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AVICENNA'S CANON OF MEDICINE. RESEARCH METHODOLOGY AND ETHICS

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REZUMAT. ***Canonul Medicinei*** **de Avicenna. Metodologia şi etica cercetării.** Avicenna a fost unul dintre cei mai importanți medici și filosofi din Islam. El a scris peste 100 de tratate de medicină, unele dintre ele conținând doar câteva pagini. Lucrarea sa majoră, intitulată „Canonul Medicinii", a fost încheiată în anul 1025 și a inclus cinci volume. Cel de-al doilea volum al Canonului începe cu o serie de condiții generale pe care testarea de noi medicamente ar trebui să le îndeplinească, pe care le-a detaliat în capitolul intitulat „Despre cunoașterea potenței medicamentelor prin experimentare." Aceste recomandări sunt analizate în prezentul articol prin corelare cu actualele principii de etică a cercetării și de metodologie.

Cuvinte-cheie*: Avicenna, etica cercetării, metodologia cercetării*

ABSTRACT. Avicenna was one of the most important Islamic physicians and philosophers. He wrote over 100 treaties of medicine, some of them containing only a few pages. His major medical work, entitled "The Canon of Medicine", was finished in 1025, and included five volumes. The beginning of the Volume 2 of the Canon started with a series of general preconditions that the testing new medicines should fulfil, detailed in the chapter entitled "On knowledge of the potency of drugs through experimentation". These recommendations will be analysed in this article in correlation with current principles of research ethics and methodology.

Keywords*: Avicenna, research ethics, research methodology*

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Introduction

Abū ʿAlī al-Ḥusayn ibn ʿAbd Allāh ibn Al-Hasan ibn Ali ibn Sīnā or Avicenna as it is known in the Western World was one of the most important Islamic physicians and philosophers. He was born in Afsana, in present-day Uzbekistan, in 980 (Afnan, 2009). From adolescence he was drawn to the study of Greek philosophy (especially Aristotle), and medicine, which he mastered at the age of 18 according to his own sayings (Zargaran et al., 2012).

He wrote over 100 treaties of medicine, some of them containing only a few pages. His major medical work, entitled "The Canon of Medicine", was finished in 1025, and included five volumes. The first volume defined what medicine is, discussed the Elements, Temperaments, and Humors, and presented what was known at the time about human anatomy and physiology. The other Volumes treated: Pharmacology (Volume 2), Special Pathology (Volume 3), Multi-Member diseases (Volume 4), and Formulary of complex medicines (Volume 5). His main sources of inspiration were Galen (and indirectly the Hippocratic works), but also the works of other physicians from the Islamic world like Ali Ibn al Abbas al Majusi or Abu Bakr ar Razi (Tyler, 2014).

The beginning of the Volume 2 of the Canon started with a series of general conditions that the testing new drugs should fulfil (2012), further detailed in the chapter entitled "*On knowledge of the potency of drugs through experimentation*". These recommendations are presented in Table 1 and will be discussed below in correlation with current principles of research methodology and ethics.

Analogy or Experimentation?

Avicenna considered that the potency (efficacy) of a certain drug can be identified through two main methods: analogy (qiyas) and experimentation (tajribah); he recommends the later as "*experimentation leads to knowledge of the potency of a medicine with certainty after taking into consideration certain conditions*" (2012). Therefore the identification of the efficacy of a new drug needs experimentation, and the fulfilment of a series of pre-requirements (a research protocol). This approach contradicts the classical, Hippocratic approach on identifying new uses for various remedies, which was based on observation and interference, not experimental research (Miles, 2005). The use of "experimentation" in the Hippocratic works only meant the change of an ongoing treatment. For example, in the Aphorisms it/ is said: "*Do not disturb a patient either during or just after a crisis, and try no experiments, neither with purges nor with other irritants, but leave him alone*" (Hippocrates) while in Nature of Men: "*[If] it is*

clear that, of the regimen the patient is wont to use, either all, or the greater part, or someone part, is not suited to him . . . this one should learn and change . . . sometimes taking away and sometimes adding . . . and so making changes in drugging or in regimen to suit the several conditions of age, season, physique, and disease" (Hippocrates). According to Miles the experimentation in the time of Hippocrates superficially resemble modern day "N of 1" prescriptive trials (Miles, 2005), in which the first subject (N of 1) of a certain trial will test the drug for the researcher to see whether he/she will tolerate it. However, if in modern clinical trials this is just a preliminary step, in Ancient Greece this was considered as a definite proof of efficiency (Miles, 2005). The approach of Avicenna is derived from the one found in Galen works, and developed further. Galen considered that qualified experience (*dihorismene peira*) is needed in order to determine the efficacy of a drug (Galen et al., 2015). He did not give a clear list of what conditions are needed in order to obtain reliable results from the experimental procedures. However, indirect cues are found in various works; for example, in On Critical Days, he defined three condition needed for the validation of the experimental procedures: (1) to choose patients about whom one can be certain, (2) to properly identify a crisis through clear perception not reasoning, and (3) to properly identify to stage of that particular crisis (the exact day of the crisis) (Adamson, 2013; Galen et al., 2015).

