INTERNATIONAL HEALTH NEWS

William R. Ware, PhD - Editor

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The feature of this issue again involves diabetes. It is hoped that readers are not getting tired of this subject. Its prominence of late in IHN is due to the huge prevalence of this disorder, now across all age groups, its dismal long-term prognosis, and what appear to be serious problems in the efficacy of treatment if the goal is to prevent complications, which is really the name of the game. Everyone, it would seem knows a number of diabetics and probably this includes family members. Thus the importance of awareness concerning what is really going on. Next month will end the series with a short discussion specifically of the failure of medications to prevent microvascular complications with only two exceptions providing evidence of modest benefit in a sea of negative results, and the modest benefit, if in fact true, will still leave most without benefit.

In this issue the topic is diabetes reversal which means getting off medications and having normal glucose metabolism. In an earlier issue, the mainstream approach was discussed. It involves invasive procedures such as cell implants, pancreatic transplantation and bariatric surgery, the latter usually restricted to the morbidly obese. As will be discussed, bariatric surgery has provided guidance leading to a non-invasive approach. While only a small but very well designed trial has been completed, the results appear nothing short of sensational with a simple protocol and rapid, definitive results. For comparison, a discussion of the success in reversing diabetes with very-low carbohydrate and ketogenic diets is included.

Also included is a short analysis of the new mainstream push for lower mortality and morbidity in heart disease. Unfortunately, some of the major interventions recommended only provide small absolute benefits and provide no benefit for most undertaking them.

Other topics include evidence that the overuse of antibiotics for sore throat continue unabated, the association between diabetes and liver cancer, and an interesting and perhaps amusing test of the quality of open access (author pays the tab) journals carried off by the prestigious journal Science with shocking results. Finally, a short note on how the FDA is making it easier to get drugs approved by apparently encouraging one of the classical techniques used to bias results.

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

REVERSING DIABETES

INTRODUCTION

The Dec/Jan 2012-3 issue of IHN contained a discussion of the failure of diabetic drugs to impact the complications of type 2 diabetes even though good control of blood sugar is achieved. The major if not only reason diabetics are concerned about their blood sugar levels is macro- and microvascular complications. It was suggested that the conventional approach gave diabetics a false sense of security if they had their blood sugar "under control." In the Sep 2013 issue there was a brief note on reversing diabetes. In this issue this topic will be revisited in much more detail because of the importance of the topic. The calorie restriction approach used in the featured study will be compared with severe carbohydrate restriction or ketogenic diet.

Some, perhaps many diabetics do not appreciate what is widely acknowledged that diabete*s* is a lifelong, incurable condition. This was again pointed out by Professor Roy Taylor from Newcastle University in the UK in the 2012 *Banting Memorial Lecture.*[1] After diagnosis, standard medical treatment involves increasing doses and adding new drugs to attempt to lower and then control the increase of fasting blood glucose and HbA1c, the long-term average blood glucose marker. Intensive therapy involves attempting to maintain targets, generally near or somewhat above the prediabetic levels. Gerald Reaven points out that as part of the famous United Kingdom Prospective Diabetes Study (UKPDS), it was found by measuring the pancreatic beta cell insulin secretion that the study participants (type 2 diabetics) had lost approximately 50% of insulin secretory capacity prior to the initiation of the study. *Following enrolment, there was a progressive deterioration of glycemic control over the next 6 years in all groups, including those assigned to intensive glycemic interventions.* The UKPDS investigators concluded, "progressively increasing hyperglycemia, associated with decreasing beta cell function, was a marked feature irrespective of the therapy used."[2] This cohort involved newly diagnosed patients. The progression from one drug to two and then perhaps three and then also insulin is common. Thus it is common for type 2 diabetics to become insulin dependent just like the type 1 diabetics. In fact, 50% of type 2 diabetics require insulin within 10 years of diagnosis. This should suggest to diabetics the nature of the problem they face.

The fact that attempts to control glucose levels do not impact complications adds an additional depressing dimension. What Reaven and others, including pharmacists who observe diabetics over long periods as their customers, are saying is that diabetics take their pills but they do not really get better. Quite the contrary, they increasingly face terrible complications that will significantly impact their quality of life. However, there appear to be alternatives to the conventional approach to treatment. These involve diet, but not the diets suggested by mainstream medicine. This is the feature topic of this month's issue.

