INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

NUMBER 234 **FEBRUARY 2013** **22nd YEAR**

The main theme in this issue is diabetes control. A four-year study is reviewed which found a low-carbohydrate diet enabled type 1 diabetics to maintain normal blood glucose levels and fluctuations, and lower their insulin requirements. A second study examined the question of lifestyle interventions such as calorie restriction and exercise inducing partial or complete remission in type 2 diabetics. Another question of importance in diabetes control is the use of insulin alone in type 2 diabetics. While it is highly unlikely that insulin would ever become the first treatment upon diagnosis unless the patient had severe glucose control problems, it may be an attractive option when drug therapy fails. Another approach to glucose control is the ketogenic diet where carbohydrates are severely limited to produce ketogenesis, something the Atkins initiation diet attempted. The results are quite interesting.

Several vaccination issues are also examined in this issue. The most recent U.S. Centers for Disease Control report on this flu season is discussed along with a recent meta-analysis which claims to present the best yet picture of the effectiveness of flu vaccines. In addition, the impact of vaccinations on infants and children is discussed. One study examined trends in hospitalization among infants according to the number of vaccine doses received in year one. Another study critically examines aluminum exposure from early childhood vaccinations and the incidence of autism.

Finally, a surprising and somewhat hard to believe study is discussed which connects mortality and cancer incidence to the use of sleeping medications. Even if the risks are overstated, the study discussed should raise serious reservations about the medication approach to insomnia.

This issue also reviews four recent books judged by your editor to be of significant interest. One, the cholesterol myth book, is of particular interest because a well-known cardiologist is taking an obviously very public position of what is still an ongoing controversy with most of mainstream medicine adhering to the cholesterol hypothesis and ignoring the critics and their evidence.

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

Wishing you and your family good health,

William R. Ware, PhD, Editor

Highlights

GLUCOSE CONTROL IN TYPE 1 DIABETICS

There is considerable evidence that when intensive insulin therapy is employed with type 1 diabetics, it is possible to approximately normalize blood glucose fluctuations and HbA1c, an indicator of long-term glucose

control. This is accompanied by a significant decline in the rate of progression of kidney damage, clinically evident neuropathy, and degeneration of the retina. However, intensive therapy increases the risk of severe hypoglycaemia episodes which can have serious consequences. In one major trial of intensive glucose control, the rate of severe hypoglycaemia was increased threefold.[1] Furthermore, even with modern technology such as self-monitoring and insulin delivery devices, average glycemic control in type 1 diabetics is generally regarded as poor.[1-3]

The blood glucose fluctuations in type 1 diabetes are related to the input of glucose from food, mainly from carbohydrates. Many type 1 diabetics have difficulty matching insulin with carbohydrate intake and suffer unpredictable blood glucose levels after eating. A recent study by Nielsen *et al* has examined the short and long term impact of carbohydrate restriction and adherence to a low carbohydrate regimen on these glucose excursions and HbA1c.[4] Reported is an extension of a study done over 12 months which was prompted by reports in the literature of type 1 diabetics achieving near-normal blood glucose levels around the clock with restriction of carbohydrates to 40 g/day. The authors display a typical example of this where an individual had variations over 4 days of 108--414 mg/dL (mean 252) which within a day was reduced to 72--171 (mean 115) mg/dL and persisted with time (to convert to mmol/L, divide by 18). This rapid drop to near normal levels cannot be due to weight loss.

In the study being reviewed, a combination of rather intensive education was combined with a dietary regimen consisting of 75 g/day of carbohydrates with insulin dose adjustment. The group of 48 diabetics was followed for adherence and glucose control over 4 years. Participants had a mean age of 52 years and a 24-year history of type 1 diabetes. All the participants experienced a decline of HbA1c from a mean of 7.6% to 6.3% at 3 months, when the first assessment was made. At 4 years, those who were partly adherent had mean HbA1c values of 6.9% and for those with excellent adherence (27% of the group), the mean has dropped to 6.0%. Those unable to adhere to the regimen regressed until at 4 years HbA1c was approximately the starting value.

At 3 months, when adherence was high for the entire group, the mean weight declined only from 77.6 kg to 74.9 kg. It is interesting that carbohydrate restriction in the case of type 2 diabetes also yielded beneficial glycemic control results independent of weight loss.[5]

The authors found that only a limited number of patients in contact with their diabetes clinic were interested in the dietary change found beneficial. If those uninterested were following guideline recommendations, they would have been on a low-fat, high-carbohydrate diet. The authors point out that there is no evidence supporting this recommendation, nor is there evidence that increased protein in low-carbohydrate diets should cause kidney disease. But there is strong evidence for "aggressive development of damages to all organs in poorly regulated type 1 diabetes."

This is of course not a cure, but rather a successful normalization of glucose fluctuations with decreased need for insulin and decreased risk of hypoglycaemia. Since intensive insulin treatment in type 1 diabetics carries significant benefits in terms of at least some complications, this much more natural approach to normalization of glucose fluctuations should be better, given the more normal insulin levels.

