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THERAPEUTIC DRUGS Through History

Steve Beitler, PhD



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"A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals." *Sir William Osler (1849-1919), Canadian physician*

"A drug is a substance that, when injected into a rat, produces a scientific paper." *Anonymous*

"He's the best physician that knows the worthlessness of most medicines."
Benjamin Franklin (1706-1790), American statesman and scientist

"I owe my reputation to the fact that I use digitalis in doses the text books say are dangerous and in cases that the text books say are unsuitable." *Karel Frederik Wenckebach (1864-1940) (1)*



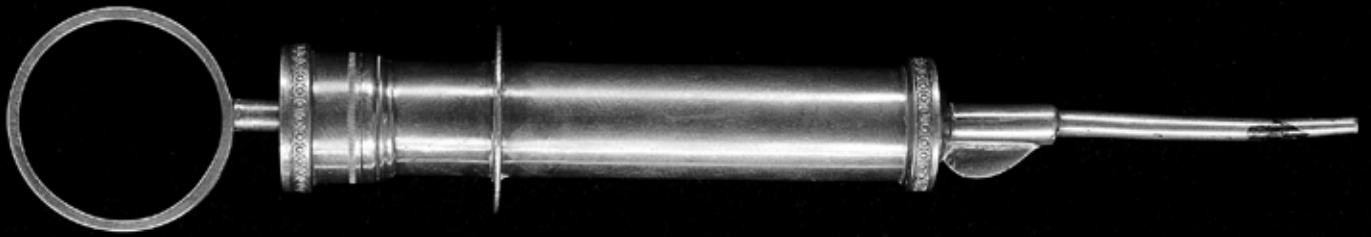
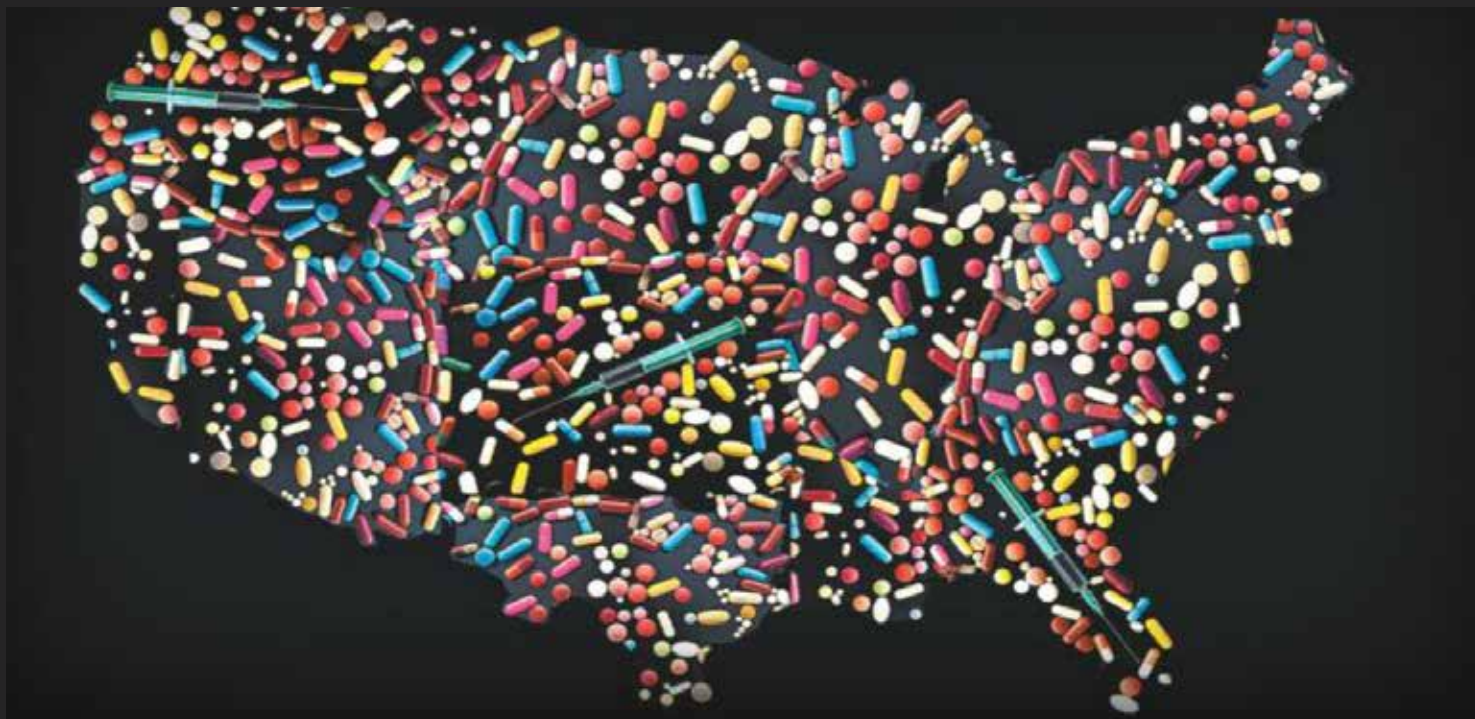


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INTRODUCTION

HIV/AIDS in the 1980s, America's opiate emergency that began in the 1990's, and the coronavirus pandemic of 2020 have reflected and reshaped eternal issues of disease, healing, and the role of therapeutic drugs. Thousands of chemical, biological, and synthetic compounds have been central to healing and the practice of medicine across human history. A full rendering of the history of drugs in medicine would reveal astounding upheaval, clear continuities, and a dense interplay of science, religion, technology, commerce, and folklore. Humanity's understanding of drugs both as therapies and carriers of clinical risk has grown alongside knowledge of disease, injury, and illness. Still, many questions about drugs as therapies, and as products of history, remain. In our own time, as genetic knowledge grows, drugs in more customized forms are joining physicians' healing toolkits. The uses and understandings of these compounds will implement evolving research findings, cultural assumptions, and clinical protocols, just as the history of drugs in medicine has always embodied these forms of knowledge, belief, and medical practice.

Even in an era of “precision” or “personalized” medicine, a defining paradox across the history of therapeutic drugs is unlikely to change. If our goal is to understand the significance of drugs in the saga of human healing, we need to move beyond even the vast history of clinical practice into political, economic, scientific, and social history. Clinicians are trained to understand drugs as therapeutic tools; historians study therapeutic drugs through different lenses. A historical understanding of medical drugs challenges doctors and historians to think about drugs as products not just of labs and factories but of hundreds of legal, political, and social decisions across many centuries. This study offers a chronological introduction that seeks to convey the topic’s vast scope and offers an historical approach to thousands of years, medical conditions, and therapeutic compounds.

Over-scheduled clinicians and overworked medical students have good reason to ask how exploring the history of therapeutic drugs will make them better doctors. One answer is that familiarity with this history can deepen a practitioner’s understanding of clinical issues (e.g., individual variability, addiction risk) that are both timeless and current. As two historians put it in 1928, “By study of the practice of medicine under conditions so different from our own, we learn something of what is truly permanent in the art of healing.” All medical history can bolster a clinician’s respect for, and humility in the face of, the complexities of disease and healing. (2)

Beyond these high-level benefits, there are practical connections among clinicians across the centuries. A history of therapeutic drugs reinforces the need for today’s practitioners to inform themselves and their patients about drugs’ powers and limitations. In addition,

while it’s not difficult to find examples of ancient therapies that now seem bizarre – e.g., chewing on a fried mouse to relieve tooth pain, or treating contusions by wrapping a person in hay and burying him up to his neck in manure – there are compelling continuities between ancient and contemporary drug therapies. In 1988 historian John Riddle compared the contents of then-current guides to pharmacy and herbal medicine to drugs mentioned in the writings of Greek physician Hippocrates between 440 and 330 B.C.E. Of the 257 drugs mentioned by Hippocrates, all but 27 could be found in one or more of the contemporary guides. (3)

Continuities across many years go beyond specific chemical compounds. Another is how clinical and social understandings of the same drug can shift. In 1898, the Bayer company introduced, and promoted aggressively, a new remedy for coughs, gastrointestinal distress, and morphine



