INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

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To answer the many questions about what is healthy to eat and what is not, nutritional studies have been the traditional source of information and answers. Evidence based medicine likes randomized controlled trials, but when seeking answers to long term nutrition related risks and benefits, such studies are difficult unless they reflect extreme reductionism and focus on one intervention such as changing the intake of some nutrient. Next in line is the so-called observational follow-up study (cohort study) which replaces randomization with the less effective statistical analysis involving confounding factors. One sees results adjusted for smoking, body mass index, income, education, ethnicity, gender, alcohol intake, and various nutritional factors. Follow-up can be as short as a few years or as long as twenty or more. Food intake is generally measured by food-frequency questionnaires, a significant limitation, and in some studies the data is updated periodically, in others only the baseline data is use, with full recognition that people change their diets over time.

What is absent from this approach is individual toxic burden which will always be highly variable given the variety of food sources, the toxic levels offered by these sources, and the human variation in the response (sensitivity) to each toxin. The individual's microbiome, the bacterial populations in the gut, is strongly sensitive to not only toxins but other important issues these studies attempt to examine, but they are generally ignored, mostly out of necessity. What is known is that over the past 20 years, humans have accumulated ever-increasing toxin burdens with a changing mix of toxins, derived from food, water, air, home furnishings, personal care products, cleaning products, pest control products, and building materials. Literally a sea of toxins with new additions monthly. Thus the toxic load in food changes and can increase over the duration of a study. While the body load tends to increase with age due to accumulation, using age as a confounding factor to correct for toxic burden would seem inadequate. The food frequency questionnaire and the other data collected attempts to characterize the cohort ignores the fact that they are systematically and inadvertently poisoning themselves to a highly variable extent, and that these poisons have far reaching consequences, partly through epigenetics, partly through direct toxicity, and that this has an effect on study endpoints for which statistical adjustments are next to impossible because the toxic load cannot be measured, and because if it could, inadequate data exists to make a quantitative connection between toxin levels and diseases, although there seems little doubt that there are significant associations. Furthermore, any attempt to take toxic burden into account also of necessity will ignore what now appears well established; problems in later life can be influenced by prenatal and even maternal preconception exposure.

Finally, as discussed in the September IHN issue, when Weston Price looked at over a dozen primitive societies living in isolation in the 1930s, in trying to explain their significant general health and healthy aging as compared to those exposed to modern civilization, including members of these societies that had migrated into the modern world, it did not appear to matter much what they ate. Some did very well mostly eating fish while other did equally well consuming mostly meat, milk and animal blood. Many ate a diet of meat, fish, fruit and plants. Their isolation from "modern civilization" suggested that what they did not eat or drink was the important factor. Furthermore, what they did not eat was mostly what resulted from the many aspects of the industrial food revolution that started in the late 1800 with refined grains and sugar and trans-fats. At that time (the 1930s), chemical toxins were not as important but trans-fats were certainly present. While nutritional studies indirectly have components that involve what was not eaten, toxins, the progressive poisoning of the cohort is not generally addressed nor is that even possible. Thus for many reasons, most of these studies are irrelevant. However, in the design of these studies, it did not help that the appreciation of the importance of epigenetics, the gut microbiome, and the importance, in spite of industrial and governmental denials of hundreds of toxic substances has only occurred recently.

Wishing you and your family a Happy Holiday Season and best wishes for the New Year,

William R. Ware, PhD, Editor

Highlights

MEAT AND CANCER ACCORDING TO THE WORLD HEALTH ORGANIZATION

On October 26 the World Health Organization (WHO) published a summary news release of a forthcoming report concerning the carcinogenicity of red and processed meat (*Lancet Oncology* online October 26). This was picked up by the media and headlines such as in *The Wall Street Journal* with "Red Meats Linked to Cancer, Global Health Group Says." The BBC was a little more precise saying "Processed Meats Do Cause Cancer—WHO" as was Reuters with "Bacon and other processed meats can cause cancer, experts say." *The Atlantic* on line said, "The WHO says red meat "probably" causes cancer." The cover of the November 9 issue of TIME had two pieces of bacon in the form of an X. Many hearing about this on the evening news probably only remember the simple take-home message that meat causes cancer. The meat industry was understandably upset. When the final report is published, it will probably be book

length since it will appear as a monograph. Thus it is of interest to examine just what the preliminary report in *Lancet Oncology* has to say in its two pages (*News* item not article. Find by searching the Lancet Oncology Science Direct website for the author "Bouvard" in October. Subscription or library access required.)