LIFESTYLE INTERVENTIONS AND TYPE 2 DIABETES REGRESSION

In the last issue of IHN, problems with drug treatment of diabetes were discussed. In addition, mention was made of the halting of the AHEAD lifestyle trial due to futility. A study just published in the *Journal of the American Medical Association* adds to the subject of lifestyle interventions. This was a large, randomized intervention trial involving over 5000 AHEAD participants followed for over 4 years.

Gregg et al [6] examined the impact of so-called intensive lifestyle intervention on remission in type 2 diabetics. Partial or complete remission were defined as a transition from meeting the diabetes diagnosis criteria to being either prediabetic or having normal glucose control, respectively. Prediabetes was defined as having a fasting glucose level of 100-126 mg/dL and an HbA1c of 5.7% to 6.5% with no antihyperglycemic medication. Complete remission required fasting glucose of < 100 mg/dL and HbA1c < 5.7% with no diabetes medications. These definitions are consistent with the American Diabetes Association guidelines as of 1997 which still apply.

The goals set in the intervention were the reduction of energy intake to 1200-1800 calories (k/cal) per day which was to be accomplished by reductions in saturated and total fat intake and increased physical activity with a goal of 175 min/week. The cohort was obese with a median duration of diabetes of about 5 years. Approximately 73% of participants were initially on oral diabetic medications and 19% were also on insulin. The definition of remission indicates that participants were also required to come off these medications to qualify.

As is common to most lifestyle interventions, weight loss was not durable but the intervention impacted glucose metabolism with some participants experiencing mostly partial remission. At 2, 3 and 4 years, respectively, 10.4%, 8.7%, and 7.3% of the intensive lifestyle participants had either complete or partial remission of type 2 diabetes compared to 2.3%, 2.2% and 2.0% for those in the so-called support and education group (essentially yearly group-sessions delivered advice on diet and physical activity). Thus in both groups, the benefits seen early were not durable. Viewed another way, 89.6%, 91.3% and 92.7% of those who undertook the intensive lifestyle intervention failed to benefit in terms of going from diabetic to either prediabetic or diabetes free at years 2, 3 and 4. The corresponding numbers needed to treat are 12, 15 and 19 to obtain any remission, and those receiving just support and education experienced very small benefit in this context.

The intervention had almost no success in bringing about complete remission. In the intervention group, at year 1 and year 4, 1.3% and 0.7% met the definition of complete remission, with numbers needed to treat of 83 and 200, respectively.

As discussed in the December/January IHN, participants in the AHEAD trial in the intensive lifestyle group experience no benefits when the endpoints were non-fatal heart attack or stroke, hospitalization for angina or overall mortality. Thus there is a disconnect between benefit measured by blood glucose levels and benefit measured by significant major event outcomes. Also, as pointed out in the last IHN, meta-analyses in the last few years suggest that the widely believed notion concerning protection from most complications based on blood sugar reduction with drugs is in fact not evidence based.

INSULIN ALONE FOR TYPE 2 DIABETES?

In 2012, Hemmingsen *et al* performed a meta-analysis regarding the question of metformin and insulin vs. insulin alone.[7] They found no evidence or even a trend towards improved all-cause mortality or cardiovascular mortality with the combination therapy compared with insulin alone for type 2 diabetics. However, the data in any of the studies included was severely limited, the case numbers very low, and the opportunity for bias judged by the authors was high. Thus the issue cannot be considered resolved. The standard practice is that insulin is added to metformin or other drugs, not the reverse, since the treatment with the oral drug is much simpler than starting injections, and the risk of hypoglycaemia no doubt much less. As discussed in the December-January IHN, intensive treatment with more than one drug, and if necessary, added insulin had no impact on most of the complications of type 2 diabetes as compared to a drug or drug plus insulin protocol that did not attempt to bring fasting glucose and HbA1c to near normal. Thus the question: what happens if only insulin is used along with diet? This would be simply hormone replacement therapy rather than attempting to modify glucose metabolism by various drug

driven programs and mechanisms. The issue is diabetic complications. A study published in 1995 appears of interest.

Ohkubo *et al*[8] examined the effect of intensive insulin therapy on microvascular complications (neuropathy, retina problems and kidney disease) in a Japanese group of type-2 diabetics already on insulin but not on diabetic drugs. They cite a number of studies starting in the mid-1980s that found intensive therapy with insulin reduced the prevalence or progression of microvascular problems in type 1 diabetics. There are more modern studies with the same results. However, at the time of the study, in Japan type 2 diabetics were treated with 1 or 2 daily injections of intermediate-acting insulin, but this approach did not normalize post-meal hyperglycemia, fasting blood glucose or HbA1c.

In this randomized study, intensive insulin therapy reduced the fasting blood glucose (FBG) from about 170 to about 125 mg/dL and the HbA1c from 9-10% to around 7 % and these results were durable for 6 years. In the usual treatment group, the corresponding values started in the same range because of randomization, and over 6 years either remained the same or slowly increased. For primary and secondary prevention of microvascular complications, the results were as follows where the comparisons are between intensive insulin therapy and standard insulin dosing. Prevalence percentages are given.

	Primary (incidence)	Secondary (progression)
Retina problems (retinopathy)	7.7% vs. 32%	19.2% vs. 44%
Kidney problems (nephropathy)	7.7% vs. 28%	11.5% vs. 32%

For neuropathy, neurological tests (motor and sensory) found that after 6 years there had been significant improvements in the intensive group, and significant deterioration in the usual care group.

