Editorial

Controlled Therapeutic Trials: Disadvantages and Advantages

The first non-double blind, non-randomized controlled trial was completed thousands of years ago and reported in The Book of Daniel. When Daniel and his young Israelites had been gathered at the King's palace, Daniel discovered that they were expected to eat the food commonly served which was against their religious beliefs. He suggested to the administrator that if his men were allowed to follow their usual diet for two weeks the administrator could himself assess the health of his young men and compare them to the health of the other young men from different regions and religions. At the end of the trial Daniel and his young men were permitted to continue to eat their own food. This experiment would not be acceptable today because it was not double blind, was not randomized, was too simple, did not cost enough and had too few subjects in the study.

This is the first recorded controlled comparison experiment. It is obvious God did not demand the modern gold standard of all trials–the randomized, double-blind, prospective experiment. Did he know something modern researchers do not know? Daniel was a faithful servant of God and surely would have run the trial differently had he been told to do so.

Afer a few thousand years hiatus the next experiment was conducted by Sir James Lind in 1747 on the effect of citrus fruit on scurvy. During April and May while cruising on HMS Salisbury he conducted the first clinical controlled trial. He treated six pairs of scorbutic sailors. The first pair were given cider, the second pair elixir of vitriol, a third pair vinegar, a fourth pair sea water, a fifth pair each were given two oranges and one lemon for six days when the supply of fruit ran out and the last pair were given an electuary consisting of a mixture of seeds. By the time the fruit ran out the two lucky sailors were much improved and a few days later were nursing the remaining ten. Lind was convinced, but the British Admiralty was not. Research would not accept that as proof and would call it anecdotal because it was not double blind and the sample was too small. Hickey and Roberts[1] described the details of this experiment. *The New England Journal of Medicine* (*NEJM*) would have rejected it because it was not double blind. A few years ago *NEJM* rejected a vitamin C study on idiopathic thrombocytopenic purpura (ITP) in which all eight of the subjects responded. The reason for rejection; it was not double-blind.

A very recent report of the beneficial effect of anti oxidant vitamins on AIDS is another example. Fawzi, Msamanga, Spiegelman et al.[2] gave over one thousand HIV-infected pregnant women either placebo or the following multivitamin mixture: 20 mg thiamine, 20 mg riboflavin, 100 mg niacin, 25 mg pyridoxine, 50 mcg B_{12}, 800 mcg folic acid, 30 mg vitamin E, and 500 mg vitamin C. They concluded " Multivitamin supplements delay the progression of HIV disease and provide an effective, low cost means of delaying the initiation of antiretroviral therapy in HIV-infected women." However the editorial accompanying this amazing report, while agreeing that the findings were significant, suggested caution, as if the vitamins were as dangerous as the anti-retrovirals. A few years after AIDS became a major problem in Canada a few patients with AIDS were referred to me and I placed them upon a multivitamin program usually with much larger doses of the same vitamins. I did not emphasize the four Foster[3] nutrients. They all responded with major improvement. They would have done better had I been aware of Foster's recent book in which he outlined in elegant detail the evidence, which led to his hypothesis that the treatment of HIV/AIDS should include four basic nutrients: selenium, tryptophan, glutamine and cysteine. A few patients who followed his program recovered. These findings suggest that the anti-oxidant nutrients are therapeutic but that the optimum therapy will occur with these four specific nutrients, the components of glutathione

peroxidase. The positive responses of a small number of patients in my series and in Foster's series should have the same value as an indicator of response as the responses of scorbutic patients to vitamin C. Is AIDS a multideficiency syndrome, lacking these four well known and easily available nutrients? Why do we need huge multi million dollar studies to prove what we already know? The reason is political.

Contrast these very simple trials with the current trials in the field of oncology. Tamoxifen has for years been considered an essential treatment for all breast cancer cases, if estrogen positive, but only for five years as after that the side-effects outweigh the therapeutic benefit. The original studies demonstrated a minor benefit, about 3% increase in days alive. The side effects were ignored except for the five-year rule. Most cancer cases did not survive the five years. This minor outcome was statistically significant because of the very large sample size which blows up insignificant clinical findings into major public announcement findings. Based on equally clinically insignificant findings it is being replaced by letrozole.