No drug is more central to medical history than opium. The earliest records of its use go back more than 5,000 years; its unsurpassed ability to reduce pain, as well as its dangers, have been known for just as long. After morphine was isolated in 1804, it supplanted raw opium as the main form of opium in medicine. In 2020, America's widely chronicled opiate emergency has resulted in more than 300,000 overdose deaths since 1999, a frightful resurgence of opium's eternal paradox: It is indispensable in treating (some forms of) pain as well as a formidable agent of dependence and addiction (for some people). (6)

addiction. Created by a simple chemical alteration of morphine, Bayer christened its new product heroin. In less than a decade its addictive potential had become clear. Heroin is not the only drug whose career has traversed medical approval, social condemnation, and an overlapping terrain between them. Ritalin is in wide use for attention-deficit/hyperactivity disorder, despite the findings

of numerous studies that show it to be close to a pharmacological twin of cocaine. Between its discovery by Albert Hofman in 1938, and its being made illegal in America in 1967, there was extensive, promising, and controversial research into the therapeutic potential of LSD (lysergic acid diethylamide). Fifty years later, there is a slow revival of studies into LSD's possible role in treating alcoholism,

post-traumatic stress, and other ailments. These examples of changed perceptions of the same drug highlight the enduring importance to clinical practice of evolving social beliefs and scientific understandings. (4)

Any short overview of drugs in medical history requires leaving out large, fascinating topics. Alcohol as a pain reliever and tobacco as a stimulant had rich therapeutic

histories before becoming the focus of social movements and public-health efforts. This article doesn't cover medicine as a profession in America, despite the vast impact of this history on how therapeutic drugs have been created, used, and understood. In addition, this study does not address the emergence of specialization (an important aspect of medicine's professional history) or the growth of chronic, "lifestyle" diseases in America after 1945. (5)

Two broad themes comprise the "spine" of this study. The first is that beliefs and practices about drug therapies in any era result from complicated interactions of scientific, technological, and social forces. What physicians and others know and believe about drugs and their effects (therapeutic or otherwise) emerge from labs, doctors' offices, people's homes, advertising agencies, schools, religious and spiritual institutions,

and more. Historians Sarah Tracy and Caroline Jean Acker described how "perceptions of illness, social forces, cultural biases, individual personalities, theoretical developments, and technological capacity all play a role in the development and dispersion of legitimized drugs as well as alcohol, cigarettes, and narcotics." Physicians' and patients' understandings of drug therapies are shaped by more than research, clinical trials, and personal experience. Today, America's ongoing opiate emergency has produced extensive media scrutiny, political engagement, and legal maneuvering that have reverberated far beyond the lab or clinic. (7)

A second theme is that, in America since 1945, a core mission of government, the medical profession, and the pharmaceutical industry has been to establish and patrol the divide between approved medical uses of drugs and their illegal, non-medical uses. This has

been an economic, political, and social endeavor of vast scale and impact. For example, the entire history of the United States's Food and Drug Administration (FDA), part of whose charter has been to regulate therapeutic drugs, is one thread in an enormous historical canvas.

In attempting to convey the scope of the history of drugs as therapies, this survey does not address a critical element of that history in America. For 400 years, understandings of drugs' medical and non-medical uses have been shaped by, and reflected in, ideas about social class, race, and gender. These dimensions have played crucial roles in public policy, media coverage, and scholarly analyses of medical knowledge and practices. In the late 1970s and early 1980s, cocaine's image as a glamorous, high-end accessory contrasted sharply with how "crack" cocaine was portrayed a few years later as

a demon scourge of the ghetto. Across American history, who is taking what drugs, and under what circumstances, has had enormous effects on clinical and other understandings of these chemical compounds. (8)

Even though this survey emphasizes the period after 1800, the history of therapeutic drugs as a focus of organized government

action goes back much further. When Columbus was preparing for his 1492 voyage, his Spanish backers instructed him to bring back opium if he found it. Plant-based substances for medical use and home remedies became staples of global trade after 1500. In the mid-19th century the British navy defeated China in two lopsided Opium Wars that enabled the British to profit

from selling opium grown in its India colony to the Chinese. Since 1900, the United States has led an international effort, built on treaties, covenants, and multi-national collaboration that have implemented drug-control regimes. (9)

But before we look at the 20th and 21st centuries, let's start at the beginning.

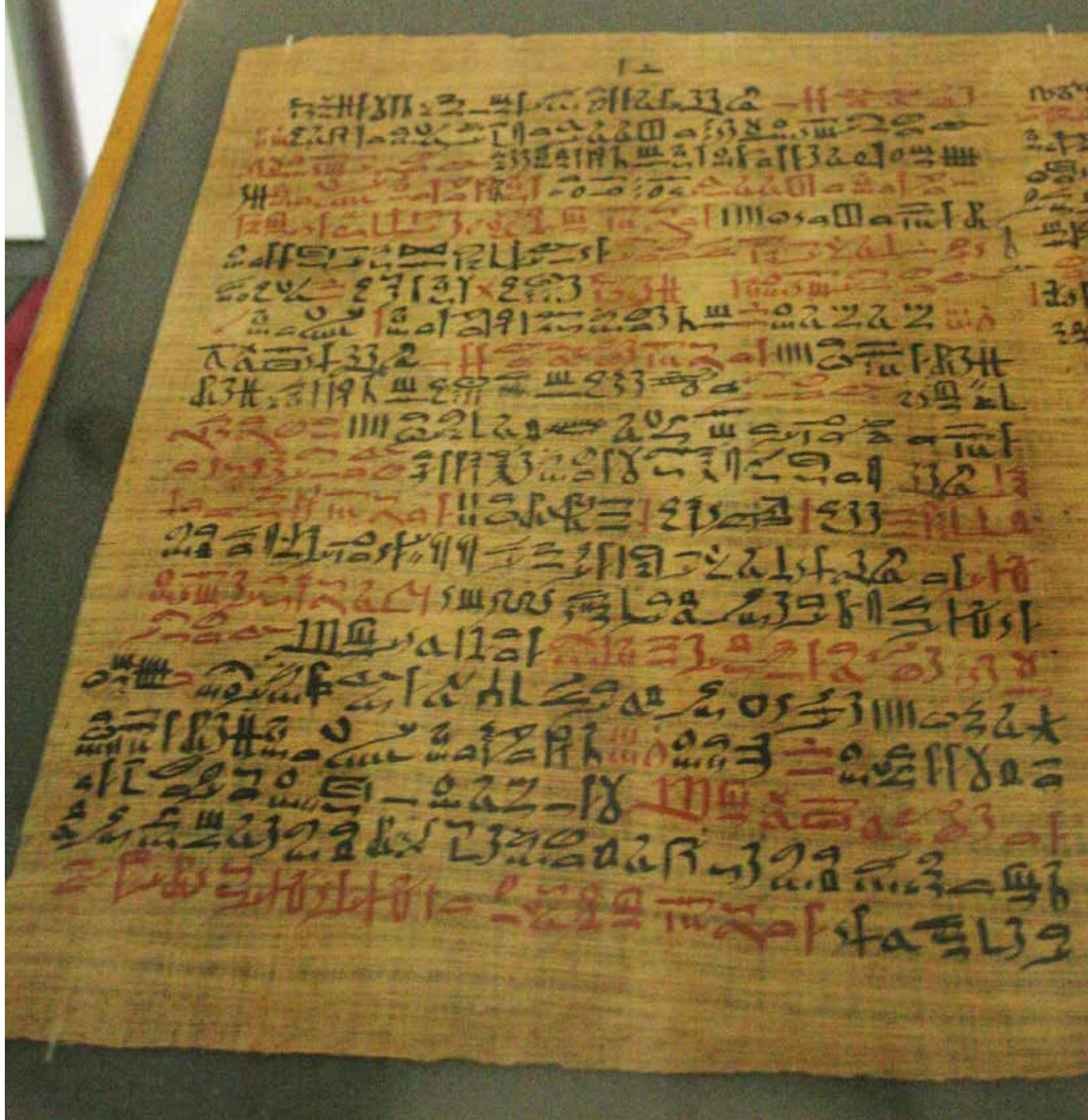
PART ONE From Spiritual to Biochemical: Antiquity to 1800

For thousands of years, healers have used plant-based drugs, in thousands of combinations, to address an equally wide array of conditions. Strong community and family medical traditions dispersed healing across society and reflected fluid boundaries separating medicines, foods, and sacraments. Ancient medicine, west and east, was holistic, stressing the importance of

diet, exercise, and lifestyle. Proper balance was the key to health, and a healer's role was to restore that balance. (10)

Our ancestors had little knowledge of anatomy, physiology, or the biochemical processes that shape how bodies work. This did not impede a vigorous quest to understand and treat disease, because epidemics grew in parallel with nomadic, and then more settled,

societies. Across history, diseases that affected crops, herds, and peoples have played a significant role. Teeth fossils from Neanderthals who lived up to 30,000 years ago have been found to contain traces of herbs, including chamomile and yarrow -- possible early medicines. In the Turkey-Syria-Iran "triangle" about 3,600 years ago, "herbal and other plant remedies were numerous; recipes included dregs



