FROM GERMS TO GENES: TRENDS IN DRUG THERAPY, 1852-2002*

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Less than a decade after the founding of the American Pharmaceutical Association, the noted American physician Oliver Wendell Holmes, addressing the Massachusetts Medical Society in 1860, made his oft-quoted statement that "...if the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind - and all the worse for the fishes."[1]

The pharmaceutical armamentarium of the middle of the 19th century was not quite so useless as the skeptic Holmes suggested. Even he qualified his condemnation by admitting that there were exceptions to his generalization, such as opium. Yet it is a striking fact that the drug therapy of the period around 1850 was in many ways more similar to that of antiquity and the Middle Ages than is is to that of the early 21st century. As historian Charles Rosenberg has noted: "Medical therapeutics changed remarkably little in the two millennia preceding 1800."[2]

This point can be illustrated by comparing the drug therapy of today to that of the middle of the nineteenth century. A useful starting point is an examination of a list of the ten most prescribed drugs of the year 2000 in the United States and their therapeutic uses (Table I).[3]

TABLE I

Ten Most Prescribed Drugs (U.S., 2000)

Drug	Use
Vicodin	Pain Killer
Lipitor	Lower Cholesterol
Premarin	Treat Menopausal Problems & Some Cancers
Synthroid	Treat Thyroid Problems
Atenolol	Treat High Blood Pressure
Lasix	Diuretic
Prilosec	Treat GERD
Albuterol	Treat Asthma
Norvasc	Treat High Blood Pressure
Alprazolam	Treat Anxiety Disorder

It is not surprising that none of these drugs were available in 1852. More importantly, however, there were no truly effective medicines available to American physicians of that period to treat most of the conditions noted in Table I, for example, cancer and thyroid problems. The physician of 1852 would not have even recognized the existence of conditions such as gastroesophageal reflux disease (GERD), high cholesterol levels, and anxiety disorder. In fact, their whole way of viewing disease and drug therapy was very different from the way we understand these subjects today.

Unfortunately, to my knowledge there are no lists of the most prescribed drugs of 1852

for the purposes of comparison. In order to give you some idea of the drug therapy of that day, however, we can examine one of the textbooks of materia medica and therapeutics of the period.

John Neill and Francis Gureny Smith's *A Hand-Book of Materia Medica and Therapeutics* is a good choice because it just happened to be published in the same year and city in which the American Pharmaceutical Association was established, namely, 1852 in Philadelphia.[4] Table II shows the classification scheme for remedies used by Neill and Smith, a classification that was not unlike that of many other books on materia medica of the period, such as George B. Wood's *A Treatise on Therapeutics and Pharmacology, or Materia Medica*.[5]

TABLE II

Classification of Remedies (Neill and Smith, 1852)

General Remedies	Local Remedies	
Astringents	Emetics	Epispactics
Tonics	Cathartics	Rubefacients
Arterial Stimulants	Diuretics	Escharotics
Nervous Stimulants	Diaphoretics	Emollients
Cerebral Stimulants	Expectorants	Demulcents
Excito-Motor Stimulants	Emmenagogues	Diluents
Arterial Sedatives	Sialogogues	Antacids
Nervous Sedatives	Errhines	Anthelminitcs
Alteratives		

Space does not permit a discussion of this classification system in detail, nor is it necessary to do so to make my point about the differences in thinking about drug action between 1852 and 2002. Although of course we recognize some of the terms in this classification system, others are less familiar to us. More importantly, this is not the way that we would find drugs organized and classified in a modern textbook of pharmacology. By and large, these terms describe broad physiological actions of the remedies, aimed at treating particular symptoms of disease. Cathartics purge and emetics vomit, while diaphoretics promote sweating and rubefacients inflame the skin. Terms such as "tonic" and "alterative" have broad and somewhat vague meanings.

Historian John Harley Warner has eloquently described the shift in therapeutics that occurred over the course of the nineteenth century, from what he calls "specificity" (or individualism) to "universalism."[6] Focusing on the United States, he shows that up to at least the 1860s, physicians viewed disease as essentially a systemic imbalance (much as their counterparts as far back as antiquity did). Although specific theories of pathology may have differed, Warner argues that they were all based on the general view that illness was usually due to either excessive excitement or enfeeblement of the body's systems. The body was viewed as an interconnected whole, and the role of the physician was to restore its natural balance. This was done primarily by stimulating or depressing the system as needed.

