Pregledni rad Acta Med Hist Adriat 2017; 15(2);261-270

Review article

RHAZES, A PIONEER IN CONTRIBUTION TO TRIALS IN MEDICAL PRACTICE

RHAZES, PIONIR KOJI JE PRIDONIO ISTRAŽIVANJU U MEDICINSKOJ PRAKSI

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SUMMARY

Medical history explains that Persian physicians used scientific methods based on clinical experiences and observations for treatment from pre-Islamic time (before 637 AD) and centuries later (in the Islamic era). Rhazes was one of the Persian physicians acknowledged as a pharmacist, chemist and prominent scientific writer on various subjects of medicine and philosophy. In this study, we aimed to investigate clinical experiences, as well as the ethical and critical views of Rhazes in medical practice. Rhazes promoted ethics in the medical profession. He expressed critical key points about ancient written texts. He broke ancient physicians' taboos in medical theories and evaluated them based on his own experiences. He designed animal and preclinical evaluations for his theories and also performed the first clinical trials with control groups in the history. His critical views about medical sciences as well as his beliefs in experiments resulted in many medical, chemical and pharmaceutical findings. Therefore, in history, he can be considered as the pioneer in using trials and experiments for approving medical methods.

Keywords: *Persian medicine; trial; Rhazes; history of medicine.*

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Introduction

Clinical and preclinical studies are the main evaluations to promote drug discoveries as well as medical methods and approaches [1]. These studies provide the most valid evidence with relevance and qualities for addressing therapeutic questions [2]. The results of several phases of clinical studies following nonclinical (laboratory) and also preclinical (animal) researches can approve the general use of medical methods and drugs for patients [3, 4]. Although, these types of evaluations constitute new terminologies in current medicine, historical evidence shows that this approach has a long history. Generally, it is believed that the first clinical study using a control group was recorded in 1537 by Ambroise Pare [5]. But, reviewing the history of Persian medicine shows that it has a longer history.

Persian medicine is a medicinal system based on the humoral theory, and it dates back to about 10,000 years ago [6]. The medical documents obviously explain that ancient Persian physicians (pre-Islamic time; before 637 AD) practiced medicine using scientific methods based on physical examination and precise clinical observation [7]. They followed a comprehensive scientific methodology founded on an experiment that is in compliance with the modern medicine [8]. In the early centuries of Islam (9-12th century AD), Persian physicians, such as Rhazes (865-925 AD), Tabari (916-986 AD), Haly Abbas (949-982 AD), Avicenna (980-1032 AD), etc., flourished in medical sciences, while some of their books were used as medical textbooks in the east and the west until the 17th century AD [9-12].

Rhazes was one of the main scholars in this period and he made a major contribution to experiments in the medical practice. In this study, we aimed to consider his contributions to experimental practices and evaluations in medicine.

Rhazes

Abu Bakr Muhammad ibn Zakariya Razi (865–925 AD), who is known as Rhazes (Figure 1) in the west, was born and died in Rey (near Tehran, the capital of current Iran). He was one of the outstanding Persian physicians, pharmacists, chemists and philosophers in the medieval era [13]. There are many discoveries in pharmacy and chemistry, such as ethanol and sulfuric acid, attributed to Rhazes [9]. Furthermore, he had many clinical achievements in medicine, such as ophthalmology [14], neurosurgery [15], pediatrics [16], as well as the treatment of kidney diseases [8], infectious diseases [15],

Fig. 1. Rhazes visiting a patient and considering his pulse and urine; in Gerardus Cremonensis "Recueil des traités de médecine" 1250-1260 AD.

hydrocephalus [17], facial palsy [18], measles and smallpox [14], etc. Rhazes also contributed to the surgical procedures performed in the airway including tracheostomy [19].

Rhazes is acknowledged as a prominent scientific writer on various subjects of medicine and philosophy [20, 21]. He wrote over 200 books and treatises [22]. His most well-known manuscripts were *Al-Hawi fi al-Tibb* (*Liber Continens*), as a comprehensive medical encyclopedia, and *al-Mansuri fi al-Tibb* (*Liber Al Mansoori*), as a medical teaching text for medical students [23].

Overall, he was known as an empiricist and emphasized clinical observations more than philosophical views [24, 25].