The following study on letrozole was published early in www.nejm.org on October 9, 2003 because it was considered so vastly important and in the November 6 issue of the *NEJM,* Goss, Ingle, Martino et al.[4]

A total of 5,187 women were enrolled (median follow-up, 2.4 years). At the first interim analysis, there were 207 local or metastatic recurrences of breast cancer or new primary cancers in the contralateral breast, 75 in the letrozole group and 132 in the placebo group–with estimated four-year disease-free survival rates of 93 percent and 87 percent, respectively, in the two groups (P<0.001 for the comparison of disease-free survival). A total of 42 women in the placebo group and 31 women in the letrozole group died (P=0.25 for the comparison of overall survival). Low-grade hot flashes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group, but vaginal bleeding was less frequent. There were new diagnoses of osteoporosis in 5.8 percent of the women in the letrozole group and 4.5 percent of the women in the placebo group (P=0.07); the rates of fracture were similar. After the first interim analysis, the independent data and safety monitoring committee recommended termination of the trial and prompt communication of the results to the participants. The 18 authors concluded that compared with placebo, letrozole therapy after the completion of standard tamoxifen treatment significantly improves disease-free survival. I am not impressed except with the careful use of percentage changes to make something appear more effective than it really is. Out of approximately 2,600 women on placebo 42 died in 2.4 years and out of 2,600 treated 31 died. In other words one would have to give 2,600 women letrozole to show a decrease in deaths of only 11. This is statistically significant but in my opinion not clinically significant and is a play on statistics that I dislike.(Lies, Damn Lies and Statistics.)[5] The only hard data and most important end point is death. Side effects increase with duration of use and it is clear that these are minimal figures that will increase.

Effective treatment will be demonstrated by relatively short term studies. The first patient given insulin for diabetes responded. No double blinds needed. The first catatonic schizophrenic patient we gave large doses of niacin in 1952 recovered in 30 days. Our first double-blind trials were on small groups and they showed that adding the vitamin doubled the recovery rate. The first schizophrenic patient in France to be given chlorpromazine responded. The first six manic patients given chlorpromazine by Dr. H. Lehmann in Montreal recovered. No double blinds needed. He is considered the father of tranquilizer treatment in North America.

It is obvious that with effective treatments small-scale studies are adequate to determine efficacy and even toxicity while for treatment which is only slightly effective very large scale trials are needed. David Horrobin[6]

questioned the value of large-scale clinical trials. He recommended that we should largely abandon large-scale trials looking for small effects and instead do large numbers of small trials, often in single centers, looking for large effects. So why do we use them? The reason is paradigm politics.

Controlled trials have become the main weapon used by the current drugs-only-treatment paradigm to protect itself against innovation. A recent letter to the *BMJ,* 2004; 329: 118 illustrates this very well. Earlier, Prince Charles had said, in a talk to a health care conference "I know of one patient who turned to Gerson therapy having been told she was suffering from terminal cancer and would not survive another course of chemotherapy. Happily, seven years later, she is still alive and well. So it is vital that rather than dismissing such experience, we should further investigate the beneficial nature of these treatments." Professor Michael Baum, retired, using the public press terminology blasted Prince Charles. I submitted the following reply.

The *National Post,* Friday, July 9, 2004 under the Headline "Prince scolded over coffee enema "cure" wrote "A prestigious British medical journal has blasted Prince Charles over his support for controversial cancer treatments that include coffee enemas and copious amounts of carrot juice." More accurately it should have stated that it was Professor Michael Baum who blasted Prince Charles while your journal labeled it a Personal View thus publicly dissociating yourself from his views. Professor Baum is disturbed because he thinks that Prince Charles was "not exercising his power with extreme caution when advising patients with life threatening disease to embrace complementary therapies." He writes "I have always advocated the scientific evaluation of CAM using controlled trials." It puzzled me why he was so unhappy with Prince Charles's comments. According to the *Sunday Observer,* Prince Charles told the health care audience he knew of one patient who had been treated successfully and added that "rather than dismissing such experience, we should further investigate the beneficial nature of these treatments." If Prince Charles was correctly quoted he and Professor Baum are in perfect agreement that alternative cancer therapies should be properly tested with good controlled clinical trials. Prince Charles did not recommend that patients seek out the Gerson treatment. He said we should further investigate such experiences.