Treatment tended to be highly individualistic. The patient's health, or natural balance, was affected by such factors as climate, age, ethnicity, socioeconomic position, and habits. The idea of disease-specific remedies, which disregarded the idiosyncracies of patient and place, was

not generally accepted. Though physicians were increasingly recognizing the existence of specific diseases, they believed that various environmental influences could change one disease into another and that a single disease could take on a variety of forms. They also believed that the physiological action of remedies could be modified by various influences. Warner notes that:

> "Two patients with the identical disease could require opposite treatments. This was precisely the point that Harvard professor John Ware made in admonishing his students to distinguish between 'a pathological and a therapeutic diagnosis.' The name that pathological diagnosis assigned to a disease was not a trustworthy guide in therapy, he urged, for 'cases of which the pathological character is precisely the same may require a treatment diametrically opposite.'"[7]

Such views made it difficult to apply knowledge gained in one situation to another context. For example, Warner states, "...it was not at all clear that the findings of therapeutic research in urban hospitals were applicable to the vast majority of sick Americans."[8] The rapid growth of experimental medical science in the last decades of the nineteenth century, however, was to undermine the principle of specificity and usher in a more universalist approach to therapeutics.

Advances in chemistry and physiology, along with the emergence of such biomedical disciplines as pharmacology, bacteriology, and immunology, dramatically altered the understanding of disease and of the human body. Returning to Table II, we can see, for example, that there is no category for antimicrobial drugs in the classification scheme. This is not surprising, of course, given the fact that the germ theory of disease had not yet been established in 1852. A very few drugs which we now know to have antimicrobial action, most notably

quinine, were in use at this time, but their therapeutic efficacy was empirically discovered and their mechanism of action was not understood. In the mid-nineteenth century, there was also no understanding of such vital components of the body as vitamins and hormones, although there was at least a vague recognition that certain factors in the diet could help prevent some diseases. The drugs that were available to the medical and pharmaceutical professions usually treated only the symptoms of disease rather than getting at the causes.

In an introductory lecture given to the medical class of 1856-1857 at Harvard University, Professor of Materia Medica Edward Clarke warned his students about the dangers of assuming that all they needed to cure disease was the right drug. He noted that one might get the impression from reading the treatises on materia medica of the day that one could find in these works all "the needful weapons with which to combat or manage disease." He went on to add:

> "It is true that experience and observation will soon disabuse you of your error. Before the first decade of your life as a practitioner has passed, perhaps before you have made a year's acquaintance with the sick room, you will have learned that though Senna will purge, and Ipecac vomit, and Calomel salivate, and Opium stupify, yet that neither Senna, Ipecac, Calomel or Opium will *cure* disease except in rare instances."[9]

Clarke, in fact, was pessimistic enough to express the view that not only did drugs not cure disease in most cases, but "judging from the discoveries of modern science, we have no reason to expect that they ever will."[10] Lest we be too harsh on Clarke for this judgement, let us remember that "modern science" had yet to substantially modify drug therapy in 1856, though it was on the eve of transforming medicine. What were the best medicines available to physicians in the mid-nineteenth century? Physician-historian Ronald Mann has summed up the most

useful drugs of the mid-nineteenth century as follows:

> "The best of the first British Pharmacopoeia of 1864 must seem to be ... digitalis, opium, atropine, a salt of morphine, quinine sulphate, ether, chloroform, ferrous sulphate, iodine, sodium bicarbonate, salt and a few other household remedies."[11]

Except for the then newly-discovered anesthetics ether and chloroform, most of these drugs had been used in Western medicine, at least in their crude natural form if not as pure chemical compounds, for centuries. For example, the use of opium to ease pain dates back to antiquity, and cinchona bark (the source of quinine) was introduced into European medicine to treat malaria and other intermittent fevers in the seventeenth century.

