

Hy's Law

People have been medicating themselves and poisoning each other, and vice versa, for thousands of years; however, there is no doubt that the era of greatest therapeutic misadventure thus far is currently upon us, at least in affluent developed countries. That is not to say that the concoctions of ancient pharmacopeias were safer than the drugs of today—but morbidity and mortality caused by medications,¹ mostly from side effects but also because of erroneous prescription or inappropriate administration,^{2,3} have created a silent epidemic of great concern to health policy makers,⁴ health care givers,^{5,6} and even patients.^{7,8} That such events occur should be no surprise, because drugs, poisons, and toxins have much in common—except, one hopes, for the “therapeutic intent” of the “prescriber.” Like medicinal potions, poisons are usually administered orally, albeit surreptitiously; in fact, the word itself derives from the Old French *puison*, which originally meant “a drink” or “a draught,” and later, in the 14th century, was used to refer specifically to poisonous draughts. As with drugs, poisons and toxins may also be given parenterally, usually delivered by a remotely guided missile (*e.g.*, a dart or an arrow) but occasionally at short range on the sharpened tip of an umbrella or walking stick. The latter device is much-favored in the “cloak and dagger” world of international espionage, as was the case with the ricin murder of Bulgarian dissident Georgi Markov in 1978 on London’s Waterloo Bridge, which was presumably initiated by the KGB. The word *toxin* is derived from the Greek word for bow (τόξον), the weapon of their oriental enemies, often used to shoot arrows tipped with poisons. Poisons may also be administered by inhalation, as occurred in the tragic poisoning with sarin gas in three Tokyo subways in 1995. In contrast, poison administration through the external ear, which was exhibited in the murder of Hamlet’s father and made possible because of the common occurrence in the Middle Ages of chronic otitis media (as presumably Shakespeare knew), is a distinctly unusual practice nowadays even in the pages of Patricia Cornwell novels.

It is only fair to point out that the medication–poison sequence is not a one-way street, because poisons have also been used as cures from ancient times to the present. Aureolus Phillipus Theostratus Bombastus von Hohenheim (1493–1541), immortalized as Paracelsus,⁹ rea-

soned that “All substances are poisons; there is none which is not a poison.” Paracelsus thought that it was dose alone that differentiated a poison from a remedy, thereby preempting by 500 years what we now refer to as true, predictable, or intrinsic hepatotoxicity.¹⁰ His dictum “Dosis sola facit venenum” (“the dose alone makes the poison”) guided Paracelsus in the use of mercury to treat syphilis, for which he was denounced in his day but which nonetheless remained the therapy of choice for the next 300 years until Erlich’s discovery of arsenic-derived arsphenamine (Salvarsan) in 1910.¹¹ Many modern drugs are also derived from poisons, starting with the neuromuscular blocking agents that followed naturally from Claude Bernard’s famous experiments with curare,¹² the poisonous alkaloid found in the South American vine *Chondrodendron tomentosum* that was said to have been brought to Europe first by Sir Walter Raleigh. The host of antitumor antibiotics used in clinical oncologic practice today, all derived from “natural” products^{13,14} (mostly plants, fungi, and bacteria), lends support to Paracelsus’ hypothesis of poisons, and includes asparaginase, a bacterial enzyme; etoposide, a semisynthetic derivative of podophyllotoxin from the stems and roots of the mayapple (*Podophyllum peltatum*); irinotecan, isolated from the Chinese ornamental tree *Camptotheca acuminata*; paclitaxel, a taxine originally obtained from the bark of the Pacific yew tree *Taxus brevifolia* (now made synthetically); vincristine and vinblastine, vinca alkaloids from the Madagascar periwinkle *Catharanthus roseus*; and the anthracyclines bleomycin, dactinomycin, daunorubicin, mitomycin, and others isolated from various *Streptomyces* species, to name but a few.

