58 approved.[21] The median time to final approval from designation as either breakthrough or otherwise was 5.2 years vs. 7.1 years. There was no statistically significant difference between breakthrough and non-breakthrough drugs in progression-free survival times or relative risk reductions for solid tumor growth. Breakthrough drugs were not more likely to act via novel mechanisms of action. Rates of deaths and serious adverse events were almost identical for both designations. The authors conclude that breakthrough-designated drugs were associated with faster times to approval, but that there was no evidence for improvements in safety or novelty. In addition there was no evidence for statistically significant efficacy advantage when compared to non-breakthrough drugs.

Thus there was no evidence that the cancer drugs approved under this new designation met the expectations used to justify the new protocol. While the FDA required additional post-approval clinical trials in order to approach what is normally required, this paper

provided no indication that any of these had reported. Patients of course want these drugs and are presumably unaware that they were far from having been tested by the standard protocols. But even these have in fact historically produced a mix of effective, ineffective and dangerous drugs with the latter ending up being withdrawn even though approved by the standard protocol. Vioxx is the poster child of this phenomenon. The internet provides an up-to-date list of these drugs with both the generic and trade names. Patients can determine from the internet if a new drug they have been advised to take or prescribed has this designation. Google NDA and BLA approval reports > breakthrough therapy approval. Unfortunately, patients do not have the resources or training to do the sort of evaluation needed to make an informed decision. Lack of real superiority compared to existing drugs is important. Knowledge of unknown serious adverse side effects and even known but played down or censored effects compared to drugs that went through the standard approval process can be critical. It is also possible that these new drugs may be much more expensive than equally effective older drugs.

A CANCER DRUG TREATMENT SIDE EFFECT: PROFOUND FINANCIAL TOXICITY

According to the National Cancer Institute the cost of most of the cancer drugs approved between 2009 and 2014 were priced at more than $100,000 per year of treatment. More recently costs in excess of $400,000/year have appeared. For perspective, in the US the median annual income is about $50,000 before taxes. Thus it is not surprising that the major reason for bankruptcy is drug costs. But the financial toxicity is greater than just bankruptcy. Homes are lost, families forced to move in with relatives to survive, and the psychological stress is very great and far from ideal when one is fighting cancer. Yet the decision to undergo expensive treatment is complex since the patient and family are being asked to put a financial value on life—actually in most cases added time of survival since only a few of the expensive new drugs bring about remission.

A recent study from Duke University studied patient-reported willingness to undergo a significant, if not life altering, financial sacrifice for cancer treatment.[22] In the initial data collection, at least 65% of patients were willing to make some kind of sacrifice, 38% were willing to sell their homes, and 49% were willing to declare personal bankruptcy. The study found that 76% of patients in the survey had stage IV cancer, and thus had a very low probability of any treatment helping them significantly. The lead author Fumiko Chino, MD commented to *MedPage Today* “There is a potential disconnect between the value that patients place on their cancer treatment and the benefit they stand to gain in terms of prolongation of life or relief of symptoms.” Cancer patients will pay anything for treatment, as apparently will their families, and may be unwilling to accept that some expensive treatment is in fact going to produce a trivial benefit. These decisions are made partly on the basis of an emotional reaction in the presence of a life crisis of profound magnitude. Decisions made without fully understanding the true benefits which, if discussed with the attending physician, might not be believed or even

comprehended. The following strengthens the view that the disconnect between benefit and cost is an important and growing problem.

A study published in 2014 looked at gains in progression free survival (PFS) and overall survival (OS) provided by 71 new expensive cancer drugs approved from 2002 to 2014 for solid tumors.[23] The gain in median PFS was 2.5 months and for OS 2.1 months. There were only two outliers, one at 6.7 and one at 11.1 months, and the 11.1 was labeled as estimated. Did patients taking these drugs fully understand the highly marginal benefits?

Consider the combination targeted immunotherapy for metastatic melanoma, Opdivo plus Yervoy. The former stimulates the kind of cells that fight the cancer and the other allows these cells to recognize the melanoma cells. The key clinical studies found that at 11.5 months half those treated were alive without their cancer spreading or getting worse, 9% had complete response, and 41% had partial response as indicated by tumor shrinkage or disappearance. One-year treatment costs about a quarter million dollars. Some would say, those were very good results. But the price tag would financially devastate all but the wealthy.

The above highlights one major issue which is cost-benefit of novel, expensive cancer drugs. A 2018 study examined this for novel oncology drugs that FDA approved between 2006 and 2015.[24] Benefits were derived from a clinical trial used for obtaining approval. The researchers use two benefit-scoring systems, one from the American Society of Clinical Oncologists, the other from the European Society of Medical Oncology. Costs were defined as either the actual cost of a monthly treatment or the difference between the cost of a given drug and the cost of the standard, much cheaper drug used prior to the launching of the novel drug. This was called the incremental cost. Annual costs ranged from US $60,000 to near $360,000 and incremental annual costs from $3000 to nearly $300,000. No correlation was found between benefit score and annual drug cost or incremental annual cost. As has been widely suggested by critics, novel drug pricing appears based only on the companies' view of what the market will tolerate.