The Ebers Papyrus (c. ~1550 BCE) is foundational to knowledge of medical practice and therapeutic drugs in ancient Egypt. In 1876 Georg Ebers, a professor of Egyptology at the University of Leipzig, published a partial translation. The document contains more than 800 section entries, 700 drugs and 800 formulae, 15 diseases of the abdomen, 29 of the eyes, 18 of the skin, 21 cough treatments, descriptions of heart issues and magic spells, entries on medicinal plants – including dill, fennel, and thyme – as well as clinical accounts of asthma, arthritis, and depression. (13)

of wine, prunes, and pine sap, all of which have antibacterial properties – although the addition of lizard excrement is harder to justify.” (11)

A key attribute of ancient medicine was that boundaries separating religion, magic, and medicine were fluid. Starting about 500 CE, with the Greeks, medicine slowly became more secular, and then, after about 1500 in the west, scientific. Before then, with remnants long persisting, disease was believed to be caused by the invasion of the body by

evil spirits, or the work of sinister forces. Healers needed magical and spiritual talents because cures required divine intervention. (12)

How did humans develop plant-based drugs? They watched how animals and people reacted to different plants. They experimented with mixing, cooking, and brewing roots, barks, leaves, and flowers.

Accidents revealed mind- and body-altering effects that could be healing, nutritional, or deadly. People shared information orally,

and, later, on papyri, clay tablets, parchments, and paper. An herbal medicine of antiquity was black cohosh, used by Native Americans to treat gynecological and kidney disorders, depression, sore throats, and rheumatism. Today black cohosh capsules are available without prescription for help with menopausal symptoms, osteoporosis, and acne. (14)

Over thousands of years, often in parallel, healers in Arabic-Islamic, Indian, and Chinese traditions



A chemical cousin of onions and leeks, garlic is one of the oldest plants known, and like opium, its medicinal and culinary properties have long been understood. Garlic’s recorded medical uses go back at least 5,000 years; it has been found in Egyptian pyramids and Greek temples, is mentioned in the Bible, and has been a pillar of traditional Ayurvedic (Indian) medicine for many centuries. Among its ancient indications were for gastrointestinal disorders, animal bites, and to alleviate seizures. Based on a belief in its value to those doing hard labor, it may have been a very early performance-enhancing drug, since it was given to Greek athletes in the ancient Olympics. (16)

developed plant-based remedies that were as complex and extensive as those of Western Europe and the Americas and that overlapped in crucial ways. Approximately 300 drugs appear across medical documents in Greek, Latin, Chinese, and other ancient languages. Until the 19th century, there was remarkable consistency about which therapeutic drugs could be used for which conditions. The healing arsenal of a physician in the early 1700s would have been largely familiar to a physician transported to that era from the 1200s. A key difference was a growing presence of drugs from the New World, such as balsam of Peru and tobacco. (15)

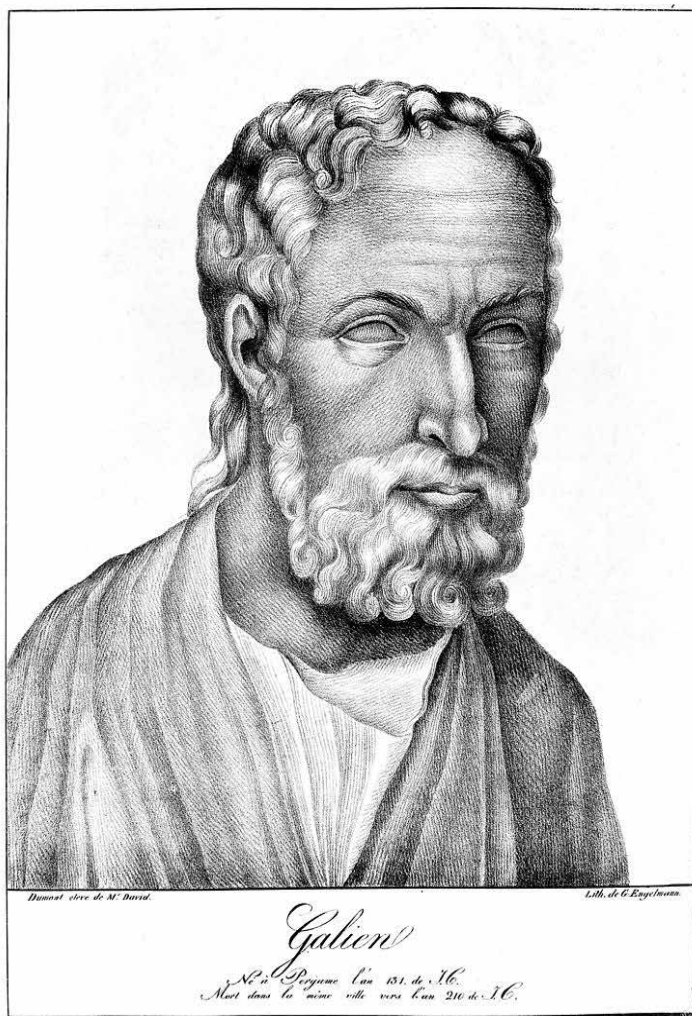
Significant commonalities across diverse medical traditions affirm similarities in disease that humans everywhere have faced. However, the roots of today's Western medicine were in ancient Greece, some five to six hundred years

before the birth of Christ. Drugs played an important role in Greek medicine. Its healers and priests used warm water, wine, oil, honey, sulfur, saffron, and resins. Opium was well-known to Hippocrates and other Greek physicians as one among many substances deployed in creams, ointments, pills, and suppositories. Compilations of Greek pharmaceuticals – medicinal plants in many combinations – reflect drugs' importance. Around 300 BCE, two treatises by Theophrastus described how some 550 plant varieties were used medically. Four hundred years later, Dioscorides, a Greek surgeon attached to Roman Emperor Nero's army, published *De Materia Medica (Concerning Medical Plants)*, five volumes of plant names, origins, habitats, their uses in treatments, and techniques of harvesting. (17)

This rich history of therapeutic botany is part of the Greeks' larger

significance in medical history. The Greeks launched a reorientation that would unfold over 2,000 years, in which medicine slowly cut its ties to religion and magic to become more secular and scientific. The Greeks were the first to put natural forces in the individual and world at the center of health and disease. Healers needed to know science and the natural world. As historian Judith Magner wrote:

In Western history, Hippocratic medicine is revered for its emphasis on the patient instead of the disease, observation rather than theory, respect for facts and experience rather than philosophical systems. ... Hippocrates had a trusted list of gentle, tried-and-tested remedies, which included olive oil, honey, and a range of more than 200 vegetables and herbs – either to be eaten whole or taken as extracts – from figs, garlic, and onion to parsley, poppy, hibiscus, chamomile, cumin, and saffron. (18)



Few people have influenced the history of medicine as much as Galen (AD 129-216). He was born in what is now Turkey, and his writings on anatomy, physiology, therapeutics, and philosophy were studied and revered for close to 2,000 years. He believed in balance as health and imbalance as disease. "Famous for his knowledge of drugs, Galen investigated the properties of simple medicines, complex concoctions, and exotics from distant places, such as 'Balm of Gilead' from Palestine and copper from Cyprus. Complex drug mixtures were later called 'Galenicals.' He recommended some "nauseating remedies, such as bile from bulls ... and a digestive oil compounded from cooked foxes and hyenas." (20)

