

Drug testing in Renaissance Florence (16th-17th centuries)

Donatella Lippi PhD¹, Francesco Baldanzi², Otto Appenzeller MD, PhD³⁻⁴, Raffaella Bianucci, PhD⁵⁻⁷

¹Department of Experimental and Clinical Medicine, University of Florence, Italy.

²Department of History, Archaeology, Geography, Art and Performance, University of Florence, Italy.

³New Mexico Health Enhancement and Marathon Clinics Research Foundation, Albuquerque, NM, USA.

⁴New Mexico Museum of Natural History and Science, Albuquerque NM, USA.

⁵Legal Medicine Section, Department of Public Health and Paediatric Sciences, University of Turin, Italy.

⁶Warwick Medical School, Microbiology and Infection Unit, The University of Warwick, CV4 7AL, United Kingdom.

⁷UMR 7268, Laboratoire d'Anthropologie bio-culturelle, Droit, Etique & Santé (Adés), Faculté de Médecine de Marseille, France.

Abstract

Background and objective: Drugs have been used since antiquity but with no controls until recently. Unpublished manuscripts from the ancient Florentine archives of Santa Maria Nuova Hospital allow scholars to ascertain how drug testing was performed on human subjects during the Renaissance.

Comment: The activity of the *Collegio Medico* led to pharmacological research. In 1498, the first official European pharmacopoeia was published with the aim of standardizing the methods of drug preparation according to approved formulas.

What is new? The accounts considered show the relevance of *empirical observations and stories of individual patients*.

Conclusions: Approval of human experiments, an extremely long process, is rooted in Medieval medicine. New evidence is given to show how drug testing in human was performed in Renaissance Florence.

Keywords:

Drug testing; Clinical trials: Informed consent; history; Renaissance; Florence

What is known and objective

The ethical approach to experimentation in man has several components; two are more important than the others, the first being informed consent [1]. Informed consent is a relatively new concept in the history of medical practice. Over the past centuries, the power of physicians to make life or death decisions remained unchallenged with the end justifying the means. By ignoring their patients' will, ancient practitioners often abused their role and carried out experiments on paupers and on the weakest members of the community (i.e. insane, women, slaves, children, prisoners). Beginning in the 18th century, this unethical behaviour gradually changed and the rights of patients were progressively recognized.

Ethical principles on human experimentation were established only in recent years; guidelines and committees were established to ascertain whether a patient had given informed consent to a specific medical treatment [2, 3]. In parallel to ethical improvements, controlled trials have been developed and both the design and the statistical aspect of such procedures have been refined [4]. Approval of human experiments, an extremely long process, is rooted in Medieval medicine. New evidence is given to show how drug testing in human was performed in Renaissance Florence.

Comment

Drug research aimed at restoring health has its ori-

Corresponding author:

Dr Raffaella Bianucci, Laboratory of Physical Anthropology, Legal Medicine Section, Department of Public Health and Paediatric Science, University of Turin, Corso Galileo Galilei, 22, 10126 Turin, Italy. Phone: +390116705939; Fax: +390116707434 E-mail: raffaella.bianucci@unito.it

gins in ancient times and has played a crucial role in health care. Over the centuries, remedies were tried and tested. During the Middle Ages, when the Arabic knowledge was added to the Classical tradition, an enhancement of both drug studies and their effects took place [5].

Although there were different kinds of healers, who practiced medicine and surgery in a not yet fully medicalized society, physicians played a major role carrying out experiments at courts, universities, and hospitals. They both used animals and human beings in the experimentation phases and drew up detailed rules for testing [6].

