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Chapter 12

ADVERSE DRUG REACTIONS, MEDICAL ACCIDENTS, and PATIENT SAFETY

Frances H. Miller¹

I. Introduction

Hippocrates enunciated the precautionary principle for medicine in 400 B.C when he said, “Primum, non nocere [first, do no harm].”² All physicians are taught that precautionary rule in medical school. Hippocrates’ advice might have worked well to safeguard patient safety in his time, when doctors couldn’t do much for (or to) patients, but medical treatment is very different now. Much has changed over the past five decades, driven by technological advance, and health care has become far more sophisticated, complex and potentially dangerous to patients than it ever was before. At roughly the same time, health sector oversight has been evolving away from the professional self-regulation and laissez faire regulatory mindset of much of the past, when the precautionary principle seemed superfluous because the risks of medical intervention were all but invisible outside the profession.

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² “As to diseases, make a habit of two things – to help, or at least to do no harm,” Hippocrates, OF THE EPIDEMICS, Bk. I, § XI (400 B.C.). (Hippocrates actually spoke Greek, not Latin, but the Latin translation has become the dominant articulation of the “do no harm” principle.) (Cf. Ozonoff 1999)

Over the past half century of dramatic medical progress, accompanied by increasing medical risks, physicians have ruefully come to acknowledge that sometimes they have to bury their own mistakes. Heightened public and professional awareness of iatrogenic (treatment caused) injury and concern for patient safety are helping to drive health system improvements today (Starr 1982). Four of these changes deserve special attention for the light they shed on the mounting governmental and public perception of medical risk, and on the regulatory and private sector responses to it.

First, computerization has been a boon to medical research and treatment, but it has also facilitated data collection revealing a high prevalence of medical accident that went unnoticed previously.³ The worrisome patient safety implications of these data have been impossible to ignore, and that fact alone has spurred precautionary reforms. Second, while technological advances have prolonged both the length and the quality of human life, many of them involve more invasive and risk-laden methods of treatment than those they replaced. In addition, modern technology often calls for more technical sophistication from caregivers than used to be required.⁴ Medical injuries thus have more opportunities to surface in the modern era, and are often more serious when they do.

Thirdly, patient awareness of medical risk has increased in tandem with the civil rights, women's liberation, gay rights, and other social movements of the latter half of the twentieth

³ *Cf.*, Dr. Lucian Leape (2004), "if a hospital has a real commitment to safety, it is going to get so much information that you don't need an [expensive] reporting system. I can talk to any three nurses in a unit for an hour about what bothers them, and come out with a safety agenda that will keep me busy for a year."

⁴ Medical Malpractice: Report of the Secretary's Commission on Medical Malpractice (The United States Department of Health, Education and Welfare's, 1973: 3) ("Few would challenge the value of these advances but they did . . . produce a concomitant number of adverse results, sometimes resulting in severe disability").

century. The patients' rights movement⁵ generated a more skeptical and risk-conscious patient culture, particularly in the US, a fact not lost on payors, providers and regulators. They have responded in ways varying from outright hostility,⁶ to cooperation,⁷ to voluntary pro-active measures,⁸ to increased governmental oversight designed to forestall medical accidents.⁹ Finally, US Congressional enactment of Medicare and Medicaid in 1965 brought a massive infusion of government funding into the US health sector, and enabled many Americans to afford medical care who had previously gone without. More patients were thus exposed to the possibility of medical accident than ever before. Medicare and Medicaid funding also sharply increased government attention to the risks - and the value - of the health services it now underwrites.¹⁰

The open-ended nature of Medicare and Medicaid funding in the US has made increased governmental oversight of the health sector partly an exercise in fiscal self-preservation. Most EU countries, on the other hand, exert tighter control over total health care spending through

⁵ See, e.g., *Wyatt v. Stickney* (1971) (involuntarily committed psychiatric patients have a Constitutional right to treatment, not just "warehousing"). See generally, Annas (2004).

⁶ Sprecher (1978) (quoting psychosurgeon who objected to proposed psychosurgery review board, "What I resent, and resent very deeply, is the idea prevalent for the last seven years that patients have to be protected from physicians.")

⁷ For example Phrma, the pharmaceutical industry trade association, has recently adopted principles by which "the PhRMA companies commit to the timely communication of all meaningful results of clinical trials, whether those results are positive or negative." <http://phrma.com>.

⁸ For example, the Joint Commission on the Accreditation of Healthcare Organizations (2005) instituted a sentinel Events Policy in 1995, which requires accredited institutions to report "unexpected occurrence[s] involving death or serious physical or psychological injury," and issues periodic Sentinel Event Alerts to its members.

⁹ For example, Congress established the National Practitioner Data Bank pursuant to the Health Care Quality Improvements Act of 1986, 42 U.S.C. § 11131-11137 (1995) to create a central repository of actions taken against physicians indicating quality of care problems. The legislation requires state licensing and disciplinary agencies to report sanctions against physicians to the Data Bank, and hospitals and other entities taking adverse action against doctors must do so as well. Moreover, medical malpractice awards must be reported to the Data Bank as well. Cf., Hallinan (2004: 1) ("corporate shield" protects negligent physician whose name never technically appears on malpractice settlement or judgment from being reported to Data Bank); Dept. of Health and Human Services Office of Inspector General (2001) raises red flags about Data Bank's effectiveness in safeguarding the public from sub-standard practitioners.

¹⁰ MEDPAC (2004) (hundreds of thousands of Medicare beneficiaries experience adverse medical events every year).

budgetary processes, so do not experience as intense fiscal pressures to implement quality improvement measures. On both sides of the Atlantic, however, payor oversight also attempts to improve patient safety and welfare. The regulatory response to medical risks has nonetheless been relatively low-key and cautious everywhere. Apart from a few subject areas - US drug and device regulation, and EU regulation of genetically modified food (see Chapter 3), for example - the precautionary principle has not found robust expression in regulatory policy focused on health care itself. In both America and the EU the reasons for this range from the difficulty of identifying iatrogenic risk, to the traditional deference accorded to self-regulation in the medical profession, to the paucity of enforcement resources.

II. Adverse Drug Reactions

Adverse reactions to drugs can be both dangerous for patients, and extremely costly to society (Classen et al. 1997). They materialize in more than 6% of all hospitalizations, and constitute almost 20% of all adverse medical events taking place in that setting (Lesar et al. 1997). One 2000 study estimated that the yearly costs associated with drug-related adverse events in the US amount to \$177.4 billion. (Ernst and Grizzle 2001). Those costs were almost double the \$91.8 billion in direct medical expenditures for diabetes care in 2002 (American Diabetes Association 2003). Estimates posit that anywhere from 28% to 95% of all adverse drug events are preventable (Agency for Healthcare Research and Quality 2001).

Some adverse drug reactions are the undesired but not wholly-unexpected side effects of the risk-benefit balancing doctors must engage in whenever they prescribe drugs (Wiener 1998). Drugs are defined as “articles . . . intended to affect the structure or any function of the body . . .

,¹¹ and the body reacts to them in both positive and negative ways. Other adverse drug events, however, are simply the result of prescribing errors, and those can be deadly. One relatively recent study determined that hospitalized patients suffering an adverse drug event almost double their risk of death (Classen et al. 1997). The highly-publicized demise of the Boston Globe's health reporter Betsy Lehman after being administered inadvertent overdoses of experimental chemotherapy for metastatic breast cancer at Harvard's Dana-Farber Cancer Institute brought that point home with a vengeance (Knox 1995; Mohl 1998). The Lehman case also proved a powerful stimulus for broad patient safety reform efforts, locally, nationally, and even internationally. (Romano 1999).