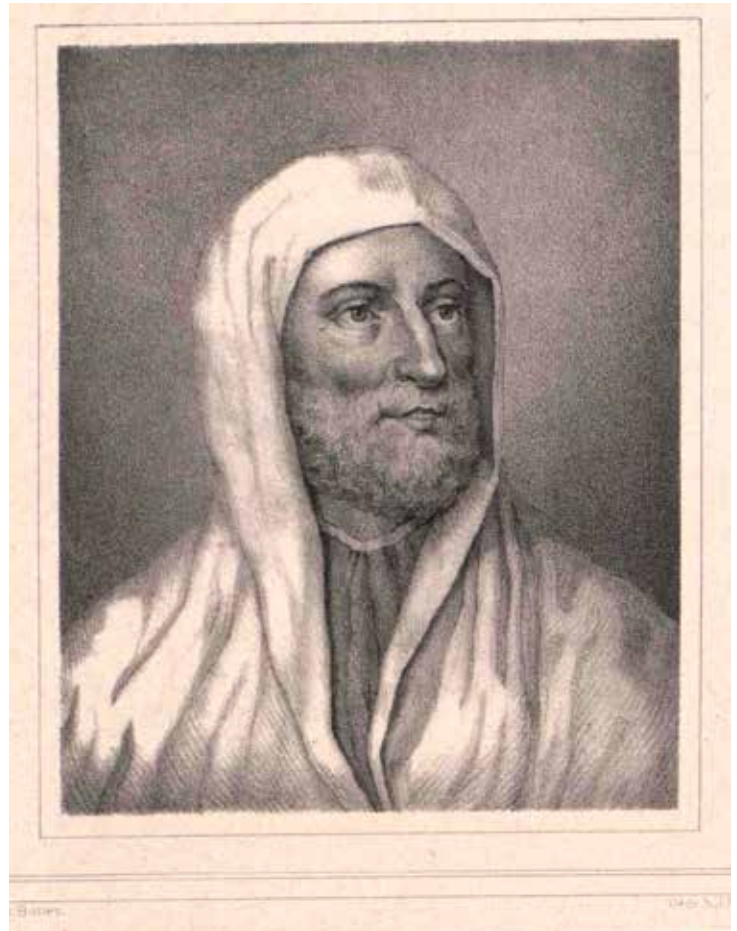
The Greeks' medical worldview is called humoral medicine, and it would shape clinical practice until about 1500. Humoralism was a rich explanatory framework in which drugs played a key role, and parallels to its ideas and practices appear in Chinese and Indian medical traditions. A key tenet of humoral medicine were functional and symbolic connections across the

four humors or bodily fluids (blood, phlegm, choler or yellow bile, and black bile), the building blocks of the world (fire, water, air, and earth), and each humor's associated quality – hot, cold, moist, and dry. Humors shaped a person's temperament and appearance. "Good health required humoral balance; symptoms reflected disruptions. Humoral theory expressed the Greek view

of the person as microcosm, a miniature that worked by the same principles as the universe." (19)

Between 300 and 1500, the Arabic-Islamic world was a center of medical practice and study whose leading practitioners expanded naturalistic approaches and plant-based therapies. Prominent physicians such as Rhazes (c. 865-925), Avicenna (980-1037),

Avicenna – (980-1037) The son of a tax collector, Avicenna was born in what is today Uzbekistan. Like Galen before him, he traveled in West Asia to study, see patients, lecture, write, and acquire funding. In 1025 he published *Al-Qanun*, *The Canon of Medicine*, which was translated from Arabic into Persian, Latin, several European languages, and Chinese. Part Two of *Al-Qanun* lists “more than 700 mineral preparations, herbal extracts, compound remedies, and other drugs and medicines.” Avicenna was among a group of Arabic physicians and philosophers who preserved medical knowledge that had faded from Europe after originating in Greece and Rome. (22)



and Averroes (1126-1198) studied Greek ideas and added their own insights in keeping these ideas and traditions alive. Arabic-Islamic physicians and scientists advanced the understanding and techniques of foundational chemical processes, such as crystallization and precipitation. They published compilations of medicinal plants and formulas, including musk, myrrh, ambergris,

laudanum (a liquid form of opium), and aloe. The formulary of al-Kindi (c. 800-870) contained drugs from Asia that were unknown to the Greeks. About the year 100, Dioscorides’ five volumes on plant- and animal-based drugs listed fewer than 1,000 entries. In the early 1200s, the compilation of Ibn al-Baytar listed more than 3,000 items, including 800 botanical drugs,

145 mineral drugs, and 130 animal drugs. (21)

While Arabic-Islamic medicine was thriving, the Crusades sparked a slow resurgence of organized medicine in Europe. In Salerno, Italy, scholars translated Arabic-Islamic texts into Latin; Salerno became a key destination for aspiring healers in the 11th and 12th centuries, including women,

who were admitted to all courses of study. Similar institutions were founded in Bologna and Padua in Italy and Montpellier, France. In the 1300s and 1400s additional medical schools opened in Europe. The growth of printing in Europe after the 1460s gave crucial support to the diffusion of Greek and Arabic-Islamic medical texts. (23)

After 1500, the growth of organized instruction and the vast impact of printing accelerated the emergence of more secular and scientific foundations for medicine. At the same time, social and intellectual ferment took many forms: the Protestant Reformation, waves of conquest and war, the growth of exploration and trade, rising population density, the migrations of soldiers and traders, and the ebb and flow of refugees and peasants. All these helped expand the range of plant medicines and establish new routes for disease vectors. By the mid-1600s, the medicinal



Quinine for malaria was a major therapeutic advance in the seventeenth century. Cinchona bark came to Europe after 1630 as an exotic centerpiece of stories of dramatic cures. In 1633, a Jesuit publication described how Peruvians used the bark of a willow tree to fend off ague, a malaria-like fever disease. About 40 years later quinine, the bark's active ingredient, was isolated, and it began to be widely used by healers and households. The first listing of cinchona in the London Pharmacopoeia came in 1677. Its success inspired medical "irregulars" to promote mysterious remedies containing Peruvian bark. (25)

garden at Oxford, begun in 1623, contained more than 600 native species and 1,000 plants brought to England from beyond. Later in the 17th century, Thomas Sydenham, a renowned British physician, concocted a recipe for laudanum,

a liquid formulation that blended opium with sherry and flavorings. This became the main form in which opium would be consumed after 1700. Sydenham's lyrical praise of opium as the healer's most trusted ally helped spark medical

interest and a vast patent- and folk-medicine industry in Britain and America. (24)

The 1700s were a key period for an important category of therapeutic drugs. By this time, smallpox outbreaks led annually to tens of thousands of deaths. Inoculation against smallpox had a long history in rural communities in Western Europe, the Middle East, North and West Africa, and Asia. In 1714 Emanuele Timoni, a doctor affiliated with the Royal Embassy in Constantinople, and his colleague Jacob Pylarini reported to the Royal Society of London on a folk practice known as ‘buying the smallpox,’ or inoculating against the disease by injecting a small amount of material taken from smallpox pustules. In 1716 Lady Mary Montagu, wife of the ambassador to Constantinople, asked the embassy surgeon (while her husband was traveling) to inoculate their five-year-old son; she and the surgeon did the same in



Starting in 1656, segments of a major medical text began to be published in Europe. Li Shizhen (1518-1593) was a Chinese physician, naturalist, pharmacologist, herbalist, and acupuncturist. His major contribution was his *Compendium of Materia Medica*, published in 1596 after decades of compilation. The book summarizes pharmacological knowledge of the prior 2,000 years and is a major treatise on botany, zoology, mineralogy, and metallurgy. (26)



Hermann Boerhaave (1668-1738) was a teacher, writer, and chemist who was an extremely influential physician of the eighteenth century. He taught medicine at the University of Leiden from 1701 to 1738. Boerhaave championed the evolution of clinical medicine from its roots in magic and mystery to become more scientific. He established one of the first "teaching hospitals," where he guided students by blending theoretical and practical instruction in close interaction with patients. (29)

1721 for her four-year-old daughter. In America's war of independence, the British were accused of sending infected agents into the field to spread the disease; General George Washington ordered a mass inoculation of America's soldiers. In 1796, Edward Jenner showed that an

animal disease, cowpox, worked as a vaccine against smallpox, a major, if controversial, advance in halting smallpox's deadly path. (27)

The seventeenth and eighteenth centuries were also critical for foundational advances in anatomy and biochemistry. In 1761 Giovanni

Morgagni (1682-1771) published *On the Sites and Causes of Disease*, which drew on more than 700 autopsies to show how bodily organs revealed the footprints of disease. Morgagni's work propelled a conceptual shift from seeing disease as an abnormality of the

entire organism to understanding it as residing in specific organ and tissue systems. (28)

By the close of the 1700s, global exploration had expanded the physician's therapeutic arsenal

dramatically. In London, apothecary Thomas Corbyn (1711-1791) offered more than 2,500 items, with many imported from North America, the West Indies, and Europe. With this global foundation

in place, the history of therapeutic drugs was poised to enter a new century, in which a convergence of science, commerce, and cultural upheaval would transform medical therapies again. (30)

PART TWO Science, Commerce, and Technology: 1800-1900

The 19th century was a period of vast economic and social development in a very young American nation. Between 1800 and 1860, America's population grew from five million to 31 million. A defining feature of the early 1800s was rapid industrialization. Cotton production in the South doubled between 1820 and 1825 and doubled again in the next five years. People and goods

began to travel by the new railroads and canals – and, after 1844, to communicate over telegraph wires. In 1800 the United States had about 20 daily newspapers; by 1860, there were 400. There were wars to remove Native Americans from their ancestral lands, a return to religious fundamentalism in the Second Great Awakening, and the fateful drumbeat of the conflict over slavery, growing louder and more intractable. (31)

Medical practice and therapeutic drugs underwent profound changes as well. As sociologist Paul Starr wrote, "Before the late nineteenth century ... there were three spheres of practice relatively equal in importance – the medicine of the domestic household, the medicine of the physicians, and the medicine of the lay healers." Advances in chemistry and emerging commercial opportunities began to nourish laboratory-based pharmacology.

