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How Well Informed of Participants in Clinical Trials: A Case Study of China

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Abstract

Background: With the development of globalization, the rising cost of clinical trials in Europe and the United States, and the huge drug consumption market in developing countries, multinational pharmaceutical giants have set their sights on emerging developing countries. As a leader in developing countries, China has unparalleled advantages, so more and more clinical trials are registered and carried out in China. **Objective:** The objective of the study is to understand the current practice of informed consent in clinical trials in public hospitals in Xuzhou. **Methods:** In this study, a 15-question questionnaire was distributed to 369 subjects in the affiliated hospital of Xuzhou medical university. Each question was graded on a 3-point scale (1 = no, 2 = unsure, 3 = yes). The sum of the scores for the 15 questions represented the level of awareness of clinical trials. **Results:** Valid questionnaires were received from 300 subjects. A considerable number of subjects still had insufficient understanding of clinical trials, especially concerning the nature of clinical trials, understanding of informed consent forms, contact with researchers, and ethics committee. (The "yes" rate was around or below 50%). Factors associated with responses to the survey include education, occupation, and source of medical expenses. **Conclusion:** Overall, this study showed that the implementation of informed consent in China remained room for improvement. Legislators, ethics officers, and researchers should work together to protect the interests of subjects.

Keywords

Clinical Trials, Informed Consent, Ethics-Research, China

1. Introduction

Clinical trials are playing an irreplaceable and important role in promoting the progress of medical science. China has become a vital country for conducting clinical trials considering its large population and increasing importance as a key player in global health [1] [2]. As a basic principle in modern medical ethics, informed consent is a process to ensure that participants fully understand the information relevant to the trial and then decide whether to accept or decline participation [3] [4] [5]. Informed consent is a prerequisite for enrolling human subjects in biomedical research [6] [7]. The World Medical Association (WMA)'s "Declaration of Helsinki" (DoH) [8] and the International Medical Science Organization Committee (CIOMS)'s "International Ethical Guidelines for Human Biomedical Research" [7] have provided ethical principles regarding human experimentation. China's "Good Clinical Practice" (GCP) [9] also stipulates that all research on human subjects must comply with the principles of DoH: respecting a participant's autonomy and protecting participants from harm [10].

Although the importance of the completeness of disclosure and the standardization of the procedure during the informed consent process is emphasized, informed consent is still a challenge to carry out in practice [11] [12]. Numerous studies have shown that a large number of participants cannot completely understand the content of informed consent forms because of too many obscure descriptions [13]-[18]. In addition, patient-centered barriers and researcher-centered barriers can hinder the informed consent process [19] [20]. These deficiencies lead to inadequate understanding of clinical trials and potentially threaten the safety of participants.

China remains the world's largest developing country. The economic and technological development is unbalanced between south and north, urban and rural areas [21]. Compared with southern Jiangsu, an economically advanced coastal province in China, the medical resources in the northern part are relatively poor. Xuzhou, as the "leader" of northern Jiangsu, its medical environment and implementation of informed consent show special reference to developing areas. Our study aimed to explore the protection of subjects' informed consent rights in drug clinical trials in Xuzhou and find the existing problems, so as to provide insights into the deficiencies and misunderstanding of the informed consent process and provide a sound basis for the standardization of the informed consent process in China.

2. Materials and Methods

2.1. Study Design

This study used a quantitative survey design. The survey study of patients was conducted between July and August of 2021. We selected the affiliated hospital of Xuzhou medical university as the field site in Xuzhou. This hospital was chosen because its medical capacity and services are considered to be the highest in

northern Jiangsu, and numerous patients from other parts of China, especially from adjacent less developed cities and provinces, seek medical care in this hospital. Participants must fulfil four criteria: 1) in-hospital patients after signing the informed consent forms; 2) aged over 18 years; 3) patients who voluntarily enrolled in this study; 4) conscious patients without psychiatric disorders. In total, 369 in-hospital patients have participated in the study. The questionnaires were sent to them to investigate their basic information and their understanding of informed consent for clinical trials.

2.2. Questionnaire Development

The understanding assessment part of the questionnaire was limited to 15 questions with a three-point response scale. The comprehension score was evaluated from level 1 to 3, with higher values indicating better understanding. A questionnaire scored 1 point if the participant chose "No", 2 points if the participant chose "Unsure", 3 points if the participant chose "Yes". The sum of the scores for the 15 questions represented the level of awareness of clinical trials. The reliability of the questionnaire was 0.718, which implied that the questionnaire was well designed.

In addition to the understanding questions, sociodemographic data (gender, age, education, occupation, source of medical expenses, source of participation in clinical trials) were also collected.

2.3. Data Collection

Data was collected using a questionnaire in Chinese, the language spoken by the study participants. The questionnaires were provided by researchers who have solid experience in conducting interviews during a face-to-face discussion with the study participants.

The risk of participating in this study was small and low levels of discomfort may occur due to the setting of the questions. Before participants filled in the questionnaire, the researchers briefly described the purpose and significance of the study and explained that the questionnaire is anonymous. Researchers who conducted clinical trials were unable to obtain positive or negative responses to the questionnaire, and participation in clinical trials was unaffected. During the process, participants were not in a hurry. When they had questions or didn't understand something, they were given an answer.

2.4. Data Analysis

Statistical analysis was performed with SPSS 25.0 software. We performed descriptive statistics, univariate analyses of variance (ANOVA), and multivariate analyses of variance (MANOVA). Statistical significance was set at 0.05.