All these results were durable when the follow-up was extended 2 years.[9] They also observed the following thresholds for hyperglycemia-induced microvascular problems: HbA1c > 6.5%, FBG > 109 mg/dL, and 2-hour post meal blood glucose > 180 mg/dL. All-cause or cardiovascular mortality were not endpoints for this study.

Since as discussed, there is evidence that intensive drug therapy does not impact complications, there is the possibility that in the case of type-2 diabetics, when insulin becomes necessary, or even earlier, there might be merit in switching just to insulin. The only difference from the Japanese study would be that the modern patient would have been exposed to a number of years of drugs that, among other actions, mimic insulin, modify insulin and glucose secretion and influence insulin sensitivity.

KETOGENIC DIET IMPROVES GLUCOSE CONTROL IN TYPE 2 DIABETICS

A recent study compared a low-calorie vs. a low-carbohydrate diet to examine the impact on glucose metabolism and blood lipids in type 2 diabetics.[10] The low-calorie diet (LCD) limited intake to 2200 cal/day with no intentional carbohydrate restriction. The ketogenic diet (KD) severely limited carbohydrates to 20 g/day. Over 6 months, the change in fasting blood glucose (in mmol/L), was from about 162 to 135 mg/dL for the LCD, and 162 to 113 mg/dL for the KD. For HbA1c, the LCD diet group went from 8.2% to 7.5% whereas those on the KD went from 7.5% to 6.3%. The weight loss over 6 months was 6% in the LCD, 12% in the KD. These changes were accompanied by clinically significant decreases in the use of anti-diabetic medications. Thus the KD resulted in results similar to those reported in many studies where increased doses and types of medication were use in the intensive treatment of hyperglycemia in type 2 diabetics.

For blood lipids, diabetics on the KD experienced declines in triglycerides, increases in HDL and decreases in LDL, but for the LC the changes in triglycerides and HDL were small or negligible. Both diets

produced about the same changes in LDL. Thus the KD with its high fat content improved the blood lipid profiles.

The impact on complications either over the 6-month period or the long-term appears unknown for either dietary approach. Presumably the results achieved by the KD could be maintained even with adjustments in carbohydrate content, but the 6 month intervention did not eliminate the need for medications, at least in the view of the patients and their physicians.

It is interesting in this context that a recent study found a moderate low-carbohydrate diet (38% of energy) achieved remarkable reduction in urinary albumin excretion, a marker of early phase diabetic kidney disease, over a 12 month period in type 2 diabetics who had evidence from microalbuminuria of this disorder at baseline.[11]

FLU VACCINES—A RECENT ANALYSIS OF EFFECTIVENESS

The U.S. Centers for Disease Control and Prevention (CDC) in the Jan 11, 2013 *Morbidity and Mortality Weekly Report* provide an estimate of flu vaccine effectiveness for this season. Cases were based on the presence of flu related viruses. The cohort was made up of 1155 children and adults with acute respiratory infections (ARI). A total of 133 cases were identified among 544 vaccinated patients whereas 238 were found among 611 non-vaccinated patients. The vaccine effectiveness calculated (1—Odds ratio) was about 62%. However, the absolute risk reduction (283/611 –133/544) was 0.219% and the number needed to vaccinate prior to the flu season to prevent one verified flu case was 46. The data collected thus far did not permit stratification by age or vaccine type. The authors comment correctly that this corresponds to the results of the latest meta-analysis of flu vaccine effectiveness. This meta-analysis of flu vaccine effectiveness was published recently in *Lancet Infectious Diseases.*[12] It differed from earlier studies because of the use of restrictive study inclusion criteria to minimize bias and confounding. In this study only very specific outcome endpoint data for laboratory confirmed viral caused flu were used, just as the CDC did in the analysis described above. Many studies failed to meet this inclusion criterion, but the investigators believe that the results of their meta-analysis provide the most accurate estimates of efficacy and of flu vaccines licensed at present in the US.

There are two types of vaccine commonly used—trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV). This study found no randomized controlled trials meeting their inclusion criteria showing efficacy of TIV in people age 2-17 and over 65. For LAIV there were no randomized controlled trials showing efficacy for people aged 8-59 years, but LAIV provided consistently the highest levels of protection for children ≤ 7 years of age. The studies included in the analysis, excluding LAIV in younger children, show a substantial variability by season and age group that cannot be attributed to difference in study design or measures of outcome. In some flu seasons and especially in some age groups, the level of protection was low or not evident.

An analysis by your editor of pooled, unweighted studies of TIV in adults aged 18-64 included in the meta-analysis found a vaccine effectiveness of 58% which is close to the weighted meta-analysis in the study, but the pooled absolute event rates were 1.18% in the treatment group and 2.73% in the controls. This translates into 65 needed to vaccinate to prevent one case. However, for children 6 months to 7 years of age, the LAIV vaccination had an effectiveness of 82% and yielded a number needed to treat to prevent one case of only 8. Thus for the TIV vaccination in the 18-65 age group, the results were indeed similar to the CDC short term results, even though the CDC used as a study cohort patients with ARI whereas the studies used in the meta-analysis involved vaccinated and non-vaccinated individuals drawn from a healthy population.