In October 2015 twenty-two scientists from ten countries met at the WHO International Agency for Research on Cancer in Lyon, France to examine the question of meat and cancer. This working group had examined more than 800 relevant studies (!) and the greatest weight was given to follow-up studies involving the general population. By far the largest body of data concerned colorectal cancer (CRC) and the summary focused on this. However, it mentions in passing that data were also available for more than 15 other types of cancer with positive associations seen between the consumption of red meat including cancers of the pancreas and prostate and for processed meat in connection with stomach cancer. No documentation was provided. However, their main conclusion is based on the CRC studies. Red meat refers to unprocessed mammalian muscle meat from beef, veal, pork, lamb, mutton, horse, or goat. Processed meat has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavor or improve preservation. Examples include bacon, ham, hot dogs, salami and sausage.

The preliminary consensus report presented the conclusion that processed meats are significantly associated with the risk of CRC but red unprocessed meats lack adequate evidence but may offer some risk. The principal epidemiological evidence cited was a meta-analysis (an analysis based on weighted pooling of studies) published in 2011 by Chan *et al*.[1] For processed meat only three out of nine studies used were statistically significant but the meta-analysis yielded a significant 18% *relative* CRC risk increase. For unprocessed red meat it was 17%, also statistically significant. However, this key meta-analysis was very strongly influenced by one follow-up study by Norat *et al* in 2005.[2] For CRC and processed meat it was given 34% of the weight in the meta-analysis. For red meat the weight was 45% and only one study out of eight or nine was significant. Such large weights are somewhat unusual.

Given the importance assigned to this one very large study in the key meta-analysis used by WHO and the impact it presumably had on the pooled results, it seems justified to take it as a source of perspective on absolute benefit. Norat *et al* followed a large group of 478,000 individuals from a number of European countries for about 5 years. In the entire group 0.3% were diagnosed with CRC. In the paper (p 912), the authors give the *absolute* risk of CRC extrapolated to 10 years as 1.71% for heavy red meat consumers and 1.28% for very low levels of consumption. This gives a 0.43% absolute risk increase. Thus over 10 years, the action of eating very small vs. large amounts of red meat required 230 to adopt this strategy to avoid one incident event of CRC (i.e. 1/0.0043). Put another way, for 99.6%, there would be no benefit. This can be compared with the 17% *relative risk increase* found with the same data. A risk increase of about 0.4% would not get the media very excited. The inherent deceptive nature of relative risk has been discussed frequently in IHN as well as in the medical literature.

However, there are other serious concerns associated with this study given very heavy weight in the key meta-analysis. Comparison of high vs. low (reference) intakes of red and processed meats taken together when adjusted for all confounders considered relevant yielded a non-statistically significant association with CRC based on the hazard ratio, a standard way of expressing adjusted results which generates the relative risk reduction numbers. The same was true for red meat alone but processed meat did yield a significant result (42% relative risk increase). All sub-group analyses of types of either red meat or processed meat also failed to find statistically significant associations with CRC.

More importantly, when a subgroup with a carefully calibrated intake was analyzed, again a non-significant result was obtained for red meat and the trend with the amount consumed was also not significant, but the significant association remained for processes meat. But the hazard ratio indicated a very low absolute risk increase of about 0.2%. However, WHO did not rate the quality of evidence for red meat as high as for processed meat but nevertheless termed it "substantial epidemiological data showing a positive association between the consumption of red meat and colorectal cancer," a stronger statement than appears justified. In fact, it appears that the WHO case rests on a foundation of results that imply a very small absolute risk increase with just processed meat consumption, mostly because of low prevalence of CRC in large populations. Recall the 0.3% prevalence of cases in Norat *et al* for nearly a half million subjects.

Some of the chemicals viewed as potentially carcinogenic in processed meat can also be generated in red meat by the cooking technique used, and the levels increase with the extent of cooking, the temperature and whether or not the meat was barbequed. These become confounding factors for which statistical adjustment is difficult or impossible due to lack of information. These toxins are minimized by undercooking without surface burning. Nevertheless it may be correct that red meat carries a small risk of cancer if overcooked or barbequed.