Rhazes' ethical views in medicine

Rhazes made a great contribution to spiritual medicine and believed in ethical issues. His views on the subject can be seen in his books and also in his practice [26]. He wrote about medical ethics: the duty of physicians is in the treatment of enemies even much more than friends [27]. Rhazes taught his students to observe the virtues and ethical principles in the medical profession and patients' care. He visited poor patients for free and even gave them money [28]. He respected all the patients during his visits and the decision making process [25].

As a result of his ethical beliefs in the medical profession, he did not prescribe harmful or unknown drugs to patients [25, 29, 30]. He preferred to use appropriate foods and drinks for the treatment of diseases instead of drugs, and suggested that physicians use this method as the first line, and then, they use simple drugs followed by compound drugs as the last line [31].

Rhazes' critical assessment of previous physicians' theories

Rhazes has helped evidence-based medicine in different aspects such as the critical assessment of the previous physicians' theories; rejection of the books and theories that were not based on clinical experiences; using science, new advances and researches in medicine instead of ancient published texts and beliefs as well as the assessment of his medical theories [25, 28, 29, 32]. He noted his comments and constructive scholarly criticism on the theories of Greek masters like Galen. Moreover, he gathered all of his opinions in the book *A- Shukuk ala Jalinoos (The Doubt on Galen)*, with respect to Galen [33]. This book was successful in the presentation of Rhazes' views on the Galenic experiences. Rhazes rejected Socrates and Aristotle's theories about mental health [26]. He opposed their theories on the formation of the ventricles, spinal cord, and the brain in pairs. Rhazes expressed that hemiplegia is related to ventricular involvement in opposition to the theory of Galen [21, 25]. Despite that, he believed humoral theorists like Galen, he used the principles of Hippocrates in attending to his patients [23].

Rhazes also warned that some physicians with higher education did not have the ability to respond to medical problems and could not cure sicknesses [25, 28].

Rhazes' manner of rejecting wrong theories of previous physicians and his critical assessment of previous medical books are the reasons for the accuracy of his knowledge as a physician who provided an early description of evidence-based medicine [32]. He believed that contemporary scholars and scientists are far more aware, knowledgeable and equipped than the ancient ones. He attempted to achieve the advancement of science, technology and arts and avoided to blindly follow ancient sages [25].

Animal research

Rhazes was a pioneer in testing his theories on animals, and presenting the concept of experimental medicine [25, 28, 29, 32]. He did animal experimentations with new drugs, checked out their effects and toxicity before prescribing the medicine to his patients [26]. It is thought that he carried out experiments on animals to assess the effects of the drug and its side effects.

As an example, he investigated the effect of quicksilver on apes [34]. He was the first to investigate the therapeutic effects of a drug using experimentation on animal subjects. He wrote: "Although, I was aware of the impact of pure mercury on the human stomach, I reviewed its impact on monkeys and monitored its use in patients with intestinal blockage" [35].

Rhazes' reports of clinical trial in the evaluation of medicine approach

Rhazes introduced controlled experiment, clinical observation and rejected medical theories unverified by experimentation in the 10th century. Rhazes reported about his own experiences with his patients. For example, Rhazes comprehensively discussed various aspects of otorhinolaryngologic concepts in *Al-Hawi* [36]. It contains 33 clinical case reports that were reported by Rhazes [36, 37]. He used the word "*Tajriba*" for these cases. "*Tajriba*" means experience [32, 38]. Also, he designed the preliminary versions of clinical trials with control groups. He wrote about the early stages of meningitis in his book: "When the symptoms of meningitis are observed, conduct a phlebotomy. I treated a group of people who showed such symptoms using phlebotomy for one group and no phlebotomy for the other group, and

compared the results. The success of my treatment was proven. All patients who had not undergone bloodletting developed meningitis" [32, 39].

Rhazes' findings contribution in developing medical sciences

Rhazes played a great role in the progress of medical sciences with the help of his critical look at the science as well as his insistence on experiment, and evaluation. The current findings shed some light on his findings in medical sciences. He showed clinical capabilities in lesions treatment, prediction and diagnosis. He described treatment options as well as clinical observations emphasizing the relation between the anatomical location of the lesions and the clinical symptoms [23]. Rhazes merged findings related to cranial and spinal cord nerve anatomy [23]. He mentioned small and chicken pox based on the original experience and direct observation of clinical methods [40].