A. Safety and Efficacy Evaluation

Ever since 1962 when efficacy requirements were added to the newly-strengthened safety requirements of the Federal Food, Drug and Cosmetic Act of 1938,¹² the US Food & Drug Administration (FDA) has generally been considered the international gold standard for rigorous pre-marketing safety and efficacy evaluation of pharmaceutical products (Pina and Pinds 2002). That golden reputation became tarnished in the wake of several FDA safety and conflict of interest controversies over the past few years, and has yet to recover (Thomas 2006).

The precautionary principle had theoretically been paramount in FDA policy until the 1990's (Olson 1995),¹³ unlike the retroactive focus of most medical practice oversight. The FDA's 1999 precautionary measure instructing blood banks not to accept blood from donors who had spent more than six months in the UK between 1980 and 1996, for fear of their transmitting

¹¹ 21 U.S.C. § 321 (g) (1).

¹² 21 U.S.C. § 355. Congress passed the 1938 Act, the foundation of modern US food & drug law, in the wake the deaths of more than 100 people who ingested a product named elixir sulfanilamide, a sulfa drug (Pina and Pinds 2002).

¹³ (consumer safety trumps other interests in FDA new drug approvals).

bovine spongiform encephalopathy virus, serves as a relatively recent example of the agency's historically guarded approach toward low-probability medical risk (Goodman 2004; U.S. FDA 1999a; Wiener and Rogers 2002 and Chapter 5 in this volume).

Precaution was the FDA's official watchword in part because Congressional oversight committees habitually announce hearings to rake the agency over the coals whenever the media accuses it of failing to protect the public from unsafe drugs and devices (Hutt 1996). As a recent case in point, Merck's "voluntary" withdrawal of its blockbuster Cox 2-inhibitor pain medication Vioxx in 2004 after studies were published showing significant cardiovascular risk associated with its use (Oberholzer-Gee and Inmader 2004) immediately hit the front pages of the popular as well as of the medical presses. The negative publicity was not lost on politicians. Other studies soon raised similar questions about the safety of all Cox-2-type pain medications. That Cox-2 inhibitor controversy, along with roughly contemporaneous and highly-publicized debates over the safety of prescribing SSRI's for depressed adolescents (Brent 2004; Expert Group on Safety of Selective Serotonin Reuptake Inhibitor Antidepressant, 2004; U.S. Food and Drug Administration 2004b) predictably triggered high-profile Congressional investigations of allegedly lax standards and conflicts of interest associated with the FDA's recent drug regulatory activities (Davis 2005).

In response, the FDA hurriedly announced that it was asking the Institute of Medicine to evaluate independently the way the agency assesses and monitors adverse events associated with drugs currently on the market (U.S. Food and Drug Administration 2004a). Even more recent revelations about the integrity of the clinical studies on which the FDA based its approval of Vioxx, about conflicts of interest on FDA Advisory Committees, and most recently about the safety of cardiac devices, have generated further calls for FDA safety reform (Strom 2006)(Ray

2006). A similar legislative reaction took place in Great Britain when the House of Commons Health Committee (2005) held a series of hearings on the influence of the pharmaceutical industry, including the unsafe use of SSRIs and Cox-2 inhibitor drugs.

The Institute of Medicine issued *The Future of Drug Safety: Promoting and Protecting the Health of the Public*,¹⁴ in response to the FDA's request to evaluate its adverse event reporting program. The Institution's comprehensive report critiques the entire drug regulatory process, and recommends a broad range of reforms encompassing 1) increased drug safety funding, 2) expanded FDA authority, 3) better post-market pharmacovigilance, and 4) upgraded management practices.¹⁵ In essence, the IOM advocates a shift in the FDA's regulatory oversight from a relatively hands-off posture after new product approval (barring significant problems), toward more stringent continuing responsibility for monitoring drug safety throughout all approved products' marketing life cycle.¹⁶ The FDA's unusually detailed 2007 response accepted many of the IOM's recommendations,¹⁷ but stopped short of fully embracing its far-reaching proposals for significantly enhanced drug safety, transparency, independence and proactivity.¹⁸

In May of 2007 the US Senate responded to mounting public concern over drug safety by passing the Food and Drug Administration Revitalization Act¹⁹ by a stunning vote of 93 – 1.

The bill basically accepts the Institute of Medicine's recommendation for a philosophical shift in

¹⁴ Committee on the Assessment of the US Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, A. Baciu, K. Stratton & S.P. Burke, eds, National Academies Press (2007).

¹⁵ Mark McClellan, *Drug Safety Reform at the FDA – Pendulum Swing or Systematic Improvement?*, N. Engl. J. Med 355;17 356;17 (April 26, 2007).

¹⁶ Bruce M. Psaty and Sheila P, Burke, *Institute of Medicine on Drug Safety*, N. Engl. J. Med 355;17 (October 26, 2006).

¹⁷ Food and Drug Administration. *The Future of Drug Safety: Promoting and Protecting the Health of the Public: FDA's Response to the Institute of Medicine's 2006 Report*. US Dept of Health and Human Services, January, 2007. (<http://www.fda.gov/oc/reports/iom013007.html>. Accessed March 1, 2007.)

¹⁸ See analysis in Bruce M. Psaty and R. Alta Charo, *FDA Responds to Institute of Medicine Drug Safety Recommendations – In Part*, JAMA, May 2, 2007 – Vol 297, No. 17, at 1917.

¹⁹ S. 1082, 110th Cong., 1st Session.

direction toward a more active post-approval safety role for the FDA. It gives the FDA responsibility for actively overseeing safety throughout the life cycle of a drug, and provides funding for the job. The bill also gives the FDA explicit post-marketing authority to order manufacturers to conduct additional studies and make labeling changes including warnings, and to limit drug distribution when the agency believes that to be warranted. The House must pass a companion bill before the final legislative details can be hammered out, but a veto-proof statute is expected to pass both Houses before the end of September. If it does not, authorization for the crucial prescription drug user fees that fund FDA drug approval will run out, and no affected interest group wants that to happen.²⁰

Much of the US's pre-1962 food and drug legislation was enacted in reaction to widespread public health disasters (Hutt 1996), and Congress similarly passed the 1962 safety and efficacy amendments to the drug approval process largely in reaction to the rash of thalidomide-caused birth defects in Europe (Hutt 1996). The US had fortuitously avoided experiencing a parallel rise in birth defects because by the time neonatal deformities began surfacing in Europe the FDA still had only awarded thalidomide investigational new drug status. The problematic drug was thus not then widely available in America (House of Commons Health Committee 2005).

While the US remains more stringent than the EU with respect to general safety and efficacy standards, notwithstanding the recent safety controversies, it has relaxed its more rigorous precautionary approach over the past ten or fifteen years (Olson 2002). Knowledgeable providers and their sick patients have been able since the 1980s to work their way around regulatory barriers keeping them from access to experimental therapy in certain circumstances. They could end-run formal approval processes and obtain investigational drugs without enrolling

²⁰ Robert Pear, *Senate Approves Tighter Policing of Drug Makers*, N.Y. Times, May 10, 2007, A1.

in clinical trials by securing ‘treatment INDs’ (Investigational New Drug Applications, which permit experimental drugs to be shipped in interstate commerce prior to FDA approval). Before these treatment INDs became available, sick patients could obtain access to experimental drugs only by enrolling in formal clinical trial protocols and risking assignment to placebo or “standard therapy” arms of the studies,. Those receiving placebo or standard care were obviously precluded from access to the experimental medication, although since most studies are blinded they would not know for sure to which arm of the study they had been assigned.²¹ Alternatively, patients suffering from certain serious diseases (AIDS, for example) could secure experimental drugs through the FDA’s ‘parallel track’ policy, which permits seriously ill patients to take investigational drugs for treatment purposes.²²

Congress passed The Prescription Drug User Fee Act (PDUFA) in 1992 in response to mounting criticism - especially from AIDS activists - that the FDA’s process for approving new drugs had become unduly lengthy and burdensome in comparison with faster European regulatory schemes (Andersson 1992; Gao 1980).²³ The FDA had been devoting much of its limited personnel and resources to generic drug approvals at that time, which meant that staff dedicated to evaluating new drug applications was stretched thin. PDUFA introduced substantial user fees for new drug applications, earmarked for hiring more FDA reviewers for clinical studies (Carpenter, et al. 2003). In return for this increased funding the agency promised to expedite review processes (Pina and Pinds 2002). The review cycle did indeed speed up in the aftermath of PDUFA and its follow-up legislative companion, the Food and Drug Modernization Act of 1997 (FDAMA). According to at least one analysis the review cycle accelerated by 50% (Kaitin 1997; Shulman and Kaitin 1996), but the number of adverse drug reactions reported to

²¹ Treatment INDs were permitted by FDA regulation in 1987, and incorporated into statute by FDAMA.