3. Results

In order to eliminate possible interference factors, this survey selected all sub-

jects (a total of 369 participants) who participated in the third batch of clinical trials in the drug clinical trials institution of Xuzhou Medical University Affiliated Hospital. However, 69 surveys were discarded because responses to questions in the questionnaire were incomplete. Therefore, only 300 patients from the study were included in the analyses.

3.1. Sociodemographic Data of the Sample

Sociodemographic data of the sample are presented in Table 1. The proportion of male and female participants was 51.7% and 48.3% respectively. The results of this survey showed no significant gender bias. Most participants were aged between 56 and 70 (32.7%), were peasantry (28.3%), had less than 15 years of education (85.3% didn't attend college). More than half of the participants (53.7%) paid their medical bills mostly by themselves. 62.4% of the patients got access to participation in clinical trials from doctors.

3.2. Participants' Understanding of Clinical Trials

Responses to the 15 questions relating to the understanding of clinical trials are presented in Table 2. The validity of the questionnaire was 0.767, which could truly reflect the participants' understanding of clinical trials. Regarding the participants' understanding of the risks and benefits, less than 50% (49.7%) of participants agreed that clinical trials provide free treatment with both risk and benefit. Quite a lot of participants (45.6%) answered "not sure". Also, roughly a third of participants (33.7%) were unsure about whether there are related laws of scientific and ethical issues in clinical trials. Similar percentages were recorded for the questions evaluating the participant's subjective understanding of the informed consent form. The same number of participants answered "not sure" when asked about whether they could fully understand the informed consent form after the doctor's explanation and 20.7% answered "No". Regarding the purpose of research, 77.7% of participants agreed that clinical trials are meaningful for the medical development and treatment of future patients. Almost all patients (95.7%) knew that they would sign the informed consent forms before attending clinical trials. Additionally, nearly all of the respondents (99.0%) said that they were voluntary to participate in clinical trials. The percentage of participants who agreed that they were free to withdraw at any time during clinical trials is also above 90%. Roughly 90% (87.3%) agreed that doctors would keep their information confidential during clinical trials. However, regarding the contact with researchers in charge or with the ethics committee, the rates of "Yes" drop sharply and fluctuate around 50%. 64.3% were sure that they had the contact information of the doctor or nurse in charge of the trial. When it comes to the ethics committee, only 56.0% knew that they could appeal to the ethics committee if they get injured during the trial. Based on this, only 53.3% said that they were aware of the phone number of the ethics committee. Concerning details in the process of clinical trials, more than one-third of participants were not aware of or unsure about the meaning of "placebo" (10.3%, 23.3% respectively).

What's more, 7.3% were not aware of the fact that they would be randomly assigned to a control group or treatment group and 21.0% were not sure.

Table 1. Sociodemographic data of the sample.

Variable	Number
Gender	
Male	155 (51.7%)
Female	145 (48.3%)
Age	
25 and below	25 (8.3%)
26 - 40	81 (27.0%)
41 - 55	78 (26.0%)
56 - 70	98 (32.7%)
70 and above	18 (6.0%)
Education	
Junior high and below	132 (44.0%)
Senior high	124 (41.3%)
College graduate	35 (11.7%)
Postgraduate and above	9 (3.0%)
Occupation	
Worker	49 (16.3%)
Peasantry	85 (28.3%)
Educator/healthcare worker	24 (8.0%)
Employee in state-owned enterprises	24 (8.0%)
Freelancer	54 (18.0%)
Retired	19 (6.3%)
Service employee	11 (3.7%)
Student	11 (3.7%)
Others	23 (7.7%)
Source of medical expenses	
Mostly paid by the company or insurance	122 (40.7%)
Mostly paid by myself	161 (53.7%)
Borrowed	12 (4.0%)
No source of income	5 (1.6%)
Source of participation in clinical trials	
Doctors	187 (62.4%)
Family and friends	39 (13.0%)
Social media	10 (3.3%)
Others	64 (21.3%)

Table 2. Participants' understanding of clinical trials.

Question	No	Unsure	Yes
Clinical trials provide free treatment with both risk and benefit.	14 (4.7%)	137 (45.6%)	149 (49.7%)
Clinical trials are meaningful for medical development and treatment of future patients.	16 (5.3%)	51 (17.0%)	233 (77.7%)
I will sign the informed consent forms before attending clinical trials.	3 (1.0%)	10 (3.3%)	287 (95.7%)
I am voluntary to participate in clinical trials.	0 (0.0%)	3 (1.0%)	297 (99.0%)
Doctors will keep my information confidential during clinical trials.	2 (0.7%)	36 (12.0%)	262 (87.3%)
I am free to withdraw at any time during clinical trials.	10 (3.3%)	17 (5.7%)	273 (91.0%)
I will get compensation of damage as a result of clinical trials.	3 (1.0%)	44 (14.7%)	253 (84.3%)
There are related laws of scientific and ethical issues in clinical trials.	23 (7.7%)	101 (33.7%)	176 (58.7%)
I think the informed consent form is sufficiently detailed.	44 (14.7%)	33 (11.0%)	223 (74.3%)
After the doctor's explanation, I can fully understand the informed consent form.	62 (20.7%)	101 (33.7%)	137 (45.7%)
I have the contact information of the doctor or nurse in charge of the trial.	50 (16.7%)	57 (19.0%)	193 (64.3%)
I can appeal to the ethics committee if i get injured during the trial.	44 (14.7%)	88 (29.3%)	168 (56.0%)
I am aware of the phone number of the ethics committee.	113 (37.7%)	27 (9.0%)	160 (53.3%)
I am aware of the meaning of "placebo".	31 (10.3%)	70 (23.3%)	199 (66.3%)
I am aware of the fact that i will be randomly assigned to control group or treatment group.	22 (7.3%)	63 (21.0%)	215 (71.7%)