The second half of the nineteenth century, however, witnessed the beginnings of a biomedical revolution that was to eventually transform drug therapy. Developments in the medical sciences led to the identification of specific causes for specific diseases and a better understanding of the action of drugs. So, for example, infectious diseases were shown to be caused by specific microorganisms. The cause of diphtheria is the same in everyone who contracts the disease, namely the diphtheria bacillus and the toxin it produces, and generally speaking the same remedy (in this case the diphtheria antitoxin that was developed in the 1890s) is used to treat the disease in each patient. Disease is not due to some general imbalance of the system, to be treated largely by stimulation or depression.

To the extent that space permits, let us briefly review some of these advances in medicine and the consequences for drug therapy. One of the most important developments in this period was the demonstration that infectious diseases, which had long been the major medical causes of mortality, were caused by specific microorganisms. In the decades of the 1860s through the

1880s, Louis Pasteur in France and Robert Koch in Germany firmly established the germ theory of disease. A whole new science of microbiology grew up as a result of germ theory, and investigators began to isolate the pathogenic organisms that caused infectious diseases. For example, in 1882 Koch isolated the tubercle bacillus and demonstrated that it was the causal organism of tuberculosis.[12]

The science of immunology was another offshoot of the germ theory. Although smallpox inoculation had been practiced for centuries, and Edward Jenner had introduced the safer technique of vaccination into medicine at the end of the eighteenth century, there was no understanding at the time of how immunization worked. Utilizing his knowledge of germ theory, Pasteur was able to develop vaccines against anthrax and rabies in the 1880s. Vaccines against other diseases followed in the ensuing decades. In the last decade of the nineteenth century, Emil von Behring and his colleagues in Germany used immunological principles to develop an antitoxin for the treatment of diphtheria, a major advance in drug therapy. The twentieth century witnessed the development of preventive vaccines against a host of illnesses, such as polio and measles, as well as the eradication of smallpox through a worldwide vaccination campaign.[13]

An understanding of the cause of infectious diseases also led to the development of chemotherapy in the early years of the twentieth century. German-Jewish physician Paul Ehrlich established the principles of the chemotherapy of infectious disease as he sought to discover compounds that would destroy pathogenic microorganisms in the human body without unduly harming the host cells. In 1910, he introduced Salvarsan, a specific chemical agent for the treatment of syphilis and the first synthetic chemical drug that proved efficacious against an

infectious disease. Ehrlich was also instrumental, along with Englishman John Newport Langley, in developing the receptor theory of drug action at this time.[14]

The development of organic chemistry in the second half of the nineteenth century had already enabled biomedical researchers to unravel the chemical structure of some drugs, and there had even been some synthesis of new drugs, such as aspirin by the end of the century. Modern experimental pharmacology also was established as a discipline in the late nineteenth century, enabling researchers to better evaluate and understand the physiological action of drugs. The symbiotic relationship between chemistry and pharmacology also promoted the beginnings of research on the relation between the chemical structure of a molecule and its pharmacological action. This kind of structure-activity thinking had played a crucial role in Ehrlich's work.[15]

In the early decades of the twentieth century, developments in physiology and biochemistry led scientific investigators to become more aware that disease could be caused not only by the presence of something in the body, namely germs, but also by the absence of some vital physiological constituent. Although there were earlier attempts to associate certain diseases with dietary deficiencies and earlier studies on glandular extracts, the concepts of hormones and vitamins did not clearly emerge until this time, when a number of such entities were isolated and used therapeutically. The first hormone to be isolated in a pure form was adrenaline (or epinephrine) in 1901, and the term "hormone" (from the Greek for "I excite") was introduced in 1905. One of the most dramatic examples of hormone therapy was insulin for the treatment of diabetes, introduced by Banting and Best and their colleagues at the University of Toronto in the early 1920s. The term "vitamin" (originally "vitamine") was coined in 1912, and researchers in the United States soon determined that one of these vitamins, what we now call vitamin A, was

present in butterfat. Other vitamins were soon discovered and found their way into medical practice for the treatment of dietary deficiency diseases such as scurvy, rickets, and beriberi.[16]