²² Articulated via an April, 1992 Public Health Service Notice.

²³ 21 USC §379 (2002).

the FDA also tripled within the ensuing five years (U.S. Dept. of Health & Human Services 1998).

At least a third of those reported adverse events were deemed ‘serious,’ and ten drugs receiving FDA approval after PDUFA’s 1992 passage were removed from the market for safety reasons in the four years between September of 1997 and August of 2001. This compares with the *twenty* years (between 1974 and 1993) it took for the same number of drugs to be withdrawn from the market pre-PDUFA (Olson 2002). This indicates that the accelerated review processes seem to have added not-insignificant safety costs.

In addition, troublesome conflict of interest questions have increasingly been raised in connection with FDA approval (Harris, 2005) Many members of the expert advisory panels which recommend to the FDA whether new drugs should be approved turned out to have direct or indirect financial interests in the drug or category of drugs they were asked to evaluate (Cauchon 2000). Even more pointed conflict of interest questions have now been raised concerning British, French and European Medicines Agency (EMA) pharmaceutical approval processes as well, because those authorities have historically invited direct industry participation in the decision of whether to grant licensing approval (Mossialos 2004). The European agencies are also funded far more substantially by fees paid by the pharmaceutical companies they regulate than is the FDA. In 2001, for example, 70% of the EMA’s budget was projected to come from industry fees, whereas only 10% of the FDA’s budget was dependent on industry sources (Garattini and Bertele 2004).

Some of the increase in adverse drug reactions leading to US withdrawals post-PDUFA can be accounted for by the fact that more (and more novel) drug products were being marketed in the 1990s than during the ‘70s and ‘80s (Olson 2004). Nonetheless, an FDA policy switch

which altered the cost-benefit ratio for drug approvals to weight considerations other than unalloyed patient safety, stemming in part from a desire to compete with faster (and more drug industry-involved) European approval policies, had to bear some responsibility as well.

Health care professionals, the pharmaceutical industry, and consumer groups lobbied for five years after PDUFA was passed to persuade Congress to enact additional reform via the Food and Drug Modernization Act of 1997 (FDAMA).²⁴ FDAMA further streamlined and accelerated the whole US review process for new pharmaceutical products, and codified the statutory fast-track approval process for those drugs and biologics targeted for serious or life-threatening diseases which had achieved surrogate endpoints.²⁵ The average time for fast-track drugs to progress from development through approval was in fact reduced by 2 to 2 ½ years soon after FDAMA was enacted (Tufts Center for the Study of Drug Development 2003; U.S. Food and Drug Administration 2003). Congress explicitly lowered the regulatory barrier imposed by the FDA's historically precautionary approval policies in response to pressure to 'get innovative drugs to critically ill patients faster,' and to harmonize global approval processes. By doing so, it moved the US regulatory approach officially closer in spirit to that of its less precautionary and more approval-friendly European counterparts (Wiktorowicz 2003). This has not, however, proved an unmixed blessing for patients, as witness the increased number of recalls (Olson 2004).

The thalidomide tragedy of the early 1960s had illustrated the need for more stringent drug regulatory schemes throughout Europe as well as in the US. Great Britain implemented its

²⁴ 21 USCA § 353a (1998).

²⁵ According to the Tufts Center for the Study of Drug Development (2000), between 1995 and 1999 biotech drugs had faster approval times going through the European Medicines Evaluation Agency than they did being evaluated by the FDA.

own “modern” drug regulatory processes in 1963,²⁶ and its regulatory agencies have generally been influenced more by the demands of industry through a “corporatist tradition of negotiation and accommodation” (Wiktorowicz 2003) than has been seen in the US. British drug and device regulation have recently been merged to create the current Medicines and Health Care Products Regulatory Agency (MHRA).²⁷

The MHRA’s approach toward pharmaceutical companies has been perceived as more precautionary than that of other European countries, notwithstanding the historically corporatist British tradition. (Wiktorowicz 2003). This stems in part from a complex relationship between government and drug manufacturers wherein the Department of Health sets the level of profits which the pharmaceutical industry is allowed to make from drug sales within the country as a whole, but does not (yet?) overtly limit the drugs available for NHS patients (Mossialos, 2004). As the byproduct of a cooperative initiative between industry and a newly safety-conscious British government, the MHRA now has enough influence and resources to enforce heightened safety standards. Although the agency has the capacity to generate stricter standards, it nonetheless still allows the industry to wield critical influence to soften regulatory policy (House of Commons 2005). Some believe this may be inevitable since drug companies provide the largest percentage of MHRA funding through user fees, as is also the case in other European countries (Abraham 2002).

France instituted a formal system of drug regulation in 1945, much earlier than did the British, albeit a system with more limited powers. The legislation required “the pharmacy profession to conduct its activities in the public interest and assume legal responsibility for them”

²⁶ The Committee on the Safety of Medicines (CMS) consisted of a group of experts responsible for reviewing product applications before sending them to the Medicines Division of the Department of Health and Social Security with their recommendations, which issued the actual drug licenses.

²⁷ *About the MHRA* (available at www.mhra.gov.uk/aboutmhra/htm).

(Wiktorowicz 2003), but the government's role in this decentralized system was merely to police the self-regulatory activities of professional and trade associations. These controls have developed into an extensive set of formal rules, which cover most manufacture and marketing processes. Since one of the pharmaceutical industry's goals was to gain increased access to international markets, both government and industry have worked cooperatively to enhance the rigor of the regulatory system – but not too much. When France introduced mandatory review of products marketed prior to 1990, the change failed to provoke any significant industry protest (Wiktorowicz 2003).

The European Union, attempting to bring a measure of uniformity to European drug approvals, established the European Medicines Evaluation Agency (renamed the European Medicines Agency - but retaining the EMEA acronym - for purposes of simplification in 2004²⁸) in the 1990s as a centralized regulatory body to evaluate drugs, devices and veterinary products for all member countries (Garattini and Bertele 2004).

All pharmaceuticals manufactured using certain biotechnological methodologies or utilizing gene therapy must be approved by the EMEA before they can be marketed throughout the EU. In addition, orphan drugs and “any medicinal product containing an entirely new active substance . . . for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disease or diabetes” must now also go through the centralized licensure process.²⁹ Moreover, by May of 2008 all medicinal products intended for treatment of viral diseases, auto-immune diseases and other immune dysfunctions must also be approved by the EMEA. A high degree of scientific expertise and sophistication is necessary to evaluate these treatments, and the requirement for central approval is designed to “preserve

²⁸ Regulation (EC) No. 176/2004 of the European Parliament and of the Council of 31 March 2004 (2).