The main difference appears to be that Prince Charles would like to see these trials conducted sooner rather than later and Professor Baum is content never to do them for he expects the alternative practitioners to conduct them even though they have no resources, no institutes, no research grants, and no time to conduct these trials. I think Professor Baum would be in a much stronger position if he were to use his influence to initiate these trials.

Is this another case of Royalty to the rescue? Sir Thomas Sydenham M.D.,[1] (1624–1689) was confronted with small pox. In 1667, 1,196 died and 1,468 the following year in London with a population of only 500,000. Sydenham observed that the death rate from small pox was much higher when the patients fever was increased. This was the standard treatment of that day. He wrote "By such means, greater slaughters are committed and more havocke made of mankinde every yeare than hath bin made in any age by the sword of the fiercest and most bloody tyrant that the world ever produced." Sydenham allowed his patients to stay out of bed for four days after the onset of the fever, allowed them liberal fluids, particularly small amounts of beer, a few bedclothes and, in a few cases of youths, bleeding. His treatment was designed to keep the fever down. This was a new idea in medicine. The medical profession did not particularly like what Sydenham was doing since it went against theory and practice going back nearly 1,500 years. He was challenged to a duel. He had been Lieutenant in Oliver Cromwell's army. The medical association

threatened him with loss of his license. Had the double blind randomized prospective methods been known they would have demanded that. Dr Sydenham appealed to the first Earl of Shaftesbury in 1669 where he described the controversy, his data and the results he was getting. I like his sentence "It fares not always soe well with Truth and Right as not to need a patronage, new truths especially such as stand in the way of received maxims and general practice, and like trees sprouting up in the middle of the beaten road, which however useful or pleasant is not fenced while they are young and defended till they are growne too sturdy for common injury, are sure to be tramped on in the bud and to be trod into dust and forgetfulness..."[7]

Controlled trials are not needed when the treatment being tested is aleady acceptable to the paradigm. Even open clinical trials are quite acceptable. The schizophrenic paradigm believes that this condition is caused by a defect in the neurotransmitters and receptors in the brain and this they believe explains why the modern drugs have an effect. Therefore the idea that any other type of compound might be useful, for example vitamins or minerals, is unbearable. When we first reported that niacin improved the outcome of treatment in 1957, during the era when psychiatry still considered schizophrenia a way of life and not a disease, the conclusion we reported was totally unacceptable. Even the use of drugs was not acceptable since the leaders of the NIMH were mostly psychoanalysts and were fearful of the drugs. It required political action by many congressmen and senators and the Mary Lasker Foundation to remove these psychiatrists from their position of influence and to allow the drugs to come in. The drug effect is so powerful that no one could miss it even with one or two patients. They were all double blinded anyway at terrific cost of time and money. The cost of bringing a new drug to market has been estimated to run between 350 and 750 million dollars. The numerous double blinds merely provided more evidence for activity that was already well known and accepted by psychiatry. They were and are redundant. The reason is political.

The rule seems to be as follows. If the treatment falls within the established paradigm, clinical studies, double blind or not, are acceptable but toxicity studies would have to be much more rigorous. Thus for many years after it was reported that tranquilizers caused tardive dyskinesia this observation was totally rejected. If the treatment is outside the paradigm double blinds will be demanded repeatedly as a way of protecting the paradigm. This is especially effective in preventing studies of non-patentable compounds like vitamins since the double blind clinical trials are so expensive. Only billion-dollar corporations can afford to do them and of course they will not test compounds they do not own. Claims about toxicity of these out-of-the box substances will be accepted with alacrity, even with no evidence whatever. World wide, oncologists believe that the anti-oxidant, vitamin C, decreases the value of chemotherapy and radiation. They have no fear of antioxidants that are not vitamins. The medical literature contains around 70 reports. One paper, based upon one case, suggested that vitamin C might decrease the value of chemotherapy. This has become a law in the field of oncology. Sometimes toxicity is invented, such as the false idea that vitamin C causes kidney stones.