In establishing these procedures, the physicians with “qualified experience” (*diōrismenē peira*) followed Galen’s principles and Galen’s works became the benchmark of medieval academic medicine [7]. Galen’s fundamental notions on drug testing were taken up by many Muslim medical authors and further developed by the Latin Scholastic Medicine [8]. Actually, detailed rules for new drug experimentation are found in the second book of Ibn Sīnā’s *Canon*. Ibn Sīnā (circa 980–1037) was a Persian polymath, who authored the *Canon of Medicine (Al-Qanun fi’-t-Tibb)*, a compendium of medical knowledge, a standard medical textbook in the Islamic world and Europe until the 18th century. In Ibn Sīnā’s work, seven rules were followed while performing the drug-testing experiment; rule no. 7 established that, in order to fully understand the strength and effect of a drug, this needed to be tested on human being [9, 10].

A renewed interest in this “experience-based” approach flourished a few centuries later. During the evaluation of drug efficacy in therapeutics, Peter of Spain (Petrus Hispanus, 13th century) and John of Saint Amand (circa 1230–1303) followed Ibn Sīnā’s *Canon*; their set of rules is very similar to those described by Ibn Sīnā three hundred years earlier [11]. In the 13th century, when Greco-Arabic authors’ masterpieces were translated into Latin, a growing need to verify the ancient affirmations, through a first-hand approach, became apparent.

Since physicians feared harmful effects to their patients, all unfamiliar practices and new drugs were test-

ed before use. A lively debate aroused about the need of establishing clear protocols with a special focus on test procedures and on the subjects used for those tests. European academic schools were particularly active in this debate and, among those, the School of Montpellier played a prominent role. This was the period in which a great amount of medical literature had become available in Latin and had to be sifted through.

In 1303, Bernard de Gordon (floruit 1270–1330) published the *Tractatus de gradibus* in which he listed a five-steps testing program for drugs based on the Galenic principles [12]. However, as a precautionary measure, he added a sixth innovative rule: *When we want to test a certain medicine on the human body, we should first test it on birds and then on dumb animals and then in hospitals and then on lesser brethren [in hospitalibus et postea in fratribus minoribus] and so on in turn, because it might kill if perhaps it were poisonous* [12].

Some years later, Arnaldus de Villanova (circa 1240–1311) completed his *Speculum medicine*. He specified that the subject of a given experiment had to be human beings; he detailed the rules to be followed to perform an *experimentum* properly and he listed the conditions that had to be observed *in experiendo* [11].

Arnaldus made a step forward in the distinction between “pharmacology” and “clinical pharmacology”; in his new protocol, distinction was made between the definition of the absolute character of a drug and the determination of its effects in a clinical context [11]. Based on “the conscientious use of current best evidence”, Bernard’s and Arnaldus’ approaches can be considered the anticipation of modern “evidence-based medicine” [13].

What is new?

Unpublished manuscripts from the ancient Florentine archives of Santa Maria Nuova Hospital allow scholars to ascertain how drug testing was performed on human subjects during the Renaissance. Manuscripts number 196 (1574–82) and 197 (1582–91) from the archive series “Affairs of the Doctors and Apothecaries Art” were analysed resorting to a dual philological–medical approach. This series reports both on the

administrative tasks of the ancient corporation and gives details on the pleas addressed to the Grand Duke by the medical practitioners. In the 16th century, clinical trials were mainly carried out on condemned criminals, prisoners, orphans, soldiers, or vagrants. Baccio Baldini (1517-1589), the Director of the Laurenziana Library in Florence and a Court physician of the Medici family, used prisoners for his tests. Between September 26th and 27th, 1566, Baldini tested a poison credited to Cosimo de' Medici (1519-1574) on a prisoner, Iacopo di Gimignano who was jailed in the Bargello prison, under sentence of death [14]. The different phases of the test were recorded in details. The prisoner was administered two drachms of arsenic in order to verify the efficacy of Cosimo's antidote. When the symptoms of poisoning manifested, he was administered an antidote; the reaction to poison and to antidote were carefully noted. Unfortunately, the text is incomplete and it is not mentioned whether Iacopo survived or not. In case of survival, Iacopo would have been granted clemency.