The above provides yet another example of the use of relative vs. absolutes benefit. An odds ratio of 0.4 or an effectiveness of 60% looks great, but a NNT of 46 or 64 may dampen the enthusiasm for the treatment.

However, if the vaccination is risk free, then the NNT may be beside the point. However, the risks of flu vaccination may not be that well defined. It is not a popular area of research.

Finally, the authors of the meta-analysis also discuss effectiveness in those over 65. They excluded one study based on this age group because the identification of the viral agent was not satisfactory and found no support for benefit among the elderly. They also discuss studies of vaccination in the elderly which had mortality as an endpoint. They point out that early studies appear to have been seriously confounded, and recent studies that address this issue found that influenza vaccination reduced all-cause mortality in older persons by only 4.6% and hospitalization for pneumonia and influenza by about 8.5%.

THE ONGOING TAMIFLU SAGA

If one listens to medical experts interviewed on U.S. national network news about the flu epidemic, mention is sometimes made that one of the treatments is the drug Tamiflu. Prior to the global outbreak of the N1H1 influenza in 2009, the U.S. alone had stockpiled nearly $1.5 billion worth of the antiviral. Heralded as the key pharmaceutical intervention, it was viewed as a way to cut hospitalization and save lives and reduce the chances of complications. It is thus curious to say the least that when the FDA approved Tamiflu in 1999 they insisted the label (package insert) indicated that the drug had not been shown effective to reduce complications. The manufacturer was even cited for violating the law by making such claims.[13] Tamiflu was also not approved for the use in preventing transmission, and yet the World Health Organization proposed a plan to suppress an emergent pandemic through mass prophylaxis.[13]

The saga involves the failed attempts over several years by the Cochrane Collaboration, a famous group conducting highly respected meta-analyses of effectiveness, to obtain the complete clinical trial data form the Tamiflu manufacturer. They considered the published data inadequate and from what was seen of the actual trial data, there appeared to be significant concerns.[13] In December, 2012, the editor of the *British Medical Journal* (BMJ) challenged the chairman of the European National Institute for Health and Clinical Excellence to withdraw approval for Tamiflu until the organization had full data.[14]

The 2010 Cochrane conclusions regarding the efficacy and safety of Tamiflu in treating influenza, its transmission and its complications in healthy adults were: "Numerous inconsistencies detected in available evidence, followed by an inability to adequately access the data, has undermined confidence in our previous conclusions for oseltamivir (Tamiflu). Independent randomized clinical trials to resolve these uncertainties are needed."[15] A stronger statement was published in 2012 where the Cochrane group indicated finding a high risk of publication bias and reporting bias in the trial program for Tamiflu, and that the required full clinical study reports were still not available to the researchers.[16] A review of this report also appeared in *Forbes Magazine* (The Myth of Tamiflu: 5 Things You Should Know, H. Krumholtz).

The history of the interaction of the Cochrane group and the manufacturer has been described in detail, and the paper includes an urgent call for a debate on the ethics of data secrecy.[13] The exchanged emails between the Cochrane group and the manufacturer going back to 2009 are also available (www.bmj.com/tamiflu).[17]

TRENDS IN HOSPITALIZATION AND MORTALITY AMONG INFANTS BY THE NUMBER OF VACCINE DOSES AND AGE

In the 2012 July/August IHN a review of a study was presented concerning infant mortality and the number of vaccine doses routinely given. The correlation was strong

and amazing.[18] Now the same investigators have examined a related question, the correlation of vaccine dose and hospitalizations. The correlation found between the hospitalization rate among infants versus the number of vaccine doses received yielded an amazing correlation coefficient (R^2) of 0.91 (perfect correlation would be 1.0). The number of doses ranged from 2 to 8 and the data were drawn from the Vaccine Adverse Event Reporting System in the US. The hospitalization rate increased from 11% at 2 doses to 23.5% at 8 doses. Also, younger infants were significantly more likely than older ones to be hospitalized or die after receiving vaccines. They also confirm the earlier reported association between doses and infant mortality.

The authors point out that while childhood vaccines have individually undergone safety or efficacy studies, there is no data concerning the safety of combining vaccines during a single physician visit. They give as an example that 2-, 4- and 6-month old infants are expected to receive vaccines for polio, hepatitis B, diphtheria, tetanus, pertussis, rotavirus, influenza type B, and an anti-pneumococcal disease vaccine, *all during single well-baby visits.* This combination of 8 vaccines given at one time has never been tested in clinical trials for anything, including safety.

The problem of immunization schedules will be difficult to address, with or without studies. The issue of convenience is obviously very important, and studies that might inform on the question appear complex and potentially uninteresting to the makers of vaccines. But the nature of these schedules allow the injection of large amounts of adjuvants such as aluminum in a single visit, and this and the mortality study discussed raise serious questions that sooner or later will resonate with parents.