Government agencies like the FDA have to make very serious decisions about allowing drugs to come onto the market. An error will be the downfall of any career physician who has made it. For these people the statistical analyses became a godsend because it removed the need to use judgment. One would depend on the double blind and the probability. If it exceeded 5%, that physician could safely agree that the drug be cleared. In my opinion the greatest value of the controlled trials is to government agencies. Few questions have been raised about the scientific validity of these double blinds. Recently three letters to the editor in *CMAJ* and one in

the *NEJM* debated the issue on the best type of clinical trials. Wright,[8] a pharmacologist, defends the double blind design. Pijak, Gazdik and Hrusovsky,[9] three clinicians, argue that observational studies (not double blinds) are simpler, and just as effective. Delaney,[10] a statistician accepts that double blinds have an important role but other methods can be as effective. Concato, Shah and Horwitz[11] compared the efficacy of five clinical topics in 99 reports between 1991 and 1995. The average results of the observational studies were remarkably similar to those of the randomized controlled trials

H. Butler in the *British Medical Journal* Rapid Response Section for July 11, 2004 discovered to her surprise and to mine, that Sir R.A. Fisher(1890-1962) in his 1925 book "Statistical Methods for Research Worker" arbitrarily selected P=0.05 as the important statistical variable. If P is less than 0.05 it is concluded that the difference between the two test groups is statistically significant. If the value if greeter than 0.05 it is not. There is no scientific rationale. Fisher chose it because it was convenient. Butler reports that Professor Leonard Savage concluded that this P value can boost apparent significance of implausible results by a factor of 10 or more. Have we for decades depended upon this arbitrary value which has never been scientifically tested? Will the world's medical libraries have to delete 90% of all the controlled clinical studies that claimed that their results were significant because the P values were less than 0.05? Will politicians who depend so heavily on public polls and the P=0.05 values be a bit more cautious in their interpretations of the results of these polls? I hope that this represents the beginning of a very serious debate on the merits of the gold standard, the double blind randomized clinical trial. Other questions have been raised about the use of these trials to support one's point of view or one's patented compounds, Hirsch,[12] Dean et al.[13] quotesd Jonathan Quick, Director of Essential Drugs and Medicines Policy for the World Health Organization wrote in a recent WHO Bulletin: "If clinical trials become a commercial venture in which self-interest overrules public interest and desire overrules science, then the social contract which allows research on human subjects in return for medical advances is broken." Self-interest already is the major factor.

Ever since I directed the first psychiatric double-blinds beginning in 1952, I have been thinking about them and have published several papers highly critical of these tests. They have never been tested to prove that, in fact, they achieve what it is claimed they do, i.e. to remove bias and to allow small samples to accurately describe what will happen with large populations. They do not remove bias, nor disallow strong biases. Most of these studies are not really blinded as this is so difficult. They interfere with the doctor patient relationship since the treating physician is asked to lie to their patients and since it is really difficult to treat the patient with hope when he knows that half of them or more are getting an inactive compound, the placebo. It is considered by many today that such trials are unethical, perhaps illegal in terms of informed consent and I think they are immoral. But they will have to be done as tradition demands. Are the double blind therapeutic trials like the increase in fever used for centuries in the treatment of small pox? They are a major factor in the high cost of drugs today and they do not always lead to the correct conclusions. Had we depended only on double blinds, L-Dopa would not be in use today for treating Parkinson's disease.

Recently a report from England showed that additives in foods created problems in children, increasing behavioral and learning disabilities. A three-year double blind controlled study showed that children were "markedly more active, inattentive and short tempered when fed a diet heavy in food additives and noticeably calmer when their diet was stripped of additives." Forty years ago, Dr. Ben Feingold, a well-known allergist, reported that these additives made some children develop

problems. His work was totally rejected except by parents who found their children became better when these additives were removed. A panel of the United States National Institutes of Health determined in 1982 that there was no scientific evidence to support these claims. The majority of clinical studies done at that time including some that were controlled all showed that Feingold was wrong. The paradigm at that time opposed his conclusions.

The paradigm is now changing and the recent study in England, also controlled, shows that Feingold was right. As the paradigm changes it becomes easier to insinuate these out-of-the box studies and to get them accepted. Most people do not realize that to the medical professions, "scientific" means it has been accepted by the paradigm. If it outside the paradigm it is not scientific.