3.3. Factors Associated with Responses to the Survey

Univariate analyses showed that education ($P = 0.009$), occupation ($P = 0.001$), source of medical expenses ($P < 0.001$) were significantly correlated with the level of patients' understanding (Table 3). To be specific, college graduates had the highest understanding of clinical trials. Meanwhile, junior high school graduates and elementary school graduates had the lowest understanding of clinical trials. In terms of occupation, educators, healthcare workers or employee in state-owned enterprises showed the highest level of understanding of clinical trials. Otherwise, workers and peasantry had the greatest difficulty in truly understanding drug clinical trials. Another influencing factor was the source of medical expenses. Statistics showed that participants who paid medical expenses by insurance had a better understanding than those who paid by themselves or borrowed money. Other factors such as age, gender, source of participation in clinical trials were not found to be related to patients' understanding of clinical trials ($P > 0.05$).

Multivariate analyses showed that the source of medical expenses had the greatest impact on the understanding of clinical trials and was the only independent factor affecting the level of informed consent (Table 4). Participants who paid medical expenses by insurance had a better understanding of clinical trials.

Table 3. Univariate analyses of subjects' understanding of clinical trials.

Variable	Number	X2/t	P
Gender			
Male	155	1.627	0.105
Female	145		
Age			
25 and below	25		
26 - 40	81	0.199	0.939
41 - 55	78		
56 - 70	98		
70 and above	18		
Education			
Junior high and below	132		
Senior high	124	3.943	0.009
College graduate	35		
Postgraduate and above	9		
Occupation			
Worker	49		
Peasantry	85		
Educator/healthcare worker	24		
Employee in state-owned enterprises	24	3.552	0.001
Freelancer	54		
Retired	19		
Service employee	11		
Student	11		
Others	23		
Source of medical expenses			
Mostly paid by the company or insurance	122		
Mostly paid by myself	161	6.431	P < 0.001
Borrowed	12		
No source of income	5		
Source of participation in clinical trials			
Doctors	187		
Family and friends	39	0.91	0.436
Social media	10		
Others	64		

Table 4. Multivariate analyses of variables associated with understanding of clinical trials.

Variable	Unstandardized Coefficients		Standardized Coefficients	t	P
	β	Std.Error	β		
Sex	−0.763	0.468	−0.092	−1.631	0.104
Age	0.115	0.277	0.03	0.414	0.679
Education	0.766	0.393	0.143	1.947	0.052
Occupation	−0.021	0.107	−0.012	−0.2	0.842
Source of medical expenses	−1.206	0.401	−0.184	−3.011	0.003
Source of participation clinical trials	−0.245	0.201	−0.072	−1.219	0.224

4. Discussion

Informed consent is vital in protecting participants' rights in human research. However, it is a challenge to ensure subjects are adequately informed and fully understand the research, and able to make a voluntary decision in taking part or declining participation [22]. There is still a big gap between the findings of this study and those of previous foreign studies [23] [24] [25]. In our study, only three questions reached an approval rate of 90%. The approval rate of the two questions was even no more than half. The disapproval or uncertainty rate of the nine questions reached 20%.

To determine factors associated with responses to the survey, we focused on four variables deemed central to patients' understanding of clinical research: age, education, occupation, and source of medical expenses. Univariate analyses showed that education, occupation, and source of medical expenses were associated with responses to the items selected. In terms of education, participants who only attended junior high school or below showed a poorer understanding of clinical trials than those who attended senior high or college. More educated participants were more likely to understand the purpose of research, the methods, the content of the informed consent form, the contact information of the researchers in charge, risks and benefits, and other clinical trial information. It can be presumed that participants with superior education are more willing to contribute to the promotion of medical science. Regarding occupation, educators, healthcare workers, or employees in state-owned enterprises showed the highest level of understanding of clinical trials. Otherwise, workers and the peasantry showed a poor level. Educators, healthcare workers, or employees in state-owned enterprises are more likely to receive higher education, understand and accept advanced things. They have more information, a broader vision, and a mind. While education and occupation are important, multivariate analyses indicate that source of medical expenses has a greater influence on patients' perceptions about clinical research. Participants who paid medical expenses by insurance had a better understanding than those who paid by themselves or bor-

rowed money. With less pressure to pay for their own medical treatment, participants feel more comfortable trying advanced clinical trials. Even if clinical trials fail, reverting to present treatments will not add to the financial burden. These findings provide insight regarding strategies to improve the recruitment of patients from diverse socioeconomic backgrounds. More importantly, it reflects the necessity of improving China's medical insurance system.

In China, current laws on clinical trials include the relevant provisions of "Law on Licensed Doctors of the People's Republic of China" and "Drug Administration Law of the People's Republic of China". Administrative regulations include "Measures for Ethical Reviews of Biomedical Research Involving Humans". Generally speaking, the legislative level is relatively low and the content is inadequate, especially the provision of informed consent. In practice, not all clinical trial participants truly understand the informed consent process. Apart from participants' own issues like educational issues, researchers may be to blame. In many cases, informed consent has become expedient for researchers to shirk their responsibility. At the same time, in China's profound cultural heritage, some traditional beliefs in Confucianism are contrary to the requirement of subjects' autonomy in informed consent [26] [27], which subtly increases the difficulty of subjects' autonomy. In China, doctors and subjects in clinical trials are more like parents and children (researchers recruit subjects and standardize all the procedures in the trials), rather than participants who actively hope to participate in clinical trials, and fully fulfill their rights and obligations informed by researchers.

To promote the practice of informed consent in China's health care system, we provide several possible solutions.

