An Expensive New X-ray Dye, Shown by Statistics to Reduce Serious Side Effects (*Chapter 9: The Nurses are Innocent – The Digoxin Poisoning Fallacy, Dundurn Press, 2011)*

Key words: adverse reactions, anaphylaxis**,** arteriography, biased statistics, contrast agents, Elliott Lasser, injections, imaging, ionic, IVPs, Japan, MBT (mercapto-benzothiazole), natural rubber seal contamination, non-ionic, osmolality, Stuart Houston

Up to the mid 1980s, the X-ray dyes used for IVPs, arteriography, and cardiac imaging studies were slightly irritating to the vessels into which they were injected, causing some burning pain for a short time after the injection into an artery, or vein. It was also known that the injection of these X-ray dyes was associated with adverse reactions that varied from nausea and vomiting, to anaphylactic shock, and sometimes death. Very serious allergic reactions were known to occur about once in 1,000 injections, with one death in about 100,000 injections.[1] Naturally, when allergic reactions occurred with these injections, they were attributed to allergy to the dye being injected. These were believed to be chemically pure pharmaceuticals, with no one considering the possibility of their contamination, especially by allergenic and/or toxic material.

In the mid 1980s, a new variant of these dyes came on the market. The injection of these new dyes was characterized by fewer minor side effects (nausea and vomiting, and burning sensation in the injection site). This decrease in minor side effects was considered to be due to their lower osmolality (relative absence of the tendency of molecules to break up into ions). These new dyes were therefore termed nonionic dyes, while the older ones were called ionic dyes. The main deterrent to the routine use of non-ionics in radiology departments was the price; the non-ionics were six to ten times more expensive than the older ionic dyes.

Great pressure was brought to bear on the users of these X-ray dyes when the results of a very large Japanese series (337,647 patients nationwide) were published,[2] comparing adverse reactions to the older ionic dyes to the adverse reactions when the very expensive new non-ionics were employed for IVPs. At the time of the study (September 1, 1986 to June 30, 1988), the injections of non-ionics showed significantly fewer adverse reactions. Particularly important was the determination that there were significantly fewer severe life-threatening reactions associated with the injection of the newer nonionic dyes, although no deaths occurred with either variety of dye in this series.

Quite naturally, the manufacturer promoted the newer, expensive nonionic dyes, not only for IVPs but also for the ever- increasing numbers of arteriograms, X-ray dye heart studies, and CT scans being performed. Medical, legal, and, creatively, philosophical, and even theological pressures were being injected into the promotion formula for advocating the universal use of these expensive non-ionics,[3] with the implication that it would be unethical, and even sinful — contrary to religious teaching — to use the much less expensive and, apparently, the more dangerous ionic dyes.

It was implied (though never said) that it could be malpractice to use the less costly dyes,

because of the results of the large Japanese comparative series. This large study was used as a tool in the marketing of nonionic dyes, and reprints of the article were dispersed freely to any radiologists who might contemplate using these X-ray dyes.

Most hospitals in Canada and the U.S. switched to the exclusive use of non-ionics at great cost to their radiology departments. This change added many millions of dollars to health care costs every year, while filling the coffers of the manufacturers of the very expensive non-ionic X-ray dyes.

However, there was a flaw in the statistical reasoning being used. This was not just a minor flaw. It was a large flaw. In truth, it was an enormous flaw. One extremely pertinent factor was operating, biasing the comparative X-ray dye study,[4] unknown to the Canadian health care system, and unknown to the health care systems in the U.S. and globally, unknown to those in Japan injecting the dyes — but the manufacturers should have been aware of it.

This very large study was not done in Canada. It was not done in the U.S. The country that may have been carefully selected for this seemingly defining study was Japan.[5]

In any statistical study used to investigate effects and their causes, true scientists take extreme precautions to make sure some unconsidered factor is not skewing their results, making their studies invalid.

Consider the following facts:

- The very large series that showed decreased severe allergic reactions to the costly nonionic dyes was carried out in Japan.

- Japanese disposable syringes, since 1985, were all made with non-MBT, non-latex non-allergenic and nontoxic synthetic rubber syringe plunger tips.

