Control of Medical Journal Content: Suppressing the MBT Contamination Warning *(Chapter 8, The Nurses are Innocent – The Digoxin Poisoning Fallacy, Dundurn Press, 2011)*

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Much has been written in the last few years about the control that powerful pharmaceutical companies exert on the medical profession and its journals. Frequently it has been said that the largest lobby group in Washington D.C. is the pharmaceutical industry. It is believed that thereare more lobbyists representing it than there are members of Congress.[1] This type of infiltration of Washington would not occur if it didn't result in legislation that benefited the industry.

This kind of influence has spread to infiltrate our medical journals. In 1999, there was an impression that the Massachusetts Medical Society had placed the reputation of its prestigious journal, the *New England Journal of Medicine (NEJ)*, at risk when it seemed to succumb to changing its direction from a not-for-profit journal to one that was profit-driven, with drug company advertising representing a significant component of the operating costs. A profit motive could render the *NEJ* more vulnerable to the interests of the pharmaceutical industry than most medical journals already appeared to be.

In 1999, the journal created new specialty journals under the logo of the *New England Journal*. This manoeuvre is said to have increased the profits of the NEJ from $386,540 per year (known profit in 1979) to an estimate of $20,000,000 for the year 2000.[2] The editor at this time, Dr. J.P. Kassirer, decided that he did not want his name associated with a practice he felt would jeopardize the journal's and his own ethical standards, by becoming vulnerable to lucrative forces with vested interests in promoting the use of pharmaceuticals. In a move that was generally considered to be a result of this ethical stand, Dr. Kassirer lost his position in 1999.

On February 20, 2006, John Hoey, the decade-long editor of the *Canadian Medical Association Journal (CMAJ)* was fired, as he said, because of "the censoring by the CMA of a report describing the difficulties Canadian women had in obtaining a Plan B (a nonprescription generic) drug from pharmacists."[3] Deputy editor Stephen Choi was named acting editor-in-chief, but when the CMA refused to adopt ten principles of editorial independence, Dr. Choi resigned, as did the editorial fellow and two associate editors.

Dr. J.P. Kassirer, now Editor Emeritus of the *New England Journal of Medicine*, and others writing in the *CMAJ*, the journal they were criticizing, cited the actions of the *CMAJ*'s owners and managers as "raising serious concern about the integrity of the journal, its reputation, and its viability in the community of top medical journals."[4]

It is worth noting that members of the Canadian Medical Association should take great care not to allow their journal to come under the control of any pharmaceutical corporation, because that should be recognized as being detrimental to the judicious practice of therapeutic medicine. Journals, especially our *Canadian Medical Association Journal*, are expected to exemplify the highest medical ethics.

It seems apparent that the editors of the *New England Journal* were expected to keep functioning

strings attached, or they would be cut loose (fired, in these cases) by the medical societies operating the journals. Is it right for the journals' owners to allow their advertisers to manipulate the strings that govern the actions of the editorial staff, and thus dictate the contents of journal articles whenever they see fit? By sacrificing independence, a journal would be forfeiting relevance as a scientific source of medicine. Would journals thus become more like advertisers for pharmaceutical products?

On July 10, 2010,[5] and on July 13, 2010,[6] Gardiner Harris of the *New York Times* wrote that a major clinical trial (the "Record Study") of a popular anti-diabetes drug, Avandia (manufactured by GlaxoSmithKline) received "a scathing review." This trial, which was used by GSK to argue that the drug was safe, was examined by Dr. Thomas Marciniak of the Food and Drug Administration (FDA), finding "a dozen instances in which patients appeared to suffer serious heart problems that were not counted in the drug's tally of adverse events," something that "should not be found as single occurrences" in such studies. Dr. Marciniak said that, when interpreted correctly, instead of supporting Avandia's safety, "the study supports critics' contentions that Avandia may cause heart attacks and strokes."

Although the FDA had originally endorsed the Record Study in 2007, it was only after independent researchers, reviewing thousands of clinical cases, found Avandia to be associated with many dangerous side effects, that Dr. Marciniak undertook an examination of the cases studied in the Record — a multinational study of 4,447 patients in 23 countries, with type 2 diabetes — a study that was funded by GlaxoSmithKline, the manufacturer of Avandia.

In 2010, the *New England Journal* accused GSK of interfering with the trial's results,[7] while Dr. Jerome Kassirer, the former editor of the *NEJ*, raised the legitimate question of "whether the entire system is corrupt."

In 1999, a secret study on Avandia by GSK compared it to Actos, manufactured by Takeda. This study indicated that not only was Avandia no better than Actos, but that there was definite evidence that Avandia showed increased cardiovascular risks. Internal documents have proven that Avandia's manufacturer "spent the next 11 years trying to cover up" its own trial results.