First of all, improve details and hierarchy of laws. At present, there is no targeted basic law, most are regulations and departmental rules whose legal effect is still insufficient. Moreover, the existing regulations on informed consent are still incomplete. For instance, the signing authority of the subject and his/her guardian is not clear. Although the role of "legal representative" in clinical trials was abolished in the 2020 version of GCP, it is likely that the guardian will replace the subject himself to decide whether to participate in a clinical trial, especially in the cases that subjects are children or people who have limited capacity to make decisions. Therefore, for children and people with limited capacity, the protection of their informed consent rights needs to be further increased.

Second, strengthen the supervision and examination of informed consent. The core purpose of an ethics committee is to protect the interests of subjects. One of the responsibilities of the ethics committee is to supervise and examine approved studies and to promptly address complaints and adverse events during the process of clinical trials. In order to ensure the practical implementation of informed consent, the ethics committee should not only strictly examine the informed consent form, but also continuously strengthen the protection of informed consent in the process of trials. The ethics committee can regularly send

personnel to supervise the process of clinical trials. They can inquire about the implementation of informed consent, and randomly examine whether the researchers have fulfilled the obligation of informed during the trials.

Third, strengthen training for researchers. At present, a number of Chinese researchers have insufficient cognition of clinical trials, which leads to the violation of protocols. Effective clinical trials training can improve researchers' awareness. The sponsor and the principal researcher should provide systematic and comprehensive training to all the researchers on possible problems and considerations in the process of trials before implementation. Furthermore, humanistic training in areas, such as communication skills, medical ethics, and professionalism, should be given more weight in the medical school curriculum and licensing process by medical policy-makers [28].

Finally, improve subjects' autonomy in participating in clinical trials. In many cases, although participants in clinical trials sign informed consent forms, they are not fully aware of their rights and duties. Chinese subjects' understanding of their autonomy is still in its infancy. Because of the lack of awareness, participants are prone to over-safeguard or be in a weak position, which requires ethics officers to tell the subjects proper measures. In addition, in order to enhance the self-consciousness of potential subjects, we suggest that ethics officers regularly go to communities to carry out relevant universal education.

Several limitations of this study must be considered. First, our sample was relatively small and all the participants were obtained from one single clinical trials institution. Although this institution is the biggest and the most authoritative one in Xuzhou, it is difficult to ensure complete consistency among patients in all developing areas. Further study should be carried out to assess the understanding of informed consent of patients from multiple clinical trials institutions. Second, our study lacked the information of those patients who refused to participate or failed to be included in the valid number. Third, the assessment may not accurately reflect the perspectives of our subjects.

5. Conclusion

This small-scale study gained an insight into patients' understanding of clinical trials by assessing their responses to a questionnaire. The results showed that factors influencing participants' understanding of the clinical trial were the level of education, occupation, and source of medical expenses. The findings also revealed weak points of the current informed consent process and a need to improve it. We suggested that legislators, ethics officers, and researchers should work together and put more effort to help participants achieve a better understanding of informed consent. Only with joint forces will they ensure that participants' decision-making is meaningful and that their interests are protected.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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A Concise History of Islamic Medicine: An Introduction to the Origins of Medicine in Islamic Civilization, Its Impact on the Evolution of Global Medicine, and Its Place in the Medical World Today

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Abstract

The practice of medicine in Muslim nations dates to the millennia before the advent of the religion of Islam. As far as the pre-Islamic period is concerned, what evidence is available indicates the medical evolution began nearly 6000 years ago in Mesopotamia, where medicine for the first time in history became a recognised profession. In ancient Egypt, it was practised by priest-physicians who demonstrated astonishing knowledge in various medical subjects. The origins of medicine in ancient Persia (Afghanistan, Iran, and parts of Central Asia) span the 6th century B.C. and to the Zoroastrian religious book of Avesta, which delved into such topics as preventive and clinical medicine. In reference to the account of medicine in the Arab peninsula, limited information exists. In terms of post-Islamic ages, the foundations of Islamic science were laid during the reign of the second Abbasid Caliph, al-Mansur, and the establishment of Baghdad as its capital in 762 A.D., when the Arabic translation movement commenced. During the next six centuries, medicine and other fields of science flourished, and prominent physicians such as the Bukht Yishu family, Râzī, Majūsī, Avicenna, Jorjânī, Al-Zahrāwī, and other scientists emerged. In both the pre- and post-Islamic ages, Islamic medicine was heavily influenced by Mesopotamian, Egyptian, Persian, Indian, and, predominantly, Greek medicine. Nevertheless, the advancements and innovations in

medical science and healthcare systems that were achieved during the early and medieval Islamic ages have indubitably made an invaluable contribution to the evolution of medicine throughout the world, and to the invention of numerous procedures and practices which are still widely performed today. Hence, the value of comprehending the pivotal role Islamic medicine played (and indeed still plays) in the progression of medical practice across the globe cannot be overstated.

Keywords

History of Medicine, Islamic Civilisation, Balkhi, Razi, Avicenna

1. Introduction

Studying history is vital, as it is history that allows us to understand how people and societies have developed. It is history that gives us the opportunity to learn about our predecessors and their achievements, as well as their struggles. Most importantly, it is through acknowledging the past that we can hope to learn from our mistakes and prevent their recurrence, and hence build future success. Understanding the history of the practice of medicine is of paramount importance; it is the practice of preserving and optimising the most valuable thing human possess-health.