The 2012 guidelines of the American Cancer Society also address meat as a cancer risk.[3] The cited evidence is the same as already discussed, [1-3] but they give only relative increases and do not mention the very small absolute risk such as that calculated by Norat *et al* and discussed above. They cite 15% and 20% increased cancer risk for red and processed meat for consumption of 50 g and 100 g respectively. They are generating concern and fear by deception through omission, the standard practice in drug marketing.

In 2013, Ioannidis and Schoenfeld published a paper in the American Journal of Clinical Nutrition in which they ask "Is everything we eat associated with cancer."[4] They were able to find more than 10 studies addressing the risk for each of the following: wine: tomatoes, tea, sugar, salt, potato, pork, onions, olives, milk, lemons, eggs, corn, coffee, cheese, carrots, butter, bread, beef and bacon. Most had a mix of positive and negative results. When they looked at meta-analyses that used data from follow-up studies, 93% found either non-significant associations or weakly or strongly decreased risk (protection). They also point out that nutritional research is generally exploratory with protocols and analysis modified in an iterative fashion. This implies potential for bias and the generation of nonsense and is part of the motivation for the pre-study registration of all the details of the study protocol and data analysis as now required for publication by reputable journals.

A lot of effort has been devoted to studies of red and processed meat consumption and mortality and these have generally included cancer-related mortality which is different from incidence, the issue in the above discussion. A just published set of such meta- analyses is thus of interest.[5] For red meat, when the highest vs. the lowest intake was compared, an analysis of eight studies yielded no association for cancer mortality whereas for processed meat analysis of eight studies found the risk was increased by a small factor of 1.08 (8% *relative* risk increase) which was statistically significant. No absolute data was presented. This study also looked at all-cause and cardiovascular mortality and found the same pattern, for processed meat there was a significant association whereas for red meat it was absent. Thus studies where only total meat intake is examined which yield statistically significant risk results, it is most likely due to processed meat, and attention should be paid only to studies that separate the two.

In a review in press on red meat consumption and healthy aging, the authors were unable to cite any evidence concerning a significant association of unprocessed red meat and all-cause

mortality or coronary heart disease mortality or stroke incidence in middle-aged in older subjects.[6]

BOTTOM LINE

Over the years, processed meat has frequently come up as a health hazard and thus the above results are not surprising. Since processed meat contains chemicals from a variety of sources, it can be argued that limiting consumption of this food is wise. It is a common mainstream recommendation. It would be nice to have more information on absolute risk increases for all the disorders where the issue has been studied. It appears they may be quite small. For red meat, the evidence so far, not only from the studies cited herein, suggests that if one wants to worry about red meat, it should be in the context of over-cooking and the presence of antibiotics, hormones, herbicide and pesticide residues from feed, issues with GMOs in feed, and other possible toxins where just on general principles, avoidance is wise. Thus it is better to eat grass fed meat which presumably has much lower levels of toxins and seek out antibiotic and hormone free meat. Follow-up studies like the ones discussed above may not tell the whole story since the levels of toxins in red meat may be have increased significantly after some of the studies were finished and in addition, cancer generally requires years to become symptomatic and death from cancer or other causes even longer. Humans are omnivores and eating meat has been normal for eons. However, since the industrial food revolution, it is not the same food. In the time period of evolution, this is just an instant. However, the changes in meat have been profound in terms of the nature of the fat and the content of chemicals and genetic material never before encountered by humans. It may take a few more decades for health risks to become more apparent. Eating free-range chicken and grass fed beef and other sources of red meat, free of hormones, antibiotics, and pesticide and herbicide residues seems sensible. Those who can find reliable sources should consider themselves lucky.

SHOCKING PREVALENCE OF DIABETES AND PREDIABETES

Data from the National Health and Nutrition Examination Survey (NHANES) concerning the prevalence of diabetes and prediabetes as of 2011-2012 has just been published.[7] The results are given in the table below.