Drugs became significant industrial commodities, and drug companies evolved from small manufacturing pharmacies in the 1820s to firms with regional markets by mid-century. More products and improved manufacturing techniques, along with military purchases at the beginning of the Civil War, drove industry growth. In Europe, plant drugs such as opium were subjected to systematic chemical analysis: the result was the synthesis of codeine, heroin, nicotine, caffeine, morphine, and later, cocaine. By 1900 companies were turning lab-made developments to profit -- as in the case of aspirin, marketed by Bayer in Germany beginning in 1898. (32)

At the same time, clinical medicine was becoming increasingly science-oriented. One marker of this trend was the fitful growth of partnerships between pharmaceutical companies and academic researchers. Another was the expansion of organized

medical education. From a few medical schools in 1800, 22 were operating 30 years later, and more than twice that number by the start of the Civil War. Across the 1800s, therapeutic drugs' creation and use were shaped by the rising influence of experimental sciences and laboratory practices in medicine. At the same time, American hospitals

became the venue at which "insurance-based health care accessible to the working class would be routinely provided." (33)

Against this backdrop, therapeutic drugs increasingly became a social problem and state project. "In the United States, relatively few Americans were aware before the 1850s either of the vast opium

(Opposite) A powerful response to massive changes in 19th-century America was a vigorous cultural critique, a flowering of experiments in communal living, and new paths of spiritual expression and self-exploration. One historian wrote that "the Jacksonian romantics ... read the biblical promises in nature itself." Poet and essayist Elizabeth Barrett Browning (1806-1861) gave expression to an evolving focus on personal identity. Browning was one of many writers and artists who experimented with, and grew to like, opiates. Thomas de Quincey's *Confessions of an Opium Eater* (1821) described his use of laudanum to enhance long walks around London or the opera. "Ether frolics" at American colleges in the 1830s foreshadowed a change in which artists, spiritual seekers, and the curious experimented with drugs for deliberately non-medical purposes. (35)



traffic or its devastating human effects.” This changed dramatically after the Civil War. Medicines that had begun life as therapies – e.g., opiates and cocaine -- slipped the bounds of medical practice and entered the wider culture as intoxicants, euphorants, and, increasingly, agents of dependence and addiction. The 19th century also witnessed a paradoxical contrast between significant advances in medical science and a “golden age” of medical flimflam, in which unlabeled patent medicines containing alcohol, cannabis, opium, and cocaine became a large and very profitable business

sector. (34)

After 1850 in the United States, opium (usually in the form of laudanum) and morphine came into wider non-medical use and scrutiny by journalists, social workers, and law enforcement personnel; drug

abuse was becoming a national problem. Data on opium imports show consistent growth between 1840 and the end of the century, with per capita imports of crude opium reaching their peak in 1896. Opium smoking increased significantly in the United States in the 1870s and 1880s, and health officials in several states studied the extent of addiction. An 1872 article said, “Opium and morphia are not only freely used in patent and commercial medicines, but they have now become common ingredients in many family remedies ... such as cough mixtures, tooth

The 19th century also witnessed a paradoxical contrast between significant advances in medical science and a “golden age” of medical flimflam ...

washes, lotions, liniments, enemas, poultices, healing tinctures and decoctions.” While the American Civil War (1861-1865) did not

launch widespread opiate use, addicted Civil War veterans, a group of unknown size, helped to spread the awareness and visibility of opiate addiction. (37)

Technology advances played a pivotal role in medical and non-medical uses of drugs. After 1850, subcutaneous injection of morphine during the US Civil and Franco-Prussian wars “granted the syringe both legitimacy and familiarity to doctors and laymen.” The syringe enabled medics to apply morphine paste to a wound from a knife, or inject morphine directly. Improvements in micros-

copy helped researchers extend their studies of organs, tissues, and

cells. “In the mid-1800s a series of new diagnostic instruments – the stethoscope, the ophthalmoscope, laryngoscope – began to expand



In 1804 a 21-year-old pharmacist's assistant in Germany, Friedrich Serturmer (1783-1841), solved a problem that had baffled scientists for centuries and has profoundly affected medical therapy ever since. Serturmer isolated morphine, the active ingredient in opium, through painstaking trial-and-error and, eventually, self-experimentation. He published his findings in 1806, and the news was greeted with wide indifference. Serturmer continued to pursue his experiments and to warn of the dangers of addiction that accompanied morphine's unparalleled ability to relieve pain. (36)

the physicians' sensory powers in clinical examination." (39)

These advances in the science and technologies of medicine occurred in parallel with a massive, uncontrolled therapeutic experiment: legal, inexpensive, socially approved, and widely available opium, alcohol, cocaine, and cannabis in hundreds of home remedies and commercial preparations for pain, fever, and other ailments. In 1859, proprietary medicine sales in the US were about \$3.5 million; by 1904 they had grown by more than twenty times. In the 1860s, "a Nashville-made Ambrosial

Oil was marketed which could cure thirty-eight specified human ailments, not to mention ten equine ones." A drug trade journal counted about 28,000 such medicines on the market in 1905. The next year a witness before a Congressional committee estimated that there were 50,000 such remedies sold in the United States. One consequence was that by about 1900 – the peak of America's first opiate epidemic – there were about 250,000 people addicted to opiates. These developments helped fuel a growing fear of drugs as social menace among Americans. (40)

As patent medicines reached their peak, pioneering research was reshaping fundamental medical understandings of disease in ways that would expand drug development after 1900. Historian Steve Parker wrote, "Discoveries about bacteria and other disease-causing microorganisms multiplied almost as fast as the bacteria themselves in the late 19th century. Scientific researchers peering into microscopes recorded all sorts of new bacteria, yeasts, protozoa (single-celled, animal-like organisms), micro-worms and others." The work of Louis Pasteur (1822-1895)



In April 1853, England's Queen Victoria took chloroform as she gave birth to Prince Leopold. "The effect was soothing, quieting & delightful beyond measure," is how the Queen described the experience in her journal. In 1831, chemists working independently in America and Europe had synthesized chloroform. After its dramatic demonstration in 1846, "anesthesia became accepted, but ether, which irritated the lungs and caused vomiting, was soon displaced by chloroform, which was powerful and easy to administer." One account says that James Young Simpson (1811-1870), professor of surgery in Edinburgh, had been testing chemicals with his assistants when one of them knocked over a bottle of chloroform. On bringing in dinner, his wife found them all asleep. Simpson tried it out on a woman in labor (half a teaspoon on a rag, applied to the nose), and was so pleased that he gave it to more than two dozen patients within a week. There were opponents to the use of chloroform as an anesthetic on religious and medical-safety grounds. Cardiac and toxicity issues would make chloroform obsolete as a surgical anesthetic in the United States by the 1930s. (38)

and Robert Koch (1843-1910) was pivotal in establishing a theoretical and methodological basis of the new science of microbiology. Koch discovered bacillae that produce anthrax, tuberculosis, and cholera. In March 1882, Koch announced that he and his team had identified the tubercle bacillus. The dramatic news spread quickly; discovery of the causal organism

put to rest the confusion that had long surrounded tuberculosis, also known as consumption and phthisis. Established folk remedies for the disease included "wolf's liver boiled in wine, weasel blood, pigeon dung, and essence of skunk; eating live snails was said to prevent the disease." In the 1880s, Pasteur "established the fundamentals of disinfection, sterilization,

immunization, and procedures for the development of vaccines." (41)

By the close of the 19th century, the growth of the United States as an industrial power; a profusion of scientific advances, technology development, and commercial expansion; and the rise of non-medical drug use had profoundly altered the landscape of drug therapies in medicine. In

the 20th century, America's changing role in global politics would expand popular and professional scrutiny of therapeutic medicines. The excesses and social alarm that drug use had produced in the second half of the 1800s would move the country to increasing drug regulation. No drug would be more central to this shift than heroin, which Bayer had introduced in 1898 as a remedy for coughs, diarrhea, and morphine addiction. America's changing role on the world stage, along with the vast growth of the therapeutic arsenal, would shape the 20th century and beyond. (42)