This script details the origins of medicine in Muslim territories. How medicine evolved in these countries and the approach Islamic medicine took to health and illness will be discussed. The paper will focus on the history of medicine in the Arabian Peninsula, the Middle East, Egypt, Syria, Afghanistan, Iran, and Central Asia. It is divided into two sections: the first focuses on the pre-Islamic history of medicine, whilst the second concentrates on medicine after the rise of Islam, Islamic medicine, and its influence on the evolution of global medicine. The paper will also outline the main centres of medical education as well as some of the most influential physicians of these periods.

2. Medicine in the Pre-Islamic Period

The evolution of medicine on earth started about 6000 years ago in Mesopotamia (a region that included Iraq, Kuwait, part of Turkey, and Syria), 4000 years before Greek medicine emerged [1]. It was in the region of Mesopotamia where the world's earliest civilisation developed [2]. The Babylonians who inhabited Mesopotamia between 1894-1594 Before Christ (B.C.) were advanced in medicine, which possibly for the first time in history became an established profession. The Code of Hammurabi composed circa 1755-1750 B.C. (regarded as the "origin of medicine" [3]) enshrined a code of ethics that challenged physicians to attain higher standards of practice. Both the Babylonians and the Assyrians, who conquered the Babylonians between 1270 and 538 B.C., believed gods inflicted illness upon humans as a punishment for sins, whilst other gods cured disease as

a reward for good behaviour. Assyrian belief maintained that three demons were responsible for disease—the demons of phthisis (or decay), liver diseases, and abortion or infant death. Treatment was largely channelled through prayer and incantation. However, emetic drugs were also utilised, nauseating patients at their sight or smell. It was believed that this would disgust the culprit's evil spirit, causing it to flee the diseased part of the body [1].

In ancient Egypt, evidence suggests that the possession of medical knowledge carried incredible status. Medicine was practised by priest-physicians with remarkable knowledge in a wide range of medical fields including anatomy and rheumatology [4] as well as surgery, neurosurgery [5], and pharmacology [6].

The origins of medicine in ancient Iran (including Afghanistan, today's Iran, and parts of Central Asia) can date back to ancient times. The first written source is Avesta, the Zoroastrian religious book, the contents of which were revealed by God to Zoroaster, a native of Balkh, Afghanistan [7] around the 6th century BC, who in turn relayed the contents of Avesta to Gushtāsp, king of Bactria (Balkh), the patron of the Faith [1]. Avesta covers many aspects of health including anatomy, disease prevention, and pharmacology. Avesta describes three types of human vessels: those through which red blood passes (arteries), the vessels containing black blood (veins), and those without blood (nerves). According to Avesta, diseases can be caused by a host of factors including a demon named Ahriman, sin, poor diet, uncontrolled sexual appetite, nervous tension, or by the god Ahura Mazdā. Zoroastrian medicine recognised three methods of analgesia: namely the use of either herbs (pharmacology), the knife (surgery), or word (psychotherapy) [8]. Hence there existed three kinds of practitioners: healers by holiness, healers by knife, and healers by instruction, the latter of whom performed health-related instruction. Physicians who specialised in "preventative" medicine were called *Durustpat* or "Masters of Health" and aimed to remove the causes giving rise to disease, whilst those treating diseases and physicians practising "clinical" medicine were referred to as "*Tan Beshazak*" or "Healers of the Body"; the latter group treated disease once it had manifested. Physicians hailed from noble families who studied theology and medicine. The Zoroaster Code of medical practice expected physicians to be experienced in their profession, to be god-fearing, to communicate well with patients, to listen to their concerns, to be sweet-tongued, gentle, friendly, zealous of the honour of their profession, and averse to greed [1].

The first medical school in pre-Islamic ancient Iran was the Jundi Shapur ("Beautiful Garden") medical school, located in modern-day Khuzestan, north-west Iran, founded by the Sassanid Emperor Shapur I (239-270 Anno Domini (A.D.) [1] [9]. It was originally established as a prison. Nevertheless, over time, it became a refuge for intellectuals from different regions and included Greeks, Syrians, and Nestorians [10] [11]. The School of Edessa (in modern Urfa in south-eastern Turkey), also known as the School of the Persians in Edessa [12], was destroyed by the Byzantines in 457 A.D. and was subsequently closed by Emperor Zeno in 489 A.D. [10] [13]). This and the further closure of

the Athenian Academy by the Byzantine Emperor Justinian in 529 A.D. led to the emigration of learned Nestorians and Greek physicians to Jundi Shapur, where they sought refuge under the patronage of Shapur II [10] [11]. Subsequently, in approximately 555 A.D. a medical centre and hospital were established by king Khosraw Anushirawan the Just [14]. It was here that a uniquely tolerant and peaceful meeting point for the study of the philosophical and medical traditions of Persians, Greeks, Indians, Zoroastrians, Jews, and Nestorians developed, serving as the foundation for the incredible medical advancements under Muslim rule. In fact, Hārith bin Kaldah al-Thaqafī, the Prophet Mohammed's (^{PBUH}) physician, trained at Jundi-Shapur [1] [15]. The Jundi Shapur medical school remained one of the greatest centres of medical teaching throughout the Islamic world until the growth of caliph Al-Mansur's capital Baghdad in 762 A.D. [1] [16].

As far as medicine in the Arab peninsula is concerned, there is very little information available. However, it appears that Arabs were familiar with treating septic wounds and ulcers with disinfectants and understood that contagious diseases were prevented by the isolation of infected patients [1].