Table. *Diabetes prevalence per 100 adults in the US general population*

Group	Diagnosed %	Undiagnosed %	Total %	Prediabetes %	Grand Total %
Age ≥ 65	21.3	11.6	32.9	49.5	82.4
Age 45-64	11.6	5.8	17.4	44.9	62.3
Age 20-44	2.7	2.4	5.1	28.2	33.3
Overall	9.1	5.2	14.3	38.0	52.3

Diabetes defined as HbA1c ≥6.5%, fasting glucose ≥ 125 mg/dL (7.0 mmol/L) or 2-hour glucose of ≥ 200 mg/dL (11.1 mmol/L). Prediabetes as HbA1c 5.7 to 6.4%, fasting glucose ≥ 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) or 2-hour glucose of 140 to 199 mg/dL (7.8 to 11 mmol/L).

The focus here is on prediabetes and is prompted by the huge prevalence both in the adult population as a whole and in the age group 45 or older. Prediabetes and diabetes represent a continuous deterioration of glucose metabolism. Thus the threshold for declaring diabetes is

somewhat arbitrary, but determined mostly by the threshold for the significant increase in risk of complications. The so-called natural history, a term which implies no treatment or intervention, is that individuals who cross the threshold into prediabetes simply progress to diabetes which then continues to progress until insulin is required to control elevated blood sugar. This progression is relentless and medication has little impact. The risk of complications is present even in the prediabetic state. If one ignores the recent amazing achievement of Taylor and colleagues at the University of Newcastle in the UK which involved curing type 2 diabetes, mainstream medicine is only able to slightly delay progression but not change the ultimate progression to diabetes because neither lifestyle (diet and exercise) or drug interventions are effective for a large percentage of patients. Blood glucose and HbA1c levels can be decreased but few prediabetics revert to normal and even fewer diabetics are "cured." Progression is the norm. As discussed in IHN several times, the sensational results of the Newcastle diet and the results of bariatric surgery challenge the conventional wisdom that diabetes is incurable.

One aspect of this disease needs clarification. The fasting blood glucose is determined mostly by the insulin resistance of the liver whereas the response to the glucose generated from food which controls the HbA1c (3-month blood glucose average) and the oral glucose tolerance test results (the so-called 2-hour glucose) involve muscle insulin resistance and the functioning of the beta cells of the pancreas. The former strongly depends on how much fat there is in the liver. The latter two become more and more important as the disease progresses. Thus the prediabetic can have impaired fasting glucose or impaired glucose tolerance or both, the latter revealed by the oral glucose tolerance test as well as the HbA1c, which reflect the excursions in blood sugar after eating, excursions which increase in magnitude and duration with increasing impairment. When both are present the rate of progression as well as the risk of complications is increased.

In a perspective in the journal *Diabetes Care,* Phillips *et al* point out that mainstream medicine currently wastes the first 10 years of the natural history of diabetes since if prediabetes was diagnosed early the progression could be delayed or in some individuals, prevented.[8] Most of the evidence comes from trials where lifestyle change and/or glucose-lowering drugs decreased the rate of progression from diabetes to prediabetes. However, the only long-term results involved the use of drugs. Studies show that very low-carbohydrate or ketogenic diets reduce both fasting glucose and HbA1c, an almost universal characteristic of such diet studies is their rather short term, poor adherence and the convergence of results for the diet vs. control groups toward the end of the trial. Furthermore, most of these studies involved diabetics and the reductions in HbA1c in some cases took the subjects into the prediabetic range, this was not the case with fasting blood sugar (see the November 2013 issue of IHN for a detailed discussion and documentation). A recent study which included prediabetics and used a very low carbohydrate diet (ketogenic) did not include enough prediabetics to allow any conclusions to be drawn.[9]

Phillips *et al* discuss several key drug trials. The DREAM trial was placebo-controlled using rosiglitazone for prediabetics and follow-up was 6 years, but the drug intervention stopped at about 3.3 years. After the first year, the cumulative increase in incidence of diabetes in the treated group ran more or less parallel to the control but with a 4-month delay at the end of 6 years. Similar results were found in the US DPP trial and the prevalence curves again then ran parallel and then tended to converge with a delay at the end of 4 years of 6 months. Thus drug intervention produced a small, sustained benefit even after the drug treatment was stopped, but nevertheless both during and after the drug treatment, progression was present at roughly the same rate. While the benefit was termed sustained, the clinical significance of this for the patient seems small. Progression to diabetes and a health disaster was delayed by only a few months.