In discussing the reversal of diabetes, it is important to be familiar with the official definitions while recognizing that these are widely used because they are convenient and that other criteria can provide more information.

NORMAL GLYCEMIA – HbA1c ≤ 5.6% **AND** Fasting blood glucose ≤ 99 mg/dL (5.5 mmol/L)

PREDIABETES – HbA1c 5.7%-6.4% **OR** Fasting blood glucose 100 to 125 mg/dL (5.6 to 6.9 mmol/L)

DIABETES – HbA1c ≥ 6.5% **OR** Fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L)

SEVERE CALORIE RESTRICTION

In the March issue of IHN the subject of curing diabetes was briefly reviewed, but the approaches discussed were rather specialized and invasive. However, in the section on metabolic or bariatric surgery, it was pointed out that this approach could result in a rapid return to normal glucose metabolism along with the elimination of the metabolic abnormalities associated with type 2 diabetes and the need for medication. The profound metabolic changes became evident within a week and before significant weight loss had occurred. However, bariatric surgery is generally indicated only for very obese or morbidly obese patients.[3]

Bariatric procedures go back several decades. A systematic review in 2004 found that for the various levels of restriction or bypass, the resolution of diabetes ranged from 99% (bilo-pancreatic diversion, the most radical), 84% for gastric bypass and 48% for gastric banding. In an early series described by Pories *et al*, 86 out of 88 obese type 2 diabetics receiving bariatric surgery reverted to normal glucose tolerance within 4 months and remained normal over 6 years follow-up.[4]

In a study reported in 2006, individuals with a mean weight of 334 lbs and a BMI of 54 (i.e. morbidly obesity) underwent bilo-pancreatic diversion bariatric surgery. One week after surgery, weight loss was about 13 lbs, which was considered insignificant. However, blood glucose levels normalized in this 7 day period as well as insulin sensitivity. The subjects were subsequently declared free of diabetes and the effect was durable.[3]

There are huge implications associated with the above observations of diabetes reversal which have recently received attention.[1] Taylor points out that the widely believed mechanism for producing normal glycemia with bariatric surgery involves a direct effect on the incretin hormones, but that this cannot be the case due to these regulatory hormones falling significantly short of such capability. Rather, he associates the reversal to a sudden, large negative calorie balance which forced the body to draw on reserves. Fatty acid intermediates that inhibit glucose metabolism and pancreatic beta cell function were suddenly desperately needed as fuel. With the inhibition rapidly destroyed along with other changes, metabolism returned to normal with either fat or glucose then supplying the fuel according to needs.[1]

This hypothesis advanced by Taylor and associates is elaborated in a view of the natural history of type 2 diabetes outlined below, starting with an individual with normal glucose metabolism but muscle insulin resistance (adapted from a paper by Taylor).[5]

- Positive energy balance occurs
- Progression of insulin resistance
- Development and increase in liver and pancreatic fat
- Increased blood triglyceride levels
- Unrestrained glucose production by the liver
- Elevated blood glucose becomes apparent (hyperglycemia)

- Pancreatic beta cells exposed to excessive triglycerides
- Decreased pancreatic insulin secretion in response to glucose signals
- Chronic elevated blood glucose
- Critical pancreatic beta cell loss and dysfunction

At this point, the individual has diabetes. All but the last step can last months to years. The last step is noteworthy for being abrupt and rapid, e.g. about 2 years. In the 2012 *Banting Memorial Lecture,* Taylor discusses the Whitehall II study which followed individuals for 13 years prior to the onset of type 2 diabetes.[1] For those destined to become diabetic, there was a slow linear increase in fasting blood glucose up until about 2 years prior to diagnosis whereas for the controls the level was constant. Then the blood glucose shot up abruptly. It was also found that the liver serum enzyme ALT increased significantly in the last two years to diagnosis and while in the reference range, nevertheless was abnormal compared to controls (26-33 U/L vs. low 20s).