PART THREE

New Drugs, New Rules: 1900-present

Several events converged in the late 1800s and early 1900s that would have profound, long-term impacts on therapeutic drugs in medicine. One was the previously mentioned arrival of heroin in 1898. Also emerging from Bayer, some two weeks after heroin, was the formulation of aspirin that would make it a global staple of pain and

fever relief. Thus, two of the most important drugs in the history of the 20th century arrived almost simultaneously. In the same year, as a result of the Spanish-American War and related diplomatic initiatives, the United States became responsible for the Philippines, Hawaii, Guam, and Puerto Rico, a change that would propel the United States into a leading role

in the global regulation of drug trafficking. In addition, beginning with the barbiturates in 1903 (see below), the history of therapeutic drugs in the 20th century was shaped by vast expansion of doctors' healing toolkits. (43)

In 1898, Bayer's launch of aspirin and heroin led off a flood of new therapies. Doctors getting started during the 1930s could deploy



Descriptions of patients experiencing extreme thirst and copious urination date back thousands of years, and in the first century, this condition was termed diabetes. In the 1670s, the diabetic's urine was found to contain sugar. In 1889, the role of the pancreas in the disease was established, and a decade later, a disorder of the pancreas's endocrine portion had been found to "drive" diabetes. In 1921 the active principle of the Isles of Langerhans was isolated by Fred Banting [1891-1941] and Charles Best (1899-1978). They were working in the laboratory of John Macleod (1876-1935), professor of physiology at Toronto, who had given them the run of his lab and gone off on holiday in Scotland. In January 1922, after some self-experimentation, Banting and Best injected fourteen-year-old Leonard Thompson, who was dying of diabetes in Toronto General Hospital. "Almost immediately his blood-sugar level fell; within days, he was out of bed, and within weeks, home and well, although dependent on insulin injections." There was a huge controversy over the 1923 Nobel Prize. which went to "the fisherman Macleod, while Best and [biochemist] J. B. Collip, got nothing." Eventually the Nobel committee gave Best more credit and recognized Romanian physiologist Nicolae Paulescu, who had discovered insulin (or pancreatine) in cows in 1916 but had not found a way to use it in humans. By 2000, more than 300 insulin analogues were available, derived from animals and humans or synthesized by DNA technology. (48)

aspirin for rheumatic fever, digoxin for heart failure, the hormones thyroxine and insulin for an underactive thyroid and diabetes respectively, salvarsan for syphilis, bromides as a sedative, barbiturates for epilepsy, and morphine for pain. Thirty years later those dozen remedies had grown to more than 2,000. (44)

Not only were new therapies pouring out of labs; there were completely new categories of medicines. The barbiturates are a good example. Veronal and Barbital were introduced in 1903 as sedatives and anti-seizure medications, a new category based on exploitation of barbituric acid. Since 1903 more than 2,500 derivatives have been synthesized; about 50 were still used at mid-century for anxiety, insomnia, anesthesia, and seizures. Barbital was superseded by a phenobarbital, Luminal, in 1912. Barbiturates were commonly

prescribed until the 1950s, when Librium, Valium, and related benzodiazepines appeared, bringing with them more specific action, fewer side effects, and lower potential

Starting with penicillin in 1943, antibiotics, the long-hoped-for “magic bullets” against specific diseases, launched an often-described “golden age” of cultural authority for medicine and the pharmaceutical industry.

for abuse than barbiturates. In their many versions and fluctuating clinical career, barbiturates are a prime example of the “same” drugs that have had long careers medically and non-medically. (45)

Other new categories, and dramatic successes, followed between 1920 and the 1970s. As described by medical journalist James Le Fanu, “there were antibiotics, anti-hypertensives to fend off strokes, anti-coagulants, anti-arrhythmics, anti-histamines, anti-depressants, and anti-convulsants. There were steroids,

including cortisone, for arthritis, bronchodilators, ulcer cures, endocrine regulators, and cytotoxic drugs against cancers.” Starting with penicillin in 1943, antibiotics,

the long-hoped-for “magic bullets” against specific diseases, launched an often-described “golden age” of cultural authority for medicine and the pharmaceutical industry. In the late 1940s and 1950s, films of hobbled victims of rheumatoid arthritis getting out of bed and walking were dramatic promotional devices for cortisone. (46)

The flood of new remedies meant that by the 1960s a global pharmaceutical industry was expanding rapidly in financial size and cultural impact. By 1979, 80 percent of the 25 single-ingredient



Demonstration of the efficacy of imipramine and iproniazid in the 1950s created a new therapeutic category: mood- and emotion-altering medicines. Psychiatrist Nathan Kline wrote of iproniazid, "Probably no drug in history was so widely used so soon after the announcement of its application in the treatment of a specific disease." In 1952, researchers had noted that patients became "inappropriately happy" when given an analogue of iproniazid. The latter was being supplanted as an anti-tubercular, and the company was ready to stop production. But in April 1957, presenters at a Syracuse, NY conference described successes in treating depression with iproniazid. It was approved for use as an antidepressant in 1958. The drug prevents the breakdown of norepinephrine, the brain-neurotransmitter substance concerned with emotional stimulation. Iproniazid was taken off the market because of its ability to harm the liver. Still, the drug had established a relationship between psychiatric disorders and the neurotransmitters. At the same time, imipramine was discovered in 1951 and was introduced for medical use in 1957. It was the first tricyclic antidepressant (TCA) in history. Imipramine "took some years to catch on. ... it turned out both drugs were antidepressants." Imipramine and the other TCAs have decreased in use in recent decades due to the introduction of selective serotonin reuptake inhibitors (SSRIs), which have fewer side effects and are safer in overdose. (50)

drugs most frequently prescribed in the United States had come to market after 1950, with half of these introduced after 1960. "By 2002 the combined profits for the top ten drug companies in the

Fortune 500, at \$35.9 billion, would be greater than those for all the other 490 businesses combined." In 2019, Americans were spending about \$270 billion annually on prescription medications, and another

\$34 billion on over-the-counter remedies. (47)

In the 1950s and 1960s, one of the most heralded new drug categories addressed psychological and emotional states. Clinicians



1. Can of Dextri-Maltose, early 20th century. Evansville's Mead Johnson & Company introduced the first successfully mass-produced infant formula, in 1911.
2. Bottle of Elixir #53 (catnip and fennel), Eli Lilly and Company, c. 1920
3. Carton of Pabulum, c. 1935. Mead Johnson & Company introduced the first fortified, pre-cooked baby formula, Pabulum, in 1933.
4. Bottle of Elixir #29, Eli Lilly and Company, c. 1920
5. Tube of Sulcop, an early sulfa-based over-the-counter antibiotic, Allied Labs, Indianapolis, c. 1930
6. Bottle of Passaloria (mild narcotic for treatment of insomnia, hysteria, and epilepsy), Eli Lilly and Company, c. 1920
7. "Acterosol, For the Prevention of Rickets," 1929. By the 1920s, Mead Johnson & Company was a national leader in the production of infant formula, vitamins and nutritional supplements.
8. "Additional Diets for Infants," Mead Johnson & Company, c. 1930
9. Salesman's sample of Dextri-Maltose, c. 1930

Before the "miracle" anti-bacterial drugs of post-WWII America, sulfa drugs had blazed the trail. Eventually more than 5,000 derivatives of the sulfanilamide molecule included more than 20 sulfa drugs that have proved useful as anti-bacterials. Prontosil was synthesized in 1908 as a red dye to color leather and fiber products. As recounted by historian Steve Parker, "In 1931, Gerhard Domagk, working at IG Farben in Germany, set out to identify a drug effective against a wide range of bacterial infections. Two years later, when his four-year-old daughter developed a bad infection on her hand, for which the only treatment up till then had been amputation, she was cured by prontosil. In 1935 research showed that inactive Prontosil is converted within the body to sulfanilamide, an active antibacterial. In 1936, Prontosil cured President Franklin Delano Roosevelt's son, Franklin Jr., after near-deadly complications of a streptococcal throat infection." (52)

began to learn about and prescribe drugs that promised to calibrate mood, affect, behavior, and internal cacophony. These new psychotropic agents included the major tranquilizers – antipsychotics

such as chlorpromazine and reserpine, and the minor tranquilizers, such as meprobamate and the benzodiazepines (Xanax). By the 1960s and 1970s, Valium, a minor tranquilizer, became the most

widely prescribed drug in America and a cultural touchstone. These therapies, their successes and their downsides, revived questions, within medicine and far beyond, about the boundaries between legal mood and

behavior enhancement and illegal pursuit of “escape,” pain relief, or self-directed mood modification.