²⁹ Regulation (EC) No. 176/2004 of the European Parliament and of the Council of 31 March 2004 (8).

the confidence of patients and the medical profession in the evaluation.”³⁰ It also prevents unnecessary duplication of expensive scientific and regulatory expertise throughout the 25 European member countries.

Manufacturers of other drugs can seek EMEA marketing approval as well, and EMEA approval permits the subject pharmaceuticals to be marketed directly in all member states (Mossialos et al. 2004). Manufacturers can still seek local approval through a decentralized process using the member states’ own regulatory mechanisms if they choose, relying on mutual recognition procedures to provide marketing access thereafter in other member states. The expanding scope of mandatory EMEA jurisdiction presages the eventual withering away of most member states’ own evaluative and licensing processes. However, notwithstanding recent constitutional uncertainties, differences in regulatory standards among member states still continue to be relevant. Individual nations tend to compete (for licensing fees) on the basis of whose approval cycle is the fastest and most likely to result in a favorable outcome. This indicates a less-than-meticulous regard for scientific processes of evaluation in some countries (Abraham and Lewis 1999), although they have begun to converge toward a more uniform model since issuance of harmonizing directives and regulations governing the EMEA. In truth, very few applications for approval are actually denied at either the EMEA or the member state level. Most manufacturers prefer to withdraw individual applications if they sense disapproval in the offing rather than having to face an outright central agency rejection. That way they can keep dossier information confidential, and perhaps thereafter apply for approval in a more lenient venue (Garattini and Bertele 2004).

³⁰ Regulation (EC) No. 176/2004 of the European Parliament and of the Council of 31 March 2004 (7).

B. Post-marketing surveillance

The efficacy of post-marketing surveillance leaves much to be desired in both the US and the EU. Theoretically the trade-off for relaxing safety and efficacy requirements pursuant to PDUFA and FDAMA was to increase US pharmacovigilance in the post-marketing period (Noah 2000; U.S. FDA 1999b), but the Vioxx controversy and other recent events have underscored the woeful inadequacy of current post-market safety screening. FDA has had the power to require Phase IV (post-approval) studies when new drug approvals (NDAs) are granted for years, and in fact has conditioned one-third to one-half of its approvals on the manufacturers' agreements to conduct Phase IV trials (21 CFR §310.303(a); Mattison and Richard 1987). Those agreements have been honored more in the breach than in the performance, however, with one study finding that only 13% of those drug companies required between 1990 and 1994 to conduct post-marketing studies had completed them by the year 2000 (Sachich et al. 2000). A more recent Congressional review determined that the FDA required 91 further studies on 42 products approved between 1993 and 2004, but as of mid-2005 only 46 had been completed, while half of the unfinished studies had not even begun.³¹

Manufacturers learn about adverse drug events (ADEs) primarily from adverse drug reports (ADRs) from the physicians and institutions who first detect problems, and then take sufficient interest and the time to notify them and the FDA. In 1993 the FDA introduced the MedWatch Medical Products Reporting Program, designed to encourage doctors to report suspected problems with medical products to the agency voluntarily, as well as to the manufacturer. Although the quantity of ADRs has increased dramatically over the years,³² and

³¹ *Conspiracy of Silence: How the FDA Allows Drug Companies to Abuse the Accelerated Approval Process*, Staff Summary, Rep. Edward D. Markey (D-MA), Energy and Commerce Committee, US House of Representatives, June, 2005.

³² Noah (2000) (from 40,000 reports in 1985 to almost 160,000 in 1996).

in fact went up by 14% between 2003 and 2004 according to recent estimates,³³ underreporting by professionals is still perceived to be the norm rather than the exception.

The FDA has issued several Guidances to Industry designed to support and reinforce timely ADE/ADR reporting, but the promptness and effectiveness of the FDA's post-marketing surveillance still depends on voluntary reporting (even if technically mandatory for manufacturers), and according to informed observers still leaves much to be desired (Struve 2005). Moreover, many have been pessimistic about FDA's willingness and ability to take action on the basis of what it does learn through a flood of often incomplete and sometimes inaccurate ADRs, ADEs and other reports, absent the external pressure generated primarily by media scrutiny following well-publicized patient injuries. Critics point out that chronic understaffing hampers the agency's capacity to do thorough analyses and take appropriate action in all but high-profile or very serious cases (Noah 2000).

The thalidomide disaster of the early 1960s spurred the development of systematic adverse drug reaction reporting throughout Europe as well as in America. Widespread misconceptions about the damaging potential of medications had prevented the medical community from identifying the now-apparent causal relationship between phocomelia and thalidomide when those birth defects first began appearing. In 1963 The Sixteenth World Health Conference passed a resolution reaffirming the "need for early action in regard to rapid dissemination of information on adverse drug reactions" (World Health Organization 1973). The project's goal was to devise a transnational system that would detect "previously unknown or poorly understood adverse effects of medicines."³⁴ The effort produced the WHO Programme

³³ The latest FDA adverse event data is available at <http://www.fda.gov/cder/aers/extract.htm>.

³⁴ Handbook of resolutions and decisions of the World Health Assembly and Executive Board, Vol. 11948-1972. Geneva: World Health Organization (1973), WHO 16.36 Clinical and Pharmacological Evaluation of Drugs.

for International Drug Monitoring, which maintains the world's largest medicine database located in the Uppsala Monitoring Centre in Sweden. This database contains nearly 3 million recorded instances of adverse drug reactions, but once again a paucity of sufficient analysts to make sense of these data hampers their effective utilization.

In 1971 WHO organized a conference on international drug monitoring, advocating creation of national centers for drug monitoring within its Member States (World Health Organization 1972). Shortly thereafter, European nations began to introduce adverse drug reporting systems, largely modeled after Britain's 1964 voluntary patient reporting program, commonly referred to as the "Yellow Card Scheme" (Otero et al. 2000). Today, most European nations employ similar yellow card schemes, and medications have been altered or removed from the market pursuant to these early warning signals.³⁵ However, the systems are often overburdened and understaffed, as has been the case virtually worldwide, which impedes the ability to analyze data and then react appropriately.

The furor over allegedly lax post-marketing pharmacovigilance stirred up by the Cox-2 inhibitor and SSRI controversies of 2004, along with allegations of conflicts of interest infecting FDA drug approval processes in the US, prompted the recently-appointed Secretary of Health and Human Services to establish an independent Drug Safety Oversight Board to monitor pharmaceuticals in early 2005.³⁶ The board, composed of government medical experts and FDA employees, will confer with outside medical experts along with consumer and patient groups in carrying out its monitoring function. Pointedly omitted from those to be consulted are

³⁵ The Yellow Card Scheme linked Remoxipride to spontaneous reports of aplastic anemia, causing the medication be withdrawn from the market after it had been used by 10,000 patients; the non-steroidal anti-inflammatory drug Tiaprofenic acid to acute cystitis; and high lipase pancreatins for cystic fibrosis to colonic strictures in children, a condition that disappeared after the Committee on Safety of Medicines (CSM) recommended against the use of high strength enzymes in 1995.

³⁶ FDA 11/18/04 press release, available at <http://www.fda.gov.cdr/fedreg/fr19921211.txt>.

representatives from the pharmaceutical industry. The Board's primary task at the outset will be to gather and analyze information about drug safety from a broad range of sources (including the public), analyze it, and devise ways to minimize suspected risks and improve drug safety.

Whether it will have adequate staff and expertise to process this information, let alone recommend appropriate remedial action, is a matter of conjecture. Critics contend that this initiative is structurally flawed, and inadequate to cope with the important safety task (Ray 2006).

Direct-To-Consumer Advertising of Prescription-Only Pharmaceuticals (DTCA) is prohibited in the EU (Directive 92/28/EEC³⁷ Article 3). Although no mention of precaution is made in any of the EU regulatory instruments related to DTCA, banning DTCA is clearly a precautionary measure based on the uncertain risks (to economic interests, to patient – doctor communications, to healthcare outcomes, etc.). However, little research has been conducted in the EU on this issue.