This hypothetical mechanism is somewhat complex, but what is interesting is that it has been tested in moderately obese diabetics simply by severe short-term calorie restriction, which produces the same metabolic results as bariatric surgery. The hypothesis, which the Counterpoint Trial was designed to test, was that the chain of events leading to diabetes could be broken and then reversed by abruptly decreasing the liver fat content and cutting off the free triglycerides generated in the liver which were impacting beta cell function and cell numbers.[6] In simple terms, this is accomplished by a sudden and severe calorie restriction, which forced the body to burn triglycerides at a large rate because of the calorie restriction, and because once the small supply of glucose is used up, that is all there is to burn. The notion was that this would "wake up" the beta cells by removing the triglyceride inhibitors and thus reverse the diabetic condition.

In the trial, Taylor and colleagues put eleven type 2 diabetic individuals (9 male, two female, mean BMI 34, mean age 50) on a 8-week 600 calorie per day diet containing about 70 g of carbohydrate (47% of energy intake). This is essentially a starvation diet and can only be used short term without serious consequences. Like the bariatric study, the weight loss was judged insignificant at the end of one week but fasting glucose had dropped from 166 to 106 mg/dL and HbA1c from 7.4% to 7.1% (note it is a 3-month average). Over 8 weeks, the fasting blood glucose fell to 102 mg/dL, HbA1c to 6.0% and the average weight loss was 33 lbs. MRI techniques were used to obtain organ fat content. Liver triglyceride content decreased by 30% during week 1 and continued to decline over the study period to reach the normal range for non-obese individuals. Pancreatic triglyceride content declined steadily over the 8 weeks. Insulin response to a two-step challenge with glucose went from very abnormal (no phase 1, attenuated phase 2) to normal over 8 weeks. Suppression of liver glucose output improved from 43% to 74% vs. baseline. Benefits were seen in all patients and the participants were typical type 2 diabetics. The return of beta cell function also indicates that with up to 4 years duration of diabetes, it is not permanently destroyed.

These results are consistent with the hypothesis being tested, i.e. that the abnormalities of insulin secretion and the presence of liver insulin resistance that underlie type 2 diabetes have a single, common cause, excess lipid accumulation in the liver and pancreas. The detailed metabolic results and direct beta-cell function assessment also considerably strengthen the conclusion indicated by just the fasting blood glucose and HbA1c that diabetes was reversed.[6]

The investigators then made it possible for participants to report long term results via email. Eight responded. HbA1c was reported at 5 to 8 months since the end of the study and ranged from 5.4% to 5.7%, consistent with the absence of diabetes. Two participants reported fasting blood glucose values of 92 mg/dL and normal 2-hour glucose tolerance tests. Some patients continued to lose weight on their self-selected diets, but most gained from 5 to 17 lbs, but even the participant who gained 17 lbs maintained a normal HbA1c of

5.2%. The authors emphasize that this is a small, anecdotal sample, but nevertheless very informative.[7]

Thus severe calorie restriction alone for a short period reversed diabetes as judged by a number of indicators. This result is consistent with the above hypothesis regarding the natural history of the disease and as well, provides an explanation for the almost identical effects of bariatric surgery. At 8 weeks the participants could be described as somewhat prediabetic and a few months after the end of the diet, became non-diabetic with quite low HbA1c values well in the normal range.

In Taylor's lecture,[1] a number of questions were discussed. (1) Is longstanding diabetes reversible? The Counterpoint Study involved only two people with short duration, and he cites evidence of reversing longstanding diabetes by either severe calorie restriction or bariatric surgery. (2) Is reversal possible if the BMI is normal? Taylor points out that in the classical presentation of type 2 diabetes, one generally finds evidence of a fatty liver in individuals with normal weight. Its presence is a key aspect of the hypothesis that explains the success of dietary reversal. (3) Will the diabetes recur? No as long as the individual's personal fat threshold for type 2 diabetes is above that maintained. (4) What is the best advice to prevent weight gain after this diet? Exercise, consume a diet that does not contain excess calories and possibly specific foods. He comments that the latter issue now needs formal testing.

