

Perspectives in Pharmacology

Experimental Therapeutics in the Renaissance

STATA NORTON

Department of Pharmacology, Toxicology and Therapeutics, University of Kansas School of Medicine, Kansas City, Kansas

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ABSTRACT

Detailed accounts of therapeutics at the time of the European Renaissance written by the participants have not survived in large numbers. One manuscript, dated 1562, was written by friars in a religious order in Italy dedicated to the care of the sick. Their remedies, methods of preparation, and uses were detailed by the friars and offer a glimpse into the beginnings of

experimentation with drugs and rejection of tradition and authority in determining the effectiveness of a remedy. These developing concepts were combined in the manuscript with traditional treatments dating back through the Middle Ages to the medical methods of Greece and Rome.

The powerful methods of modern experimental therapeutics, especially prospective, controlled studies of human populations and statistical analysis of data, are developments of the 20th century. Other methods of determining the usefulness of remedies, however, can be used to distinguish cause (administration of a drug) and effect (recovery from illness) from association without causation. In examining older studies of experimental therapeutics, particularly those before the development of statistical analysis, other criteria must be used. This is essential in studying drug development during the transition of alchemy into chemistry beginning in the European Renaissance.

Paracelsus (1493–1541) was an innovative physician and alchemist of the late Renaissance in Europe who has been credited with spreading interest in the synthesis of drugs through his doctrine of iatrochemistry (Strathern, 2000). The aim of iatrochemistry was to investigate the composition and action of chemicals used in medicine (Thompson, 2002). In this period of European history, experimental therapeutics was beginning as alchemists used their knowledge of synthesis of chemicals to produce drugs. Not all Renaissance alchemists were dedicated to the search for the fabled Philosophers' stone that would transmute base metals into gold. At the time when Paracelsus was wandering in Europe, proclaiming his doctrine of the importance of chemicals as drugs and denouncing Galenists and others who used herbal remedies for illnesses, a religious group, the friars of the Order of Saint Jerome, was using chemicals that they had synthesized as well as herbal preparations to treat the sick. This order

was founded about 1350 in Italy and was dedicated to the care of the sick. The order was disbanded about 300 years later. A manuscript¹ now in the Kenneth Spencer Research Library of the University of Kansas (University of Kansas, Lawrence, KS) was compiled by Friar Giovanni Andrea, dated 1562 in Lucca, Italy. The manuscript, entitled *Libro de i Secreti e Ricette (Book of Secret Remedies)*, has about 400 pages of remedies, including methods of preparation and details of use, probably collected over the 200 years of existence of the order before this materia medica was written down by Andrea. It is known as the *Gesuatti Manuscript* after the popular name of the friars, the "Gesuatti". As far as is known, this manuscript is the sole record of their materia medica.

Although well known individuals are identified historically with major changes in science, in any great shift in concepts, there is a broad base of persons, often unidentified, who contribute to the change. None of the friars of the Order of Saint Jerome is historically famous, but the *Gesuatti Manuscript* offers information on the ways in which drugs were used and how their effectiveness was examined by members of the order engaged in daily care of the sick. The descriptions of the remedies vary markedly in style of writing as well as content. Most of the writing is in Renaissance Italian along with some in Latin. The compilation gives a view of practical therapeutics emerging from the rigid traditions of the Middle Ages and early Renaissance during which there was strict adherence to authorities such as Galen. The manuscript con-

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¹ The manuscript, Pryce MSE1, is in the Department of Special Collections, Kenneth Spencer Research Library (University of Kansas, Lawrence, KS). The author is responsible for the transcription and translation of the hand-written manuscript.

tains about 1500 remedies for a long list of illnesses, including serious conditions such as malaria, tuberculosis, cancer, gout, infected wounds, epilepsy, kidney stones, asthma, and syphilis, and less threatening conditions such as toothache, cataract, ringworm, poor memory, and gray hair. The authors of these remedies, based on internal evidence, had varied backgrounds, suggesting that physicians, apothecaries, and alchemists were numbered among the friars.

Many of the remedies and some of the text, included as background material for the friars in their examination of patients, were mixtures of modern (for them) and traditional information. A discussion of digestion could have come from the new teachings of Vesalius, who lectured in the medical school of Padua from 1537 to 1543.

The first digestion [of food] is made in the stomach. It digests the food and the nutritive value of the food is passed to the liver through certain veins which have sent the mixture. The second digestion is made in the liver and the nutrition which the stomach has sent to the liver is converted into blood and the liver sends it to the veins. . . . The excess of the first digestion is the feces which nature sends to the bowels. The excess of the second digestion is the urine which the liver sends to the kidneys and then the kidneys distill it to the bladder through 2 pores which lead to ureters that are suspended in the flesh (folio 24r).