3. Medicine in the Post-Islamic Age

Following the introduction of Islam in the 7th century, an intellectual and cultural transformation in the Arab peninsula began. Islam, from its foundation, stressed that the pursuit of knowledge was a divine command, professing that knowledge brings mankind closer to God, representing the " ultimate happiness" [17]. The foundation of Islamic science was laid during the Abbasid Caliphate and the foundation of Baghdad as its capital by Caliph al-Mansur in 145 A.H./762 A.D. It is reported that Caliph al-Mansūr suffered from an abdominal disease and asked for a skilled physician in his realm to find a remedy for his illness. He was told there was no other physician more accomplished than the Nestorian physician Jirjis bin Bukhtyishu. Subsequently, Jirjis, then Chief of the Jundi-Shapur Hospital, was summoned to Baghdad. Jirjis treated the Caliph Mansur and was appointed the court physician [1] [18]. During the succeeding years, many scientific texts were translated into Arabic from works from the Syriac, Greek, Sanskrit, and Pahlawi languages [1] [19]. Scientists such as the Jewish Masha' Allah al-Yahudi, Al-Muqaffa', a Zoroastrian who converted to Islam, and physicians including the Bukhtyishu family and the Nestorian Hunayn ibn Ishāq, were summoned to Baghdad [20]. During the next six centuries, medicine alongside other fields of science reached its peak, and prominent physicians and scientists emerged in the Islamic lands to give immense contributions to global civilization.

4. Hospitals

The first Bimâristân (hospital) in the post-Islamic era was built in Damascus in 88 A.H./707 A.D. [15]. The first Bimâristân in Baghdad was built during the

reign of Caliph Harun Al-Rashid (170-193 A.H./786-809 A.D.) with Jibrail Bukhtyishu as its head physician. Subsequently, three more hospitals were built in Baghdad, including the Bimâristân al-Sa'di (279A.H./892 A.D.), Bimâristân al Sayyidah (306 A.H./918 A.D.), and the Mansūrī hospital (981 A.D.) with Al-Razi as its principal physician [21]. The first hospital in Afghanistan (Ghazni) was built during the reign of Sultan Mahmoud of Ghazni (998-1030 A.D.), which also had *Darul-Majânīn* ("madhouse") or a mental health section [22]. The first hospital in Iran (Isfahan), with Abu Ali Sina as its chief physician, was built during the reign of Ala'ud Dawla (1008-1041 A.D.) [8]. The first hospital in Marrakesh was built in 1199 A.D. The first hospital in pre-Ottoman Turkey was constructed in 1205 A.D. in Kayseri; two more were erected in Sivas in 1217 A.D. and Amasya in 1308 A.D. [23]. The Al-Mansuri Hospital in Cairo was built in 1284 A.D. with a capacity of 8000 beds [24], whilst the first hospital in Grenada was built in 1397 A.D. [25].

5. Influential Physicians

The **Bukht Yishu** family of the Syrian, Nestorian background produced ten extraordinary physicians who served between the 8th and 11th centuries. There is very little information available about the founder of the family, Bukht-Yishu I, who was born in Baghdad [26]. His name was Syriac, meaning "Jesus hath delivered" [20] or "Jesus saved" [19]. His son Jirjis I (died 152 A.H./769 A.D.) served as the court physician of Caliph al-Mansūr (754-75 A.D.); and his grandson, Bukht Yishu II (died 185 A.H./801 A.D.), the court physician of Caliph al-Mahdī (775-85 A.D.) and Hārun al-Rashīd (786-809 A.D.) [27]. Jibra'il ibn Bukht-Yishu II (died 213AH/828/9 A.D.), son of Bukht Yishu II, served as the court physician of Hārun al-Rashīd, al-Amin (809-813 A.D.) and al-Ma'mun (813-833 A.D.). Other members of this eminent physician family included Bukht-Yishu III ibn Jibra'il (died 256 A.H./870 A.D.) the court physician of Abbasid Caliph, al-Mu'taz (866-69 A.D.); Yahyā or Yuhanna, Bukht-Yishu IV (died 329 A.H./941 A.D.), the court physician of Caliph al-Muqtadir (929-932 A.D.); Ubaydullāh ibn Jirjis II, the court physician of al-Muttaqī (940-944 A.D.); and finally, Jibrail ibn Ubaydullāh and his son Abu Sa'id Ubaydullāh [20].

Hunayn ibn Ishāq al-Ibādī (died in 260 A.H./873 A.D.) known as Joannitus was a Christian scholar, born in Baghdad, and the pupil of Yahyā (or Yuhanna) Mâsawayh of Jundi Shapur. Hunayn translated many Syriac and Greek works into Arabic [18] [27] [28] [29] including Fusūl or Aphorisms of Hippocrates [20].

Ishāq bin Imrān (died c. 903-9 A.D.) was an Arab physician born in Tunisia who composed the *Al-maqāla fil-malīkholyâ* (the treatise on melancholy) [30] which was the first written treatise on melancholy in Arabic strongly influenced by the Rufus's "On Melancholy" [31].

Ahmad bin Sahl Abu Zayd Balkhī (849-934 A.D.) born in Balkh, Afghanistan [18] [19] [32] was the founder of the Balkhī School of Geographers in Bagh-

dad [33], and the author of seventy books [27] [34] including the book of *Masâlih al-Abdân wa al-Anfus* ("Sustenance for Body and Soul"). Balkhi was one of the first physicians to define panic attacks (*al-faza*), phobia (*al-khawf*), and obsessive-compulsive disorders (*al-waswasah*). Balkhí, 1100 years ago, brilliantly differentiated between *al-huzn* (normal sadness), and *al-jaza* (depression); the former being reactive—"the causes clearly known, such as loss of a loved relative, or loss of something"—and the latter being endogenous depression, that "has no reasons; it is a sudden affliction of sorrow, which persists all the time preventing the afflicted person from physical activity, or feeling any happiness or enjoying any pleasure" [35] [36] [37]. It wasn't until 1899 A.D. when Emil Kraepelin introduced "psychogenic depression" and Kurt Schneider in 1920 A.D. "reactive" depression. The term "endogenous" came into existence around 1893, proposed by Paul Julius Möbius. Endogenous depression was described by Emil Kraepelin as a form of depression that tends to come out of the blue [38]. When comparing the two, it is remarkable how similarly Balkhi and Kraepelin describe endogenous depression.