- The ampoules of the new expensive nonionic dyes were sealed with synthetic non-MBT, non-latex, non- allergenic, and nontoxic synthetic rubber. The inexpensive ionic dye ampoules were sealed with natural rubber requiring allergenic and toxic MBT, and allergenic latex in the manufacturing process.[6]

- The first of my two severe anaphylactic shock reactions was proven to be from allergenic/toxic MBT from disposable syringes containing natural rubber (that just happened to be associated with the injection of cheaper nonionic X-ray dye).

- The second case of anaphylactic shock was from MBT leached into the dye from MBT in dye ampoule seals (again, associated with a cheaper ionic dye). In light of this information, one would not have to read this Japanese article to know what the results would show. One would predict exactly what the authors would find in their study from September 1, 1986 to June 30, 1989, which was as follows:

> The injections of "nonionic contrast media (X-ray dyes) significantly reduce the frequency of severe and potentially life-threatening ADRs (adverse drug reactions) to contrast media at all levels of risk, and that use of these media represents the most effective means of increasing the safety of contrast media examinations." ——— Those who knew what we have learned about allergenic MBT contamination and the presence of allergenic latex in medical natural rubber would have written their conclusions somewhat differently: The contamination from natural rubber of any X-ray dyes by MBT, or latex, significantly increases the frequency of severe and potentially life-threatening ADRs (adverse drug reactions) to these contaminated contrast media at all levels of risk and that the elimination of natural rubber contact (made with the allergens MBT and latex) represents the most effective (and by far the least expensive) means of increasing the safety of any injections (ionic and nonionic contrast media, in this case).

In Japan, the risk of exposure to allergenic MBT had been eliminated in the case of the expensive non-ionic dyes, whereas the risk of allergenic MBT (and latex) exposure remained prevalent in the ampoule seals of the much less expensive ionic component of this study, thus introducing a very large bias towards causing allergic reactions with the cheaper ionic dyes, reactions that would be due to MBT, or latex, not to allergy to the ionic dyes. It was in the midst of this study that I encountered anaphylaxis from MBT contamination from the rubber ampoule seals, following an injection of one of the much less expensive ionic dyes.

Again one must be reminded of a type of intentionally introduced bias that led to that often-quoted saying, usually applied to political statistics, that there are three graduated kinds of lies: lies, damned lies, and statistics. Those knowingly speaking or writing falsehoods are generally classified as liars. It is important to note that these words do not refer to the Japanese researchers involved in this study; they were unaware of the insidious MBT-latex-natural-rubber aspect to the adverse reactions being reported.

However, there may be, indeed, major medical, legal, ethical, and religious implications at the root of this saying (and there may be significant repercussions to each of these, as can be gauged from the second-worst type of lie) that conceivably may be factored into this statistical equation, if such prior knowledge was used by the manufacturers in the testing parameters and then in the marketing the expensive nonionic dyes.

Thoughtful, health cost-conscious, well-read radiologists in Saskatoon came to a somewhat different conclusion than their more credulous counterparts.

Just as there were reduced adverse reactions to costly nonionic dyes in the Japanese series, an anticipated reduction in the incidence of reactions to X-ray dye injections was being noticed, not in Japan, but in Saskatchewan, at the Royal Victoria Hospital in Saskatoon. However, this drop in serious reactions was not associated with the newer expensive nonionic dyes, but a reduction clearly was evident in the incidence of allergic reactions when the much less expensive ionic dyes continued to be used. The Saskatoon radiologists had understood a significant underlying increased risk factor in the reactions

encountered with X-ray dye injections, and they realized that it was no longer present with the less costly ionic dyes.

Since 1990, they had known that MBT-latex-natural-rubber was no longer present in the disposable syringes they used to inject the dyes, and the seals on the cheaper ionic dye ampoules no longer leached MBT or latex, because they too were MBT- free, just as occurred when the costly nonionic dyes were injected in Japan.

Professor C. Stuart Houston of Saskatoon is a giant of Canadian diagnostic radiology, a six-year editor of the *Journal of the Canadian Association of Radiologists*, the author of five books on medicine, the history of medicine, and Canadian Arctic history, and a world-recognized authority in ornithology. With sound medical, economic, and ethical reasons, the Department of Radiology of the Royal Victoria Hospital in Saskatoon did not succumb to the exclusive use of the expensive nonionic dyes, but continued to use ionic dyes.