In April, the UK indicated they had reached the point where the pricing situation had become intolerable, that is, unaffordable. The problem was the Cancer Drug Fund (CDF) which provided funding to individuals needing drugs which were considered of low value, i.e. not cost effective because of small benefits. In early 2016, 45 drugs were cut from the CDF to protect the solvency of the fund due to high and increasing costs. One of the drugs cut had been "universally embraced by oncologists"[25] but the drug achieved only approximately 6 months of PFS. Even then the UK, the world's fifth largest economy, could not pay for all drugs that improve PFS and OS. In 2016 in the US, the cost of this drug was estimated at $100,000 for this rather insignificant increase in PFS. Very few cancer drugs produce a cure. However, they have the potential to bankrupt individuals and ultimately may exceed the ability for governments and other insurers to pay. Cancer patients do not deserve to be put in the position where total financial disaster is added to the disaster of their cancer.

Prasad *et al* from the University of Oregon Department of Public Health and Preventive Medicine and from the Sloan Kettering Cancer Center have discussed what appears to be the underlying role of industry in a discussion of the UK action.[25] They propose that in the era of double-digit percent profits, high prices for drugs result from payers who are unwilling to say no, except when they can no longer say yes. The approval by the FDA of drugs with truly marginal survival benefit has been the result of the initial willingness to pay. The authors wonder whether the fact that companies can charge so much and get marginal drugs approved so readily is driving an epidemic of pseudo-motivation where new, costly, and heavily promoted drugs come to market but offer little real benefit for patients. Cancer drug development over the past decade, with very few exceptions, has been able to discover only a negligible number of drugs that cure cancer. In addition, if they had discovered more, it is unclear how the pricing and the interaction with governments and the insurance industry would have played out. Today, the pricing of a novel drug that appears to put a certain cancer in durable remission is priced for millionaires and governments unable to withstand public pressure to allow it to be covered.

To put the melanoma drug combination in perspective, a 94-year-old woman with stage 4 melanoma given a very pessimistic prognosis was treated with an inexpensive combination of natural products (Salvestrol) was symptom free after 6 months and at one year an examination revealed she was cancer free.[26] The protocol for this treatment used today is much more aggressive in that it involves a higher dose and makes use of the synergistic effect of vitamin C and other supplements taken concurrently. Tumor regression was seen after only a few months which provided encouragement that the Salvestrols were working. Compared to the cost of the immunotherapy, the cost is almost negligible. Furthermore, there was metastasis to some other site and the therapy effectively treated this. This is a natural product. Only case histories are currently available and case history evidence is not regarded as evidence based. It is fact viewed with contempt.

METFORMIN VS. LIFESTYLE FOR PREVENTION OF PREDIABETES PROGRESSION

If one puts the words prediabetes and guidelines into PubMed and limits the search to article title, nothing recent appears, and from 2006 to 2015 guidelines appear only for Spain, Indonesia, Europe, and India. A review in 2015 discusses lifestyle and pharmacotherapy, with the latter discussing various anti-hyperglycemic drugs.[27] The most common first-line treatment of diabetes is metformin, a drug of longstanding popularity. Thus it is not surprising that there have been controlled studies of lifestyle as well as metformin in the context of preventing progression from prediabetes to type 2 diabetes.

A recent systematic review and meta-analysis deal with prevention of progression to type 2 diabetes in prediabetics.[28] The researchers included 25 studies, 21 of which tested lifestyle interventions alone, two metformin alone and two assessed both. Studies

all had controls. In 2017 Dennis Maki from the University of Wisconsin School of Medicine and Public Health performed an analysis of the data in this trial to obtain reliable numbers needed to treat (NNT) to prevent one case of progression to diabetes.[29] For lifestyle interventions, 20 studies covering a range of intervention durations yielded a NNT of 15. For studies over 3 to 6 years, the number was 12. Only one metformin study was examined which had a follow-up of 1 to 3 years. The NNT was 14. These NNTs correspond to absolute risk reductions of between 7% and 9%, and in comparison to modern results for intervention trials, this is quite good even though close to 90% did not benefit and progressed to type 2 diabetes.

In this issue of IHN, in a discussion of why obese individuals do not all get diabetes, evidence is presented to the effect that the Newcastle diet is effective in reversing diabetes, except in the case of long-standing disease (duration over 6-8 years). It is believed that the reversal proceeds in stages from diabetes to prediabetes to normal glucose control. Although not yet tested in a clinical trial, it is thus likely that the diet would also be effective in preventing prediabetes from progressing to full-blown diabetes. It is also quite possible that even shorter diet periods than used in the clinical trials would totally reverse early diabetes, probably permanently.