By contrast DTCA is allowed in the USA and research carried out by the Centre for Drug Evaluation and Research of the US Food and Drug Administration (US FDA)³⁸ has investigated the impact on the physician – patient relationship with broadly positive conclusions. However, harms have been identified and the evidence of benefits seems

³⁷ Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use. See website <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31992L0028:EN:HTML> (accessed on 22.11.2006)

³⁸ See for example: Direct-to-Consumer Advertising of Prescription Drugs: Physician Survey Preliminary Results 1/13/2003 Kathryn J. Aikin, Division of Drug Marketing, Advertising, and Communications (<http://www.fda.gov/cder/ddmac/globalsummit2003/>)

weak (such as an increased uptake of new drugs with significant benefits to patients [e.g. statins³⁹]).

So with regard to DTCA, the US seems less precautionary than the EU. However, in the aftermath of the Vioxx controversy, both the pharmaceutical industry and Congress have been toying with the idea of banning DTCA for the first two or three years after a new drug has gained approval⁴⁰. The hiatus would provide time for more safety data to accumulate before advertising campaigns stimulate widespread patient demand.

Computerization has somewhat eased the burden on reporting centers on both sides of the Atlantic, and the 2004 EC regulation reorganizing and streamlining EMEA procedures now requires electronic transmission of adverse reaction reports, which helps to simplify their analysis.⁴¹ Britain's MHRA currently operates an Adverse Drug Reactions On-Line Information Tracking (ADROIT) database as well. ADROIT has increased the incidence and effectiveness of reporting, analysis and hazard detection, but its effectiveness is hampered, as elsewhere, by lack of sufficient staffing to do sophisticated analysis of causation and other issues (Bruno, Stricker and Psaty 2004). Although one could argue that the precautionary principle is now at work with

³⁹ However, note that Steven Findlay has commented negatively on the example of statins and elevated blood cholesterol levels example. (Steven Findlay, 2001, *Pharmacoeconomics* 19(2): 109-119) He points out that the number of people taking these medicines has mushroomed in the last two decades and adds "it is entirely possible that the cost of having every American with elevated cholesterol levels take a drug for extended periods (years to decades) would exceed the benefit derived (in reduced fatal and nonfatal cardiovascular events) compared with other interventions, such as insurance-paid dietary counselling programmes." Quoted in "Direct-to-consumer advertising of prescription medicines: a review of international policy and evidence - A report for the Royal Pharmaceutical Society of Great Britain" by Colin Meek - November 2001 See website at: <http://www.rpsgb.org.uk/pdfs/dtcarep.pdf> (Accessed on 23.11.2006)

⁴⁰ Brian Vastag, *Congress Considers Tightening Regulations to Direct- to-Consumer Advertising*, 97 J. of the National Cancer Institute No. 24, 1807 (Dec. 21, 2005).

⁴¹ Regulation (EC) No. 176/2004 of the European Parliament and of the Council of 31 March 2004 (7).

respect to post-marketing surveillance, pharmacovigilance in its present form functions as only a weakly protective mechanism against adverse drug reactions, and a retroactive one at that.

III. Medical Accidents and Patient Safety

Medical accidents, defined for the purposes of this chapter as treatment-caused patient injuries or ‘near misses’, tended historically to be viewed as isolated, rare, and relatively unpredictable events (Leape 1994). Licensing authorities in all countries have usually made sure that physicians met basic standards of education and training before they were permitted to practice medicine, but beyond that historically did little to regulate the quality of care their licensees actually delivered (Jost 1997). The public usually learned about medical accidents anecdotally, if at all, and then often only after a mass disaster or an injured patient had initiated a medical malpractice lawsuit. Although individual hospitals had a somewhat better sense of the prevalence of iatrogenic injury, and payors had a more informed sense of the societal costs of medical accidents, neither tried very hard to prevent patient injury until relatively recently.⁴² These institutional players were reluctant to intervene because physicians had traditionally dominated the health sector (Starr 1982), and legislation prohibiting corporations from practicing medicine reinforced that dominance by raising legal obstacles to many of their ameliorative efforts (Chase-Lubitz 1987).

External oversight for medical accidents was thus relatively sparse and basically reactive in both the US and in Europe until the mid-1980s, and precautionary measures apart from those of the Food & Drug Administration were sporadic. Oversight after the fact of medical injury

⁴² The Leapfrog Group Consortium (2005) of large employer-purchasers of employee health insurance has issued “Purchasing Principles”, including standards for providers designed to improve patient safety. These standards include 24/7 coverage of intensive care units by intensive medicine specialists, computerized order entry of medication orders and referral of patients needing high-risk procedures to medical centers meeting volume criteria. See Freudenheim 2000.

consisted primarily of institutional and professional licensure sanctions (Kusserow et al. 1987; Relman 1985), malpractice litigation (Studdert, Mello, and Brennan 2004; Mohr 2000)⁴³, and occasional reimbursement penalties⁴⁴. These measures were neither effectively proactive, nor sharply focused on anticipating future medical accidents and safeguarding patient welfare (Miller 1997), apart from the odd safety regulation directed to such issues as radiation exposure⁴⁵ or the blood supply.⁴⁶ To the extent that providers failed to improve medical safety on their own,⁴⁷ the public had little choice but to rely on these *ex post* quality control mechanisms. Whatever deterrent effect was generated by retroactive punitive measures and the relatively few instances of direct governmental safety regulation focused on medical treatment was difficult to quantify.⁴⁸

Since little reliable information about the widespread extent and increasingly systemic origin of medical accidents existed, few believed that much of great significance could be done to prevent them.⁴⁹ Accordingly, little pressure for precautionary reforms existed until the US's medical malpractice insurance crisis of the mid-1970s stimulated comprehensive fact-gathering about the extent and severity of medical accidents (United States General Accounting Office 1986). Similar pressure was not felt in Europe because medical malpractice lawsuits were relatively rare, and thus their signaling effect weak. To the surprise of many interested parties,

⁴³ For a comprehensive survey of the medical malpractice liability system and the Harvard Medical Practice Study on New York hospitals, see Weiler et al. 1993.

⁴⁴ 42 U.S.C. § 1320c-2 (1982).

⁴⁵ For example, 21 CFR § 1020.31, *et seq.*

⁴⁶ Groopman (2004) (commenting on two articles on new testing options in same issue of NEJM: Zou et al. (2004) (2004) (on benefits of using \$5 test to reduce the risk of these infections) and Stramer et al. (2004) (on benefits of testing to reduce recipient infection in the window period before seroconversion)). For an account of the post-1982 AIDS policy disputes involving blood screening, see Feldman and Bayer (1999).

⁴⁷ Bosk (2003) (sociological description of the way surgeons recognize mistakes, and penalize those who make them).

⁴⁸ One economist examining the deterrent effect of malpractice litigation estimated that "only a 4 percent reduction in the rate of negligent injury is required to justify the costs of the tort system" (using 1974 estimates of claims frequency and patient compensation). Danzon (1985). See also, Bovbjerg (1986) (general discussion of malpractice litigation's deterrent effects).

⁴⁹ *Quality of Health Care in the United States: A Chartbook*, by Leatherman and McCarthy (2002) contains a number of relatively current medical error study summaries.

the American studies showed that a great deal more medical negligence actually took place - in hospitals at least - than ever culminated in litigation, notwithstanding a more litigious legal culture in the U.S (Bok 1983).