Similar cases are reported in the literature: a young man who had received monkhood (aconite) and Bezoar, after having developed serious symptoms and having recovered, was granted clemency or another young man, who was first administered monkhood and nux vomica (which contains strychnine), was later given an "Archducal powder" to antidote the poison and was set free [15].

Also the famous anatomist Gabriele Falloppio (circa 1523-1562) carried out experiments on poisons and administered opium to death-row inmates. He performed an experiment in Pisa on a man sentenced to death. His aim was to show that fevers could neutralize the noxious effect of opium, which was considered a cold poison. The man was given a first dose and survived whereas the second dose was lethal [16].

In general, prisoners were not ideal candidates for drug trials. Therefore, from the Middle Ages onward, hospitalised patients became the most suitable subjects for experiments. This practice is attested also in Florence. In the centre of Florence, at Santa Maria Nuova, stood a vast hospital where surgical training had been first established and where the *Collegio Med-*

ico (College of Physicians), the prominent state organization for the supervision of medicine and medical professions, was active.

The double-function of this structure created the ideal conditions for the development of pharmacological research within the boundaries of legality and efficacy. In 1498 (Florentine calendar), the first official European pharmacopoeia, the *Receptario fiorentino*, was published with the aim of standardizing the methods of drug preparation according to approved formulas. The legal nature of this text is confirmed by the presence of penalties for rule violations. Pharmacists were compelled to buy an official copy of the *Receptario fiorentino* from the Art of Physicians and Apothecaries. The second edition of the Florentine *Receptario* was commissioned by Cosimo de' Medici to the *Collegio Medico* and was published in 1550, and a third version was published in 1567. Further editions appeared in the following years. Apothecaries were compelled to follow carefully the instructions for drug preparation and administration so that the medicines prescribed by the physicians were correctly prepared and safe.

In this perspective, Cosimo de' Medici issued a special law on May 8th, 1562: whoever dealing with drugs and medicines had to get subpoenaed in front of the Officials of the Art of Doctors and Apothecaries [17]. This law was applied also to charlatans, quacks, and tumblers, who travelled across the State, selling sweet, bitter and opiated tinctures, soothing and purgative medicines, preserves, locs (a type of thicker syrup), syrups and juleps, robs (a type of medicinal syrup), troches (dried tables of drugs), powders, pills, *sieffi* (medicines composed by different powders kneaded with rubbers), collyria (a medical eye wash), ointments, plasters, oils, drugs with epithem (powdered drugs mixed with a liquid for external use) and cordials. Since several frauds were perpetrated by charlatans, the promulgation of this law was aimed at preventing the circulation of counterfeited drugs that may have caused harm.

Also Cosimo's successors tried to crack down this pharmacological abuse and the task of analysing and testing the products sold by the illegal practitioners was delegated to the *Collegio Medico*. Before testing the

drugs on hospitalised patients, the properties of the drugs were analysed by the members of the *Collegio Medico* who followed Galen's rules (i.e. the analyses based on the smell and taste of the drugs). Meanwhile, the secret cures of lay healers, handed down through generations, represent a precious heritage that had to be verified and, in some cases, preserved; if a prescription worked, no one could force the owner to reveal the chemical formula.

Many documents attest that unqualified empirics could apply to the *Collegio Medico* in order to be authorized to practice Medicine. The *Collegio Medico* examined their requests and returned the decision [17]. When the effects of a given drug were uncertain, the Grand Duke himself could order to proceed with a clinical trial on hospitalized patients. Many documents exemplify the legal procedures followed by the appellants who asked to show their skills in the treatment of specific diseases. Some of those documents are held by the Archives of the Hospital of Santa Maria Nuova. Usually appellants requested to be authorised to practice medicine, to test their drugs on patients and to maintain the secret of their formulas, in this specific order. The terms *Esperienza / sperimentarlo / esperimento / sperimentia* (experience, experimenting, and experiment) which were used to describe the tests had an interchangeable meaning; these terms acquired a different significance in contemporary literature [18].