A study of 227,571 Medicare patients, conducted by an FDA reviewer,[8] concluded that "Avandia increased the risks of stroke, heart disease, and death."

I direct the members of the Ontario Medical Association to another example of control of content of a medical journal by corporate interests. This came from personal experience. Because of my publications on allergic reactions associated with contamination of X-ray dye injections and the fastidious reporting of reactions to the Ontario Medical Association's Adverse Drug Reporting Program, I was asked to write an article for the OMA's journal, the *Ontario Medical Review*, on the contamination of pharmaceuticals by MBT leaching from the pharmaceutical rubber of syringes and ampoule seals.

Because the journal took great pride in its involvement in the reporting of adverse reactions to drug administration by OMA members, there always was a section devoted to the OMA's Adverse Drug Reporting Program. Our OMA journal had been dedicated to keeping Ontario physicians alerted to the importance of these adverse drug reactions, so this requested article should have been an informative one about the possibility of severe adverse reactions from MBT — an entirely appropriate article for the journal.

The article was carefully written and referenced fully, detailing my experiences with the two anaphylactic reactions to an injected X-ray dye contaminated by MBT. It was pointed out that this was just a glimpse of the MBT contamination that must have been occurring with injections of pharmaceuticals, IV solutions, immunization desensitizing "shots," and blood transfusions everywhere in the world. The final editing changes were made and accepted by the editorial staff. It was now in the form that would appear in print within a couple of weeks, warning of the potential for severe adverse reactions, an integral component of this journal's format and its *raison d'être*.

There should have been an aura of anticipation and pride among the offices of the *Ontario Medical Review*, as they were about to publish the world's third report on the topic. The article was to warn physicians about anaphylaxis events that had been occurring for years, but with the many severe reactions and many deaths worldwide being invariably blamed on the injected pharmaceutical, rather than the insidious contaminant, MBT. This was a very significant article indeed!

I read the galley proofs and made the suggested editorial changes. Two days after the final changes were made and approved, I was dumbfounded to receive a call from the editor, Dr. David Fletcher, who said that the journal could not publish the article because of the threat of being sued.

It must be said that Dr. Fletcher's reaction was the direct opposite of that of Tony Smith, the deputy editor of the *British Medical Journal* in the early 1980s. In answer to a similar threat of a lawsuit by a major drug company (Eli Lilly), Dr. Smith had the fortitude and integrity to firmly say, "In that case we'll see you in court."[9] The drug being cited by the BMJ as a cause of severe liver damage, benoxaprofen, was banned in the U.K. soon after the article was published. In the U.S., because of this reported hepatotoxicity, benoxaprofen was withdrawn in the same year it was marketed, 1982.

After pursuing a discussion with the editor for a few minutes, I realized that an absolutely final decision had been made — the requested, edited, revised, and approved article would not be seen in print.

I brooded and boiled over this development for hours, over the years of labour I had put into pharmaceutical rubber research, over the work I had done on the paper, and over the almost impenetrable barrier that continued to be erected to conceal the MBT hazard. Almost all members of the medical, dental, and nursing professions, and the public were destined to be kept unaware of the potentially lethal MBT hazard — with a respected medical journal aiding and abetting what seems to be an imposed restriction of medical teaching

It is obvious that the only groups that could sustain damage if the article were to be published would be the syringe manufacturers, and particularly the pharmaceutical industry, which had millions of pharmaceutical doses, prepackaged in unit dose syringes across the world, and, probably a billion or more pharmaceutical ampoules with natural rubber seals.

It was obvious also that no lawsuit would have been considered, even remotely, because a court case of this significance would have resulted in many newspaper articles that would have the effect that they so badly wanted to avoid — the revealing to the public of the hazard that pharmaceutical rubber had exposed them to, and was continuing to. One should not expect that the pharmaceutical industry would be willing to sacrifice the health and possibly the very lives of patients for the sake of profits.

I had an uneasy feeling that the word "lucre" lingered somewhere not very far offstage, just hanging in the air. Pharmaceutical advertising is very lucrative for medical journals.

There are other facets to the manipulation of journals, brought about by their great economic power. The tampering with medical journals — even to the extent of attempting to prevent the publication of factual articles that the pharmaceutical industry would not like to appear — is well-recognized in our "free enterprise" world, not just my personal experience.

In 2006, a Toronto researcher, Joel Lexchin, writing in the *British Medical Journal*,[10] documented several examples. Lexchin cited one notable instance of what appears to have been economic punishment. After the publication of an article that "critically examined the scientific accuracy of advertisements for drugs in ten leading medical journals,"[11] the journal, using similar statistics from four other comparable journals, calculated that it had lost 1 to 1.5 million dollars in drug company advertising revenue from what seems to have been a punitive economic form of retaliation.