The proclivity of humans to seek cures for their ills in the worlds of nature and alchemy appears to have been as strong and universal among the ancients as it is today, judging by the content of their documents that have survived on clay tablet, papyrus, silk, and parchment from Mesopotamia, Egypt, China, and Europe, respectively. The Egyptian Papyrus Ebers, dating from 1500 BCE, set forth 811 prescriptions in the form of salves, plasters, and poultices; snuffs, inhalations, and gargles; and fumigations, suppositories, and enemas—all derived from minerals, plants, and so-called “organic” material that “plumbs the depths of human credulity”¹⁵ and does not bear description here. The extensive *Materia Medica* of Chinese medicine¹⁶ (itself predated only by the medicine of Babylon and Egypt) was well-documented (over 1200 drugs) in the centuries between 1100 BCE and 659 CE, in the Wu Shi Er Fang and the Herbals of Shennong and

Tang, as was the Indian Ayurvedic System^{17,18} on which the Gyu-zhi of 8th century CE Tibetan medicine was based. Plainly, physic in Western medicine began with the Greeks and Romans as described in the Hippocratic writings of approximately 400 BCE, and in the contributions of both the philosopher-scientist Theophrastus (approximately 300 BCE) and the peripatetic physician Dioscorides (1st century CE), as well as with Claudius Galen (131–201 CE) and his complex medicinal concoctions or “galenicals.” During the Dark and Middle Ages, the remedial expertise of Greco-Roman civilization was preserved in the monasteries of England, Ireland, France, and Germany but was promoted by the Arabs, as exemplified by the *magnum opus* of the Persian physician, philosopher, and poet Abu Ali al-Husain ibn Abdallah ibn Sina (981–1037 CE),¹⁹ who was known as Avicenna, the Prince of Physicians, in the Persian empire; and by the voluminous writings of the physician, philosopher, and rabbi Moses ben Maimon (1135–1204 CE),²⁰ who was known as Rambam or Maimonides.

It is tempting to dismiss the pharmacopeias of old simply as collections of potentially dangerous nostrums and placebos, as Voltaire hinted when he described the art of medicine as a means of “amusing the patient while nature cures the disease.” Despite the contemporary penchant for so-called “alternative” or “complementary” medicine, it is salutary to note that approximately 80% of the world’s inhabitants still rely mainly on traditional medicines for their primary health care.²¹ Also, many of the important medications now in use in developed countries were discovered as a direct result of isolating the active principles from plants used in traditional medicine, which over the centuries has given us drugs used to treat malaria, pain, heart failure, dysrhythmias, hypertension, infection, depression, cancer, and, of course, constipation.²² Yet for all the apparent perspicacity of the healers and apothecaries of old, it was difficult for them to recognize the toxic effects of their remedies. Alexander the Great came close to the mark when he complained that he was “dying from the treatment of too many doctors.” (In truth, he probably died of alcoholic pancreatitis!)

It may come as a surprise nonetheless to learn that the phenomenon of hepatitis due to drug sensitivity was not firmly established until the mid-20th century. In the Lowell Lectures delivered in Boston, Massachusetts, in March 1947,²³ Himsworth felt it necessary to present the case of a 37-year-old woman suffering from thyrotoxicosis who developed a severe illness that was indistinguishable from infective hepatitis and was characterized by fever, jaundice, and hepatomegaly after a second test dose of aminothiazole was given (a transient fever caused by the first dose had been disregarded). At the time of Him-

