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INTRODUCTION

Joseph Lister, Ignaz Philipp Semmelweis, Albert Woolley, and Cecil Roe are probably the most famous names linked to the history of contamination. While Lister and Semmelweis evidenced, in 1850–1860, the importance of asepsis in dealing with surgical instruments and patients to avoid infections, Woolley and Roe were victims of contamination with a chemical contaminant inadvertently infused during spinal anesthesia 100 years later, in 1947. In the late nineteenth century, practices such as hand washing with a solution of chlorinated lime to reduce the incidence of fatal childbed fever, and spraying instruments, surgical incisions, and dressings with a solution of phenol to reduce the incidence of gangrene were neither accepted nor recognized as means of avoiding the transmission of microorganisms. Microbial contamination was simply not an issue. In contrast, a chemical contaminant delivered to Woolley and Roe along with an anesthetic, which caused both to become paraplegic, was recognized as such, although the explanation for the case does not seem fully plausible and has not been totally elucidated even today. Curiously, it was the phenol solution, in which the ampoules of the anesthetic had been immersed for asepsis, that was the supposed contaminant! According to the trial conclusion, contamination occurred by the penetration of the contaminant through invisible cracks in the glass ampoules of the anesthetic.

Nowadays, microbial contamination is, with rare exceptions, well recognized through immediate and specific bodily reactions. Chemical contamination, on

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the other hand, is not so widely recognized, except when ill-fated episodes like the Woolley and Roe case occur. Chemical contamination rarely provokes an acute bodily reaction, and therefore, its manifestation is not promptly linked to the contaminant. This absence of an immediate response hampers the recognition of chemical contamination, making a substantial amount of evidence necessary in order for the effect of a chemical to be acknowledged and measures for its eradication to be taken. Aluminum was irrevocably recognized as causative of dementia dialytica in 1976, 3 years after clinical manifestations of the syndrome had emerged. The water used for hemodialysis was considered to be the primary source of aluminum, but it was only after 20 years that precautions to eliminate aluminum in the water were routine and the syndrome ceased to be a threat. In other situations, even when data indicate the presence of a contaminant and research has demonstrated that it could be harmful, risks are taken because no viable or satisfactory solution exists. Diethylhexyl phthalate, a polyvinyl chloride (PVC) additive that makes the polymer flexible and functional is recognized as causing infertility and endocrine disruption in rats. Despite all studies indicating this hazardous effect, it is still the chief plasticizer for the PVC used in medical devices such as infusion lines and catheters. A strong argument favoring its permanence is that, without plasticizers, PVC is useless and substitute candidates could even be more hazardous than the phthalate itself.

Physical contamination, a third type of contamination, entails the presence of solid particles suspended in liquid formulations. Particulate matter is a problem because the introduction of particulate matter into the bloodstream may result in phlebitis or cause damage to vital organs. The most common particulates in intravenous preparations are glass fragments, from the opening of glass ampoules, particles from rubber stoppers and intravenous equipment, and particles from plastic syringes.

Of all the recalls linked to contamination issued by the United States by the Food and Drug Administration over the last 5 years (2007–2011), 33% were due to particulate matter, demonstrating that, although it may be controlled through careful inspection, this is not a solved problem (Fig. 1.1).

Of the remaining recalls, 32% were related to microbial contamination and 29% were related to chemical contaminations. Contributing to increased rates of chemical contamination were the recalls of toothpaste (contaminated by diethylene glycol) in 2007, heparin (contaminated by oversulfated chondroitin sulfate) in 2008, and Tylenol (contaminated by 2,4,6-tribromoanisole) in 2010. The remaining 2% of chemical contamination involved iron in a lens care solution and a cross contamination of several drug products by penicillin.

With the advent of biopharmaceutical drugs, new modalities of contaminants have arisen. Since most of them are proteins, minimal changes in their conformational structure are sufficient to introduce a new entity in the formulation, which, able to trigger adverse reactions, is deemed to be an undesirable species and therefore a contaminant. Allergic and adverse reactions accounted for more than 40% of recalls over the last 5 years (2007–2011) (Fig. 1.2).

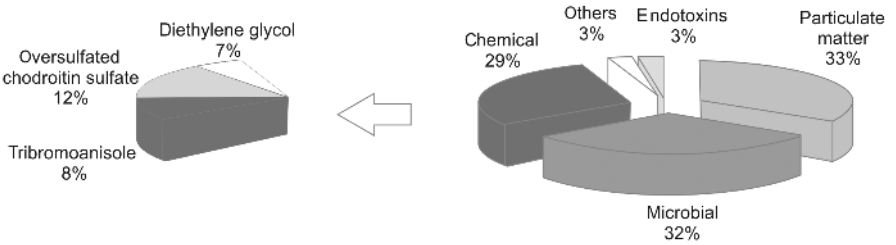

FIGURE 1.1 Food and Drug Administration drug recalls linked to contamination over the last 5 years (2007–2011).