The results of the Counterpoint Trial, which seems to suggest a simple solution to the diabetes epidemic, should stimulate large studies with longer follow-up. But proponents of this approach face an uphill battle since this is not a drug based approach and involves temporary near starvation which will be viewed by many as *a priori* a horse that will never run. ***Readers are warned that trying this approach without stopping diabetes medications presents a risk of serious hypoglycaemia***.

COMPARISON WITH LOW-CARBOHYDRATE OR KETOGENIC DIETS

In the past few years there have been calls (from the wilderness) for a return to the old approach used for decades for treating mostly type 1 diabetes, the adoption of carbohydrate restriction.[8-13] It is therefore of interest to compare the above results of short-term severe calorie restriction with either very low-carbohydrate or ketogenic diets. A number of studies have appeared in the past decade which allow one to address this issue. Eight studies are of interest and summarized below. Some of the studies in the table were randomized but there was considerable variation in the control diets. Thus, since the changes of fasting blood glucose (FBG) and HbA1c are the indicators of interest, only the very low-carbohydrate or ketogenic results are presented. Incidentally, a number of studies have been omitted simply because the carbohydrate restriction was too small to be of any real significance (range 33-40% energy from carbohydrates, or for a 2000 calorie diet, 165 to 200 grams/day). The term low-carbohydrate is obviously meaningless. This illustrates a big problem with studies on so-called low-carbohydrate diets, i.e. many are not really low-carbohydrate, and most do not involve severe enough restriction to offer the hope of a significant impact on glucose metabolism.

Summary of trial results for low-carbohydrate and ketogenic diets in patients with type 2 diabetes

Study	Weeks	CHO (g)	HbA1c (%)	FBG (mg/dL)	Calories	∆W (lbs)
Gannon[14]	5	142	9.8→7.6	167→119	2800	4
Gumbiner[14]	6	39	ND	227→144	1635	0
Boden[14]	2	21	7.3→7.0	135→114	2146	4.4
Yancy[14]	16	45-34	7.3→6.3	164→136	1470	20
Krebs[15]	12	20 start*	7.4→6.1	127→82	Ad lib	22
Westman[16]	24	20	8.8→7.3	178→153	Ad lib	23
Stern[17]	52	120	7.4→6.6	166→138	1462	11
Hussain[18]	24	20 start*	9.2→6.0	165→108	Ad lib	26

**Atkins diet, FBG - fasting blood glucose, CHO - dietary carbohydrate content, ∆W - weight change from baseline*

The Atkins model involves an induction phase that is ketogenic (the body is forced to metabolize ketones from triglycerides because of low glucose levels), which is followed, after an intermediate weight target is reached, with increasing carbohydrate intake by 5 g increments provided weight loss continues. Typical final carbohydrate consumption is 50-100 g/d. Thus these diets are only initially ketogenic.

Two of the three very short-term studies were able to bring the FBG down to the top of the prediabetic range but not the HbA1c. Longer-term studies had mixed results but no actual reversal of diabetes. These studies were obviously not severely calorie restricted (see table) and thus one might conclude that even though the carbohydrate restrictions were mostly similar and some smaller than in the Counterpoint Trial, severe calorie restriction appears essential for diabetes reversal. The two studies (Krebs and Hussain) with the best results used the Atkins protocol and had fairly large changes in weight, but no information was collected regarding calorie intake and the metabolic changes left the patients prediabetic, suggesting that the approach may not have normalized pancreatic function which is the key to reversal.[19] Nevertheless, these were very good outcomes and in some studies patients found it possible to cut medications, in some cases drastically.

What is really at issue here is creating conditions which will dramatically alter the dysfunctional pancreas-liver-insulin system to return beta-cell function to normal, eliminate insulin resistance and strongly reduce liver fat. It appears that very low carbohydrate or ketogenic diets by themselves can approach but not accomplish this when the total energy intake is 1500-2800 calories. It is the virtually starvation level temporarily induced which forces the rapid, in fact remarkable loss of liver fat and the ultimate removal of the postulated cause of beta cell dysfunction. Thus while the carbohydrate-insulin connection is valid, the mechanism of diabetes and its relentless progression, which is the target for modification, appears too complex for severe carbohydrate restriction to result in total reversal. The fasting blood glucose and HbA1c markers provide guidance, but the changes in the liver and pancreas and the normalized insulin secretion profile in response to glucose are what appear to count.