Another DDP study compared lifestyle, metformin and placebo interventions. While there were large changes in the cumulative prevalence of diabetes at the end of the study, the cumulative incidence over 4 years showed a delay of about 2 years for lifestyle and one year for metformin. Thus the use of drugs to lower blood sugar levels does not appear to solve the problem of progression in prediabetics but merely delays the diagnosis of diabetes for a period depending on the intervention. The fact remains that it takes roughly 10 years from the initial crossing of the prediabetic threshold to the appearance of diabetes. This is not surprising since the threshold for diabetes is an arbitrary point in a continuous progression which is not significantly impacted by "managing" blood sugar levels. In this time frame, the above delays appear of little significance and the principal problem remains. Biomarkers rather than cause have been addressed.

Finally, why the large prevalence of both diabetes and prediabetes? Obesity, poor dietary choices and lack of exercise are frequently cited. However, in recent years environmental chemicals have received increasing attention as potential factors. These include pesticides, herbicides, dioxins and chemicals associated with plastics. When the intake exceeds the rate of natural detoxification or the body storage is efficient as is the case with fat-soluble toxic chemicals, then over the years the body burden increases and the tipping point may be reached where critical aspects of glucose metabolism become dysfunctional, including insulin resistance and beta cell function.[10-12] Sources not only include food, drinking water and chemicals from personal care items and home furnishings, but also toxins inhaled from air pollution or absorbed through the skin.[13] Among the most strongly implicated in the context of diabetes and obesity are the endocrine disrupting chemicals such as bisphenol A, phthalates found in plastics and cosmetics and chemical flame retardants. Exposure is almost universal. These observations simply reinforce the view of the importance of environmental toxins and body burden on chronic diseases and the need for aggressive detoxification and limited toxin intake.[14, 15]

BOTTOM LINE

What then is the solution to the problem of a more or less hopeless prognosis for the prediabetic if left untreated or even given conventional treatment and advice? The answer would appear to be the Newcastle Diet (see IHN October 2014). Since it was able to return many diabetics to normal (cure!) then it would be amazing if it did not work, in fact work faster and better, on prediabetics. In addition, this diet works over 8 weeks and appears permanent if the end-of-diet weight is maintained (see below for an update). Hopefully, there will be a study of this diet with prediabetics, perhaps even looking at how many weeks are required to restore beta cell function to normal. It may be less than 8 weeks. If the prediabetes is merely impaired fasting glucose, studies published thus far indicate that only a week or two might be required. Individuals with a severe weight problem that suggests bariatric surgery and at the same time have prediabetes will almost certainly return to normal glucose metabolism if they have surgery.

LATEST OPINION ON DIABETES SCREENING

This independent task force of volunteer experts operates with support from the US Department of Health and Human Services and its guidelines are very influential. The task force has just released its latest recommendations for screening for both diabetes and prediabetes.[16] They recommend screening for adults age 40-70 who are overweight or obese. However, not all diabetics or prediabetics are overweight or obese. Furthermore, as indicated above, in the US in the age group of 20-44, almost 30% were prediabetic but would be excluded because of age, and as well 2.4% who had undiagnosed diabetes. While the Task Force admits that benefits

may accrue from early diagnosis of both prediabetes and diabetes, they claim there is little satisfactory evidence by their standards. However, the risks of screening are negligible. The HbA1c test does not have false positives aside from laboratory error. Therefore, any benefit, even small, is worth considering. The recommendations also ignore the rapidly increasing incidence of diabetes in children and young persons and *a* prio*ri* prediabetes must be on the increase as well in children. It can be argued that HbA1c should be checked once every 1-2 years as part of routine checkups. The Task force also naturally ignores the Newcastle dietary cure. After all, there are as yet no randomized controlled studies that would meet their standards. The Task force recommendation appears seriously out of step with reality. However, this latest position may influence reimbursement for screening tests.