The report by Julie Deardorff[14] illustrates the difficulty the modern paradigm has in accepting findings which help children recover and which are acceptable by their children's parents, by orthomolecular physicians. Madalyn Berner of Wheaton, Ill., once routinely described her son Richie as "hyper, impulsive and distracted." By age six, he had developed a tic and had begun hitting himself, screaming at high pitches and compulsively washing his hands. Doctors diagnosed the troubled boy with attention deficit and hyperactivity disorder and prescribed medication. When Richie began to hear voices, Berner abruptly changed course.

Instead of switching drugs, Berner dropped them altogether and revamped her son's diet, eliminating wheat and dairy products. Without wheat, she said, his hyperactivity vanished. Without dairy, he could suddenly read. His rashes and constipation also disappeared. Dietary changes are far from a cure and eyed skeptically by the mainstream medical community because the scientific evidence is still shaky. Often, removing certain foods has absolutely no effect on children."You won't see it espoused in main pediatric journals," said Dr. Sandy Newmark, director of the Pediatric Center for Integrative Medicine in Tucson, which specializes in ADHD and autism. "But there is a whole community out there looking at diet." In Berner's case, the treatments - cobbled together from three health practitioners, including a chiropractor - dramatically changed her son's life. Today, Richie Berner, 8, not only is functioning in a normal classroom setting, but also is one of the best rebounders on his YMCA basketball team, a team sport he previously couldn't play. His Sunday school teacher at St. Michael School in Wheaton, was astonished to learn he'd once had behavioral problems and called him "bright, alert and involved in class."

Evaluation of Toxicity[15]

Double blind controlled therapeutic trials not only over estimate the efficacy of drugs by depending only on the P value using very large numbers but they also underestimate the toxicity of drugs because even with large scale studies toxic effects commonly occur sometime after the drugs are taken and often long after the treatment period that was used in evaluating these drugs. They make drugs appear too good by over estimating the positive effects and down playing the negative effects. The evidence is all around us and has at last been picked up by the public media. In the past few weeks we have been swamped with bad news about the most modern and most thoroughly double-blinded drugs. The *Wall Street Journal*, June 25, 2004 discussed major concerns drug companies have with the need to use placebo since so many of their drugs are no better than placebo. They hope to discover how to identify placebo reactors so that they can be deleted from clinical studies. The report pointed out that spin put on by investigators and trial sponsors distracted from the high placebo responders and led to exaggeration of the benefits of drugs and downplay of their harmful effects. Munro[16] reported that two current drugs Celebrex and Vioxx hit the market with the claim that they caused less stomach

bleeding than other painkillers. Later it was found that the company only reported the first six months of the trial. Had they reported the next six months the public would have known that these drugs caused much more ulcers than the short term had indicated.

In 2004, Health Canada, concluded that 5.2 million Canadian adults suffered from medical errors or preventable adverse effects in Canadian hospitals. Between 9,200 and 24,000 died per year. Of all the admissions one in nine ie. 468,000 patients were given the wrong medicine, or the wrong dose by doctors, pharmacists and hospitals. I assume that side effects also occurred when given the correct dose and the recommend medication. In the US about 108,000 patients died in hospitals even with the proper use of drugs. The equivalent deaths in Canada should be about 10,880. The cost of these events is devastating.

Kirkey[17] reported the dangerous effects of antipsychotic drugs under the large heading "Anti-psychotic drugs alarm doctors." This news item reported that some doctors were very concerned abut deaths, seizures, tardive dyskinesia. Who would not be worried? Unless the public gets alarmed the profession will not because it has been using dangerous drugs for many decades. Health Canada received 600 reports of suspected adverse reports; 59 died. The number who killed themselves is not known. Astrazeneca,[18] the drug company which sells Crestor, a very popular cholesterol lowering substance issued an advisory in which it emphasizes the dangers of rhabdomyolysis, a wasting disease of muscles. The rate is under 0.01% but when millions of subjects take it this means 100 patients per million. The risk arose from doses of 40 mg daily when only 10 mg is recommended. But the risks are not really known. Thus Japanese and Chinese are at an increased risk as are patients with pre existing diseases such as kidney problems, hypothyroid problems or with a history of muscle pain. Yet one of the doctors involved as advisor to the company stated "Statins are safe, are essential for the prevention of coronary artery disease". Preventing coronary disease is of course very important but the statins are not needed since niacin, a vitamin, does the same much more effectively and is accompanied by a large number of positive effects as it is a healing vitamin. It lowers cholesterol, lowers triglycerides, elevates HDL, lowers Lipo A, extends life substantially and does not cause terminal complications. All it needs is a doctor who knows how to use it.