sworth’s practice, the hepatotoxicity of chlorinated hydrocarbons (*e.g.*, chloroform) was recognized²⁴ (although it had taken almost 50 years to do so²⁵), the risk of liver and kidney necrosis caused by phosphorus and arsenic was well known,²⁶ and the fatality of mushroom poisoning had been appreciated since the time of the Roman Empire,²⁷ at least. It is not certain when drug hepatotoxicity was first recognized as an entity, but it may have been Bang’s observation in 1774²⁸ of an association between chronic liver disease and arsenic, the use of which was fashionable then as a drug and cosmetic. During the first half of the 20th century, incidental occurrences of hepatic drug injury began to be noticed, like the first case of an idiosyncratic reaction on re-exposure in a patient who had taken cinchophen for gout,²⁹ and the first 12 cases of drug-induced cholestasis³⁰ when arsphenamine was still being prescribed for syphilis. During the third quarter of the 20th century, practitioners noticed that an increasing number of drugs injured the liver, and they published their observations as case reports and in small series. The distinction between intrinsic hepatotoxicity and what Hippocrates called *idiosyncrasy*, referring to a person’s own peculiar (constitution *ιδιος* (idios) one’s self, *συν* (syn) together, *κρσις* (crasis) mixture) was acknowledged and the range of hepatotoxic drug reactions was extended to include cholestasis, steatosis, and even tumors. Studies on the mechanisms, prevention, and treatment of drug hepatotoxicity were initiated and monitoring and regulatory agencies were enfranchised in many countries. Yet the field lacked cohesion, systemization, and leadership until 1978, when the publication of his now landmark monograph on hepatotoxicity³¹ established Hyman J. Zimmerman as the doyen, guru, oracle, and high priest of that realm.

Hyman Joseph Zimmerman, or “Hy” to all who knew him (Fig. 1), was one of the most beloved and respected members of the founding elite of hepatology in the second half of the 20th century. The twinkling eye, warm disposition, magnetic charm, signature bow tie, gravelly voice, and Edward G. Robinson-like countenance and stature made this “Little Caesar” of hepatotoxicity unique and always recognizable, no matter how large the gathering. Hy was born, raised, and educated in Rochester, New York, but he was given the chance to study medicine in the balmy clime of Stanford, California, as an unexpected consolation or bonus for the ethnic (Jewish) quota that precluded his admission to medical school in his oft-snowbound native city. Drafted into the army during World War II, he completed his medical studies on a reserve commission. Then, after superb training in tropical medicine that the army had arranged, and with the vision, insight, and planning that only the military mind



Fig. 1. The four faces of Hy Zimmerman (July 19, 1944–July 12, 1999). **Above left:** Outside the 239th General Hospital at Châlons-sur-Marne during his military service in World War II in a composite picture created by his son Philip from contemporary photographs. **Above right:** Teaching on ward rounds. **Below left:** For his sayings, he was known as Chairman Hy. **Below right:** Hy was devoted to his wife Kitty, here shown in a photograph by Ms. Robin Megibow.

can exercise, Hy was sent to a field hospital in France at Châlons-sur-Marne, near the venue of the Battle of the Bulge. There, while some of his superiors were engaged in their own personal evaluation of the neuropsychiatric effects of fermentations of the grape and the barley, he was free to treat and study over 300 soldiers with acute infective hepatitis, which resulted in a seminal publication³² (the second in his distinguished bibliography) and a personal commitment to hepatology. His first article on drug hepatotoxicity came just a few years later,³³ to be followed by over 100 more publications on his chosen topic alone in his career. During his time in the army, he exploited his fondness for animals and his disdain for pompous authority by naming one of his dogs Colonel, which gave him the excuse to create the illusion of shouting and even cussing at a superior officer without fear of retribution.

Soon after leaving military service, Hy began his 50-year attachment to the Veterans' Affairs hospital system and his cherished association with the liver pathologists at the Armed Forces Institute of Pathology in Washington, DC. In an illustrious career that included chairmanships of departments of medicine, memberships of numerous associations and societies, service on editorial boards, and consultation for study groups, government agencies, and pharmaceutical firms, he was one of the very few Distinguished Physicians of the Veterans' Affairs system and was a recipient of the Distinguished Achievement Award of the American Association for the Study of Liver Disease.³⁴ He was a famed teacher whose many anecdotes, maxims, and epigrams were sometimes referred to as "the sayings and aphorisms of Chairman Hy" (Fig. 1).