In the interest of medical ethics, one wonders if the pharmaceutical and medical rubber manufacturers could, or should, be alerted to the contents of medical journals before their publication, and then, inscrutably, almost cherry pick which articles get published (with reprints of these "vetted" articles being circulated to practicing physicians by pharmaceutical representatives as advertisements of their wares).

Nonetheless, the many millions (even billions) of pharmaceutical doses, insidiously in contact with natural rubber, were now destined to be used up on patients, with the attendant risks of severe adverse reactions that my patients had experienced, and the many deaths worldwide. The *Ontario Medical Review* apparently was aiding and abetting this unacceptable state of affairs by refusing to publish a pertinent article that they had requested I write.

One needs only to leaf through all medical journals to realize that almost all the advertising, and therefore, a significant percentage of the costs of the journals' publication, would be borne by advertising by the pharmaceutical industry.[12] This suggests that the real threat to the OMA's journal would not have been a lawsuit, but rather a stern warning that these manufacturers would withdraw their advertising if the MBT article were published. If this were the case, this would represent a glaring example of interference with the publication of an article that may have been detrimental to drug industry profits, but of great benefit to the interests of public health — the derailing of the dissemination of important information that warned of life- threatening MBT contamination.

It has been suggested, quite recently, that the practice of corporate power being exerted on journals, even to having articles "ghost written" by professional writers hired by the pharmaceutical industry,[13] may no longer exist. One questions, however, whether this behaviour has vanished, or ever will vanish, because it is so economically beneficial to the mutually interested parties. However, it is very degrading to the science of therapeutics in medicine and to the willing participants in this action.

Until even now this widespread MBT/rubber contamination problem has been largely buried — with hardly a headstone to disclose that it even existed. MBT was primarily written up in scientific journals that physicians almost never read, or refer to (e.g. the *Journal of Biomedical Mass Spectrometry*, or the *Journal of Chromatography*). It is deeply disturbing that such an important and pervasive public health problem can be so hard to uncover and virtually impossible

to expose in print — and thus it has been so hard to protect patients from.

Benzothiazoles have been used in rubber manufacturing since the 1920s. The Canadian Worker's Compensation Board has for many years recognized MBT as a significant contact allergen in workers in rubber manufacturing. However, what has been discussed here is not just exposure to MBT through skin contact, but exposure by the far more dangerous systemic (injection) route. To my dismay, to this day, MBT remains as a widespread hazard, virtually unknown to the medical profession, perhaps intentionally kept that way, with the active acquiescence of our health protection agencies, clinical scientists — and our medical journals.

Just as the MBT experience may be interpreted as a window to a far greater problem suggesting manufacturers ignoring, and perhaps actively suppressing, vital medical information, the recent travails of Dr. Nancy Olivieri, a world-recognized hematologist, may be seen to display a similar theme of improper corporate control. When a researcher reveals the adverse effects of treatments with a drug produced by a major manufacturer, the writer may find his or her position — and even a university appointment — at risk.

While receiving funding from the large pharmaceutical manufacturer, Apotex, for a drug trial on deferiprone, a treatment for a severe congenital anemia, Dr. Olivieri found that it may lose its efficacy with prolonged use. After consulting the hospital's research ethics board, she followed their advice and revised the consent forms for the patients enrolled in the drug trial, to inform them of this fact. (This had the potential to damage the marketability of deferiprone.)

Apotex forthwith not only terminated the two trials that Dr. Olivieri had in progress in Toronto, but they simultaneously terminated her consulting contract for a third international trial. Seemingly, Dr. Olivieri's scientific honesty had no place in the workings of this particular pharmaceutical corporation.

Some time after the trials were terminated, she found that there were instances of increased liver damage, with fibrosis, associated with this drug, above and beyond the liver damage from the increased iron storage that developed during therapy for her congenital anemia (thalassemia major) patients. This should not have been entirely unexpected, since congenital iron storage disease (hemochromatosis) is known to cause liver damage — and damage to the heart ("iron heart") and to the pancreas, with increased skin pigmentation ("bronzed diabetes"). In keeping with normal ethical standards,[14] she informed all of her patients and drug regulatory bodies of this risk.[15,16]

During this time, negotiations were underway with Apotex for the largest corporate donation ever given to the University of Toronto and its affiliated hospitals. Apparently, Apotex persuaded the U of T's president to write to the Liberal prime minister and four Liberal cabinet ministers regarding proposed new drug patent regulations, stating that "Apotex advised us that the adverse effect of the new regulations would

make it impossible for Apotex to make its commitment to us." The president asked these officials "to do what is necessary to avoid the serious negative consequences to our very important medical sciences initiative."[17] The president apologized later for this conduct.

Conforming to the behaviour of a true scientist, Dr. Olivieri published her clinical trial findings on deferiprone. This action was motivated by the justifiable Ciceroic ethical axiom that the welfare of patients takes precedence[18] over the interests of a corporate donor (Apotex) — and the

donation's recipient (her employers, the Toronto Hospital for Sick Children and the University of Toronto).