ALUMINUM EXPOSURE AND AUTISM

A paper by Tomljenovic and Shaw from the University of British Columbia concerning this topic was
recently published in the *Journal of Inorganic and Biochemistry*.[19] It may be significant that this is not a journal where one expects to find papers that concern toxicology and epidemiology! The authors justify this investigation partly because aluminum (Al) is an experimentally demonstrated neurotoxin, something that has been recognized for decades. In introducing the topic of the paper, they comment that in adult humans, a variety of conditions encompassed by the so-called autoimmune/inflammatory syndrome can be induced by exposure to aluminum at levels found in vaccines. They also cite as an example the observation that exposure to as little as 20 µg/kg of body weight of Al is sufficient to cause neurodevelopment delays in preterm infants. In addition, Al is a strong stimulator of the immune system, and this is the reason it is almost universally used as an adjuvant (active additive) in vaccines. In view of this, they comment that it is surprising that little is known about the toxicology or pharmacokinetics of Al compounds in infants and children. Furthermore, the mechanisms of the interaction of Al adjuvants with the immune system are not clear. Yet Al adjuvants have been used for decades in vaccines. They also point out the interesting fact that in vaccine efficacy and safety studies the placebo contains the adjuvants or is another adjuvant containing vaccine. It seems clear that the assertion of safety of Al adjuvants is not based on experimental evidence.

Tomljenovic and Shaw examine the correlation between childhood exposure to Al from vaccines and the prevalence of autism in seven countries where pediatric schedules for vaccination were available. Perspective can be gained by considering that an adult receiving a Hepatitis B (HB) vaccination is exposed to about 7 µg/kg of body weight of Al whereas the comparative figures for an infant receiving a single HB vaccination is 74 µg/kg and a two month old receiving the commonly recommended set of vaccinations is exposed to 173 µ/kg which is equivalent to 24 HB doses on a single day for an adult.
Perspective can also be gained by considering the following total number of vaccine doses

given up to one year of age in the following countries included in this study: Sweden, 12; Iceland, 12; Finland, 13; UK, 19; Canada, 24; Australia, 24; US, 26.[18]

This study found: (1) children from countries with the highest autism prevalence appear to have the highest exposure to Al from vaccines; (2) the increase in exposure to Al adjuvants significantly correlates with the increase in autism prevalence in the US observed over the past two decades; (3) a significant correlation was found between the amounts of Al administered to preschool children and the current prevalence of autism in the seven countries included in the study. The correlation coefficients (R^2) found were high with many in the range of 0.7 to 0.9, numbers which are rarely seen in epidemiology but often in the physical sciences. When they apply a commonly used set of criteria for judging causality, they conclude that the correlations found suggest that Al is a causative agent for autism.

In a study by DeLong published about the same time as the study discussed above, a positive and statistically significant relationship was also found between vaccination rates and the prevalence of autism in the US from 2001 to 2007.[20] The author comments that although mercury has been removed from many vaccines, other "culprits" may link vaccines to autism. Clearly Al is a prime candidate.

Which brings us to a simple question. Why isn't everyone screaming "do something" when the autism prevalence in the US is reported to be an astounding 1 in 8 children. Even if this partly represents overdiagnosis it is a crisis.

DANGERS ASSOCIATED WITH SLEEPING PILLS

The use of sleeping pills and potions has a long history. Today one may think of barbiturates and benzodiazepines (e.g. valium) but a general list would also include sedative antihistamines (e.g. Benadryl) and in fact a large number of other drugs, all lumped under the general term *Hypnotics.*

There has been strong suspicion, based initially on data several decades old, that hypnotics enhance the risk of both overall mortality and cancer.[21] This hypothesis has been considerably strengthened recently with the publication in the *British Medical Journal* (*BMJ OPEN*) of a study by Kripke *et al* that directly addressed this question.[22] Data came from the electronic health records of a large integrated healthcare system in the U.S. Over 10,500 subjects (mean age 54) were patients who had received hypnotic prescriptions. They were matched with over 23,600 patients with no such prescriptions and followed for an average of 2.5 years. Only patients with hypnotics frequently prescribed were included and the prescription had to be for insomnia with dosage instructions indicating bedtime use. Patients with cancer were excluded. The aim was to estimate mortality risk and cancer risks associated with specific, currently popular hypnotics.

It was found that for overall mortality, the groups prescribed 0.4-18, 18-132 and > 132 doses/year, had enhanced risk as indicated by hazard ratios of 3.6, 4.3 and 5.3 relative to non-users of hypnotics. Not only the large enhancement of risk (up to > 5 times) but also the dose dependence was viewed as highly significant. For zolpidem (Ambien), there were 265 deaths out of 4336 users, temazepam (Restoril) 143 out of 2076, and for non-users 295 out of 23671 (data in Supplementary Table 9). These differences in incidence seem hard to believe.

In the supplementary material Kripke *et al* list 24 studies concerning the association of sleeping pill consumption and mortality. Of 22 listing risk ratios, only one failed to exceed 1.0, the no effect result. Risk ratios ranged up to 12.0 with several having the same range as this study, but the diversity of studies made meta-analysis impossible.

Stratification for hypnotic type indicated enhanced statistically significant mortality risk for eszopiclone (Lunesta), zaleplon (Sonata), triazolam (Halcion) but not flurazepam (Dalmane), but the number of events were very small compared to the two popular medications. In addition, hazard ratios for barbiturates and antihistamines were 2.8 and

4.6, respectively, but again the number of events was small.