In *Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver*,³¹ Hy succeeded in producing the most comprehensive catalogue of adverse drug reactions in the liver available at the time of its publication, based on facts retrieved from his almost insatiable consumption of the medical literature and drawn from his extensive experience as a consultant. His legendary astronomical memory and uncanny ability to see pattern and order among that morass of data allowed him to specify the characteristics of drug-induced liver injury and thereby to construct a classification scheme that is still valid today. Hy's scheme readily lends itself to modern mechanistic explanations using recent discoveries in cellular and molecular biology.³⁵ While he clearly distinguished between intrinsic and idiosyncratic hepatotoxicity, he also emphasized that his was an oversimplification, as there is a spectrum of adverse reactions between the two pure extremes. Host factors can modulate the impact of intrinsic hepatotoxicities, as has been shown by the effect of high chronic alcohol consumption on acetaminophen hepatotoxicity,³⁶ and there are growing numbers of examples. Also germane to the classification of drug hepatotoxicity was the appreciation of the many differences, especially in outcome, between hepatic and cholestatic drug reactions. He also pointed out that drugs can cause cholestasis by a variety of mechanisms that differ depending on the intrahepatic site where the brunt of the injury falls³⁷ (*e.g.*, hepatocellular, hepatocanalicular, ductular cholestasis, and so forth).

Perhaps more important than any of the foregoing insights was Hy's unique realization that when drug-induced hepatic reactions cause sufficient hepatocyte injury to affect global liver function and, in particular, to cause jaundice because of impaired bilirubin transport by the liver, the hepatotoxicity of this severity is likely to lead to patient death, especially if the offending drug is not stopped.³⁸ Stated more simply, Hy's rule was that aminotransferase elevation accompanied by bilirubin elevation (without significant alkaline phosphatase elevation) can be ominous, whereas aminotransferase elevation alone may be less specific in detecting serious injury. The importance of this simple rule was not lost on the officials of the U.S. Food and Drug Administration (FDA), who are naturally concerned about any drug hepatotoxicity that can lead to death. Over the years, the approval of several drugs has been refused (*e.g.*, ibufenac, perhexiline, dilevalol, and tasosartan), other drugs have been withdrawn after approval (*e.g.*, iproniazid, ticrynafen, benoxaprofen, trovofloxacin, bromfenac, and troglitazone), and still more bear serious warnings that limit their use, all because of hepatotoxicity.³⁹

Although guidelines for detection of hepatotoxicity due to drugs and chemicals were discussed over 20 years ago at a Fogarty conference,⁴⁰ these have not been entirely satisfactory in striking the balance between the overconservative approach, in which patients may be deprived of an important and relatively safe drug, and the other end of the spectrum, in which severe liver injury is discovered only after a drug has been approved and marketed. With this dilemma in mind, Dr. Robert Temple, Director for Medical Policy at The Center for Drug Evaluation and Research of the FDA, concluded long ago that Hy's simple prediction about the outcome of jaundice with hepatocellular enzyme elevation was valid and useful. Thus he elevated it to the status of a law (which he dubbed "Hy's Law") under which the FDA has been operating to a great degree for many years.³⁹ Clearly this practice is somewhat arbitrary, and modifications will be needed to enhance specificity and sensitivity and to ensure validity. It is hoped that this will be achieved by the recently funded NIH National Institute of Diabetes, Digestive and Kidney Diseases-sponsored multicenter "Hepatotoxicity Clinical Research Network."

In addition to his prowess and preeminence as a physician, clinical scientist, mentor, role model and communicator, Hy Zimmerman was above all a devoted family man. The consummate husband of Kitty, who predeceased him by 10 years, and forever changed by the passing of his son Robert in 1993, he remained an adored father to his three other children. He lived to complete the writing and see the proposed cover of the much-awaited second edition of his book,⁴¹ which was published 2 months after his death. How much better can we summarize Hy's achievements than to paraphrase Winston Churchill's famous comment* on the Soviet Union's intended actions in the very war that guided Hy toward a career in liver disease: "A landmark law wrapped in a landmark book inside a landmark human being."

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*In a speech in the House of Commons [May 13, 1940], Churchill said "I cannot forecast to you the action of Russia. It is a riddle wrapped in a mystery inside an enigma."

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