CONCLUSIONS

Thus the Counterpoint Trial and the related bariatric surgery approach emphasize the importance of a short term but sustained very low calorie shock to the system if diabetes reversal is the objective, and the data suggests remarkable if not sensational results.

The Counterpoint Study also provides insight into why medications which lower blood sugar do not impact complications. It may be because the medications are treating symptoms by targeting specific mechanisms for glucose generation or metabolism rather than eliminating fundamental causes and returning glucose metabolism and beta-cell function to normal, as appears to be the case with severe calorie restriction. Thus the underlying pathology is not addressed by the drug approach and the disease progresses.

With both the very low carbohydrate or ketogenic diets as well as the severe calorie restricted diets, the long term durability needs to be studied, and this is complicated by weight gain and resumption of old dietary habits. However, with the severe calorie restriction the changes in metabolism may bode well for a long-term "cure" since the natural history of the development of diabetes progression is slow and easier to reverse, especially when early signs appear such as turning prediabetic.

Some will certainly find 8 weeks of more or less starvation difficult to cope with. There is currently a new fad diet called the Fast Diet, where for two days a week one "fasts," which really means 500-600 calories, the latter for men. There are now a number of meal plans available in books and on the internet with 500 calories diets, and this leaves room for 100 calories of snacks. The internet provides many snack suggestions that contain no more than 50 calories. Calorie counting is as old as diets themselves and the cell phone aps provide a simple solution.

The Fast Diet proponents presumably assume, no doubt with some justification, that 500-600 calories a day is unacceptable except for a short period followed by a longer reward period. If one has type 2 diabetes, then the reward is not 5 days of a more normal diet per week as in the Fast Diet, but rather total reversal within 8 weeks of a serious disease with a bleak long-term outlook and a return to normal glucose metabolism, which is then durable if weight regain is limited, but not required to be zero. No more pills, no more insulin injections, no more concern about hypoglycaemia. Furthermore, presumably no more worry about complications, although this has not been tested, but it is just a very reasonable assumption given how many aspects of the disease are eliminated. That should be enough to provide motivation for 8 weeks of not eating very much. However, the diabetic must fully appreciate what is probably in their future if their disease progresses, as it most certainly will. One should probably take supplements during the diet. However, 8 weeks is too short to raise concerns about malnutrition. It would be prudent to undertake such an intervention under the supervision of a physician, especially since stopping medication or rapidly reducing dose levels is obviously required in order to avoid hypoglycaemia.

AMERICAN HEART ASSOCIATION CALL TO ACTION ON CARDIOVASCULAR DISEASE

The AHA has just issued a call for action from an advisory committee in connection with achieving a goal of 20% reduction in CVD mortality and a 20% improvement in CV health by 2020. The emphasis is on three areas:[20]

- Preservation of CV health through promotion of healthy lifestyle choices.
- Treatment of unhealthy behaviors like smoking, poor diet, and physical inactivity in addition to risk markers like adverse blood lipids, high blood pressure, hyperglycemia and obesity.
- A combination of individual level and population based health promotion initiatives to improve cardiovascular health.

This program appears to have some problems. Consider the hypertension recommendation. A recent Cochrane analysis of pharmacotherapy for mild hypertension (140-159/90-99 mmHg) found that in primary prevention successful intervention failed to significantly reduce mortality or morbidity associated with coronary heart disease, stroke, or total cardiovascular

events.[21] As regards lipids, meta-analyses of 11 studies concerning primary prevention found statin therapy had no effect on mortality, an absolute risk reduction of 1% for major CHD events (100 needed to be treated for one to benefit) and no benefit for stroke.[22] This is consistent with a number of other analyses and has been discussed repeatedly in IHN. Concerning hyperglycemia, as discussed in the Dec 12/Jan13 issue of IHN two large, major studies, ACCORD AND ADVANCE, and recent two meta-analyses found no cardiovascular benefit associated with intensive vs. non-intensive blood glucose control, and two trials of metformin, the most frequently used drug and the first-line response to diabetes diagnosis, one a large placebo controlled trial, the other a withdrawal controlled trial, failed to find evidence of significantly preventing complications, including cardiovascular events, and the key study is viewed by critics as so flawed that it might be difficult today to publish it.