At the end of the 16th century, Jacopo Choppa, a practitioner from Modena, applied to the *Collegio Medico* to be authorized to practice medicine in Florence. The *Collegio* rejected his application. Jacopo, then, appealed directly to the Grand Duke and cited the privileges given by the *Collegio Medico* in Padua and by the Republic of Venice [17]. The Grand Duke ordered a trial. Two patients were selected and Jacopo performed the experiment but failed.

Other unpublished documents dating back to the 16th century confirm the application of the above procedures. In March 1573 (according to the Florentine calendar), Mariotto di Deo wrote a plea to the Grand Duke claiming to possess a secret healing cancer drug (*segreto particolare sopra el guarire el canchero*). In order to obtain the license to practice medicine (*libera*

patente di poter medicare), he asked permission to show the efficacy of his remedy on patients without revealing his formula (*senza che lui habbia a manifestare detto suo segreto*).

The Grand Duke Cosimo authorized the experiment: *il Reverendo Spedalingo di Santa Maria Nuova gli dia un par di quei simili malati di cancro, che ne faccia esperienza*. However, no cancer patients were present at that time in the Hospital of Santa Maria Nuova: *non havendo nel nostro spedale da di molto tempo in qua havutone, ne di presente havendone che habbino tal male, non ho possuto darli tal cura, ne sperimentarlo*. Nevertheless, the *Spedalingo*, the director of the hospital, testified that many patients had been cured by Mariotto in the past and they were healed (*bene posso riferire a quella come io ho veduto di quelle persone che di tal male sono state da lui curate et altutto liberate*). Thanks to the attestation of the *Spedalingo*, who was a very influential person, Mariotto received the license one year later (*Facciasegli la patente di poter medicare quel male*) [19].

In 1585, when Francesco I de' Medici (1541-1587), Cosimo's son, ruled Florence, the *Collegio Medico* interceded for Giovanbartolomeo Ghesio, an empirical practitioner from Piacenza. Ghesio claimed to have a "special water" that healed both ulcers and blisters (*havere alcuni segreti d'una acqua fatta da lui, con la quale asserisce guarire volatiche et ulceri incurabili*). The Grand Duke gave his authorization and three patients were assigned to Giovanbartolomeo to demonstrate the efficacy of his remedy: *il Collegio de Medici gl' assegni dua o tre malati di simil male et guarendoli faccisi il privilegio* [20]. The dossier concerning the outcomes of Ghesio's experiments is incomplete and, unfortunately, no conclusion can be drawn.

Conclusion

Testing drugs was a common practice during the Renaissance. Prisoners and hospitalized patients, the majority of which belonged to the lower classes, were the most suitable subjects as they manifested a great variety of diseases. Each clinical trial had to be performed on a subject who suffered from a peculiar ailment and the relevant drugs had to be administered. Galen's and

Ibn Sīnā's rules required to test drugs on sick people and never on healthy subjects in order to evaluate the properties of a medicine against the “unbalanced” (humoral theory of medicine) conditions of a patient [20]. Once the nature of the disease was identified, the physician administered a drug, whose primary qualities had already been established by the *Collegio Medico*, to the patient and the drug would have neutralized the disease.

Over time, detailed records of experiences and cases were collected, paving the way for the new literary genre of *curationes* and *observations*. These accounts of individual cases and other occurrences of medical interest represent *an important sign of the new significance of observation in medical culture* [21, 22] and show the relevance given to *empirical observations, to the stories of individual patients, and to the knowledge of particulars rather than to universal theories* [15].

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References

[1] Beecher HK. Ethics and Clinical Research. *N Engl J Med* 1966; 274:1354–1360.

[2] Dowling HF. The dilemma of human experimentation with drugs: a historical perspective. *J Clin Pharmacol J New Drugs* 1967; 7(5):248-50.

[3] Murray PM. The History of Informed Consent. *The Iowa Orthopaedic Journal* 1990; 10:104-109.