The concept of the cause of disease, however, was still mired in the Hippocratic school of the four humors: choleric (warm and dry), phlegmatic (cold and humid), sanguine (warm and humid), and melancholic (cold and dry). The traditional way to establish the validity of a remedy for a specific disease was to end the description with the terse phrase, “E provato” (it is tested), meaning that it had been obtained from an authority. When a friar attempted to evaluate a remedy directly, possibly one that he had devised, it was necessary to employ more modern ways of evaluating the outcome of treatment of a particular disease. Although some of their arguments seem superficial or naive, their attempts at least represented a break with tradition as the only source of truth. The friars did not have statistical methodology at hand, the common method required today in which treated individuals are compared with a control group. Instead, the friars resorted to the logical arguments defined much later by the statistician A. V. Hill, who set forth nine ways in which correlation could be linked to causation (Hill, 1977). Hill called these nine types of evidence: reproducibility, strength of association, specificity, relationship in time, biological gradient, biological plausibility, coherence of evidence, analogy, and experimentation. The friars used each of these types of evidence to argue for the value of remedies. It would have been most effective to use, as Hill intended, several of these types of evidence to document the value of each remedy, but only a brief account of each remedy was written down in their *materia medica*. The following examples of their innovative attempts in therapeutics and discard of tradition are drawn from these brief accounts.

Reproducibility

When a remedy is used under differing conditions, the more often a cure is achieved, the greater the reproducibility. The *Gesuatti Manuscript* has numerous examples of this.

One remedy for ringworm contained lard, juice of cabbage leaves, vinegar, and a few herbs. It was stated that “this recipe has been very, very useful, many, many times and is approved by me, Maestro Andrea” (folio 16v). Another remedy was a cure for difficult urination in older men. Several herbs were prescribed to be given in the morning and evening with “wonderful effect”. The patient “will be cured of such infirmity which many persons have tested” (folio 44v).

Strength of the Association

The more precise the observed relationship between the remedy and the cure, the more likely the association is causal. Some obvious associations are implied in the manuscript rather than stated. In one remedy, a prayer to cure a broken foot was assisted by tying the foot to a board after pressing the broken bone in place. The author commented that, after the prayer, the binding of the foot should be good and tight, “because in the binding lies the cure” (folio 92r). The prayer was given less emphasis than the binding. In another remedy for broken arms or legs, the practitioner was advised to wet the bandage with powdered red clay to make a good binding and keep the injured member quiet (folio 92r). It is an interesting sidelight on the level of knowledge of treatment of broken bones by some practitioners that it was thought necessary to describe these methods.

Specificity

To demonstrate causation, it is best if a remedy is recognized as specific for that condition. This is found fairly often in the manuscript where remedies were selected for a specific illness. In one remedy, a mixture of marine animals (sponges, sea urchins, starfish, and cuttlefish) was dried in the oven, powdered, and taken as pills for several days in the spring and in the fall as a remedy for goiter (folio 11r). This was the only condition for which these animals were used, and the remedy may have been effective if the iodine content was adequate.

The manuscript contains many remedies for wounds of all kinds, reflecting the frequency of these problems for the friars. Many remedies were used for all kinds of wounds, but some required unusual ingredients for specific purposes. One remedy called for live yeast culture, mistletoe, and ammonium chloride. The mixture was warmed, mixed with olive oil, and rubbed on the flesh in which iron, wood, or spines had become embedded (folio 74r). The use of yeast is interesting in this unguent because recent research has indicated that autolyzed yeast extract has the ability to induce antimicrobial peptides in epithelial cells and it has been suggested that the active ingredient in the yeast is isoleucine (Fehlbaum et al., 2000).

A very specific way to open abscesses using chemical cautery was described in detail (folio 75r). The materials used for this “cold burning” were lye from oak ashes, ground eggshells, quicklime (calcium oxide), and orpiment (native arsenic trisulfide). In the early 20th century, similar escharotics were still described in the *materia medica* (Funk, 1917).

Relationship in Time

The closer in time that the effect of a remedy is to the cure, the easier it is to attribute the benefit to the remedy. A rapid

cure from one remedy was described. The remedy, a mixture of St. John's wort, turpentine resin, saffron, and olive oil, was said to be powerful for stomach pain and for healing all wounds. The friar recommended it highly, stating "a few days ago, I used it and in one and a half hours everything was cured" (folio 105r). At no point in the manuscript was the possibility of a placebo response considered. Successful treatment implied causation.

Some remedies were expected to be slow to act. A distillate of plants was used for scrofulas, and the technique was to "give 3 ounces to the patient every morning. . . and continue it for one month and it will help greatly" (folio 12r). It was recognized that there were differences in the rate of healing and that, generally, treatment at the onset of an illness was more successful than treatment of chronic conditions. With one remedy, however, the author assured the reader that "even if it is an old illness it is possible to cure it in a few days and if it is a recent illness it will be cured rapidly" (folio 48v).