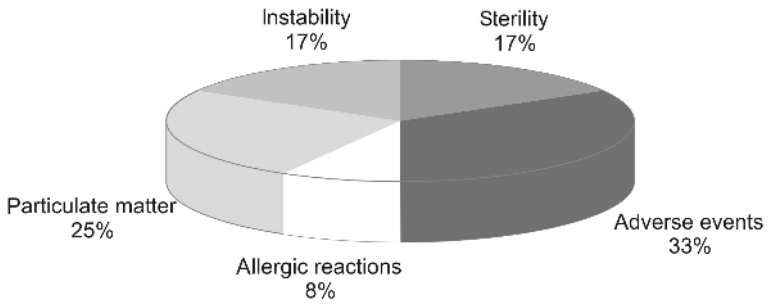

FIGURE 1.2 Food and Drug Administration biologic product recalls linked to contamination over the last 5 years (2007–2011).

The number of drug recalls due to contamination over the last 5 years clearly indicates that contamination of drug products is a topic that demands discussion (Fig. 1.3). Thus, the goal of this book is to gather together data regarding contamination sources associated with the production, storage, and delivery of pharmaceuticals.

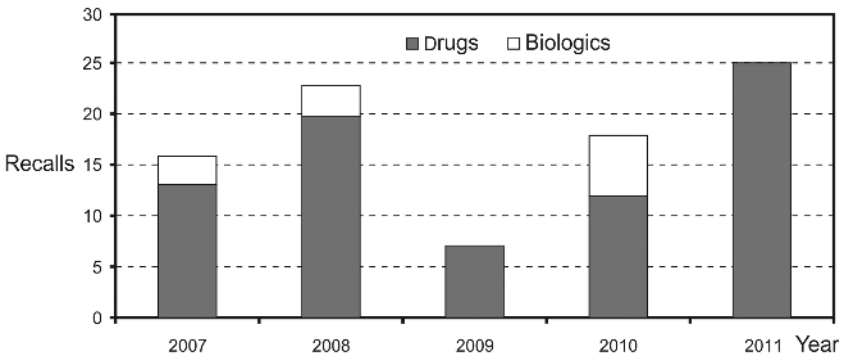

FIGURE 1.3 Number of drug recalls due to contamination over the last 5 years (2007–2011).

Below is a brief synopsis on Lister and Semmelweis's discoveries and the Woolley and Roe case.

Joseph Lister was born on April 5, 1827 in Upton, England. He entered the University College of London in 1844 and received his college degree in 1847, at the age of 20. When Lister began his education, there was a mortality rate of over 50% for surgery. He dedicated his career to changing the hitherto accepted conventions of surgery.

He began researching inflammation. Lister was aware that inflammation was the first stage of many postoperative conditions and, although many theories of inflammation existed, almost all of them were devoid of facts. Lister studied the varying effects of irritation on the skin and the resulting inflammation. His conclusion was that "the tissues of the affected parts have experienced to a proportionate extent a temporary impairment of functional activity or vital energy," and, in 1857, he published "An Essay on the Early Stages of Inflammation."

In January 1860, Lister became Regius Professor at the University of Glasgow. As a professor of surgery, he encountered extreme filth and unfavorable conditions in the wards of Glasgow Hospital. The problem that vexed Lister the most was that of sepsis following compound fractures, a fracture in which the skin is broken and the bone is exposed. Such a problem required surgery and had an extremely high mortality rate, especially when the individual remained in the hospital following the surgery.

In 1865, he read about the work done by Louis Pasteur on fermentation and microbes. Based on Pasteur's ideas, Lister deduced that wounds had to be thoroughly cleansed to avoid the entry of germs into the body. He tested spraying instruments, surgical incisions, and dressings with a solution of phenol, which at that time was used to deodorize sewage. He used it on a small boy with a compound fracture in his leg. The wound did not suppurate following surgery, and the only injury was that the acid burned the boy's skin. Lister explained the case and subsequent ones in a series of articles on the "Antiseptic Principle of the Practice of Surgery" in the *British Medical Journal*. Lister was also able to successfully remove abscesses, a surgery considered an unnecessary risk during those days, with astonishing survival rates. The number of patients operated on by Lister who died fell dramatically from a rate of 46% to 15% after the introduction of Lister's asepsis measures.

By 1890, nearly the entire surgical community had accepted Lister's innovation, and microbes that caused sepsis had been identified and cultured. Lister died on February 10, 1912.

Ignaz Philipp Semmelweis was born in Buda (now Budapest), Hungary, on July 1, 1818. He received his education at the University of Pest between 1835 and 1837.