There are some Rhazes' clinical experiences in medical history that had not been reported before him. Rhazes described measles in the book of "*Al Jodari vaal Hasbah*" for the first time [41]. He clinically differentiated between measles and small pox [40]. He also discovered constriction of the eye pupils to light [23, 29, 32]. Rhazes developed an ancient method of treating hydrocephalus from his own experiences [17, 32]. He correctly defined facial palsy [18]. Rhazes made propositions about some anatomical descriptions for the first time, such as the recurrent laryngeal nerve as a motor nerve and mixed sensory [21]. Rhazes reported the connection between the brain and the spinal nerves [23], and described the concussion and distinction between brain injury and abnormal physiological conditions [21, 23, 42] as well as spina bifida for the first time [26]. He helped to diagnose and treat many renal and bladder diseases [8, 32]. Also, he presented treatment methods for nocturnal enuresis and described its symptoms [43]. Rhazes described the importance of nutrition and diet in the prevention of diseases as well as treatment of patients [31, 44]. He explained rhinites allergic occurred after smelling the roses for the first time. He described the emergence of gonorrhea in detail [26, 45] and defined fever as a natural defense mechanism of the body against disease [26]. Rhazes showed differences between gout and rheumatism [26].

Rhazes as a hospital physician and his clinical roundups

Rhazes was a hospital physician and had sufficient patients in the hospital to visit and care for. He made a big contribution to hospital medicine.

He built a hospital in Baghdad, the Capital of Abbasid Caliphate. When he wanted to select a place to build the hospital, he ordered that spiced meat should be put all around the city, and he located the hospital on the place where pieces of meat rotted later than on the other places. He believed that the place had a better and cleaner environment and weather [46].

In the hospital, when he sat at his place, his students sat below him, and further down, their students took their places. Rhazes created a competitive space for medical students when a patient arrived. New patients were attended to by the first group of junior students and if they were unable to diagnose and treat him/her, senior students would take over and this cycle continued until finally, Rhazes acted in challenging diseases, which others could not diagnose or treat [23, 47].

Conclusion

It appears that Rhazes was the pioneer of the experimental views in clinical practice. He had an interesting critical view on science and believed in animal and human studies to evaluate medicines and medical methods. Therefore, he accessed many new findings with the help of his unique scientific view. He broke Galenic taboos, challenged ancient beliefs and presented new advancements in medical sciences and practice. It seems that he believed in his experiments more than in philosophy of his opinions and decision makings in medical practice. It was a great critical point in the medicine development in history. Also, the history of medical evaluations including preclinical evaluations, animal researches and clinical studies should be reconsidered, and Rhazes can be credited as the first person who included such views into medical practice.

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Sažetak

Medicinska povijest pokazuje da su se perzijski liječnici služili znanstvenim metodama u liječenju, temeljenim na kliničkim iskustvima i promatranjima još od predislamskog vremena (prije 637. godine) i stoljećima poslije (u islamskom dobu). Rhazes je bio jedan od perzijskih liječnika priznat kao ljekarnik, kemičar i istaknuti znanstveni pisac o različitim temama iz medicine i filozofije. U ovom radu nastojali smo istražiti klinička iskustva, kao i etičke i kritičke stavove Rhazesa u medicinskoj praksi. Rhazes je promovirao etiku u medicinskoj struci. Iznio je kritične ključne točke o antičkim pisanim tekstovima. Srušio je drevne liječničke tabue u medicinskim teorijama i procijenio ih na temelju vlastita iskustva. Provodio je evaluacije za svoje teorije na životinjama i u predklinici te proveo i prva klinička ispitivanja s kontrolnim grupama u povijesti. Njegova kritička stajališta o medicinskim znanostima, kao i vjerovanje u eksperimente rezultirali su mnogim medicinskim, kemijskim i farmaceutskim otkrićima. Stoga se Rhazesa u povijesti može smatrati pionirom u korištenju ispitivanja i eksperimenata za odobravanje medicinskih metoda.

Ključne riječi: *perzijska medicina; medicinska ispitivanja; Rhazes; povijest medicine.*