A. Rates of Medical Errors in the US and the EU

Collecting data on iatrogenic injury was especially difficult in the era before computerization, not least because medical care is delivered in fragmented settings ranging from large teaching hospital centers, to doctors' offices, to patients' own homes. The California Medical Society and the California Hospital Association underwrote the first large-scale (27,000 hospital admissions) investigation of the extent and impact of medical error in California hospitals in the 1970s. The study was designed to collect data providing the foundation for medical malpractice reform legislation in that state (Mills 1977).⁵⁰ The cost and personnel requirements required for such comprehensive research undertakings deterred further wide-ranging studies until the New York State Legislature funded the now-famous 1990 Harvard School of Public Health report analyzing adverse medical events in 31,000 New York hospitalizations during 1984 (Harvard Medical Practice Study (1990)). Once again, this research was undertaken to provide the factual underpinnings for malpractice reform legislation in the wake of yet another US medical malpractice insurance crisis, this time in the mid-1980s.

Both the landmark California and New York investigations revealed a surprisingly high incidence of adverse medical events related to hospitalization (4.6% of all hospital admissions in California and 3.7% in New York), and a relatively low incidence of malpractice claims related

⁵⁰ (one in 126 California hospital admissions produced injuries due to negligence, but less than one-tenth of those injuries resulted in a malpractice claim)

to those adverse events the reviewers determined were caused by negligence.⁵¹ A similar large-scale Harvard School of Public Health investigation carried out toward the end of the 1990s in Colorado and Utah produced comparable statistical results both for inpatient injury (Thomas, Studdert and Burstin 2000) and for malpractice claims related to those injuries (Studdert, Brennan and Thomas 2000; Studdert et al. 2000). Numerous other studies on smaller patient bases have produced additional evidence of widespread patient harm caused by medical treatment (Classen et al. 1997; Steel 1981).

The Harvard analyses, comparing medically adverse events with malpractice claims filed within the relevant limitations period (as well as the resolution of those claims), concluded that the tort system was an inefficient means of compensating injured patients (Brennen, et al 1996). These and the many other smaller studies reinforced the insight that far more iatrogenic injury occurs in hospitals than the public perceived (Romano et al. 2003). In the words of three respected researchers writing about the Colorado and Utah findings, who have also analyzed the data on adverse medical events from other investigations, “the burden of iatrogenic injury is large, enduring, and an innate feature of hospital care in the United States” (Studdert, Brennan and Thomas 2003: 1643, 1662; Zahn and Miller 2003).

The latest large-scale analysis of adverse medical events in the US was released in mid-2004 (Health Grades Quality Study 2004). That investigation applied the Agency for Healthcare Quality and Research’s Patient Safety Indicators (Agency for Healthcare Research and Quality 2004) to approximately 37 million Medicare discharges between 2000 and 2002, and then used other peer-validated research techniques (Zahn and Miller 2003) to assess the morbidity,

⁵¹ The Harvard study found that 8 times more negligent adverse events occurred in 1984 than malpractice claims were eventually filed related to those events (Localio et al. 1991).

mortality and costs of the adverse events uncovered.⁵² Its extrapolated findings that “an extra \$19 billion was spent, and over 575,000 preventable deaths occurred as a result of the 2.5 million patient safety incidents that occurred in US hospitals” in those three years were well-publicized, again capturing public attention (Davies 2004).

As patient care has increasingly migrated to out-patient settings over the past two decades, it has carried the burden of medical accident with it. In the case of ambulatory surgery, for example, an investigation of adverse incident reports to the Florida Board of Medicine between 2000 and 2002 documented a startling ten-fold increased risk of iatrogenic injury (including death) for procedures performed in doctors’ offices instead of in ambulatory surgical centers (Vila et al. 2003).⁵³

On the other side of the Atlantic, a four-part television documentary in 2000 entitled *Why Doctors Make Mistakes* (BBC 2000), exposed a similarly high incidence of medical errors in Britain. (Martyn 2000). According to this documentary, 40,000 of the estimated 320,000 adverse medical events occurring there each year kill patients. This equals 10 times the number of people who die yearly in automobile accidents on British roads. *The British Medical Journal* (*BMJ*) also published a special issue in 2000 devoted entirely to medical errors and patient safety, “calling for a rethink of health care systems and training to cut the number of mistakes made by doctors to the low levels observed among pilots or nuclear plant workers.” In a contemporary BBC interview the editor of the *BMJ* attributed many of these problems to

⁵² Health Grades, Inc. (“a health care ratings and services company”) conducted the study, which excluded obstetric patients.

⁵³ Claude H. Organ, the editor of that journal, wrote an editorial six months letter commenting on the controversy the article engendered, and reprinting the American College of Surgeons’ evolving “*Patient Safety Principles for Office-Based Surgery Utilizing Moderate Sedation/Analgesia, Deep Sedation Analgesia or General Anesthesia* (2004).

Britain's faulty "culture in medicine which doesn't quite acknowledge that all these errors happen". (BBC News 2000)

In 2001, a retrospective pilot study conducted by the clinical risk unit of University College London examined 1,000 randomly drawn case records from two hospitals in the London area. Their analysis showed that "10.8% of patients had experienced an adverse event; half of these events were preventable; and a third of adverse events led to either serious complications or death" (Vincent et al. 2001: 517). While this investigation was small and limited to two hospitals, it indicated that adverse medical events appear to be as pervasive in England as they are in the US - perhaps even more so.

These medical mistakes are costly in terms of both the unnecessary suffering and deaths they cause and the resources they drain. They cost Great Britain "approximately £2 billion a year in hospital stay alone, over £400 million in clinical negligence settlements and £1 billion in hospital-acquired infections a year" (Emslie 2002). Despite increased patient safety awareness in recent years, one in ten British patients will still contract a staph infection while in hospital, 40% of which are resistant to antibiotics. Moreover, within Europe only Greece has a higher incidence of hospital-acquired methicillin-resistant staphylococcus aureus M.R.S.A. than has Britain. (Alvarez 2004).

European doctors fail to report medical error adequately, whether for fear of economic consequences, licensure sanctions, or public humiliation, a failing shared by their American counterparts. The voluntary reporting schemes for medical accident almost all countries use, compounded by a lack of sufficient computerization to pinpoint and analyze the causes of iatrogenic injury, are partly to blame. Britain's original 1955 guidelines for reporting medical errors merely required that adverse events (later expanded to include 'near-miss' incidents (Shaw

and Coles 2001)) be reported to a hospital “as soon as possible” (Ministry of Health 1955); that injured parties and witnesses be named; that “the full facts” (Ministry of Health 1955), be provided; and that appropriate action be taken to remedy the situation (Shaw and Coles 2001). But little follow-up apparently took place and the under-reporting persists.

A 1999 survey conducted by Britain’s National Health Service (NHS) demonstrated significant inconsistencies in the frequency and procedures used in incident reporting at local levels (Dineen and Walsh 1999). Similar inconsistencies and communications failures were brought to light during the 1994 *Allit Inquiry* into a hospital’s failure to uncover a serial-killer nurse (Dyer 1994; NHS Executive 1994). They also surfaced in the *Kent and Canterbury Screening Report* of 1997, revealing that cervical screening services failed to detect cancers in hundreds of women (Wells 1997).

B. Policy Response in US and EU

All of these factors and many other investigations have formed the statistical backdrop against which the patient safety movement began to achieve both prominence and momentum in both the United States and Europe as the millennium arrived. As evidence about sub-optimal medical care causing medical accidents was accumulating, medical researchers were simultaneously detecting substantial variations in medical practice that could not be accounted for by demographics or other ‘rational’ scientific explanation. For example, in the US Dartmouth’s Dr. John Wennberg found a 50% variation in the rates of hysterectomy in one geographic market, a 45% variation in the rates of prostatectomy in another one, and a 62% variation in the rates of tonsillectomy in yet another (Wennberg 1984; Wennberg et al. 1982). Lynn Payer’s 1996 book, *MEDICINE AND CULTURE* explored dramatic differences in treatment

modalities among countries as well. Other researchers soon found other evidence of excess, inappropriate and non-validated medical treatment, indicating that the overall quality of both US and European medical care left much to be desired (Chassin et al. 1986; Kemper 1988; Shroeder et al. 1973).