REFERENCES

1. Gray N, Picone G, Sloan F, Yashkin A. Relation between BMI and diabetes mellitus and its complications among US older adults. *South Med J* 2015;108:29-36.
2. MedPage Today.Interview of Porfessor Roy Taylor. How Weight Loss Wakes Up the Beta Cells in Type 2 Diabetes. 22-7-2018.
3. Taylor R, Barnes AC. Translating aetiological insight into sustainable management of type 2 diabetes. *Diabetologia* 2018;61:273-283.
4. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med* 2013;30:267-275.
5. Taylor R. Type 2 diabetes: etiology and reversibility. *Diabetes Care* 2013;36:1047-1055.
6. 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;54:2506-2514.
7. 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.
8. Lean ME, Leslie WS, Barnes AC et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2017.
9. Taylor R, Holman RR. Normal weight individuals who develop type 2 diabetes: the personal fat threshold. *Clin Sci (Lond)* 2015;128:405-410.
10. White MG, Shaw JA, Taylor R. Type 2 Diabetes: The Pathologic Basis of Reversible beta-Cell Dysfunction. *Diabetes Care* 2016;39:2080-2088.
11. Ribe EM, Lovestone S. Insulin signalling in Alzheimer's disease and diabetes: from epidemiology to molecular links. *J Intern Med* 2016;280:430-442.
12. Steven S, Lim EL, Taylor R. Population response to information on reversibility of Type 2 diabetes. *Diabet Med* 2013;30:e135-e138.
13. Salunkhe VA, Veluthakal R, Kahn SE, Thurmond DC. Novel approaches to restore beta cell function in prediabetes and type 2 diabetes. *Diabetologia* 2018.

14. Mulla CM, Middelbeek RJW, Patti ME. Mechanisms of weight loss and improved metabolism following bariatric surgery. *Ann N Y Acad Sci* 2018;1411:53-64.
15. Knop FK, Taylor R. Mechanism of metabolic advantages after bariatric surgery: it's all gastrointestinal factors versus it's all food restriction. *Diabetes Care* 2013;36 Suppl 2:S287-S291.
16. Steven S, Carey PE, Small PK, Taylor R. Reversal of Type 2 diabetes after bariatric surgery is determined by the degree of achieved weight loss in both short- and long-duration diabetes. *Diabet Med* 2015;32:47-53.
17. Corley BT, Carroll RW, Hall RM, Weatherall M, Parry-Strong A, Krebs JD. Intermittent fasting in Type 2 diabetes mellitus and the risk of hypoglycaemia: a randomized controlled trial. *Diabet Med* 2018;35:588-594.
18. Corrigan-Curay J, McKee AE, Stein P. Breakthrough-Therapy Designation - An FDA Perspective. *N Engl J Med* 2018;378:1457-1458.
19. Pusthumana M, Wallach J, Ross J. Clinical Trial Evidence Supporting FDA Approval of Drugs Granted Breakthrough Designation. *JAMA* 2018;320:301.
20. Kesselheim AS, Woloshin S, Eddings W, Franklin JM, Ross KM, Schwartz LM. Physicians' Knowledge About FDA Approval Standards and Perceptions of the "Breakthrough Therapy" Designation. *JAMA* 2016;315:1516-1518.
21. Hwang TJ, Franklin JM, Chen CT et al. Efficacy, Safety, and Regulatory Approval of Food and Drug Administration-Designated Breakthrough and Nonbreakthrough Cancer Medicines. *J Clin Oncol* 2018;36:1805-1812.
22. Chino F, Peppercorn JM, Rushing C et al. Going for Broke: A Longitudinal Study of Patient-Reported Financial Sacrifice in Cancer Care. *J Oncol Pract* 2018;JOP1800112.
23. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics-the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. *JAMA Otolaryngol Head Neck Surg* 2014;140:1225-1236.
24. Saluja R, Arciero VS, Cheng S et al. Examining Trends in Cost and Clinical Benefit of Novel Anticancer Drugs Over Time. *J Oncol Pract* 2018;14:e280-e294.
25. Prasad V, Mailankody S. The UK Cancer Drugs Fund Experiment and the US Cancer Drug Cost Problem: Bearing the Cost of Cancer Drugs Until It Is Unbearable. *Mayo Clin Proc* 2016;91:707-712.
26. Schaefer BA. *Salvestrols. Journey to Wellness*. Clinical Intelligence Corp., 2013.
27. Bansal N. Prediabetes diagnosis and treatment: A review. *World J Diabetes* 2015;6:296-303.
28. Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions. *BMJ* 2017;356:i6538.
29. Maki DG. Review: HbA1c has low accuracy for prediabetes; lifestyle programs and metformin reduce progression to T2DM. *Ann Intern Med* 2017;166:JC41.

For a FREE SUBSCRIPTION please contact us with your name and e-mail address at
editor@yourhealthbase.com

Editor: William R. Ware, PhD

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

ISSN 1203-1933 Copyright 2018 by Hans R. Larsen

INTERNATIONAL HEALTH NEWS does not provide medical advice. Do not attempt self-diagnosis or self-medication based on our reports. Please consult your healthcare provider if you are interested in following up on the information presented.