The arrival of emotion-modifying medicines helped drive considerable growth in medicine as a profession and field of employment in the decades following World War II.

Paul Starr noted that “between 1950 and 1970, the medical work force increased from 1.2 million to 3.9 million people. National health care expenditures grew from \$12.7

billion to \$71.6 billion [as] medical care became one of the nation’s largest industries.” (49)

As barbiturates (relaxants), amphetamines (stimulants), and emotion-altering drugs such as Valium came into wide, ongoing use, they quickly became “street” drugs whose non-medical use mushroomed. This change helped drive a wide-ranging effort to set and enforce boundaries between legal and illegal use, both at home

and abroad. After 1945, the enormous economic and cultural stakes attached to drug therapies in medicine fueled collaboration and conflict among regulatory agencies, the pharmaceutical industry, law enforcement, and the medical profession in establishing lines of authority and control over the definition and deployment of legal and illegal drugs. Between 1900 and 1930, the United States played a key role in creating a global-control

Amygdalin is a naturally occurring component of apricots, apples, plums, and more. Since the early 1950s, amygdalin and a modified form named laetrile have been promoted as effective against cancer. Studies have shown them to be clinically ineffective in treating cancer, as well as potentially lethal when taken by mouth due to possible cyanide poisoning. But by the end of the 1970s 10 states had passed laws allowing their residents to procure and use laetrile. The battles that produced those laws hearkened back to folk medicine traditions and signaled new forms of organized patient activism to challenge “mainstream” science and assert patients’ authority in medical decision-making. (55)



regime through treaties, covenants, and national laws. This effort included international agreements in 1909 and 1912; the United States's Pure Food and Drug Act (1906) and Harrison Narcotics Act (1914); expansion of federal drug legislation and regulation from the 1930s through the 1970s; and America's self-declared war on drugs, launched in 1971. Agreements reached in 1961, 1971, and 1988 that were overseen by the United Nations helped structure the global effort to delineate and police the boundaries between legal and illegal uses of drugs. Clinicians, working through professional groups such as the American Medical Association, fought hard and consistently to maintain decisive authority over prescribing medicines as a defining dimension of medical practice. (51)

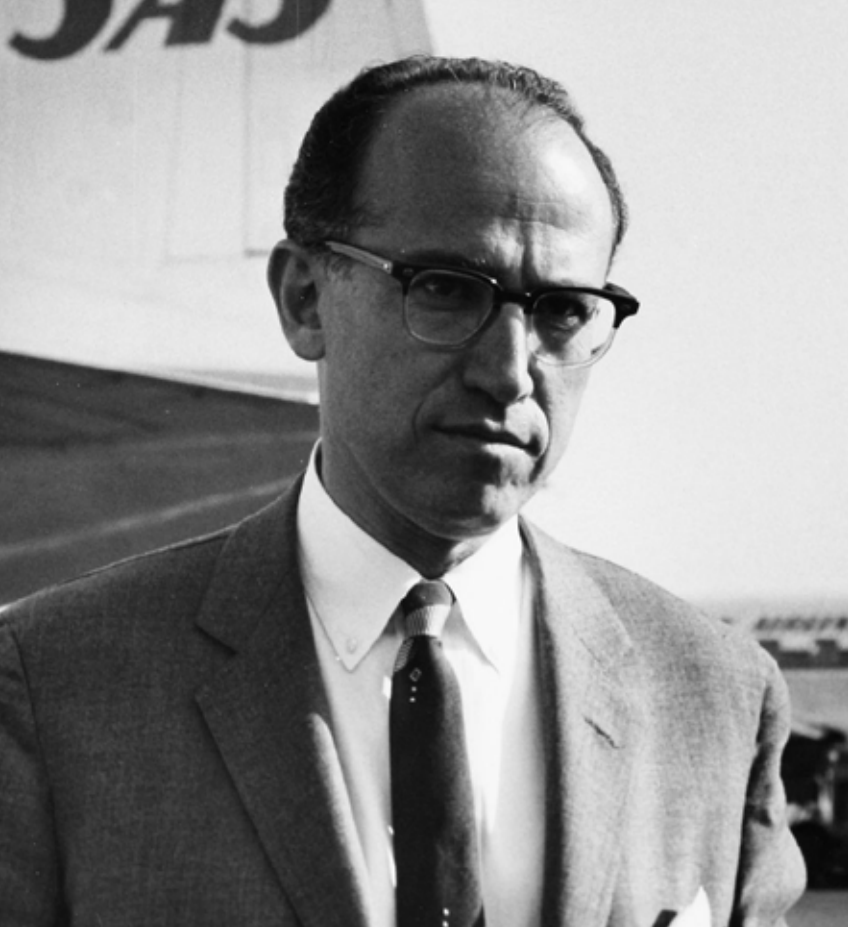
For drugs whose medical use had evaporated and whose non-medical use had been criminalized, such as cocaine and heroin, a key goal of

these efforts was to inhibit supply. The operational belief was that suppressing supply would make drugs so expensive and hard to get that their abuse would no longer be sustainable. For those who still managed, harsh punishment would await. But growing acceptability of some forms of non-medical drug use, as well as laws of supply and demand, would confound this strategy and drive the growth of massive drug-policy budgets, regulatory and enforcement bureaucracies, the prison industry, and, in parallel, vast untaxed profits for traffickers.

The first steps in this control effort were taken in the first decades of the 20th century. In 1906, the Pure Food and Drug Act required manufacturers to list the ingredients of any medicines that were shipped across state lines.

Within a few years, sales of patent medicines fell by more than 30 percent, as people learned what they had been taking for decades. The

Harrison Narcotics Act, which took effect on March 1, 1915, sought to control nonmedical sale and use of opiates and cocaine. The law allowed distribution of heroin and cocaine only by doctors, druggists, manufacturers, and wholesalers who registered with the federal government, paid taxes on the transactions, and kept careful records. The Harrison Act was America's national response to global commitments it had made in the treaties of 1909 and 1912. A question that the statute left unresolved was whether the provision by doctors of heroin and cocaine to known addicts was legitimate medical practice. The federal government sought, and the courts approved, an expansive reading of the Harrison Act's implicit police powers in the five years after its passage. A set of court cases decided that such maintenance of addicts was not legal – a key turning point, by 1920, in setting contemporary boundaries between approved



Scares about Sudden Acute Respiratory Syndrome (SARS), Ebola, avian flu, and 2020's novel coronavirus pandemic had been foreshadowed in 1950s America by poliomyelitis. By then, polio was a dreaded summertime stalker of children for which no prevention existed and whose effects could be devastating. An inactivated polio vaccine, developed by Jonas Salk, came into use in 1955. An oral polio vaccine was developed by Albert Sabin and became available in 1961.

The vaccines have eliminated polio from most of the world and have reduced the number of cases reported each year from an estimated 350,000 in 1988 to 33 in 2018. As the efficacy and safety of the Salk vaccine emerged from a massive clinical trial in 1955, "people observed moments of silence, rang bells, honked horns, blew factory whistles, fired salutes, kept their traffic lights red in brief periods of tribute, took the rest of the day off, closed their schools or convoked fervid assemblies therein, drank toasts, hugged children, attended church, smiled at strangers, forgave enemies." (56)



and illegal use. (53)

With the Harrison Act in place and interpreted judicially, a federal framework for drug control was steadily built out long before President Nixon declared the war on drugs in 1971. In 1932 the Uniform Narcotic Drug Act made possession of opiates, cocaine, and cannabis for non-medical use illegal, and over the next decade most states adopted this law. Responding to an increase in heroin use in cities after World War II, federal law in 1951 mandated a minimum sentence of two years in prison for a first conviction of heroin possession, five to 10 years for the second offense, and 10 to 20 years for third-time violators. The Narcotic Control Act of 1956 raised these minimums and allowed juries to impose a death sentence to adults convicted of selling heroin to a minor. The Controlled Substances Act of 1970 established the framework within which federal

drug policy still operates. Since 1971, the war on drugs has grown massive in its budgets and impacts, such as America's prison population of 2.3 million in 2020. By the mid-1990s, 40 federal agencies or program – in seven of 14 cabinet programs – were involved in drug enforcement (54)

It was also in the mid-1990s that the United States began a new chapter in its long history with one of humanity's oldest therapeutics – opium. Of course, neither a clinical focus on pain, nor awareness of opium's powerful, dual nature, was new. In 1996 the FDA approved Purdue Pharmaceutical's submission for OxyContin, a time-release opiate. Soon after, about two dozen similar formulations followed. These were marketed as less addictive than older opiates because they were time-release, but they contained larger amounts of opiates than earlier compounds.