The stage was thus set for government and health insurers to begin ‘managing’ care, using evidence-based practice guidelines (Field and Lohr 1990; Rosoff 1995). These guidelines are standardized specifications for managing clinical problems, ideally developed by the medical profession. They are designed to improve the quality (and presumably the safety) of the medical care that government, health insurers, and employers underwrite. Guidelines are also intended to reduce the cost of care, so that government can offer broader benefits for its covered citizens, insurers can stem the rate of increase in subscriber premiums, and employers will continue to subsidize health insurance for their employees.⁵⁴

Britain’s National Institute for Clinical Excellence (NICE), was established in the past decade to produce evidence-based guidance for Britain’s National Health Service in three areas: clinical guidelines, technology assessment, and diagnostic or therapeutic interventions.

Although NICE was set up to reduce unwarranted variations and improve the quality of British health care, critics contend that it has failed to fulfill its original mandate to identify the most effective, and presumably safe, treatments for medical problems (Maynard et al. 2004; Rao 2004). Some argue that NICE clinical guidelines should take not only cost-effectiveness for individual patients into consideration, but should also take the most efficient and equitable use of

⁵⁴ The US consumer backlash against managed care in the late 1990s dampened private insurers’ enthusiasm for managing care, however, so in the US private payors are for the moment less likely to continue being a strong driving force for quality improvement, and therefore patient safety (See Robinson 2001; Swartz 1999).

limited health care resources for all patients into account since NICE guidelines function as *de facto* requirements for NHS purchasing decisions. (Wailoo, et al 2004) (Devlin, et al 2003).

Differing national ideologies have dictated the way different European countries attempt to prevent and remedy medical errors. England and Scotland, for example, sanction deterring negligence by suing for malpractice, notwithstanding a generally less litigation-prone patient population than can be found in the US. A lawsuit after the fact of medical accident falls short of achieving the theoretical tort objectives of deterrence and compensation in Britain, however, because “less than 1% of people suffering preventable harm receive compensation through the tort system, and there is little relationship between successful litigation and the degree to which negligent practice has contributed to harm” (Runciman 2003:974).

Tort law’s perceived shortcomings persuaded policymakers in several other European nations to enact no-fault compensation schemes for medical accident many years ago. No-fault regimes, whereby a party suffering iatrogenic injury theoretically need only establish a causal relation between medical treatment and subsequent injury in order to recover, have been available for the past thirty years in Sweden, for almost 20 years in Norway, and for lesser periods of time in both Denmark and Finland as well (Gaine 2003). In the words of one commentator, the “socialist legal ideology” of Scandinavia opts for insurance rather than litigation to provide compensation when dealing with medical error (Gaine 2003: 997-998). Several other countries, including England and Scotland, have considered enacting no-fault as well.

These no-fault systems have hardly proved a panacea for injured patients, however, since nearly half of all Scandinavians who seek no-fault redress for medical accident fail to meet the eligibility criteria (Gaine 2003). While Scandinavian doctors do not have to face being hauled

into court when they are implicated in iatrogenic injury cases, provider behavior still matters within the system. Although physicians do not incur monetary penalties for their medical negligence, they report experiencing painful losses of personal and professional integrity when named as parties to medical accident claims (Raef 2002). By way of contrast, “[i]n France, medical negligence claims against the state are handled under an administrative law scheme, separate from the civil justice system, and patient compensation for hospital mistakes is automatic” (Gaine 2003: 997-998).

While post-hoc inquiries into systems failures have increased in frequency and scope since the UK’s first ‘modern inquiry’ was commissioned in 1967, their conclusions about medical accident causality have remained remarkably consistent.⁵⁵ By equating errors with blame, health systems sometimes reprimanded individuals for statistically unavoidable mistakes, yet failed to uncover and prevent often rampant, pervasive and persistent failures within the systems themselves.

Findings of the public inquiry into Pediatric Cardiac Surgery at the Bristol Royal Infirmary published in 2001 (Kennedy 2001), for example, bore a striking resemblance to those reported by the inquiry into “allegations of abuse and ill treatment of vulnerable long stay patients” in Ely Hospital, Cardiff more than thirty years previously. (Department of Health and Social Security 1969). Both investigations described problems of “poor clinical leadership, and isolated and inward looking culture, inadequate management structures and systems, and inadequate recourses” (Department of Health and Social Security 1969). A 2002 article in the *BMJ* concluded that the “consistency with which inquiries highlight similar causes suggests that their recommendations are either misdirected or not properly implemented” (Walsh and Higgins

⁵⁵ A *BMJ* study identified two inquiries in the 1970s, five in the 1980s, and 52 from 1990 through 2002 (Walsh and Higgins 2002).

2002: 894). These reports have been influential not only in shaping more recent British policy, but they have also led to calls for improvement in patient safety throughout much of Europe as well.

In 1998, after almost a decade of little heeded hand-wringing and escalating pleas for reform from expert analysts of medical error, the US patient safety movement finally took off with the Institute of Medicine's (IOM) landmark publication, *TO ERR IS HUMAN: BUILDING A SAFER HEALTH SYSTEM* (Kohn, Corrigan, and Donaldson 1999). The Executive Summary's flat statement that the 98,000 yearly "deaths due to medical errors exceed the number attributable to the 8th leading cause of death" was a riveting show-stopper, which the media immediately picked up and publicized. (The HealthGrades study six years later estimated that the annual number of iatrogenic deaths was in fact almost double that number. *See*, text accompanying note 26, *supra*.) The book's next statement that "[m]ore people die in a given year as a result of medical errors than from motor vehicle accidents (43,458), breast cancer (42,297) or AIDS (16,516)" (Kohn, Corrigan, and Donaldson 1999:1) put the problem sharply in context for a lay audience. Almost immediately a sizeable segment of the public grasped the magnitude of the medical error problem, and public attention became focused for the first time on serious efforts to avert it (Leape 2001). The IOM report was more than just a compendium of adverse medical events and their consequences – it went on to offer "something new" in the way of attacking the prevalence of iatrogenic injury; systems reform designed to forestall it completely.

TO ERR IS HUMAN changed the dynamics of reform rhetoric by down-playing the traditional fault-finding approaches to curing medical error that had achieved only limited success, and showing that defective and inefficient health care delivery systems (as distinguished from mere personal error) could be a large contributing factor to medical injury. The report

sought to refocus reform efforts away from concentrating on fault-finding, blaming and punishment. Instead it advocated devising new systems and incentives for *preventing* errors before they have a chance to materialize.⁵⁶ If the systems approach could increase accountability and avert errors, there would be less need for the relatively ineffective blaming mechanisms of punishment after the fact of medical injury.

The Institute of Medicine followed up public acceptance of that first comprehensive foray into the patient safety issue with a second book, *CROSSING THE QUALITY CHASM: A NEW HEALTH SYSTEM FOR THE 21ST CENTURY* (2001). This second publication sought to capitalize on the spotlight *TO ERR IS HUMAN* had focused on medical error by making thirteen specific recommendations for systems improvement (Institute of Medicine 2001) and articulating “Ten Simple Rules for the 21st Century Health System” (Institute of Medicine 2001). These rules and recommendations are designed to shift provider and payor behavior toward performance predicted to improve patient and population health outcomes.