First Principle – the Tested Drug Should be Free of Excipients Able to Change the Properties of the Active Substance

An active drug can be associated with various other, pharmacologically inactive substances like anti adherents, coatings, colours, binders, disintegrants, flavours, lubricants, preservatives, sorbents, sweeteners, vehicles. All these excipients have important roles in the presentation, preservation of bioavailability of the active substance at the target site/sites. However, in the time of Avicenna the chemical interactions between most substances were unknown, making an absolute necessity, in order to properly asses the usefulness of a certain active drug, to separate its effect from the effect of other substances.

The excipients are detailed in the guidelines depending on their temperatures (heat and cold). See Table 1. Avicenna defines the constitution of a person as a mix between humours, temperatures and elements; similarly, remedies had different constitutions, making them allowed or disallowed for a certain patient depending on its particular constitution. However, before combining them with substances able to change the constitution of the mix, the physician/researcher should have been certain about the constitution of the active substance.

Second Principle – the Subject Must Suffer from a Single Condition

According to Avicenna, a composite disease is not represented by an association of disease, but on an association of morbid states that concur and generate a single disease. For example: "*the following kinds of morbid state go together to make up an inflammatory mass: (1) a disorder of temperament, this being associated with matter, (2) a perversion of form, (3) unhealthy configuration – one never meets with an inflammatory deposit without there being disfigurement, change of size and there is often displacement as well, (4) loss of continuity. This is the necessary accompaniment of the discharge of superfluities into the tissue spaces, penetrating as they do into them all, and separating one from the other in order to make space for themselves*."

In order to assess the efficacy of a certain disease, the researcher nowadays tries to limit the subject selection criteria in a fashion that will minimize potential biases and maximize the statistical significance of the obtained results. This is the reason why we use concepts such as inclusion and exclusion criteria, placebo or randomization. Van Spall, in a review analysing eligibility criteria for randomized clinical trials showed that one of the strongly justified reason for exclusion is represented by the fact that the effect of intervention is difficult to interpret (Van Spall et al., 2007). In the Canon, Avicenna suggests that the experiment should be performed on singular conditions; this would apparently mean that they would seek cures for symptoms rather than for diseases per se. More likely, keeping in mind however the next principles, he considered that by properly identifying a specific imbalance he would be able to bring the body to a healthy state, and to properly identify the original cause and/or the condition that would be affected by the drug "*if the condition consists of two opposite diseases and the drug is tried and found beneficial in both, we cannot infer the real cause of the cure*".

Third Principle – the Drug Should be Tested on Contrary Conditions

According to this principle, testing the efficiency of a certain drug requires two study groups, having opposed conditions. A drug would be considered effective only if it would have effect on only one condition; otherwise "*is possible that the drug acted directly against one disease, and acted against the symptom of the other*" In this principle we see two important elements: the first one is the need for two study groups, a fundamental element in today's clinical trials; if however today we assess the effect of an active substance in relation to a control group (either placebo or other active agent), in Avicenna's time the "control" group was represented by subjects with a different condition. If there was a difference in the effect of the drug on those two conditions, one could speculate that the

drug was active; if not, most likely more research was needed, the test being made on different conditions. The second element is represented by the need to counteract the source of the disease (the cause) and not only one of its symptoms (its effects); the reason for this approach has been detailed in the analysis of the second principle.

Fourth Principle – the Dosage/Potency Should be Correlated with the Severity of the Disease

In order to minimize the harm and maximize the efficiency of a certain remedy, the physician had to gradually increase the dosage until an optimal concentration was determined. This approach is similar to the one found in current day Phase 1 trials, in which the test subjects receive often sub-therapeutic active drugs, in increasing doses, in order to assess safety, tolerability, pharmacokinetics and pharmacodynamics of the agent. The prima-facie reason for this approach in Avicenna's time was however not non-maleficence, as is today, but beneficence (*If some of the drugs are inadequate with regard to heat when compared to the coldness of an illness, they will not be able to effect a cure*)

Fifth Principle – Time Needed to Determine the Effect

Avicenna considered that, if a drug determines a positive effect immediately, it acted on the disease itself; if however, the effect took longer to achieve, or if the results are contradictory, such a speculation could not be made.

Sixth Principle – Reproducibility

If the effect of a certain drug varies in different cases, the drug might not determine the effect, but more likely to be an accidental event. Translated in current day practice, this principle is highly similar with reproducibility, one of the main principles of the scientific method. The idea was most likely taken from Aristotle, who considered that there is no scientific knowledge associated with isolated occurrence; however, the name associated usually with the recognition of the reproducibility in science is Robert Boyle, who considered that the foundation of knowledge should be based on experimentally produced elements that should be believed by the scientific community based on their reproducibility.