RESULTS FROM THE SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL (SPRINT)

The eagerly awaited results of the so-called SPRINT blood pressure trial have just appeared in the *New England Journal of Medicine*.[17] The trial was halted early because the results were viewed as very good. This study provides a good example of what in mainstream medicine is a "big deal" deserving two editorials and a perspective in the same issue of the *Journal.* The trial addressed the question of the benefit of using a systolic blood pressure target of 120 mm Hg in an older population at high risk for cardiovascular disease but free of diabetes. This exclusion was due to the results of the ACCORD trial which had already shown no benefit of this intervention for diabetics. The SPRINT trial was randomized with the control a comparison group where the target systolic pressure was 140 mm Hg. The inclusion criteria were age >50 with high blood pressure and increased cardiovascular risk defined as clinical or subclinical cardiovascular disease other than stroke or chronic kidney disease or a 10 year risk of cardiovascular disease > 15% according to the Framingham risk score, or an age ≤75. The primary composite endpoint was heart attack, stroke, and acute coronary syndrome not resulting in an occlusive heart attack, heart failure, or death from cardiovascular causes. Secondary outcomes included individual components of the primary endpoint and all-cause mortality. Over 9000 subjects were randomized into the treatment and comparison groups; the latter termed the standard treatment group. Both had baseline average systolic blood pressure of 139 mm Hg and the comparison group maintained an average treated systolic pressure of about 135 throughout the study after a few months. The intensive treatment group maintained an average pressure of about 120 mm Hg.

The results are summarized in the following table which represents a mean of 3.3 years treatment. RRR and ARR represent relative risk reduction and absolute risk reduction. The numbers needed to treat (NNT) to prevent one event over 3.3 years are those provided by the authors in the paper and yield the ARR as 1/NNT. NO BENEFIT results from (100 – ARR) %.

Table. *Absolute and relative risk reductions in SPRINT blood pressure trial*

Outcome	RRR (%)	ARR (%)	NNT	No Benefit (%)
Primary endpoint*	25	1.6	61	98.4
All-cause mortality	27	1.1	90	98.9

**See text above for components*

The numbers make one question why the results were such a "big deal." It needs to be emphasized that these results apply to the select patient group based on the inclusion criteria and therefore do not apply to the general population. There is a risk that the media projected the false notion that lower is better for everyone with hypertension. In fact, one editorialist estimated that only 1 in 5 individuals treated for hypertension would even have qualified for inclusion. It is also important to realize that the follow-up was short and that it would be expected that for 10 years, the absolute risk reductions for the primary endpoint and all-cause mortality would increase to about 5% and 3.3% respectively with associated small decreases in NO BENEFIT. Absolute risks for adverse events ranged from small decreased risk but 13 types of event with positive risk including 1.8% for acute kidney injury or acute kidney failure and 1.4% for hypotension. These numbers would also presumably increase with time the same way one would expect to see in the benefits. Thus one can raise valid questions regarding the risk/benefit balance.

In this study we have an impressive relative risk reduction in the two above endpoints, but small absolute benefit and a most of the treated cohort did not benefit. Patients who meet the inclusion criteria and are provided with the absolute results, not the 25% or 27%, will need to weigh the adverse events that had absolute risk increases compared to standard treatment that were ≥ 1%, given the absolute benefit of 1.6%. In addition, individuals with hypertension should worry about being advised to seek a target of 120 if they do not meet the trial inclusion criteria since they might not experience even the small benefit with an intervention is not without risk. A commentary in www.medscape.com pointed out that the authors of the report failed to discuss the need for lifestyle changes to be added to the medications they found to have such a small benefit, and mentioned specifically that the cohort was on average at the threshold of obesity.

One of the comments in the same issue of the *Journal* (James S. Yeh, case vignette) presented a case of a 75-year-old women who did not meet the criteria and in fact had a Framingham risk score of 7% and a normal glomerular filtration rate, a measure of kidney function, did not have a history of heart disease or smoking and exercised regularly. The commentary gave opposing view from two physicians as to the advisability of getting the systolic pressure down to 120 with one making a case for doing this based on the relative risk reduction. The amazing and sobering thing is that the J*ournal* even published the position of a physician recommending in the face of the above presentation that SPRINT justified treating this patient to the new target. This may illustrate a systemic problem with overtreatment.