At the same time, patient groups, drug-policy reformers, and targeted industry promotion were, from different perspectives, telling clinicians that they had been under-treating pain, in part due to legitimate fears about patients becoming dependent or addicted. The new opiates enabled doctors, according to manufacturers and some advocacy groups, to prescribe more freely, including for chronic pain. This was a radical departure from opiates' long-standing roles in treating acute post-surgical pain, cancer pain, and end-of-life issues. The result was an explosion in opiate prescribing, which peaked in 2012 at about 260 million prescriptions written, and has declined by about 20 percent since then. (57)

The epidemic of overdose deaths that began in the late 1990s reprised several themes in the history of therapeutic drugs. As in the second half of the 1800s, opiates were

flourishing within medicine and were widely used far beyond clinical practice. Battles over appropriate pain management reflected ancient contests over patient autonomy, clinical authority, and medicine's eternal engagement with pain.

These contests had been intensified by a growing understanding after 1945, among clinicians and patients, of pain as deeply subjective. What does medical expertise mean when it comes to endlessly diverse forms of pain? The opiate epidemic also highlights the vast commercial power of modern pharmaceutical companies. They have kept regulators and legislators at bay while high-powered opiates produced billions in profits and hundreds of thousands of deaths.

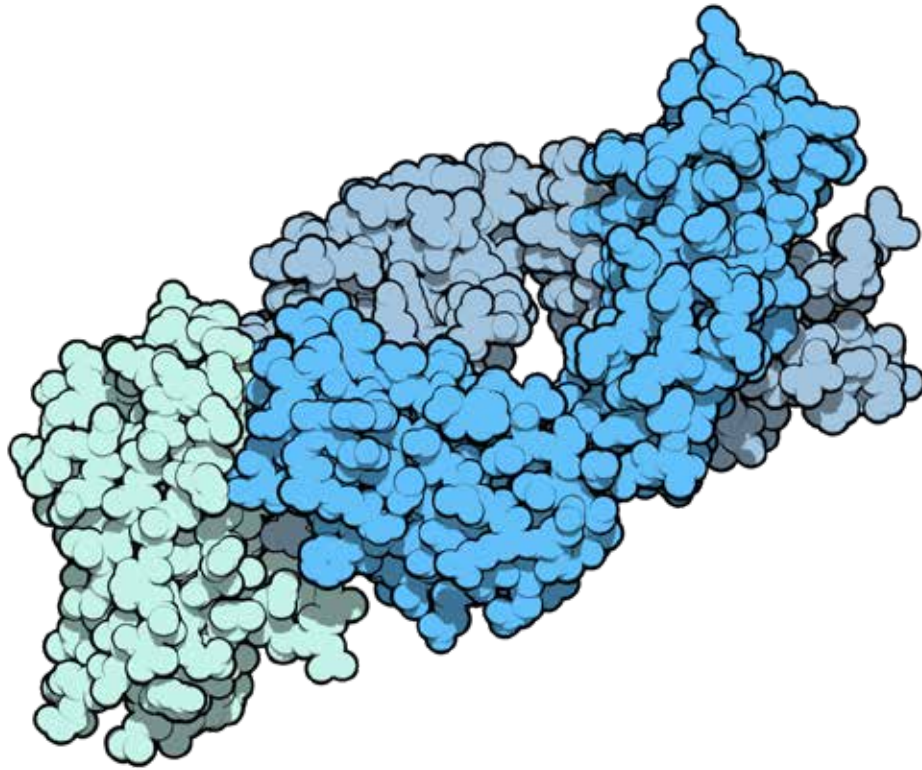
The opiate emergency brings us back to the themes of this historical survey. It shows how clinical practice and tools are affected by social, political, and cultural forces. The opiate pandemic has generated

enormous media scrutiny, hundreds of lawsuits, widespread legislative action, and vast suffering. It demonstrates, with searing emotion, the continuing difficulty of managing the boundaries between legitimate and illegitimate drug use, since at its heart is a deeply human experience – pain, which is often physical and just as often emotional, psychological, existential, or spiritual. The ways in which people experience, and opiates and other drugs address, non-physical pain is a crucial question for historians and clinicians.

The epidemic demonstrates as well the limits of governmental power in curbing the behavior of patients or of pharmaceutical manufacturers, who wield significant influence in Washington, D.C. It shows too how successful the medical profession has been in asserting its authority over clinical practice.

Long before the current opiate epidemic, the quest for powerful, non-addictive pain relief has been

an elusive research goal. In the 21st century, this effort has taken what could be called a genetic turn. As the structure, functions, and interactions of cells and their products have steadily come into view, work to understand how genes predispose, signal, and cause illness (including pain) has increasingly defined research and infiltrated clinical practice. Even though the terms are often used interchangeably, personalized medicine considers patients' genetic make-up with attention to individual preferences, beliefs, attitudes, and the social setting. Precision medicine is a health-care delivery model that relies heavily on data, analytics, and information. It emphasizes careful assessment of molecular, environmental, lifestyle, and behavioral factors in health and disease. In 2015 the federal government sought to boost precision medicine when President Barack Obama announced the



Monoclonal antibodies are manufactured versions of immune system proteins (antibodies) that are designed to attach to a specific target. An example is Herceptin, which attaches to the HER2 protein on cancer cells, which can help stop the cells from growing. About a quarter of all breast cancers have an excess (over-expression) of the HER-2 gene that produces too many of these HER-2/neu receptors found on the surface of the tumor cell. A drug marketed in 1998 by Genentech, Trastuzumab, sold as Herceptin among others, is a monoclonal antibody, effective only for treatment of HER-2-positive tumor cells. By 2008, there were about 30 monoclonal antibodies available, with global sales of about US\$30 billion. By 2014, nearly 50 were on the market. (59)

<p>PMI (Precision Medicine Initiative) Cohort Program (PMI-CP). The National Institutes of Health is assembling a research cohort of one million or more Americans from whom genetic and other data will be collected, with the goal</p>	<p>of advancing understanding of determinative patterns in genetic markers or mutations. One issue that the PMI will investigate is how to incorporate a vast and growing universe of wearable and in-home self-tracking devices, sensors,</p>	<p>applications, and networks. A major focus of personalized medicine is identifying genetic biomarkers for cancer. In 2018 personalized medicines, which seek to exploit genetic knowledge for therapies, accounted for roughly 40 percent of</p>
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all new drug approvals. Boosters of precision medicine argue that it has the ability to “democratize medical care” by making sophisticated diagnostics widely available. (58)

Precision medicine, even in its formative period, shows how a convergence of scientific, medical, economic, and social forces continues to shape the development and

deployment of therapeutic drugs.

The opiate emergency in America reminds us of the challenges involved in establishing and policing the boundaries between medical and non-medical use. The coronavirus pandemic spotlights the role of governments – local, national, and global – in coordinating not just those boundaries but humanity’s

responses to new disease threats.

What do these still-unfolding events tell us about the history, and future, of drugs in medicine? First, it is rarely wise to underestimate the power of commercial forces and motivations in shaping how people, organizations, and governments behave. Since its emergence in the second half of the 1800s, the



Checkpoint inhibitor therapy targets immune checkpoints, which, when stimulated by cancer cells, can “apply the brakes” to an immune-system response. In this way, some cancers can protect themselves from attack. Checkpoint therapy can block the ability of cancer cells to inhibit the immune system in this way. The first anti-cancer drug targeting an immune checkpoint was ipilimumab, which was approved in the United States in 2011. Currently approved checkpoint inhibitors target molecules that bind to receptors on an immune cell surface, which inhibits immune cell activity by disabling key regulatory role on T cell activities. (60)

pharmaceutical industry has had a distinctive role, unusual visibility and influence, and plenty of critics. In addition, a paradox at the heart of precision medicine can convey another lesson. Even as we extend our understanding of disease and health to the molecular, cellular, and intra-cellular levels, a timeless feature of clinical practice is

reasserting itself. This is the enormous range of individual variability that doctors see every day. Despite having the same disease, or receiving the same medication, people's courses of diseases, arcs of recovery, and reactions to medicines vary enormously. There is evidence, if not yet proof, that such variability is itself encoded in people's genes.

This would mean that the quest for ever-better medical therapies will continue to reckon with broad social forces and endless individual quirks – just as it always has.

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