This warning followed a similar warning in Europe. If any vitamin carried that small degree of risk it would have been taken off the market immediately. Anti arthritic drugs like celebrex and vioxx increased the risk of hospitalization 80% within one year of prescription because it increased risk of developing congestive heart failure. In Canada in 2003 there were 7.7 million prescriptions for cox-2 inhibitors, total value $475 million and 16 million prescriptions per year for non-steroidal anti-inflammatories.[19] One doctor said "it is really ironic that patients may be trading one side-effect, gastric bleeding, for a far more serious one, congestive heart failure. It is also ironic that niacin and niacinamide have excellent anti arthritis properties but are almost totally ignored."[20,21]

Dean et al.[13] in a major report on iatrogenic accidents in medicine concluded that American medicine frequently does more harm than good. For example, the number of people in hospital with adverse drug reactions was 2.2 million. Over a ten year period, out of an average of 16.4 million admissions to hospital, adverse drug reactions totaled 1.06 million and medical errors 0.98 million, a total of over 2 million. They concluded, "When the number one killer in a society is the healthcare system, then, that system has no excuse except to address its own urgent shortcomings. It's a failed system in need of immediate attention. What we have outlined in this paper are insupportable aspects of our contemporary medical system that need to be changed - beginning at its very foundations." Adopting orthomolecular medicine

and psychiatry is the most effective change, as it would eliminate most of the drug errors from wrong drugs and the wrong doses.

These adverse effects can not occur with nutrients. No deaths from nutrients have been reported in US in the past forty years. If the wrong vitamin is given or if the dose is too high there is no problem since they are safe and the body simply eliminates the extra amount. Orthomolecular medicine can be used to treat almost every disease known to medicine, not in a specific way but because no one can argue with the statement that no matter what the disease that person will do better if they are nutritionally well. For many conditions medication may be eliminated altogether.

A 21-year old man complained he had been depressed all his life. History and food habits suggested a dairy allergy. Based on my practice since 1950 about 75% of all long-term depressions are caused by chronic food allergies. I advised him to eliminate all dairy foods, and added some vitamins and minerals. Milk decreases the absorption of zinc for example and due to the chronic effect of the allergy on the intestine probably decreases the absorption of many nutrients. After a two-week period of abstinence he was normal. He then did the challenge test; he ate some ice cream. Two hours later he was once more depressed and one hour after that he was psychotic and his mother had to call the police to restrain him. He fell asleep 8.30am until 11.30am and has been free of depression. Had he gone to another psychiatrist not familiar with the effect of food allergies he would have started the long and dreary journey of testing one anti-depressant after another until the one could be found that would be effective and not have difficult side effects.

Impact of Double-blind Controlled Trials on Medical Curiosity and Initiative.

In general one of the most important qualities of good doctors has been subdued and perhaps destroyed. The best physicians are those how are familiar with the best in medicine but who still are able to think and to solve problems when they run across patients who do not respond to the cook book of modern medicine. Physicians are trained to remember and if what they have been taught does not help they give up, tell the patient they can not help any more and this is honest, or tell them that there is no other treatment which is dishonest or advise them to live with their discomfort. But the innovative physician will seek out other approaches and will use them provided that they are less toxic than the method which has not worked. This is the way medicine has always been practiced and the reports of these physicians in medical journals would be read and repeated by other doctors. If other doctors could confirm that would eventually become another treatment for that condition. In 1960 when we first began to publish our results using orthomolecular methods for our schizophrenic patients, doctors found it interesting and within a year or at least a dozen United States and Canadian doctors were treating their patients this way. They were not afraid of opposition from their colleagues, they were not afraid of losing their licenses and their livelihood. But after the APA report in the early 1970s and the sweep of double blind methodology into medicine the situation became entirely different and a tremendous amount of fear was generated by the position taken by the APA, by the NIMH and by other established bodies. The medical journals were promptly closed to orthomolecular physicians and these physicians were unable to report their findings. This actionwas based on the most superficial examination of the evidence which was then available. In my opinion double blinds have been generally very harmful to the medical profession and even more harmful to the patients they have been treating.