What about individuals who have already had a heart attack or stroke, i.e. secondary prevention? This was reviewed in the April 2013 IHN. For treatment of hypertension, most cardiovascular endpoints had NNT above 50, and for statin therapy, NNTs ranged from 28 to 111 (absolute risk reductions 4% to 0.9%) for men, 33 to 200 (absolute risk reductions 3% to 0.5%) for women, depending on the endpoint. It is not clear that these obviously modest benefits have anything to do with lipid lowering. Furthermore, the NNT should be compared with the risk of adverse side effects, but that data appears suppressed and limited.

Thus we are left with not smoking, eating a healthy diet (opinions differ on what this is), exercising more and losing weight if indicated. No one would question the wisdom of these interventions but they have been around for quite some time. There is little evidence to suggest that really significant progress can be made. Quite the contrary, obesity, diabetes and physical inactivity appear on the increase in all age groups, and healthy dietary and food choices face huge negative pressure from the food and agriculture businesses. A substantial fraction of the food offered in the supermarket today would not have been recognized by our grandmothers as food at all.

The AHA certainly has good intentions but one can argue that they may have reached the point of diminishing returns. There is huge resistance to lifestyle changes and drug therapy is successful mostly in the eyes of those who realize they have nothing better to prescribe.

Sudden cardiac death (SCD) is generally not discussed in the context of heart disease risk factors and prevention. Some statistics: Current annual heart disease mortality is 600,000. Coronary heart disease contributes 385,000, and sudden cardiac death, 200,000-250,000. About 80% of SCD victims have coronary heart diseases. SCD excludes death from a sudden occlusive heart attack, termed a myocardial infarct. Rather it is generally a manifestation of a fatal heart rhythm disorder. It has been known for decades that the risk of SCD is independent of serum cholesterol. Currently the left ventricular ejection fraction is the only SCD risk stratification factor used in clinical practice. Thus none of the risk factors, either defined by biomarkers or lifestyle, discussed in the AHA advisory appear to directly relate to SCD. Yet it represents nearly 50% of all heart-related mortality. It was also observed a decade ago that good omega-3 status, as determined by certain minimum levels of long-chain omega-3 fatty acids in red blood cell walls, reduced the risk of SCD dramatically. It appears that only rarely is this marker measured.

NEWS BRIEFS

OBESITY, DIABETES AND RISK OF LIVER CANCER

A study has just appeared that examined the impact of obesity and diabetes on liver cancer.[23] The researchers made use of the SEER Medicare database and found 6991 individuals ≥ 68 years of age diagnosed with liver cancer between 1994 and 2007. As a control a random sample of 255,000 individuals were selected. Odds ratios and population attributable fractions (PAF) were calculated. PAF indicates the number or proportion of cases that would not occur if the factor were eliminated.

It was found that diabetes and/or obesity more than doubled the risk of liver cancer with little gender dependence and the PAF for diabetes was about 37%. However, the PAF was much lower for obesity (5%). These numbers can be put in perspective by considering the related results for hepatitis C and alcohol related liver disease which had odds ratios of 40 and 4 with PAFs of 22% and 24%, respectively. The study did not distinguish between type 1 and type 2 diabetes, but the latter is vastly more prevalent today, especially in the age group selected.

This study also focuses the concern regarding cancer and diabetes on the liver and raises the obvious question. Is there a decrease in liver cancer risk with either severe calorie restriction which eliminates diabetes or severe carbohydrate restriction which converts diabetics into prediabetics? In the case of the association with alcoholic fatty liver disease, it appears that irreversible liver damage is the important factor but prior to this, the disorder can generally be reversed by simply stopping alcohol consumption, and this would presumably reduce the risk of cancer. In the case diabetes or obesity, reversal presumably eliminates an important insult to the liver and suggests that this might reduce the risk of cancer, but the interventions described above have not had liver cancer as a studied outcome since long-term studies would be required. Nevertheless, this may be an added benefit.

