Grey Matter

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Published 11/19/2004

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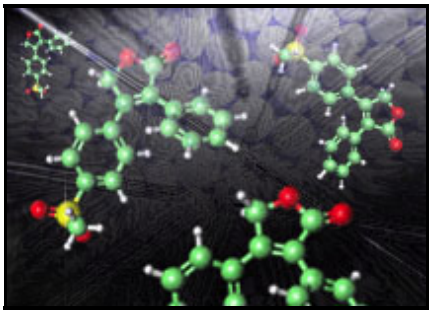

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Many people have seen the pharmaceutical company Merck's recent recall of Vioxx (rofecoxib) as confirmation of Merck's dysfunctional or dishonest management. Others see it as evidence of the FDA's dysfunction. But what the Vioxx case really highlights is the absurdity of the belief that drug safety can be guaranteed. The expected flood of lawsuits is strong evidence indeed that the American public believes Merck to have willfully and knowingly hawked a dangerous drug.

CBS's Sixty Minutes added to the misinformation last Sunday, November 14. Here's the third paragraph of their report.

> "However, according to internal Merck documents ***60 Minutes*** has seen, and interviews with outside scientists, Merck had concerns that Vioxx could possibly cause cardiovascular risks long before it was pulled off the market."

That makes it sound as if Merck hid this information, right? Certainly, CBS's report gives that impression. But here's a simple fact: **Merck was warning about the cardiovascular risks for years.** The package insert from September 2002, and reprinted in the widely used Physicians' Desk Reference, devotes two full tables and a number of paragraphs to the risk of cardiovascular problems. The package insert shows that 45 of 4,047 patients on Vioxx experienced a cardiovascular thrombotic event, compared to only 19 of 4,029 patients on naproxen. The package insert goes on to say that Vioxx is not a substitute for aspirin and that patients who need cardiovascular protection should continue taking aspirin. Printing such risks in the package insert is not a good way to hide any of Vioxx's warts. Instead, it is a way to allow physicians and patients to make informed choices.

Also, CBS led with the weakest and most implausible part of its case. The network showed a healthy, beautiful 39-year old, Janet Huggins, who died within a month of starting to take Vioxx. Yet CBS went on to say:

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> "Instead, Merck found something potentially worse: Patients taking Vioxx for longer than 18 months were twice as likely to suffer a heart attack or stroke than those taking a placebo."

But 18 months is *not* one month. Was CBS simply careless? Merck has solid evidence that Vioxx shows no additional cardiovascular risk until after 18 months of therapy. Life is uncertain and there are risks everywhere. To blame everything on Vioxx is sloppy thinking.

The fact is that pharmaceuticals are not black or white; they are grey. Consider the contemptible thalidomide, which caused serious deformities in 10,000 European babies after their mothers took it as a tranquilizer to alleviate morning sickness. After four decades of an FDA ban, thalidomide is back on the market with the FDA's blessing to treat a painful skin condition of leprosy. The FDA pulled Propulsid (cisapride), a heartburn drug, from the market in 2000 after 80 people who took it died from an irregular heartbeat. But Propulsid was also a miracle drug that allowed patients with cerebral palsy to digest food without extreme pain. A medicine that may work for one person at certain times for a given disease may not work if any of the variables changes.

Problems, sometimes serious, can arise after FDA approval. Three to ten percent of blue-eyed patients who took Xalatan (latanoprost) for glaucoma ended up with permanently brown eyes. This amazing side effect was uncovered only after the drug was approved as "safe and effective." One researcher estimated that 106,000 people died in 1994 alone from adverse reactions to drugs the FDA deemed "safe." Merck voluntarily pulled Vioxx, but most drugs on the market have problems. It is the drugs' benefits and side effects that cause physicians and patients to debate their usefulness for each specific situation.

Consider aspirin (acetylsalicylic acid). In December 2003, an FDA advisory committee couldn't determine if aspirin was useful for preventing initial myocardial infarctions (MI's), or heart attacks, even though it is approved for the prevention of second heart attacks and the committee had data on 55,000 patients. This is aspirin, after all, which has been taken over one trillion times during the last hundred years. Does this bountiful experience mean that aspirin is guaranteed safe? Not at all. Aspirin can, and does, kill people by causing gastrointestinal bleeding.

Into this world came Vioxx. People were dying due to the problems with NSAID's that blocked both COX-1 and COX-2. Scientists knew that the gastrointestinal bleeding problems were related to COX-1 inhibition, so it made sense to develop products that inhibited relatively more COX-2 than COX-1. Evidence for this theory, as for any theory, can typically be sufficient only with years

of study with large numbers of patients. At some point, the fog lifts and conclusions can be made. Then the second-guessing starts. Perhaps Merck should have run the critical trials earlier. Perhaps Merck and the FDA could have seen this problem earlier. Perhaps, perhaps, perhaps. The point is, as noted earlier, that medicines are grey. Only over time are their real characteristics known, and only then can the Monday morning quarterbacks state with ignorance-emboldened certainty that Merck and the FDA were clearly wrong. If these critics are so good at such assessments and the facts are so clear, we encourage them to venture into the murky world of drug development and identify the winners and losers years earlier. It would save everyone a lot of money and trouble. Of course, they can't.

Merck has a reputation for being the most cautious and ethical company in the pharmaceutical industry. When I (Charles) worked at Merck twelve years ago, employees proudly quoted George W. Merck's 1950-era credo: "We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear." Not for nothing did *Fortune* magazine name Merck America's Most Admired Corporation seven years in a row. Merck employees have always taken a lot of responsibility for their patients' outcomes. Indeed, it was this concern that led them to withdraw Vioxx from the market. In a less litigious society, such a move would have been unwise, given Vioxx's substantial benefits to many patients. What clearly happened here is that a cautious company withdrew a drug that had some problems. That's all.

No one except trial lawyers and a few lucky plaintiffs will benefit from lynching Merck from the nearest tree. If we forget that disease and death are the enemies and that pharmaceutical companies like Merck are on our side, we will pay for that memory lapse for the rest of our unnecessarily shortened lives.

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