Impact of Controlled Trials on Society, on Patients and their Families.

Waiting for controlled trials has been beneficial for the patient population because

it delayed introducing them to drugs that are generally of little benefit and produce major side effects. Many drugs have been taken off the market afer many years due to serious side effects. Had these drugs never been introduced the lives and health of these patients would have been saved. Ideally, drugs should never be introduced until they have been tested for many years and shown to be safe, as safe as existing medicat ion used to treat the same condition. The situation is entirely different with compounds that are naturally found in the body and are safe. With this group of therapeutic substances the wait for controlled studies is detrimental as it prevents many patients from benefiting from the treatment.

A very good example of the benefit of not waiting is the fortification of flour in about 1942 with three vitamins, niacinamide, thiamin and riboflavin–enriched flour. This was done during the first Great War because so many United States men were not fit for the armed services. Pellagra was endemic and often pandemic in the southeast United States. A small group of pioneer nutritionists recommended that the flour be enriched. Canada soon followed suit but only several years later during which it considered the addition of these vitamins to flour an adulteration and illegal. No one demanded any controlled experiments. They were not in style. It was clear that these vitamins prevented deficiency disease and no one raised the reasonable point that the evidence from few patients reported in the literature did not prove that adding it to flour would be beneficial. The additional cost of the flour was minor and the number of people saved from pellagra alone, was enormous. But suppose the controlled trial was then as popular as it is now. The FDA and NIH would demand double blind controlled experiments that would take many years and allow the epidemic of pellagra to continue until these trials were complete.

A recent example illustrates the baleful effect of demanding controlled trials long after it was well established that folic acid prevented spina bifida. Dr. Smithells in Scotland in 1981 demonstrated that giving pregnant women this vitamin decreased the incidence of spina bifida. He had earlier observed that their red blood cells were deficient in folic acid. Very little was needed. One multivitamin or B-complex pill contained enough folic acid. The immediate reaction of the medical establishment was disbelief and hostility. I remember reading an issue of one of the English medical journals, which contained six or seven letters, all condemning Smithells vigorously for his idiotic suggestion, and one even complained that the amount he used, one milligram daily, would be dangerous. Smithells wrote a book to defend his views. Ten years later after controlled trials in both the United States and England, his original findings were confirmed and since them the vitamin is being added to flour as well.

Treated with orthomolecular methods, the majority of early schizphrenic patients recover. They become free of symptoms, get on well with their families and the community and they pay income tax or are otherwise making useful contributions to society. But due to the resistance of the psychiatric establishment most of them will never have a chance to recover since given drugs alone fewer than ten percent ever can work again. Who will one day add the costs of this enormous burden of ill health to these patients and to the families? And think of the loss to our community of the contributions these gifted patients could make after recovery.

Costs

We do not know how much was saved by the American public by enriching flour. I hope that some medical economist will undertake to calculate this and to estimate the cost of delay per year. But we can estimate the cost to the United States of not enriching their flour with folic acid over a ten year period.

Here are the numbers. During those ten years, 250,000 children were born in the

United States with neural tube defects (NTD). Had all their mothers taken folic acid daily 187,000 fewer babies with NTD would have been born. A pediatrician estimated that in Canada each NTD child consumed $50,000 in medical and surgical costs over their first 12 years. Assuming equivalent costs in the US this would amount to over 9 billion dollars, A few pennies per day would have saved these enormous health costs. Can you think of any other investment that yields this same type of return?

The introduction of orthomolecular therapy has aleady saved thousands of patients from the ravages of schizophrenia and other diseases that respond to this treatment. Who will estimate the cost of delaying the introduction of this benign treatment for over forty years? The average forty-year life-span cost of treating schizophrenic men and women is two millions dollars. We do not know the cost of not treating them since up to a third will recover without treatment. This is the natural recovery rate which can be increased to fifty percent if they are provided with shelter, food and treated with respect and consideration. Dan Chaon, Author of the novel "You Remind Me of Me" *New York Times Magazine*, June 27, 2004, described his recovery from encroaching madness. He described hallucinations, both visual and auditory, felt unreal, misinterpreted words, and had problems with memory. His experience is typical of a transient schizophenic episode. Luckily for him he did not seek psychiatric help and get started on modern tranquilizers.

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