Abu Bakr Muhammad ibn Zakariyā al-Râzī (c. 865-925 A.D.) born in Ray, Iran, known also as Rhazes, was one of the greatest practitioners of the Islamic medicine to ever live. He was a prolific writer who composed more than one hundred works on metaphysics and medicine. *Firdausu'l Hikmat* (Paradise of Wisdom), *Al Faraj ba'da'sh-Shadda* "Joy after Sorrow", and Al Hāwī are amongst Razi's most famous works [27]. Alongside writing, Râzī devoted his attention to Alchemy, on which he wrote twelve books [20]. Râzī was the first who recommended clinical trials, stating "if you want to study the effect of bloodletting on a condition, divide the patients into two groups, perform bloodletting only on one group, watch both and compare the outcome". Furthermore, he wrote *Kitab fi al-Jadari wa al-Hasbah*, an influential book on measles and smallpox, and the first book on paediatrics [39]; hence, Râzī is regarded as "the father of paediatrics" [40]. In terms of neuropsychiatry, Râzī in the first part of the Al-Hāwī (in the section entitled "brain diseases") classifies neuropsychiatric disorders into the following categories: 1) "*malīkholyâ*" or melancholia [41]; 2) "*sar'a*" (seizure), and *um-al sabyān* literally meaning the "mother of a demon that hurts children" [19], infantile epilepsy; 3) "*kābus*" (nightmare) and *al-tafaza' al-nawm* (nocturnal panic disorder); 4) *al-tashannuj, wa al-tamaddud wa al-kazāz'* (spasms and movement disorders); 5) *qeranits bi' infirād wa ishterāk al-junun* (simple and psychotic phrenitis); 6) "*qhutrub*", described as an agitated form of psychosis, similar to hebephrenic or catatonic-like psychosis; 7) *mâniâ*; 8) "*hazyān*" or delirium; 9) *jami' al zurub-alsahar* (all kinds of insomnia); and finally; (10) *Al-suda'a wa al-shaqīqa wa al-ma' fil ra's* (headaches, migraine, and hydrocephalus) [41] [42].

Hakim Maysarī authored the Dāneshnāma (Medical Encyclopaedia), the only medical manuscript written poetically in Farsi-Dari (Persian) [43] [44]. There is little information about Maysarī's life, however, it transpires from the Dāneshnāma

that he was from eastern Persia (today's Afghanistan) and completed Dāneshnāma in 370 A.H./978-9 A.D. There was only one similar medical manuscript written by Yūsuf bin Muhammad, a doctor, and poet from Herat (Afghanistan) who lived during the reign of Bābur (932-37 A.H./1526-30 A.D.), the founder of the Mogul Empire in India and Homāyūn (937-63 A.H./ 1531-56 A.D.). His works span all branches of medicine [45]. Maysarī dedicates his book to emir *Nāsir al-Dīn wa'd Daula*, Sebüktegin who established the Ghaznavid Empire in 977 A.D. in Ghazni, Afghanistan [22] [46]. Dāneshnāma hence is the first known medical book written in Afghanistan. Dāneshnāma is a relatively short medical encyclopaedia comprising 4505 verses; it is an invaluable medical resource that covers a wide range of subjects including neuropsychiatry, ophthalmology, cardiology, respiratory medicine, dermatology, gynaecology, sexology, and more. The book is structured as follows: 1) on "*mizāj*" (temperament), 2) on acute pains, 3) on remedies, 4) on clinical medicine, covering a wide spectrum of health problems "from head to toe" starting with hair loss and ending with feet corns and callus; 5) toxicology, and 6) fever. As far as neuropsychiatric conditions are concerned, Hakim Maysarī was one of the first physicians to describe the symptomatology and treatment of neuropsychiatric conditions such as melancholy, *rejā* (pseudocyesis), *ikhtenāq e rahm* (hysteria), and pseudo-seizure, *shaqīqha* (neuralgia of trigemini nerve or/and migraine), *dawwār* (vertigo), *sarsām* (meningitis, encephalitis), *sobāt* (hypersomnia), *shukhūs* (syncope), *sar'a* (seizure), and *kābus* (incubus). Dāneshnāma is probably the first medical book in post-Islamic medicine that openly discusses issues that are still rather proscribed even today, such as sexual dysfunction, loss of libido, ejaculation praecox, vaginism, dyspareunia, nymphomania, satyriasis, elongation, and enlargement of the penis, contraction of the vagina, and issues around contraception [44].

Abu Mansūr Mowaffaq bin Ali Herawī (died ca. 978-88 A.D.) was a physician and pharmacologist from Herat, Afghanistan, and the author of Al-abnīya an haqā'eq al-adwīya ("Basics Facts about Medicines") written in 447 A.H./1055 A.D. This is the oldest book of pharmacology written in Farsi-Dari [45]. In this book, Herawī reviews 584 remedies, including their mode of actions, indications, efficacy, side effects, adverse effects, and geographical origins. He provides Arabic, Greek, Indian, Farsi-Dari, and Syriac names of the drugs [47] [48]. When discussing indications of the remedies, Herawī refers to other physicians including Razi and Galen but most often to Pedanius Dioscorides (ca.40-90 A.D.), the Greek physician, pharmacologist, and botanist, and the author of the monumental De Materia Medica [49] [50].