Seventh Principle – Animal Studies Have Limited Uses

Avicenna considered that the use of animal studies is of little importance, as the effects might be different on humans compared to other animals. Even if this is true, most drugs have similar metabolic pathways and action mechanisms in

all mammals. However, recognizing the effects on animals might have been much more difficult, and therefore significantly increase the rate of errors, which would determine the physicians at that time to do this recommendation.

Discussions

As we saw above, Avicenna's Canon of Medicine presents a series of clear recommendations regarding how a medical research should be conducted; these guidelines, even if based on an entirely different way of looking to medicine in general and the human body in particular, has a series of elements that are still identifiable in today's medical research like the need of at least two study groups to assess the usefulness of a particular drug, the need for reproducibility or the need of human experimentation to test the efficacy of a certain drug. The basic ethical principle underlying medical experimentation was beneficence, in the Hippocratic tradition; however, if in the Hippocratic tradition the physician was viewed as the ultimate resource for knowledge, in the Canon the knowledge of the physician had to come from experiments, as the subjective opinion of a physician can ne erroneous. The basic underlying ethical model of Avicenna's approach, as seen from today's perspective was utilitarian (Mill, 2010): the ultimate good of the sick needed human experimentation, not only animal experimentation - therefore the physician had to experiment on humans; the cause of the disease was more important than a particular symptom to treat - therefore, if a certain drug acted on contrasting conditions, it had to be tested on a third condition, otherwise its effect could not be properly assessed. Various authors considered that his philosophical approach seeks for a harmonious approach to the integration of the human being in nature, an approach with Aristotelian influences (Davidson, 1992; MacIntyre, 2003; Gutas, 2014), that is in apparent contradiction with the Kantian view that human beings capture nature through natural laws and equations (the legislating power of Reason) (Kant et al., 2000; Kaufman, 1997)

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Table 1. Principles of human experimentation as presented in Avicenna's Canon of Medicine

The drug must be free from any acquired quality: this can occur if the drug is exposed to temporary heat or cold, if there is a change in the essence of the drug, or if the drug is in close proximity to another substance. Water, although cold by nature, will give warmth as long as it is heated; euphorbium, although hot by nature, will have a cold effect when cold; almond, although naturally neutral, will have a strong effect of heat if it turns rancid; and fish, although cold, is a strong source of heat if salt is added to it.

The experiment must be done on a single, not a composite, condition. In the latter case, if the condition consists of two opposite diseases and the drug is tried and found beneficial in both, we cannot infer the real cause of the cure. Example: if we treat a patient suffering from phlegmatic fever with agaric and the fever abates, this does not mean that because it was useful for a hot illness agaric possesses the property of coldness. It is possible that the drug was effective because it dissolved the phlegm or removed it; when the [phlegm] disappeared the fever disappeared. This action represents both the direct and the accidental benefit of the drug. The direct benefit relates to the [phlegm], and the indirect refers to the fever.'

The drug must be tested on two contrary conditions. If it is effective on both, we cannot judge which condition benefited directly from the drug. It is possible that the drug acted directly against one disease, and acted against the symptom of the other. Scammony, if used to treat a cold disease, would no doubt have a warming effect and bring benefit. If we try it on a hot disease, such as diurnal fever, it would also have a beneficial effect because it gets rid of yellow bile. In these cases, an experiment would be of no help in deciding whether [the drug] is hot or cold, unless we could know that it acted directly on one disease and acted on a symptom of the other.

The potency of the drug should be equal to the strength of the disease. If some of the drugs are inadequate with regard to heat when compared to the coldness of an illness, they will not be able to effect a cure. Sometimes during their application against coldness, their function for producing warmth is weakened. So it is best to experiment first using the weakest [dosage] and then increase it gradually until you know the potency of the drug, leaving no room for doubt.

One should consider the time needed for the drug to take effect. If the drug has an immediate effect, this shows that it has acted against the disease itself. If its initial effect is contrary to what comes later, or if there is no initial effect at first and the effect shows up later, this leads to uncertainty and confusion. Actions in such cases could be accidental: their effect is hidden at first and later comes into the open. The confusion and uncertainty relate to the potency of the drug.

The effect of the drug should be the same in all cases or, at least, in most. If that is not the case, the effect is then accidental, because things that occur naturally are always or mostly consistent.

Experiments should be carried out on the human body. If the experiment is carried out on the bodies of [other animals] it is possible that it might fail for two reasons: the medicine might be hot compared to the human body and be cold compared to the lion's body or the horse's body … The second reason is that the quality of the medicine might mean that it would affect the human body differently from the animal body

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