This termination of ongoing clinical trials that may not have shown a marketable result and that revealed a risk of permanent liver damage lays bare a huge ethics problem and a grave concern about the validity of publishing trial results in a way that can create a large bias in favour of pharmaceutical products. In this way, it would be possible to undertake ten similar trials in different settings, using different investigators, and refuse to publish nine of the ten that statistically show negative effects and/or no positive effects. They then can publish the only one that may show positive findings for the trial drug.

A popular adage describes three degrees of increasingly bad lies — lies, damned lies, and statistics. One can understand how the worst variety may be published in our best medical journals. The other variety of truly valid trial results (the other nine out of ten cited above) — with the rare exception of that of Dr. Olivieri's group — may not appear in the tables of contents of our major medical journals, and may spell the demise of the careers of fine scientists (and perhaps the journals themselves), if they do appear in print.

In an action generally perceived as a consequence of her reporting of these drug trials, Dr. Olivieri, an internationally renowned medical scientist, was fired from her job as head of the Hemoglobinopathy (congenital abnormalities in structure of the hemoglobin molecule that result in anemia) Disease Unit at the Toronto Hospital for Sick Children.

There was an overwhelming outpouring of disgust from members of the medical profession and of the university academic community when they learned of this unconscionable interference with scientific integrity in research and with academic freedom. This pressure resulted in the rehiring of Dr. Olivieri, not by the HSC, but by the University of Toronto. She was not allowed to regain her previous position, because the HSC had unceremoniously dissolved it. However, she was allowed to continue her research on congenital anemias.

In recognition of her ethical stand as a scientist and as a physician who was willing to put her career in jeopardy, the University of Winnipeg bestowed on Professor Nancy Olivieri an Honorary Doctor of Science in 2006, citing that she was "one of the preeminent crusaders for academic freedom in our times," a "defender of research integrity, academic freedom, and as a critic of the increasing corporatization of the universities."[19]

This type of interference with the revealing of the true results of drug trials demands that there be legislation enacted so that those involved be absolutely obligated to register all drug trials and to publish the results, good, bad, or indifferent, if not in a journal, then in a recognized and easily accessed Internet site dedicated to revealing drug trial results. These drugs must be identified by all the generally accepted terms as to the class of drugs they represent and the purposes of treatment, so that the results do not remain hidden from other researchers, the medical community involved, or the public, some of whom will be personally involved in the treatments being investigated. The government bodies supervising the enforcement of the regulations must be immune to commercial pressures, with severe punishment for failure to abide by these principles.

Researchers, academic physicians, the editors and reviewers of medical journals and the pharmaceutical industry, in theory, should be complementary — independent forces that combine in the public interest of the prevention and treatment of disease processes, something that should be a symbiotic relationship — mutually beneficial. However, as far as the pharmaceutical industry and the medical profession and their journals are concerned, a very intimate relationship

has developed that has been compared to "dancing with a porcupine," wherein it seems that the results of research — and its publishing — must fulfill, for the pharmaceutical industry, a "fundamental need to satisfy shareholders," a powerful force that "could, and at times does, conflict with a researcher's agenda to seek and unveil truth.[20]

It seems that corporate power has always been exerted on journals, even to the extent having articles "ghost written" by professional writers hired by the pharmaceutical industry. Although it was suggested that this behaviour has vanished, it has not, as pointed out in the *Montreal Gazette*, August 24, 2009.[21] It is unclear whether it will ever vanish, because it is so lucrative to the mutually interested parties — yet so detrimental to the ethics of medicine and, potentially, so damaging to public health around the world.

Two Dalhousie professors, Elaine Gibson (law) and Françoise Baylis (bioethics and philosophy), noted that two reviews were undertaken to study the circumstances surrounding Dr. Nancy Olivieri's firing, the Naimark Review (commissioned by the Hospital for Sick Children)[22] and the Thompson Report (commissioned by the Canadian Association of University Teachers).[23] As might be imagined, diametrically opposite assignments of blame surfaced — with the Naimark Review exonerating the hospital and the Thompson Report blaming the hospital. The Thompson Report discredited the Naimark Review as being "based on incomplete, incorrect, and false testimony."

With great insight, the Dalhousie writers suggested that one must read both reports and decide "which version of events is more thorough, credible, independent and just." [24] In the final paragraph of their article, they offer words of caution to the much sought-after potential dancing partners for the pharmaceutical industry (the researchers, the academic doctors, the journal editors, and their reviewers): before accepting a dance with a potential porcupine, "one needs a clear idea of the choreography. When the music is unappealing, or the risk of missteps considerable, it is best to announce that one's dance card is full." This is an onerous responsibility heaved on the shoulders of those rendered vulnerable in the face of inadequate, or insecure funding.