Diuretic substances increase the flow of urine in various ways, but they have other effects as well, many of which are extraordinarily useful to physicians who treat a variety of disorders and diseases. There are different categories of diuretics, and diverse diuretic agents are used in medicine for well-defined purposes.

Diuretics are among the most commonly prescribed drugs in the United States today, and they have four primary uses. Some diuretics are used to remove fluid from the tissues and cavities of the body in cases of edema. Diuretics also promote the elimination of waste products and poisons from the blood. In addition, physicians prescribe them to maintain the action of the kidneys.

The use of diuretics for therapeutic purposes is not new. In the 16th century, they were used for the treatment of edema (commonly called dropsy). The renowned physician Paracelsus acknowledged mercurous chloride as a diuretic. Before the rise of modern pharmaceutical research, natural substances with diuretic properties were cataloged by physicians eager to prescribe them. For instance, in 1902, the physician Samuel Potter included diuretics in his compendium of materials for prescription writing. Most of the diuretics listed were herbal derivatives.

Potter distinguished between “refrigerant,” “hydragogue,” and “stimulant” diuretics. According to Potter’s definition, refrigerant diuretics, such as potassium salts, “modify rather than increase the urine, and exercise a sedative action upon the heart and circulation,” whereas hydragogue diuretics “increase the water of the urine” and raise “arterial pressure” throughout the body or in the kidneys. Examples of hydragogue diuretics were caffeine, digitalis, and cocaine. Finally, Potter stated that stimulant diuretics “act upon the genitourinary mucous membrane by local irritation, which in excess causes inflammation and symptoms of a violent character.” He warned against over-use of these substances, which included cayenne pepper, juniper, and corn silk.

Other 19th- and early 20th-century physicians used diuretics before the modern science of pharmacology was well advanced. Until his death in 1878, William Stokes was a pioneer in the treatment of heart failure, focusing on the beneficial diuretic properties of mercury. Stokes made many important clinical observations about mercury and provided guidelines for when and how to use it. He accurately underscored the importance of re-establishing urinary flow to ameliorate dyspnea (shortness of breath) in patients experiencing congestive heart failure.

The 20th century’s first effective diuretics were organomercurials. A Viennese medical student named Alfred Vogel discovered that when he administered sulfanilamide to heart patients, they excreted large amounts of sodium and potassium in their urine. This discovery was of incredible importance for the treatment of hypertension, and new derivatives of sulfanilamides were soon developed by the pharmaceutical company American Cyanamid.

Carbonic anhydrase inhibitors were a widely used treatment in the 1950s. But this family of diuretics had serious disadvantages. Most notably, the loss of bicarbonate led to metabolic acidosis, which could cause long-term problems. Scientists hoped to develop an agent that would inhibit the reabsorption of sodium and chloride ions.
in the kidney and increase urine production without disturbing the body’s balance of electrolytes. Researchers at Merck developed a compound called chlorothiazide, heralding a new era of diuretic drugs termed thiazides.

**Thiazide asides**

Merck shared the patent for a second-generation thiazide with CIBA, which conducted parallel research on diuretics. Hydrochlorothiazide (named Hydrodiuril and Esidrix, respectively, by Merck and CIBA) was first sold commercially in early 1959. These new drugs were marketed as effective treatments for congestive heart failure and high blood pressure. Their effect on the pharmaceutical industry was dramatic. Positive reports about the thiazides in the medical literature were reinforced by a well-financed marketing effort. Pharmaceutical companies made tens of millions of dollars on these new diuretics.

By the late 1950s, thiazide diuretics were considered superior to the organomercurials and to oral diuretics, such as the carbonic anhydrase inhibitors. One medical journal of the time insisted that chlorothiazide was the “most vital and specific weapon in the treatment of a relatively nonspecific disease.” Another claimed that the “advent of potent oral diuretics such as chlorothiazide promises to revolutionize the treatment of hypertension.”

The thiazides were introduced at an auspicious time. There was a demand for the effective treatment of edema and congestive heart failure, which, at the time, was still met almost exclusively by the use of the potentially toxic organomercurials. Physicians in the late 1950s were increasingly reluctant to use drugs with potentially harmful side effects, and thiazides offered a ready solution to their concerns. In its first year of release in 1957, chlorothiazide was incredibly popular. Thirteen million prescriptions were issued for Diuril, the trade name for the Merck drug. One million heart patients and half a million hypertensive patients took it that initial year. In 1958, sales of Diuril represented about 75% of the total market for diuretics, bringing more than $20 million to Merck Sharp & Dohme. These sales figures seemed to justify the multimillion-dollar investment in research and development that pharmaceutical firms like Merck had made in the 1930s and 1940s. Profitable drugs like the thiazides only accelerated research budgets at the top companies.

By the late 1950s, reports in medical journals confirmed the prolongation of survival in patients with malignant hypertension who were treated with diuretics. Still, many physicians questioned whether patients should be treated in the earlier stages of disease, before complications developed. The first randomized clinical trial of antihypertensive medications began in the late 1950s but was not completed until the next decade. Although no long-term clinical trials had been conducted with the new diuretics, epidemiological evidence suggested to many physicians that early treatment was justified. The characteristics of chlorothiazide as a relatively benign medication compared with the carbonic anhydrase inhibitors undoubtedly influenced such decisions.

The increasing use of thiazide diuretics had a measurable impact on death rates from cardiovascular disease. The American Heart Association and the National Institutes of Health reported declining death rates as early as 1959 that were partly attributable to the new antihypertensive thiazides. The thiazide diuretics also augmented the effects of other antihypertensive drugs. They proved to be an effective way of eliminating excess water and salt from the body and were safe when properly used. Diuretic medications introduced between 1950 and 1965 came to dominate the treatment of hypertension. Before 1950, there were no generally recommended drugs to lower blood pressure. Twenty years later, at least four major families of such drugs were widely used.

Pharmaceutical science has come a long way since physicians and herbalists used mercury and other natural substances in hit-or-miss ways to obtain diuretic effects.

**Further reading**

University of Utah: NetPharmacology; http://lysine.pharm.utah.edu/netpharm/netpharm_00/notes/diuretics.html#History.


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