After Ehrlich's success with Salvarsan, there followed a quarter of a century without much further progress in the discovery of drugs to treat infectious diseases. Then in 1935 there was a dramatic breakthrough when Gerhard Domagk in Germany announced that animal studies and clinical tests had demonstrated the curative action of Prontosil, an azo dye containing the sulfonamide group, against streptococcal infections. French scientists soon determined that Prontosil was broken down in the body, and that one of the products, sulfanilamide, was actually the active agent. This discovery paved the way for the synthesis of a whole series of compounds, the so-called "sulfa drugs," which proved efficacious against a variety of serious bacterial diseases.[17]

The sulfas were soon followed by the introduction of a yet more important class of "miracle drugs," the antibiotics. Following up on Alexander Fleming's 1929 paper reported on the antibacterial effects of an extract from the *Penicillium* mold, Howard Florey, Ernst Chain and their coworkers at Oxford University isolated penicillin in relatively pure form in 1939. Animal tests and clinical trials demonstrated the remarkable efficacy of this drug in the treatment of infectious disease. The urgent need for penicillin for the war effort spurred the development of large-scale manufacturing procedures for the drug, with the United States leading the way. Even before the war had ended, another antibiotic, streptomycin, had been discovered in the laboratory of Selman Waksman at Rutgers University. Streptomycin was especially promising in the treatment of tuberculosis. In the late 1940s, a number of broad spectrum antibiotics were introduced, including chloramphenicol and the tetracyclines. The discovery of penicillin had

ushered in the "era of antibiotics," the most useful drugs to date in the fight against infectious disease.[18]

The "era of antibiotics" was soon followed by the "era of psychopharmaceuticals." Although certain drugs, such as opium, had been used for centuries in the effort to treat mental illness, the first significant success in this area came with the introduction of chlorpromazine for the treatment of psychotic patients in 1952. Other psychoactive drugs that proved efficacious in the treatment of the mentally ill soon followed. Today we have a host of compounds, such as the selective serotonin uptake inhibitors, for the treatment of depression, anxiety, bipolar disorder, and other mental health problems.[19]

Heart disease, stoke, and cancer remain major killers in the United States, but there has been significant progress in the development of drug therapies against these diseases as we have increased our understanding of these illnesses. Taxol, for example, has proved efficacious in many cases in the treatment of breast and ovarian cancer. We have drugs available to help control the risk factors for heart disease and stroke, such as blood pressure and blood cholesterol level. Anticoagulants such as coumadin and diuretics such as Lasix are also valuable aids in dealing with cardiovascular illness.

In the limited space available, I have not been able to mention numerous other significant drugs introduced over the past 150 years. Whole categories of drug treatment have been omitted. For example, no mention has been made of the development of drugs that have proved useful in the treatment of asthma, Parkinson's disease, ulcers and other gastrointestinal problems, anemia, and a host of other medical conditions. Nor have I been able to do justice to the advances in our scientific understanding of the physiology and pathology of the human body and the mechanisms

of drug action. I have also not discussed the changes that have taken place in our methods for evaluating drugs, especially the development of large-scale clinical trials to provide more reliable statistical evidence about the efficacy and toxicity of drugs. Finally, I have not touched upon some of the negative aspects of drug therapy, such as side effects and the development of drug resistance by microbes. The reader who wishes to learn more about these developments is invited to consult the references listed in the notes section of this paper.[20]

One other point that I would like to emphasize, however, is that while we have moved, in Warner's words, from specificity to universalism in terms of our theories of disease and drug action, we have become more specific with respect to our choice of medicinals to treat a given disease. That is, we do not rely as much on a polypharmaceutical "shotgun" approach, where a prescription might consist of many ingredients, as our predecessors did. Nor do we tend to use a particular remedy to treat a host of different diseases. We rely, as much as possible, on specific remedies for specific diseases, as I indicated above. By and large, these are single-entity remedies rather than combinations of ingredients, and they are generally chemically pure substances rather than plant or animal parts in their natural state. We have, for example, vitamins and hormones to treat specific deficiency diseases, antibiotics to attack specific microbes, and so on. This development has also occurred largely over the past 150 years.