For cancer incidence, the corresponding hazard ratios were 0.86, 1.20 and 1.35, the latter statistically significant, when the use of any hypnotic was compared with non-use. When stratified by type of hypnotic, >800 mg/year of zolpidem (or >1640 mg/ year of temazepam) yielded hazard ratios of 1.28 and 1.99, respectively compared to non-users. These were to two most frequently prescribed sleeping pills. Temazepam belongs to the benzodiazepine class whereas zolpidem is a gamma-butyric acid potentiating drug.

The validity of studies like this depends strongly on correcting for confounding and in particular for comorbidities. The authors describe a number of approaches used and indicate satisfaction that residual comorbidity confounding was not a significant issue in the final results obtained. The hazard ratio calculations controlled for age, gender, ethnicity, smoking status, body mass index, marital status and alcohol use and 12 classes of comorbidity.

The authors discuss the remarkable increase in mortality risk associated with infrequent hypnotic use and point out that they were unable to discover any biases that could account for these results, but admit some residual confounding many have been present. They emphasize that control for major confounders had minimal impact on the hazard ratios and view as unlikely that confounding explains the high (extraordinary?) mortality found associated with hypnotics.

Finally, the question that no doubt has occurred to all readers—what are the causal pathways for the large increases in mortality? The authors discuss this and suggest increased depression, impaired motor and cognitive skills leading to accidents and falls and increased sleep apnea which may lead to accidents, hypertension, heart failure, arrhythmias, and cardiovascular disease. They point to two studies where participants randomized to hypnotics experienced more adverse medical events overall than those on a placebo, including infections. These rationalizations seem to strongly suggest the need for more research.

The same large effects were recently reported for a meta-analysis involving adverse events. Cognitive events were 4.78 times more common, adverse psychomotor events 2.16 times more common and daytime fatigue was found to be 3.82 times more common. Mortality was not an endpoint.[23]

One of the authors has a free book available on the internet with a much more extensive discussion of this matter.[21]

REFERENCES

(1) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993 September 30;329(14):977-86.

(2) White NH, Sun W, Cleary PA et al. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. *Arch Ophthalmol* 2008 December;126(12):1707-15.

(3) Genuth S. Insights from the diabetes control and complications trial/epidemiology of diabetes interventions and complications study on the use of intensive glycemic treatment to reduce the risk of complications of type 1 diabetes. *Endocr Pract* 2006 January;12 Suppl 1:34-41.

(4) Nielsen JV, Joensson EA. Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. *Nutr Metab (Lond)* 2008;5:14.

(5) Accurso A, Bernstein RK, Dahlqvist A et al. Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. *Nutr Metab (Lond)* 2008;5:9.

(6) Gregg EW CH. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012 December 19;308(23):2489-96.

(7) Hemmingsen B, Lund SS, Gluud C et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ* 2011;343:d6898.

(8) Ohkubo Y, Kishikawa H, Araki E et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995 May;28(2):103-17.
(9) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998 September 12;352(9131):837-53.
(10) Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition* 2012 October;28(10):1016-21.
(11) Haimoto H, Sasakabe T, Umegaki H, Wakai K. Reduction in urinary albumin excretion with a moderate low-carbohydrate diet in patients with type 2 diabetes: a 12-month intervention. *Diabetes Metab Syndr Obes* 2012;5:283-91.
(12) Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 2011 October 25.
(13) Doshi P, Jefferson T, Del MC. The imperative to share clinical study reports: recommendations from the Tamiflu experience. *PLoS Med* 2012;9(4):e1001201.
(14) Godlee F. Withdraw approval for Tamiflu until NICE has full data. *BMJ* 2012;345:e8415.
(15) Jefferson T, Jones M, Doshi P, Del MC, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: a Cochrane review. *Health Technol Assess* 2010 October;14(46):355-458.
(16) Jefferson T, Jones MA, Doshi P et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1:CD008965.
(17) Payne D. Tamiflu: the battle for secret drug data. *BMJ* 2012;345:e7303.
(18) Miller NZ, Goldman GS. Infant mortality rates regressed against number of vaccine doses routinely given: Is there a biochemical or synergistic toxicity? *Hum Exp Toxicol* 2011 May 4.
(19) Tomljenovic L, Shaw CA. Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? *J Inorg Biochem* 2011 November;105(11):1489-99.
(20) Delong G. A positive association found between autism prevalence and childhood vaccination uptake across the U.S. population. *J Toxicol Environ Health A* 2011;74(14):903-16.
(21) Kripke DF. *The dark side of sleeping pills.* Free eBook. http://www.darksideofsleepingpills.com/all.html; 2012.
(22) Kripke DF, Langer RD, Kline LE. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012;2(1):e000850.
(23) Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005 November 19;331(7526):1169.

BOOK REVIEWS

DOCTOR, YOUR PATIENT WILL SEE YOU NOW. GAINING THE UPPER HAND IN YOUR MEDICAL CARE. Steven Z. Kussin, M.D. Rowman & Littlefield, New York, 2012

It is the rare individual in the developed world that has not had repeated encounters with the medical system, including hospitals, emergency departments, the search for specialists, and the consumption of prescription drugs. The tentacles of the system constantly increase in their reach and power, and as the population ages, the need relentlessly increases.