On this subject, in December 1994, he wrote to me that he had recently attended the annual November national meeting of the Radiological Society of North America (whose journal is *Radiology*) in Chicago. Dr. Houston described a session on "Selective use of nonionic contrast material (X-ray dyes): opposing philosophies, economics and ethics." The speaker had said that the expensive nonionic dyes were preferable to ionics but, because of cost, most hospitals still used a high proportion of nonionics. "[The Mayo Clinic is still at 85 percent ionics.]"

These are excerpts from what Dr. Houston wrote to me about what he rose from the floor to say in Chicago at this annual national meeting.[7] He prefaced his remarks by saying that his diagnostic radiology department continued to use ionic dyes and that Gavin Hamilton in London, Ontario, was like "a voice in the wilderness," and then continued as follows:

...Gavin Hamilton single-handedly had forced the removal of MBT from syringes and rubber stoppers in Canada. Since then we have not had a single serious IV contrast reaction at our hospital. Formerly, we had deaths, and we had serious reactions

From the response, I suspect that no one in the audience had heard of MBT.

In the final paragraph of Dr. Houston's letter, in words that are etched in my memory, he wrote: "Please note in your memoirs that Stuart Houston is the second voice in the wilderness." In truth, this book represents a portion of my memoirs, comprising two significant areas of unfinished business in my life work, conjoined into a twin tale, as the reader is learning.

Although in 1994 natural rubber definitely had been removed from X-ray dye ampoules and from the syringes radiologists used to inject them, Dr. Houston's justifiable belief (and my hope), that natural rubber had been removed from contact with all drugs that are injected subcutaneously and intramuscularly, was not based on reality. There was, in fact, a failure to act on the acknowledged clinical concept that, although the intravenous route

can elicit the most rapid onset of a deadly allergic reaction, any other means of tissue injection is far more dangerous than the ingestion of an allergen, but even the less dangerous ingestion route can kill, as those with peanut or seafood allergy have been warned repeatedly.

Dr. Elliott Lasser, an internationally recognized authority on contrast media, tapped into the FDA's database to compare reported reactions to ionic and nonionic X-ray dyes from 1990 to 1994.[8] Perhaps someone in Dr. Lasser's group was stimulated by Dr. Houston's 1994 comment about the reduction in the incidence of severe reactions when the cheaper ionic dyes were used. Dr. Houston had advised U.S. radiologists at their Chicago national meeting that this was a period during which there had been the almost complete elimination of exposure of X-ray dyes to direct contact with natural rubber, involving both ionic and nonionic varieties.

Lasser's group showed total reported reactions per million cases of 193.8 for ionics, compared to 142.5 for nonionics, a very close relationship, much closer than earlier studies had shown, when the incidence of natural rubber contact was far more common with ionic than nonionic dyes. What is even more important is that Lasser's group showed the incidence of fatal reactions, though low, was almost twice as high when the newer, much more expensive nonionic dyes were used (6.4 per million for nonionics and 3.9 per million for the older, much less costly ionic dyes).

The Saskatoon radiologists' experience and Lasser's study form an extremely significant validation of the extent of allergic reactions and deaths from MBT contamination of injections from pharmaceutical rubber. The older, much less expensive ionic radiopaque dyes have a long history of causing severe reactions uncommonly — and deaths fairly rarely. However, although the chemical composition of the dyes remained the same in 1990–1992, the incidence of severe reactions and deaths dropped remarkably when natural rubber contact was eliminated from the ampoule seals and from the syringes used to inject the MBT leaching from MBT-latex-rubber. MBT caused many deaths worldwide and remains a threat in Canada and the U.S., but the threat is extreme in India, China, and Indonesia, where MBT-latex-rubber is in common use in syringes, pharmaceutical ampoules, and IV apparatus.

This study destroys the safety issue as a major factor in selecting nonionic over ionic dyes. The decreased overall incidence in adverse reactions was not due to the "effect of improved contrast media," as this article suggests, but was due to the elimination of contact, of both dye types, with natural rubber and its leachates MBT and latex from syringes and ampoule seals. Dr. Houston's outstanding group of Saskatoon radiologists were not only Western trail blazers in this regard, but were showing the path the world should have followed in the past and must surely follow now in the rational future use of these dyes!

We are left to wonder what motivated the pharmaceutical industry to choose Japan for the huge study on IVP X-ray dyes, which led to decisions that have cost our health delivery system so much over the last fifteen years.