Biological Gradient

None of the therapeutic descriptions involved linear regression or any type of modern dose-response analysis. The closest approach to dose-response was the recognition that children should receive lower doses of many remedies than adults. A lotion for scabies containing sublimate (mercuric chloride) and rock alum (aluminum potassium sulfate) was used by wetting the skin in the area of infection. Since the preparation settled out, it was shaken before use. "When you wish to wet [the skin of] a little child, do not shake the lotion but take from that on top, which is more clear and less strong" (folio 32v).

A remedy for worms contained nine herbs including wormseed. The dose was 1 ounce for an adult or large child and 1/2 ounce if the child was small (folio 37v). This remedy may have been effective. The plant, wormseed, was probably *Artemisia maritima* L. or a related species that contains the anthelmintic compound santonin (Goodman and Gilman, 1941).

Biological Plausibility

When a novel remedy is proposed, there may be no precedent for its action. In this case, the author of a remedy may resort to argument involving unrelated current concepts to explain effectiveness. One remedy in the manuscript seemed to be recommended by the alchemist as a result of his enthusiasm for his synthesis rather than any tests of effectiveness. The friar was working with antimony (as he called it) or possibly with stibnite (antimony trisulfide). Both are found in nature. Masses of antimony occur in veins containing stibnite (Bayley, 1917). The friar-alchemist described how to prepare his remedy by putting antimony and sulfur in distilled vinegar. The vessel was sealed and held until no more red color came out into the vinegar. Then the red vinegar was distilled. The first liquid to come out of the still was like water. "Then you will see come from the still a stupendous miracle. . . Red drops will fall like blood which you will collect. . . You will have the fifth essence. . . All the treasure of the world is not equal to it" (folio 110v). The fifth essence or quintessence was a term from the Aristotelian concept of four elements (earth, air, fire, and water) plus the fifth essence (ether), which was

the fundamental principle. Paracelsus wrote, "there is a force of virtue shut up within things, a spirit like the spirit of life, in medicine called quintessence" (quoted by Thompson, 2002). The distillate like drops of blood may have been vitreous antimony trisulfide, which is described as a transparent, ruby-red mass (Stecher et al., 1960). Clearly this friar-alchemist was impressed with the transformation of a gray mass of native stibnite to a blood-red one. He described his quintessence of antimony as a remedy that "miraculously removes the pain of every sore and heals it" (folio 110v). His evidence was that he had produced a quintessence and therefore it must be of great remedial value, an argument that in modern terms is far from plausible, but it may have carried weight in the Renaissance.

Coherence of Evidence

The association of remedy and cure should not only be plausible but should agree with other evidence. This concept of related information was not ignored by the authors of the remedies in the manuscript. Leg sores seem to have been common, based on the number of remedies. Three chemicals were repeatedly used in ointments to be rubbed on sores. These were zinc oxide, white lead (lead carbonate), and litharge (yellow lead oxide). Wax and olive oil were used to make the ointment, and sometimes resin from fir or spruce trees was added. These ingredients were accepted as useful, and various proportions of each were used in different recipes, but the comments were similar. "Many doctors use this unguent [for leg sores]" (folio 65v). "A poultice of fine lead is best for such illness [as leg sores]" (folio 64r). "An ointment for bad legs that heals any sore difficult to cure" (folio 67r) contained 2 drams of zinc oxide, and 1 dram each of litharge and white lead in a base of plant gum.

Reasoning by Analogy

One causal association can be used to strengthen the case for another similar observation. Oil of tartar is an old alchemical preparation. Chaucer (1340?–1400) mentioned it in the "Yeoman's Tale" of alchemy in the *Canterbury Tales*. The method of preparation was described in the *Gesuatti Manuscript*. The base was tartar (potassium tartrate) obtained from grapes during the preparation of wine. The recipe started with 5 or 6 pounds of tartar, dried to powder in a furnace, then placed in a sack in a large glass flask, and put in a humid location for 20 or 30 days. Then the sack was boiled in 3 pounds of water until the water was reduced one-third. This water was called oil of tartar, and several uses were given. It would remove spots of ink or wine on cloth and could be used to clean paintings and drawings. By analogy, on the skin, it removed dark marks or freckles, and "it will make the skin lustrous and clear and stretch out every wrinkle. It will make you appear younger than you are" (folio 106r).

