The origins of pharmacology in the 16th century proposed extracting the essence or "arcanum" from substances. Other medical alchemists active principles from plants and minerals. Remedies from plants went through several editions and was widely used in Europe in the 16th century was by Hieronymus Brunschwig whose first printed edition was published in 1500. Specific plant parts as described in the herbals of Gerard and of Turner trying to find better remedies for diseases. In contrast to information on the recognition (or notoriety) for the pursuit of the Philosopher's Stone that was expected to transmute base metals to gold. More certainly, cuneiform tablets from the library of Ashurbanipal, dated about 2000 BCE, contain detailed descriptions of the preparation of remedies.

The word "pharmacology" was not used in print until the 17th century, however, as far back as the 4th century, the word "pharmacum" was used to denote a medicine or drug. In the late 1600s, Walter Harris in his Course of Chymistry adapted this late Latin term to "pharmacologia". Coincident with its use in language, the study of pharmacology developed three basic principles that are used today. These concepts were formulated in the 16th century—and serve as a signpost for the origin of modern pharmacology—when the traditional beliefs of Hippocrates (460–357 BCE) and Galen (131–200 AD) were overthrown by the modern ideas of drug action. These three principles are:

1. Each disease has a unique cause for which there is a specific remedy.
2. The "doctrine of signatures" states that each remedy has an identifiable nature or essence that is obtained from the natural product by chemical extraction.
3. The administration of a remedy is based on dose-response by which the appropriate dose is determined.

Although these guiding principles are obvious to a modern pharmacist, the recognition of their fundamental nature in the use of drugs was a hard-fought battle. To Hippocrates, who were cold in the second degree and that bitter almonds were hot and dry in the second degree.

The first significant challenge to the selection of remedies that subscribed to the doctrines of Galen came in the 16th century from those apothecaries who were seeking the active ingredients in plants, minerals, and animal products. Although alchemists have achieved recognition (or notoriety) for the pursuit of the Philosopher's Stone that was expected to transmute base metals to gold. Paracelsus (1493–1541) proposed extracting the essence or "arcanum" from substances. Other medical alchemists...
Form. Many fables thus developed regarding the officinarum because the plant contains use of the four humors. For example, celandine was thought to be good for jaundice. The concept seems no more satisfactory as a way of selecting remedies than remedies showed by their form a sign.

In its simplest form, the doctrine of signatures stated that plants and other sources of remedies showed by their form a sign of the disease for which they should be used. This concept seems no more satisfactory as a way of selecting remedies than the old Galenical use of the four humors. For example, celandine was thought to be good for jaundice because the plant contains yellow juice. Also, the root of the mandrake (Mandragora officinarum), a perennial plant native to southern Europe, was thought to resemble human form. Many fables thus developed regarding the morphology of mandrake root as a

Doctrines of Signatures

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Like the doctrine of signatures, the understanding that most drugs should be taken orally developed with the interest in alchemical extraction of active ingredients. However, oral administration was by no means the only way to use a remedy. In the 16th century, peony roots were believed to be effective in epilepsy and other disorders of the mind because the thick, knobby, tuberous root was thought to resemble the brain in some way. Alas, old habits of mind die hard. Peony roots were considered effective both when taken internally and when worn as an amulet. Many remedies—not just for skin conditions—were used as ointments, poultices, and plasters for internal illness. For example, many individuals developed the swollen, hard spleen characteristic of chronic malaria, and although the cause was not known, many remedies for the spleen were placed on the skin over that organ. Fortunately, by appropriating the old doctrine of signatures (because it opposed the theory of humors and the Galenical belief that opposites cured) and refining it (by adding the novel idea that the internal essence of a plant was the true signature or contained the real remedy), medical alchemists furthered the sophistication of disease remediation.

Dose-Response

The concept that the response to a drug is dose-dependent is a basic premise in pharmacology and is an essential part of drug-receptor interaction. Nevertheless, this concept has not always been associated clearly with the use of remedies. When drugs are taken orally, the relation of dose to response is easier to see than when the remedy is applied externally or is used as an amulet or talisman. There are, of course, dose-response considerations in chemicals absorbed through the skin, and modern drugs applied in patches to the skin require some unique pharmacologic investigation (16). There is some evidence that cutaneous absorption of drugs was recognized in the 16th century. Methods for cleaning the skin and for increasing vasodilation in the areas of application of ointments and poultices were commonly employed. Warm unguents were rubbed into skin that had first been cleaned with warm alcohol (e.g., wine), and if large areas of the skin were to be covered with an ointment, the patient was advised to stand in front of the fire (17).