For example, the IOM stated that “[d]ecision making is based on training and experience” under the current approach, but under the proposed treatment rules decisions would be evidence-based. Few would contest the basic wisdom of utilizing what evidence-based medicine has to offer, but a rule shift from “professionals control care” to the IOM’s proposed ideal that “the patient is the source of control” requires the kind of 24-hours-a-day, seven-days-a-week continuous patient access to care providers that many commentators believe would be impossible to provide. Notwithstanding varying degrees of agreement with its proposed rules and recommendations, the IOM Committee professed that implementing them could help “close the quality gap and save lives.” (Institute of Medicine 2001). Most of the IOM’s recommendations remain aspirational at this stage, and few have yet found expression in formal practice or

⁵⁶ *Cf.*, Latham 2001 (provocative philosophical discussion of the IOM report’s recommendations.)

governmental regulation. The dialogue has however shifted from skepticism about the extent of the medical accident problem⁵⁷ to a cooperative search for solutions to acknowledged shortcomings in patient safety. In other words, precautionary measures have gained credibility as feasible strategies.

Whether the precautionary principle will gain momentum and the patient safety movement will accomplish a significant reduction in iatrogenic injury across the board still remains to be seen (Leape 2005). As safety expert Dr. Donald Berwick observes, “[A]ll improvement is change, and human systems resist change.” “[I]mprovement requires a source of tension, discomfort with the *status quo*, sufficient to overcome this inertia” (Berwick 2002: 1523). A few early bright spots, like the near-universal adoption of the Harvard Anesthesia Standards (which have appreciably reduced the incidence of anesthesia morbidity and mortality worldwide) show what can be achieved to improve the safety of narrowly-targeted high-risk procedures on a systems-wide basis (Eichhorn 1986).

That example bears repeating for the lessons it teaches. When the Harvard teaching hospitals began self-insuring for medical malpractice at the end of the 1970s, they analyzed where their losses were greatest, and what could be done to reduce them. Once they pinpointed that approximately 35% of their malpractice payouts were going to the 5% of their claims related to anesthesia accidents, the motivation to improve that ratio was strong. The stimulus to improve safety arose from a genuine desire to protect surgical patients from the devastating consequences of anesthesia mishaps, but an equally strong spur was economic self-interest. In essence, the Harvard teaching hospitals now had to pay for their own mistakes directly because they were underwriting their own liability insurance.

⁵⁷ Michael L. Millenson (2003) blames the medical profession for “failing to take corrective actions . . . and failing to discuss openly the consequences of that inertia.”

Harvard Medical School's Anesthesia Department accordingly analyzed every anesthesia accident occurring in recent years, and then devised eight "minimal standards" for patient monitoring during anesthesia designed to improve safety in all Harvard surgical suites. The first two standards were hardly revolutionary. They merely required that: 1) an anesthesia specialist remain in the operating room with an anesthetized patient at all times during surgery, and 2) there be continuous monitoring of patients' respiratory and cardiac functions as long as they remain anesthetized. Those unfamiliar with surgical suite procedures were startled to realize that those two simple safety rules had not been observed routinely before. The Harvard hospitals then mandated implementation of these eight standards in all of their operating rooms. Almost immediately the anesthesia accident rate dropped so significantly that the system's costs for insuring anesthesiologists for malpractice plummeted. Little more than two months after Harvard's implementation experience was published in JAMA, the American College of Anesthesiology adopted them as recommended procedures for all operating rooms..

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) now all but forces hospitals to implement similar anesthesia standards as a condition for accreditation. JCAHO accreditation is in turn all but required for a facility to be certified for reimbursement under the federal Medicare program (42 USC §§ 1395 x (e), 1395 bb), and most states have built JCAHO standards into their requirements for facility licensure as well (Tex. Health & Safety Code §222.024). The Harvard anesthesia standards are thus *de facto*, if not *de jure*, governmental regulatory requirements. The evidence supporting the dramatic difference their implementation makes is so strong that they have also been adopted as ideal patient safety precautions for operating rooms worldwide.

Recent attention to patient safety in the EU can be largely attributed to the release of *TO ERR IS HUMAN* in the United States, which prompted the international news media to focus on the extent of medical accident all over the globe. Soon afterwards, a group of experts on adverse events from Britain's National Health Service (NHS) produced the widely celebrated report *Organisation with a Memory* (Department of Health 2000), calling for a mandatory patient safety reporting system. Health Minister Lord Hunt introduced the National Patient Safety Agency shortly thereafter, advocating a fundamental change in organizational culture within the NHS "from one of individual blame to one of organizational accountability" (Emslie, Knox and Pickstone 2002). Articulating the parallel between the airlines and the health industry, Health Minister Lord Norman Warner later asserted that, "most problems affecting patient safety occur as a result of weaknesses in systems and processes, rather than the acts of individuals" (Emslie, Knox and Pickstone 2002). In aviation maintenance, which also relies on individuals to perform high-risk activities, "some 90% of quality lapses were judged as blameless" (Reason 2000: 768-770).

In February of 2004 the British National Patient Safety Agency (2004) initiated the first country-wide patient safety reporting program, the National Reporting and Learning System (NRLS). Frankly modeled after the aviation industry practices advocated by the Institute of Medicine, the program is founded on the premise that human error is inevitable and systems can be designed to help protect against them (Reason 2000). The NRLS coordinates the activities of local risk management systems in order to identify and analyze national trends. Importantly, it functions anonymously and is divorced from disciplinary procedures in order to encourage reporting (Reason 2000). Again, the model is aviation's non-punitive reporting systems; as these have proliferated, the number of serious airplane accidents has markedly declined.

This shift toward preventing error by reforming systems has thus resonated throughout Europe as policymakers have become increasingly aware of medical error's prevalence, echoing the similar movement in the US. That politicians are at last publicly focusing on this issue marks a dramatic change in approach, because professional self-regulation and after-the-fact legal remedies rather than precautionary policies were previously thought sufficient to protect patients (Leape and Berwick 2005). The patient safety movement is still in its infancy, however, and cannot yet be considered an example of precautionary activity in the true regulatory sense.

V. Conclusion

The precautionary principle has not been a widely adopted health sector concept on either side of the Atlantic. Until fairly recently most medical accidents were not thought to be foreseeable, and therefore were not considered responsive to precautionary measures. Empirical research over the past several decades has revealed the pervasive, predictable and often systemic nature of iatrogenic patient injury, however, and attempts to improve patient safety are now being undertaken in both America and Europe. Since most patient safety initiatives are still voluntary, they are not currently being addressed in precautionary principle terminology.

Neither the US nor the EU can accurately be considered more rigorous in its current approach to safety improvement, because the movement is relatively new. Both are keenly interested in observing the improvement efforts their opposite numbers are attempting, however, not least because both have substantial financial stakes in the costs of medical accidents. One can predict that their regulatory approaches will be more likely to converge than to diverge in the future, whether or not they are officially articulated in terms of the precautionary principle.

With respect to drug regulation, the situation is somewhat different. The US Food and Drug Administration has traditionally taken a more cautious stance when licensing pharmaceuticals than have its European counterparts, and thus precautionary principle terminology carries more resonance with respect to drug and medical device licensing in America. In recent years, however, under pressures from medical activists for faster access to experimental drugs and from the pharmaceutical industry for accelerated approval policies as the drug industry globalizes, the FDA has relaxed its comparatively rigorous regulatory barriers. At the same time, the EU has increasingly centralized its drug approval processes, tightening the standards in use by some of the less safety-focused member states, but not appreciably raising the level of rigor already in effect in others.

Current highly-publicized controversies concerning widely used pain medications, antidepressants and medical devices have recently precipitated a reassessment of drug approval and oversight policies on both sides of the Atlantic. As additional data accumulates, US and EU drug approval policies - as well their patient safety initiatives - are more likely to converge toward increased rigor than to grow any further apart.

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