Oil of vitriol (sulfuric acid) was produced by alchemists as early as the 13th century (Holmes, 1941). The *Gesuatti Manuscript* gives a detailed description of the apparatus and method of preparation. In this recipe, the starting material was vitriolo romano (copper sulfate), which was heated continuously in a small, specially constructed kiln (Fig. 1). The alchemist who made the sulfuric acid noted, "I say that this

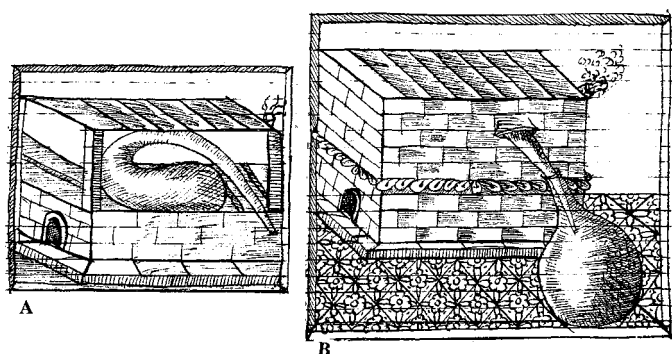


Fig. 1. Drawing of apparatus for producing sulfuric acid, from the manuscript (folios 106v and 107r). Published with the permission of the Department of Special Collections, Kenneth Spencer Research Library (University of Kansas). A, inside the kiln showing the glass retort to hold copper sulfate. B, bricked up kiln showing receptacle for sulfuric acid.

oil has so much potency that it consumes everything and it is not burned" (folio 107v). He described oil of vitriol as being composed of two of the Aristotelian elements, water (it was a liquid) and fire (it burned things). Although it seemed that such a powerful liquid must have great medical value, its practical use in remedies was limited to a few drops, well diluted.

If you put 2 drops in a glass of sweet wine, at once it will remove the sweetness and give it a certain burnt flavor, very appetizing to taste, and it gives you a very good stomach and will make you look younger, with very good breath and clears the eyesight and preserves the memory. It removes corns rapidly (folio 107v).

Again, the enthusiasm for the remedy was based on the transformation of one chemical into another with markedly different properties. Sulfuric acid continued to be used in therapeutics into the 20th century. The *Manual of Therapeutics* (Parke, Davis and Co., 1910) lists dilute sulfuric acid as valuable in chronic diarrhea, perhaps an echo of the "good stomach" of the earlier age.

Experimentation

An experiment to test a hypothesis was not a standard method in the Renaissance as it is now in science. Nevertheless, the concept of an experiment was known and was used to illustrate or reinforce a point. As such, an experiment represented the most marked deviation from reliance on authority or tradition and instead was a direct appeal to reason.

One remedy for superficial damage to the head or a head wound was prepared from two powdered herbs, scabiosa (probably *Scabiosa succisa* L.) and betony (woundwort; *Stachys* species) and was said to cure wounds rapidly. "If you wish to prove this, take a young chicken or other animal and cut the head. Then put on the powder and you will quickly see a marvelous result" (folio 13v). Except for the lack of a control animal, the experiment is very straightforward.

The manuscript contains several remedies for kidney stones and bladder stones, and the variety of ingredients in the remedies reflects both the seriousness of the disorder and the difficulty in finding cures. In one remedy, "to break the

stone in the bladder, take a fox and a hare alive and cut off the heads and carefully collect all their blood" (folio 45v). The blood was mixed with the head, feet, skin, and liver, dried in the oven, and made into powder. Taking a spoonful of powder in wine or other liquid in the morning and evening for several days was said to result in passage of the stone or gravel.

If you do not believe it, do the experiment. Take a spoonful of this powder and put it in a clean pot with wine or water or broth and also with vinegar, and put in a stone and cover it well and keep it in a warm place for 6 or 8 days. You will find the stone broken into several pieces (folio 45v).

Presumably the intent was to put a kidney or bladder stone, usually of calcium oxalate, in the test mixture. Although calcium oxalate is insoluble in acetic acid, the dilute acetic acid might have caused an impure calcium oxalate stone to break apart, allowing the friar to draw the erroneous conclusion that this would happen in a patient.

However poorly designed some of the experiments were, this manuscript represents a distinct break with the past and tells something of the state of mind, not of the famous contemporaries of the friars, but of individuals involved in daily care of the sick who wrote down their remedies for each other. The well known herbals of the period, such as John Gerard's (1633) and William Turner's (1551), extensively quoted the old authorities, Pliny, Galen, and Dioscorides, as sources of information on the value of their herbs as remedies. Their books are treasures of old traditions. Nevertheless, they lack the asides that illuminate the inquiring mind of the Renaissance individual who was personally treating the sick. The friars of the *Gesuatti Manuscript* were interested in all types of new remedies. Their descriptions are evidence of the beginnings of experimental therapeutics long before the therapeutic revolution of the 20th century.

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Address correspondence to: Dr. Stata Norton, Emeritus Professor, Department of Pharmacology, Toxicology and Therapeutics, University of Kansas School of Medicine, 3901 Rainbow Boulevard, Kansas City, KS 66160. E-mail: snorton@kumc.edu