Today we seem to be at the beginning of another new era in drug therapy, brought on by the rise of molecular biology as a result of the discovery of the helical nature of DNA and the breaking of the genetic code. Genetic engineering has allowed us to utilize microorganisms to manufacture drugs, for example, the use of bacteria to produce human insulin. Our increased understanding of the human genome has opened the possibility of developing specific gene

therapies to repair or compensate for genetic defects. Although we have not gone very far down this path yet, the potential for therapeutics is enormous. On the other hand, the ethical issues raised by genetic manipulation are a legitimate cause for concern, but that subject is beyond the scope of my paper.

These remarkable advances in drug therapy, coupled with the automation and large-scale manufacturing associated with industrialization, have had a profound impact on the role of the pharmacist. At the time that the APhA was founded in 1852, most prescriptions still involved more than one ingredient and required some compounding. Over time, the compounding function of the pharmacist has been eroded until it has virtually disappeared. Yet the introduction of all of these new and effective drugs has led to a dramatic increase in the number of prescriptions dispensed, fueling a continuing demand for pharmacists. The scientific complexities associated with modern drug therapy have forced the pharmacist to become more of an expert on the pharmacological action of drugs and the factors that affect such action. The pharmacist's responsibility no longer stops at the point where the patient takes the drug into his or her body. The pharmacy school curriculum of today contains substantial coursework in pharmacology and therapeutics, as well as clinical clerkship experiences. In many ways, the profession is still adjusting to these developments.

A recent publication of the American Chemical Society, entitled *The Pharmaceutical Centruy: Ten Decades of Drug Discovery*, makes the point that "the preponderance of drug development has taken place since 1900," for since that year "hundreds of drugs ranging from sulfanilamides to AZT have been developed, and many more are in the pipeline." Looking ahead, the publication states: "It appears that the future will allow us to rationally attack the

medical ills of the world."[21] In a resounding note of optimism, the editors predict:

> "But at the rate that our knowledge is compounding, we shall soon know how to stop cancer from spreading, how to start the body's production of insulin, how to stop osteoporosis and grow new bone material, and possibly, how to regenerate the spinal cord."[22]

Given the dramatic developments that we have seen in the field of therapeutics since the APhA was founded in 1852, I hesitate to challenge these bold predictions. We have come a long way in the past 150 years with respect to drug therapy, and yet we still have a long way to go. While I do not want to rain on the parade, I think a note of caution, derived from history, is in order here. Towards the end of the nineteenth century, medical researchers buoyed by recent advances in understanding the relationship between the chemical structure of drugs and their pharmacological activity got carried away in their enthusiasm for the near-term therapeutic potential of these developments. In lectures delivered in 1877, for example, British physician and pharmacologist Thomas Lauder Brunton expressed his belief that the time might not be far off when scientists would be able to synthesize substances that would act on the body in any given way, thus placing therapeutics on a completely rational basis.[23] In 1889, he reemphasized his hopes for therapeutics when he stated:

> "The prospects of therapeutics appears to me very bright....I think it is highly probable that before long we shall have a series of drugs which will stimulate the biliary secretion of the liver or modify its glycogenic function, arranged in order of comparative strength....We may also look for a series of remedies which will modify the circulation by dilating the blood vessels not only temporarily but more or less permanently....We may

also, I think, fairly expect to obtain a series of remedies having an action upon the heart and vessels..."[24]

In spite of the impressive advances made in drug therapy over the past century or so, we have not yet achieved the lofty goals envisioned by Brunton and some of his contemporaries. We still cannot predict the pharmacological action of any compound with certainty by merely inspecting its structural formula, nor can we yet design drugs at will for specific diseases. As Richard Klausner, former Director of the National Cancer Institute, reminded us in the celebratory publication about the "pharmaceutical century" mentioned above, predicting the future is still a risky business. In his words, with which I will close this paper:

> "'It's always amazing how, for some things, we dramatically underestimate how far they are in the future, and for other things, we dramatically overestimate them. We're not that bad at predicting things that might be part of the future, but we're really bad at predicting the timing and kinetics and path to them.'"[25]

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Notes and References

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