In oral administration, the relationship of dose to effective action was sometimes clearly stated. Prescriptions often included a statement of the amount to be used, so that a specific amount in ounces or drams should be given as a dose. One prescription from 1562, which proposed a mixture of equal amounts of hyoscyamus (Hyoscyamus niger) and opium, stated clearly that giving one dram to a person caused sleep. A precise comment about dose-response was added: "If you want him to sleep less, give him less" (18). It was often recommended that children be given lower doses than adults.

Historically, Paracelsus’ outspoken dismissal of Galen and Galenical remedies containing mixtures of plants was a catalyst that encouraged others to reject tradition and resort to experimentation. Like all successful challenges to tradition, the 16th century was a time when the desire and need for change was widespread. With the arrival of medical alchemy and the ability to extract remedies from plants or minerals by fire with various types of equipment, the age of pharmacology had arrived. The necessity for equating disease with the four humors was quietly ignored by many medical alchemists but managed to linger on unhealthily in the teachings of the medical schools where the tradition of Galenical remedies persisted for another century and where disagreement with the abrasive Paracelsus was strongest. Although Paracelsus was the most vocal critic of Galenical remedies, he did not reject plants as sources of remedies. One of his most popular prescriptions for treating patients contained opium, along with gold, pearls, and laudanum. The last ingredient was a gummy resin from a plant native to Europe, the rock rose (Cistus ladanifer), but the name “laudanum” became attached to the only active ingredient, opium, and tincture of opium is still known as laudanum.

A more important contribution from Paracelsus [found in his Seven Defenases, or the Reply to Certain Calumnations of His Enemies (19)], however, is the well-known statement that it is only the dose that makes something beneficial or harmful: “All things are poison, and nothing is without poison: The Dosis[sic] alone makes a thing not poison. For example, every food and drink, if taken beyond its Dose, is poison.” In pharmacologic terms of dose-response, Paracelsus’ statement is best described by two dose-response curves (Figure 2.1), where line A is a plot of percent response of a population for a desired effect against dose and line B is a plot of percent response for a side effect in the same population. The plot in Figure 2.1 assumes normal distribution for both lines A and B.

**Figure 2.**

* Dose-response relationship illustrating Paracelsus’ quotation using two variables. At dose $X_1$, 50% of a population shows the desired action (A) and at dose $X_2$, 50% of the same population shows an undesired action or side-
The importance of dose-response in the study of drugs is paramount in bioassays that determine the potency of preparations and that aid the development of potential drugs. As early as 1733, De Moivre published the equation for normal distribution of a variable (20). Over a century later, in 1879, Galton proposed that variation in susceptibility of individuals was related to the curve of normal distribution (21). When the percent response plotted against the log of the dose is normally distributed, the resultant symmetrical curve resembles a drawn-out S-shape. The ED$_{50}$ (dose effective in 50% of the test procedures) became important in bioassays for comparing the effectiveness of two preparations. The similar concept of the LD$_{50}$ (the dose that kills 50% of the test organisms) was also developed. Statistical methods were created for finding the best-fitting lines for ED$_{50}$ and LD$_{50}$ determinations. The statistical argument that made the 50% dose the most valuable was that variance was at a minimum at this point. Probit analysis (22) was developed for evaluating variance and was based on the assumption of normal distribution. Data were transformed into a straight line when percent responses, converted into normal equivalent deviates (probits), were plotted against doses on a logarithmic scale. Such results could be expressed as LD$_{50}$ ± S.E.

In any such calculation, the basic assumption is still that the data are normally distributed, and this is a reasonable assumption for much biological data; however, many special cases occur in which other distributions are routinely encountered. One such case is when a drug (or other chemical) may initially enhance a response followed by inhibition with increasing doses, resulting in an inverted U-shaped doseresponse relationship (Figure 3).

Figure 3.
Dose-response relationship where the nature of the response changes with increasing doses. With increasing doses the response increases from the initial conditions up to dose $X_1$. As the dose is increased further, the response decreases. Starting at dose $X_2$ the response is below the initial conditions.

Numerous examples of the inverted-U curve (also called hormetic dose-response) in immunopharmacology have recently been reviewed (23). The statement by Paracelsus on the effect of increasing doses, where a drug first helps and then harms, could be considered an example of hormesis (24).

The various applications of dose-response have been major factors in the development of modern pharmacology and in understanding the mechanism of action of drugs. The importance of dose-response goes well beyond the early emphasis on the percentile response, although this is still a powerful tool for analysis of data and has played a major role as the study of drugs emerged from the long period during which the relationship between cause and cure was not precisely recognized. Modern pharmacology can involve studies of drugs based not on populations but on individual responses to drugs, with regard to specific genetic differences. These studies would have amazed and delighted the 16th century alchemist and apothecary who often based his “proof” of the effectiveness of his remedy on success in two out of three patients. Indeed, the physicist Herman Von Helmholtz (1821–1894) said that all science is measurement and that applies to pharmacology no less than to physics.

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