Steven Kussin, M.D., a practicing physician in New York with over thirty years of experience including teaching at Albert Einstein Medical College and Columbia, has just had published a remarkable and unique book. It is a thoughtful and rigorous dissection of what is behind the name tags and titles of medical professionals, what is concealed behind the bricks and mortar that surround our hospitals and medical schools, the real nature of the private practice, the group practice and hospital run clinics. In short the whole gamut that combines into what we call modern medicine. This also includes the credibility of the evidence of evidence-based medicine, the hundreds of guidelines, who writes them and how they can be used or misused and the critical challenge to medical professionals to keep up with, critically analyse and use the huge flow of new research results that threaten to inundate them.

This dissection reveals the good, sometimes bordering on incredible with phenomenal achievements and evidence of real genius, the average, the mediocre, the poor and at the end, the ugly—so bad as to be extraordinarily dangerous. It is the old bell curve problem. In this book one finds a fair but critical and rigorous discussion of the main issues surrounding modern medicine today which contribute to controversy, distrust, dissatisfaction and concern, but are balanced by remarkable successes. The consumer needs perspective. This book provides it.

Like a traveler's guide, this book aids in the navigation of this extraordinarily complex system. But like the traveler, those attempting to optimize their medical experiences face innumerable obstacles and potential confusion. This appears to be the best handbook available for the many excursions, frequently mandated by necessity, into this dangerous, heterogeneous but potentially highly rewarding land. It is highly recommended—a must read!

THE GREAT CHOLESTEROL MYTH. WHY LOWERING YOUR CHOLESTEROL WON'T PREVENT HEART DISEASE—AND THE STATIN-FREE PLAN THAT WILL. Stephen Sinatra, M.D. and Jonny Bowden, Ph.D. Fair Winds Press, Beverly, MA, 2012

The dietary fat and cholesterol-statin controversy appears unique in medicine. It has been the subject of a number of books (look at "cholesterol myths" at Amazon.com.), an organized group of sceptics (THINCS) which includes a number of distinguished medical scientists, and a steady flow of letters to editors, most rejected. Yet the essential features and arguments are virtually unknown to the general public who consume billions of dollars worth of statin drugs worldwide in the belief that they are dramatically lowering their risk of cardiovascular disease.

This is a subject that has been discussed many times in IHN through both commentaries and book reviews. A new book has just appeared which is noteworthy by virtue of the high profile of the authors. Dr. Stephen Sinatra is a board-certified cardiologist in private practice and on the faculty of the University of Connecticut School of Medicine. Many readers are familiar with his newsletter *Heart, Health and Nutrition,* and some will have read *Reverse Heart Disease Now*, and T*he Sinatra Solution: Metabolic Cardiology.* The coauthor, Jonny Bowden, Ph.D. is a nationally known expert on weight loss, nutrition and health.

This book reviews what the authors describe as the shoddy science, manipulated research and corporate greed that have perpetuated the cholesterol myth. Discussed is what they conclude from the latest studies and clinical findings, The real culprits in heart disease include sugar but not fat, inflammation, stress and high-carbohydrate diets full of processed foods. To quote William Davis, M.D., author of *Wheat Belly*, "Anyone sceptical about the notion that there isn't more to heart disease than "cut your fat, take a statin drug" would be well served by reading this book. Dr. Mark Hyman, M.D., a well-known integrative physician and critic of modern medicine, adds, "*The Great Cholesterol Myth* finally sheds light on the true story, why millions are being harmed by statin drugs and how to really prevent heart disease. Everyone with heart disease, on a statin or with a family history of heart diseases must read this book. If you doctor recommends a statin, read this book first but don't bother arguing.

PSYCHIATRIC DRUG WITHDRAWAL. Peter R. Breggin, M.D, Springer Publishing Co. 2012

Peter Breggin is a well-known psychiatrist in private practice who is also active in forensic psychiatry and is a long-standing and recognized critic of the dominance of pharmaceutical therapy in modern psychiatry and the need for a new paradigm. This book makes sort of a trilogy. The two other books being are *Brain-Disabling Treatments in Psychiatry,* Second Ed. (Springer, 2008) a medical monograph, and *Medical Madness* (St. Martin's Press, 2008), written for a general audience. The former develops in detail with documentation the thesis that all psychiatric drugs can cause dangerous behavioral abnormalities and brain dysfunction which can be permanent. Put a different way, these drugs are presented as creating the impression of benefit by altering one or more brain function with unfortunate consequences, while the patient has the perception of improvement. Breggin points out the total absence of evidence to support one of the principal guides for psychiatric drug discovery and development. This is the notion that biochemical imbalances cause mental disease and need to be treated. No one has ever shown them to exist, but psychiatric drugs do indeed cause, among other things, biochemical imbalances. The second book introduces what he terms medication spellbinding, where mental deterioration and serious side effects are perceived as benefit and not recognized for what they really are, by either the patient or the prescriber. But the main topic of the book involves the abnormal mental and behavioral problems caused by these drugs which can lead to truly bizarre actions. Breggin provides fifty case histories.