These results illustrate the sad fact that clinical studies aimed at reducing the impact of chronic disease generally fail to benefit the vast majority of those treated. Readers may find it interesting to visit www.theNNT.com where they will find a large number of carefully documented and discussed examples provided by a group of physicians and biostatistics experts in which the results are examined in the way IHN attempts to use. For example, in the areas of cardiology and public health, about of half of the studies examined on the website, mostly focused on popular screening and preventive interventions, had no benefit or no benefit plus enhanced harm.

NEWS BRIEFS

POTASSIUM AND KIDNEY AND CARDIOVASCULAR COMPLICATIONS OF TYPE 2 DIABETES

Type 2 diabetics are at high risk of developing kidney and cardiovascular disease, complications which are life threatening. A study just published examined the hypothesis of a protective role of potassium.[18] A group of 623 Japanese type 2 diabetics free of kidney disease were involved. Urinary potassium and sodium levels were measured at baseline and the subjects followed for a median of 11 years. Urinary potassium excretion (g/d) was 1.4 in the first quartile and 2.3 in the fourth. The primary endpoint was the first occurrence of any adverse kidney or cardiovascular events. Plots of the cumulative incidence of this composite endpoint for each potassium quartile exhibited a large protective effect with the difference in event rate of 15% at 10 and 16 years for being in the fourth vs. the first quartile. At 5 years it was 9%. When a multivariate analysis was conducted taking into account confounding, potassium but not sodium was significantly associated with the primary endpoint. However, the study used only baseline (initial) levels. Nevertheless, these results suggest there may be considerable merit in maintaining high potassium status in type 2 diabetics if there is no kidney impairment in order to decrease the incidence of complications. Incidentally, blood potassium and sodium levels were essentially constant over the quartiles of urinary potassium and evidentially blood levels are not useful markers in this context.

POTASSIUM AND PROGRESSION OF EXISTING KIDNEY DISEASE

In sharp contrast to the above report, an also just published study involved a US population with kidney disease (eGFR 42-49) with half the study population diabetic. It was found that potassium and sodium urinary excretion measured annually was positively associated with kidney disease progression.[19] The absolute difference in cumulative rate over 6 years between the lowest and highest quartile was about 12%, similar to but the reverse of what was observed in the above study. However, in that study the cohort was initially free of kidney problems and the composite endpoint included both the appearance of kidney problems and cardiovascular problems. In the subgroup analysis of the Japanese study, for progression to chronic kidney disease rather than a first manifestation the adjusted hazard ratio was small and not statistically significant when the first and fourth quartile of potassium excretion were compared. However, there was a trend toward what eventually probably would have become a positive association similar to that observed in this study. In the US study there was no significant association between potassium excretion and all-cause mortality. The Japanese study did not provide a subgroup hazard ratio for cardiovascular or all-cause mortality. The two studies do not appear to be contradictory since one used urinary levels to judge intake in individuals who were free initially of kidney disease, whereas this study, as the authors point out, the association of dietary potassium intake with kidney disease progression is more complex than for those with chronic kidney disease due to the abnormal manner in which those with the disease handle dietary potassium and the confounding effect of medications. They point out that their study supports the notion that high potassium intake might cause adverse effects among patients with chronic kidney disease.

BARIATRIC SURGERY IN ADOLESCENTS REVERSES TYPE 2 DIABETES

A study just published examined the impact of bariatric surgery on 242 adolescents (age range 13-19) with an average weight of 325 pounds (BMI 53!).[20] Either the sleeve or bypass method was used. After surgery, at 3 years follow-up, the average weight loss was over 90 pounds which occurred within a year and was durable for the next two years and the differences in weight loss between the two techniques was not significant. Reversal of type 2 diabetes was

seen in 95% (94% for bypass, 100% for sleeve) of the diabetics. Prediabetes was eliminated in 76% (74% in bypass, 100% in sleeve). These are obviously very large absolute effects. Other beneficial changes included remission in hypertension (74%), dyslipidemia (66%) and abnormal kidney function (86%). These results are similar to what is obtained in adults. Bariatric surgery and the 8-week very low calorie diet (Newcastle diet) appear to be the only interventions that actually cure diabetes.