ANTIBIOTICS TO TREAT SORE THROAT IN THE US CONTINUES UNABATED

The only common bacterial cause of sore throats requiring antibiotics is Group A Streptococcus, and the prevalence of this particular throat infection is about 10%. This infection is universally susceptible to penicillin. Around 1993 the prescribing rate for adults seeking medical help for a sore throat dropped from 80% to 70%. But even at 70%, antibiotic prescribing is inappropriate in this setting. With the growing importance of resistance to antibiotics, an interesting question concerns the prescribing patterns over the subsequent years. A recent study has examined this issue.[24] The investigators determined the percentage of sore throat visits resulting in an antibiotic prescription and further stratified by emergency department visits or primary care. For all visits and primary care, the percentage has varied between 53% and 65% between 2000 and 2010. For ED visits, the percentage was on average about 54%. Inappropriate treatment continues unabated. The authors point out that the practice of prescribing antibiotics to those unlikely to benefit is not benign. In addition to the issue of drug resistance, antibiotics can cause diarrhea and in rare case a serious adverse drug reaction. In addition, they estimate that between 1997 and 2010 inappropriate antibiotic prescriptions cost about a half a billion dollars. What they fail to mention is the adverse effect on beneficial gut bacteria.

THE JOURNAL *SCIENCE* ORGANIZES AN INTERESTING STUDY

There are over 8000 “open access” scientific journals now in existence. They represent a new phenomenon. These publications make money by charging authors and all articles are available free online. Many of these journals are not covered by the National Library of Medicine (PubMed) and as a consequence provide authors only with a reference to add to their CVs. The papers go into unmarked graves. But enough are covered to raise concerns about quality and standards. The journal titles frequently appear mainstream.

The journal *Science* commissioned a researcher to create a bogus paper on a new cancer drug study with built in grave errors that any peer reviewer or editor would be expected to catch. The name of the institution was made up and based in an African capital.

The paper was sent to 304 journals of which only 255 responded and 157 accepted the fake and flawed study for publication. In many cases the paper was accepted without peer review. When a review was performed, the paper had a 70% acceptance rate. One of the journals, *PLOS One,* which while open access, has a very good reputation, was the only journal that noted the study flaws and "meticulously" reviewed it before rejection. Stanford's John Ioanniudis, a high profile academic critic of poorly designed, executed and reported medical research, commented "These aren't really science journals as pointed out by this very cute and clever hoax; they are more check cashing operations."

Conclusion: Money corrupts and don't believe everything you read in the "peer reviewed" medical literature. It is easy to check if a journal is covered by PubMed using the single citation search feature. PubMed is free and is the equivalent of Google for medicine.

"ENRICHED" STUDY ENROLMENT ENCOURAGED BY FDA

The FDA is implementing a program designed to boost the success rates in clinical trials. One of the classic biases associated with clinical trials is pre-trial participant selection to weed out non-responders and those who have adverse reactions to the intervention. For example, genetic makeup is one example that can be used for exclusion. In fact, the FDA has stated that clinical trials are not designed to demonstrate the effectiveness of a treatment in a random sample of the general population. Really! That would seem to be a good description of the traffic in and out of the offices of family doctors, GPs and in some countries, internists. The goal is to increase the chance that a study of an effective drug will be able to detect a treatment effect with smaller sample sizes than needed in an unselected population. While some will have no problem with genomic or proteomic pre-trial screening, there is nevertheless even a problem here in conveying to doctors this restriction on the interpretation of benefit. The industry has a poor record in transparency in their dealings with doctors. Witness the large number of successful criminal prosecutions and accompanying huge fines, many associated with aggressive off-label marketing. Thus while critics are crying for stricter controls on bias and cheating in clinical trials, it appears that the FDA is moving in the opposite direction.

The reader is referred to the new book *Bad Pharma* by Ben Goldacre, a physician in the UK. Chapter after chapter provides detailed and frightening insight into how biased and dishonest trials and misleading drug promotions put patients at risk of being treated with ineffective or dangerous drugs. An earlier book by Goldacre, *Bad Science*, is also recommended.

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