While the title of this latest book indicates the theme is drug withdrawal, the book in fact also provides an excellent, condensed and very readable version of the of parts of Breggin's monograph with a chapter on early and then chronic brain impairment followed by five chapters providing detailed reasons for drug withdrawal, each dealing with a different class of drug (antipsychotic, antidepressant, stimulant, sedative and mood-stabilizing drugs). After a chapter on spellbinding, the second part of the book concludes with eight chapters dealing will all aspects of managing withdrawal, with emphasis on the critical role of the therapist in achieving success and avoiding serious events or disaster. Three of these chapters involve case histories, which include both adults and children, and provide significant insight into the potential complexities of this process. It is interesting that in many cases it is not the patient but a parent or spouse that initiates the consultation regarding drug withdrawal. The fact that withdrawal is so difficult in many cases highlights the serious nature of the side effects of what is in fact the principal treatment modality in modern psychiatry, one which often leads to patients being on several drugs. Discussed is withdrawal from polypharmacy which must be carefully orchestrated with the right sequences and withdrawal rates. Also discussed is the need and success of required concomitant psychotherapy, the need for emergency psychiatric help available 24/7 and the strong dependence on support from family members.

Breggin's latest book leaves little doubt that his main thesis has great merit and significance. If one believes in some causal factor for a disorder and withdrawal of the factor eliminates the disorder, there are grounds for regarding the association as real. The results of complete drug withdrawal are frequently remarkable and correspond to the patient being finally able to lead a normal and rewarding life. This is after in some cases years of impaired or severely impaired existence which Breggin

regards as a result of medication, something that by and large was not recognized except by family members.

This book will change forever most reader's understanding of modern psychiatry, and how a hasty decision by a practitioner to medicate with one or more powerful drugs can lead to years of unnecessary suffering and agony, and sometimes to suicide, violence and crime. Readers who fail to see the full significance need to read *Medical Madness.*

Aamazon.com has the book. A signed copy of this book is also available from the author. See http://breggin.com/index.php?option=com_content&task=view&id=296&Itemid=129

UNACCOUNTABLE. WHAT HOSPITALS WON'T TELL YOU AND HOW TRANSPARENCY CAN REVOLUTIONIZE HEALTH CARE. Marty Makary, M.D., Bloomsbury Press, New York 2012

Few would challenge the proposition that modern medicine suffers from a lack of transparency and from a code of silence fuelled by fear at many levels of repercussions (interns, residents, nurses, junior attending physicians). Medical mistakes and unsafe practices, especially in hospitals, take a terrible toll underappreciated by the general public. A recent book examines this problem in detail with skill and insight.

The author, Dr. Marty Makary, is a surgeon at Johns Hopkins Hospital and an associate professor of health policy at the Hopkins School of Public Health. His research includes issues of health safety with emphasis on the hospital setting and he is a vocal advocate for transparency in health care.

This book provides comprehensive insight into issues, especially in hospitals, that directly impact the consumer, i.e. most readers of this review. Some may not want to read this book because either they regard the matter as beyond their control or they simply would rather not know, given their frequently limited choices. On the other hand, some may have more options than they realize, especially if they live in heavily populated areas.

A highlight of the book is a discussion of the results of surveys with which the author was personally involved. The intention was to obtain a picture of the inner workings and culture of a set of hospitals with an anonymous questionnaire which obtained the views of those who knew, the people that worked there. The range of responses was remarkable. For example, the percentage of hospital employees in over 60 hospitals who reported well-coordinated teamwork in their workplace ranged from about 16% to 100%. For the percentage who felt comfortable having their own care performed in the unit in which they worked, the same range was obtained. Throughout the book are displayed similar results for other issues critical to the patient. Again, the old bell curve.

The heading to Part II (The Wild West) provides insight in the scope of the book. Chapter titles tell the details: Impaired Physicians, Medical Mistakes, Ask Before You Give, Eat What You Kill and The All American Robots. The book ends with an examination of how transparency, accountability and honesty must play a role in reform.

TRANSFORMING HEALTH CARE: VIRGINIA MASON MEDICAL CENTER'S PURSUIT OF THE PERFECT PATIENT EXPERIENCE. Charles Kenny. Productivity Press, Taylor & Francis Group, New York. 2012

This book documents how a hospital in Seattle Washington, Virginia Mason Medical Center, accomplished a profound transformation in culture and day-to-day operations in the pursuit of what was termed The Perfect Patient Experience. It was not easy but opposition was slowly converted. An interesting feature of the approach was the influence of the so-called Toyota Model where employees

have a remarkable influence on quality control and the avoidance of problems and potential disasters due to management attention (listening), respect and action. A hospital taskforce actually visited a plant in Japan. Listening to patients was a critical aspect of the project. Patients even helped design a new building. The results of several years of effort were innovations in patent safety assurance, reduction in professional liability expenses, and changes enabling nurses to spend 90% of their time with patients. Patient satisfaction skyrocketed as did the hospital's reputation. There was a dramatic reduction of medical mistakes and harm. Satellite clinics managed to eliminate waiting lists. A fascinating story of determination and effort to achieve significant and lasting culture change and reform.

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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