MAINTENANCE OF BLOOD GLUCOSE CONTROL AND STABLE WEIGHT OVER 6 MONTHS AFTER VERY LOW CALORIE DIET. AN UPDATE ON THE NEWCASTLE DIET

At the American Diabetes Association Scientific Sessions Meeting in June 2015, Professor Roy Taylor's group presented new results (poster 2177) where they studied the durability of diabetes reversal over 6 months after the end of an eight week 600-800 calorie diet.[21] This study supports earlier anecdotal results collected by email. For the subjects with short duration diabetes (<4 years) weight went from 99.5 kg initially to 84.7 kg at 8 weeks and was 84.7 kg at 6 months. For HbA1c in the short diabetes duration group, the initial value of 7.2% went in 12/15 to < 6.5% and 11/12 maintained < 6.5% for 6 months. In the long duration diabetics (> 8 years) the corresponding numbers were for weight 97 kg to 83 kg to 85 kg and for HbA1c, 8.6% decreased to <6.5% (2/14) in 8 weeks and at 6 months to <6.5% in 3/14. They also measured liver triglycerides and insulin resistance and plasma insulin and found improvements were maintained over 6 months. They concluded that the study confirmed the durability of the pathophysiologic changes which permit return to normal blood control in people who previous type 2 diabetes, and the results indicate that the very low calorie diet is much more effective for those with short-term diabetes. For a detailed discussion of this diet, the original study and other results, see IHN October 2014. This study reinforces the benefit of early diagnosis of type 2 diabetes.

ANTIBIOTICS, THE GUT BACTERIAL POPULATIONS (MICROBIOME) AND FUNCTION

A paper just published examined the effect of *one* dose of either of four commonly used antibiotics on the oral and intestinal microbiome and also examined changes in gut function.[22] The study involved 66 healthy individuals in the UK and Sweden in a randomized placebo controlled clinical trial. Immediate and long-term effects (12 months) were examined. For background concerning the microbiome, see the September 2014 IHN. While the oral bacterial populations were found to be resilient and recovered rapidly, this was not the case in the gut with two antibiotics, clindamycin and ciprofloxin showing severe and long-term impact on the health-associated butyrate producing microbial community. Butyrates, short chain fatty acids, are associated with gastrointestinal health partly by acting as an energy source and partly by inhibiting inflammation, carcinogenesis and oxidative stress. In addition they decrease serum levels of glucose, decrease insulin resistance, and increase the protective effects of an important peptide (GLP-1).[23, 24] The antibiotics were also observed to increase antibiotic-resistant gene expression. The fact that long-term involved many months, this research highlights the growing attitude that antibiotics such as these should only be used when absolutely necessary, which does not appear to be the current practice nor correspond to the wishes of many patients.

BLOOD SUGAR LEVELS AND MORTALITY IN THE ELDERLY

A though provoking study has just appeared which looked at mortality rates in a group of about 13,000 subjects (41% male) in a Israeli healthcare database who in a 10 year follow-up did not develop diabetes.[25] The average age was about 80. A striking U-shaped result was found

between the death rate over 10 years and the initial 3-month blood sugar average provided by HbA1c (A1c), the glycated hemoglobin. For those without comorbidities, the death rate was 11.4% lower for those with A1c between 5.9 and 6.1% compared to those with ≤5.39 and about 5.6% lower for those between 5.9 and 6.1% compared to 5.4 and 5.89%. That is, the minimum in mortality was between 5.9 and 6.1% and it was pronounced and significant. In fact the risk at levels between 6.1-6.4% only went back up to that associated with 5.4-5.89%. Note that the thresholds for prediabetes and diabetes are ≥ 5.7% and ≥ 6.5% respectively and this study excluded diabetics. Taking into account comorbidities had little influence on these results. Risk ratios generated by multivariate analysis taking into account a number of confounders reflected the same U-shaped response when A1c between 5.9 and 6.1% was used as the reference. Most of the risk ratios were statistically significant. A1c tends to normally increase with age, and the authors suggest this may represent a physiological response to aging that is protective, a view also expressed by researchers who also found similar results. The results suggest studying the elderly with low A1c levels to seek the origin of the enhanced mortality as this might suggest therapeutic targets. In addition, it appears that the notion that for thresholds, one size fits all, is an oversimplification, given the minimum risk in mortality in an A1c range indicating prediabetes, and evidentially the "the lower the better" philosophy has limitations.

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