[4] Bhatt A. Evolution of Clinical Research: A History Before and Beyond James Lind. *Perspectives in Clinical Research* 2010; 1(1): 6-10.

[5] Abdel-Halim RE. Experimental medicine 1000 years ago. *Urology Annals* 2011; 3(2):55-61.

[6] Leong E, Rankin A. Testing Drugs and Trying Cures: Experiment and Medicine in Medieval and Early Modern Europe. *Bulletin of the History of Medicine* (Summer 2017); 91(2). In press.

[7] Bynum W. Reflections on the History of Human Experimentation. In: Spicker S.F., Alon I., de Vries A., Engelhardt H.T. editors. *The Use of Human Beings in Research. Philosophy and*

Medicine, vol 28. Dordrecht :Springer; 1988:29-46.

[8] van der Eijk PJ. Galen's use of the concept of 'qualified experience' in his dietetic and pharmacological work. In: Debru A., editor. *Galen on pharmacology: Philosophy, history and medicine. Proceedings of the 5th international Galen colloquium, Lille, 16–18 March 1995*. Leiden: Brill; 1997:35–57.

[9] *Interpreting Avicenna: Critical Essays*. Edited by Peter Adamson, Cambridge. Cambridge University Press; 2013:98.

[10] Azizi MH. Ibn Sina and the clinical trial. *Arch Iranian Med* 2009; 12 (4): 435 – 436.

[11] McVaugh M. Determining a Drug's Properties: Medieval Experimental Protocols, *Bulletin of the History of Medicine*, (Summer 2017);91.2.In press, ref. 17: The rules are given in Arnau de Vilanova, *Speculum medicine*, cap. 22: De modo cognoscendi virtutes complexionatorum, primo per experimentum, in *Opera Arnaldi* (Lyons, 1504), fols. 10ra–11ra.

[12] Demaitre L. *Doctor Bernard de Gordon, Professor and Practitioner*. Toronto: Pontifical Institute of Medieval Studies; 1980.

[13] McVaugh M. The “Experience-Based Medicine” of the Thirteenth Century. *Science and Medicine* 2009; 14: 105-130.

[14] Marinozzi S, Giuffra V, Kieffer F. Baccio Baldini (1517-1589), protomedicus on the medical court between humanism and experimentalism. *Acta Med Hist Adriat*. 2015; 13(2):345-64.

[15] Stolberg M. Empiricism in Sixteenth-Century Medical Practice: The Notebooks of Georg Handsch. *Early Science and Medicine*. 2013; 18:487-516.

[16] Gabriele Falloppia, Libelli duo. alter de ulceribus: alter de tumoribus praeter naturam. Nunc recens in lucem editi. Illustrissimo Ioanni Iacobo Phucharo...Venetij: apud Donatum Bertellum, 1563.

[17] Ciuti F., *Il Collegio dei fisici e l'Arte dei medici e speciali di Firenze: dalla Repubblica allo Stato mediceo (XIV-XVI secolo)*. *Archivio Storico Italiano* 2012; 170(1): 3-27.

[18] Pomata G. A Word of the Empirics: The Ancient Concept of Observation and Its Recovery in Early Modern Medicine. *Ann. Sci.* 2011; 68:1–25,

[19] State Archives of Florence (ASFI), Hospital of Santa Maria Nuova (OSMN), “Affairs of the Doctors and Apothecaries Art”, 196 (1574-82), Affairs 17 and 18.

[20] State Archives of Florence (ASFI), Hospital of Santa Maria Nuova (OSMN), “Affairs of the Doctors and Apothecaries Art”, 197 (1582-1591), Affair 149.

[21] Pomata G. Sharing Cases: The Observations in Early Modern Medicine. *Early Science and Medicine* 2010; 15:193-236.

[22] Pomata G. Praxis historialis. The Uses of Historia in Early Modern Medicine. In eadem and Nancy G. Siraisi, editors. *Historia. Empiricism and Erudition in Early Modern Europe*. Cambridge, MA: Mitpress; 2005:105-46.