In 1837, Semmelweis moved to Vienna and studied at the Second Vienna Medical School. He completed his studies in 1844 and remained in Vienna after graduation, becoming an assistant in the First Obstetrical Clinic of the university's teaching institution, the Vienna General Hospital (Wien Allgemeines Krankenhaus). In July 1846, Semmelweis became the titular house officer of the First Obstetrical Clinic, and his numerous duties included assistance with surgical procedures and clinical examinations. One of the most pressing problems he faced was the high maternal and neonatal mortality due to puerperal fever. Curiously, however, the Second Obstetrical Clinic in the same hospital exhibited a much lower mortality rate. The difference between them laid in their functions. The First Obstetrical Clinic was used for teaching medical students, while the Second Obstetrical Clinic was for the instruction of midwives. No clear explanation for the difference in mortality rates was forthcoming. Most women at the time delivered at home, but those who had to go to hospitals due to poverty, illegitimacy, or birth complications were exposed to high mortality rates. The disease was considered to be an inevitable aspect of contemporary hospital-based obstetrics, a product of unknown agency operating in conjunction with elusive atmospheric conditions. Semmelweis was severely disturbed that his First Clinic had a much higher mortality rate due to puerperal fever than the Second Clinic.

In 1847, Jakob Kolletschka, his friend and a professor of forensic medicine, died after being accidentally punctured with a scalpel while performing a postmortem examination. Kolletschka's own autopsy revealed a pathological situation similar to that of the women who were dying of puerperal fever. Semmelweis made a crucial association. He promptly connected the idea of cadaveric contamination with puerperal fever. He concluded that doctors and students carried the infecting particles on their hands from the autopsy room to the patients they examined during labor. This startling hypothesis led Semmelweis to devise a novel system of prophylaxis in May 1847.

Realizing that the cadaveric smell emanating from the hands of the dissectors reflected the presence of the incriminated matter, he instituted the use of a solution of chlorinated lime for washing hands between autopsy work and examination of patients. Despite protests, Semmelweis was able to enforce the new procedure vigorously and, in barely 1 month, the mortality from puerperal fever declined from 12% to 2% and remained low for the time his methodology was in practice.

In spite of the obvious conclusion, Semmelweis's observations conflicted with the established scientific and medical opinions of the time. Some doctors were offended at the suggestion that they should wash their hands, and Semmelweis could offer no acceptable scientific explanation for his findings. In 1861, Semmelweis published his discovery in the book *Die Ätiologie, der Begriff und die Prophylaxis des Kindbettfiebers* (*Etiology, Understanding and Preventing of Childbed Fever*), which received a number of unfavorable foreign reviews.

In July 1865, Semmelweis suffered what appeared to be a form of mental illness and was committed to an asylum, the Niederösterreichische Landesirrenanstalt, in Wien Döbling. He died there only 2 weeks later, on August 13, 1865.

On Monday, October 13, 1947, two patients, *Albert Woolley* and *Cecil Roe*, who were on the same operating list for a surgical procedure, developed permanent paraparesis following spinal anesthesia administered by the same anesthetist. Both patients sued the hospital and the anesthetist. At the trial, in October 1953, the court accepted evidence that the paralysis had been caused by the phenolic sterilizing solution seeping through invisible cracks in the glass ampoules of cinchocaine, the anesthetic. The court concluded that, because the anesthetist could not have been expected to know about this hypothetical risk, there had been no negligence.

An editorial in the *British Journal of Anaesthesia* at that time considered the sequence of events to be unlikely and thought it more probable that there had been contamination of the anesthetic with a different chemical. Dr. Malcolm Graham, the anesthetist, did not believe the "invisible crack theory" or the role of phenol. Phenol was known to be a chemical irritant, but no one was aware at that time of the effects of a solution of phenol in the subarachnoid space. Additionally, 1 year after the trial, the use of intrathecal phenol for the treatment of chronic pain was reported, which means that the neurological damage would be alleviated rather than caused by phenol.

In 1990, the case was critically reevaluated by Dr. Hutter [1]. His findings provided a more logical explanation for the events. He concluded that there is no doubt that the neurological damage was caused by a chemical contaminant, but that it was a mineral acid rather than phenol. Hydrochloric acid from a sterilizer could have been the contaminant. The ease with which contamination could happen, and the relatively small volume of acid that would have been required, makes this a realistic possibility. He hypothesized that the sterilizer would have been contaminated with acid on the Monday morning if, as a part of routine weekend maintenance, it were descaled (with the acidic solution) and the person undertaking this duty had forgotten to drain and wash out the acid. Needles and syringes placed into the sterilizer containing the acidic solution instead of ordinary water would have become contaminated and then used by the anesthetist.

While the reassessment conducted by Dr. Hutter absolved phenol, it continues to be accepted that the cause was some sort of chemical contaminant.

REFERENCE

1. Hutter CDD. The Woolley and Roe case. Anaesthesia 45, 859–864, 1990.