Abu'l Khayr Hasan bin Sawār, Khammār (942-1046) was a Christian physician born in Baghdad [18] [28] [29]. He was described by Nizami-Aruzi as the third after Hippocrates and Galen in the science of medicine [20] [26]. Khammār was the chief physician of the Royal Hospital in Ghazni [22], and the court physician of Sultan Mahmūd (388-421 A.H./998-1030 A.D.), Sultan

Mas'ūd I (421-32 A.H./1030-41 A.D.), and Bahrāmshāh [18].

Ali ibn Abbās al Majūsī (949-994 A.D.) known as "Haly Abbas" [51], born in Ahvaz, Iran, was a pioneering physician and surgeon who influenced the Western world with his monumental work, *Kāmil ul-Sinā'at ul-Tibya* ("The Comprehensive Book of Medical Art"). This was also known as *Kitābu'l Malikī* or "The Royal Book" [52]. Majūsī in the introduction of this book declares "what I saw in the old medical books from the time of Hippocrates until now was incomplete. A complete and comprehensive book on science and all fields of medicine has not been written until this era". His book was a medical one covering all medical subjects. The Malikī book was the main medical book used by physicians before the Avicenna's Qānūn; however, when comparing Qānūn and the Royal Book, the Qānūn was deemed stronger on the theoretical, though weaker on the practical, side [19] [20]. In psychiatry, Majūsī categorised mental disorders into: 1) *malīkholyâ* (melancholy), 2) *haymān* (love madness), 3) *qhutrub* (defined as a form of agitated melancholy), 4) *sarsām* (inflammation of the head, or meningitis), 5) *barsām* (inflammation of the chest or the "curtain located between heart and lungs"), characterised as a syndrome of delirium, 6) *sobāt* (hypersomnia, or narcolepsy), 7) *sobāt-ul-saharī* (narcolepsy or agrypnocoma), and 8) *zawāl hāfeza* (dementia). As far as the aetiology of mental disorders is concerned Majūsī's perspective is holistic and refers to the three main aetiological factors like a) "physical" factors (temperament, humour, physical predisposition, personality, etc.), b) "non-physical" factors, like excessive emotions as sadness, fear, and anxiety, and c) "environmental" factors. Furthermore, Majūsī believed "qhutrub" was hereditary, but that nonetheless melancholy was caused either by brain dysfunction, damage to the stomach, or impairment of other organs [53].

Abu Bakr Rabī ibn Ahmad al-Akhwayani al-Bokhârī (died 983 A.D., Bukhara, Uzbekistan) lived in northern Afghanistan and Bukhara, and was the author of *Hidâyat al-Muta'allemin fi al-Ṭibb* ("A Guide for Medical Students"), the third oldest medical book written in Farsi-Dari [54]. Bokhârī wrote on different subjects of medicine, including contraception [55] sarsām or meningitis [56], and made the distinction between seizure and pseudo-seizure [57]. For his knowledge of mental disorders, Bokhârī became known as *Pezeshk-e-Divanegan* [58]. Bokhârī classified mental disorders into: 1) malīkholyâ or melancholia, [54] 2) mania, 3) qhutrub, 4) "*kâbus*"—a nocturnal panic disorder, 5) "*Rejâ*" (pseudocyesis) and 6) "*Khonâqh-ul-rahm*" (hysteria) [54] [59].

Abu Mansūr Hasan, ibn Nūh al-Kamarī (died c. 999 A.D. in Bukhara), the court physician of Sāmānids (892-999 A.D.) and Avicenna's teacher, was a versatile physician and author of many books, including the *Al-Tanwīr fi al-Iṣṭilāḥāt al-Ṭibbiyya* or Enlightenment into medical terminology [60] and *Al-Ghina wa al-Muna* or the "Book of Wealth and Wishes" [8] [58] [61].

Abu Ali Hussein, ibn Abdullah ibn Sīnā, Latinised, **Avicenna** (980-1037 A.D.) born in Balkh, Afghanistan [1] [39] was described as "the Philosopher of the East, the Proof of God unto His creature" [20] [26]. Avicenna authored 450

books, including the monumental *Qānūn fi Tib* ("Canon of Medicine") and *Shefā* ("The Book of Healing"). Qānūn is amongst the most influential medical books and was a standard medical text, remaining in use until the 17th century [8]. Qānūn was so revered by physicians that Nizami-Aruzi stated that "if Hippocrates and Galen were resurrected, it would be permissible for them to prostrate before this book" [20] [26]. In anatomy, Avicenna was the first physician to prove that only humans have clavicles and was the first to locate the stomach in the left part of the abdominal cavity. Unlike Galen, who assumed the heart was on the middle of the chest, he specified that the heart was in the left side. He concluded that the spinal cord was a continuation of the brain and contained sensory, motor, and mixed fibres. He accurately distinguished between skeletal and smooth muscle functions. Avicenna accurately described the bicuspid and tricuspid heart valves, as well as the aortic valves and their functions. In describing the anatomy of the testicles, he demonstrated that there was a "fertile" and "infertile" fluid. Moreover, Ibn Sina was the first to describe the configuration of the eye muscles. In infectiology, Avicenna concluded that measles, smallpox, and plague have an infectious origin. He pointed out the existence of "small disease-causing creatures." Avicenna was the first to postulate the parasitic origin of filariasis. In surgery, he routinely performed surgeries such as removing bullets, stones, and tumours, stressing the need to excise tumours as soon as possible. Avicenna can be considered the discoverer of tracheotomy. He is one of the founders of paediatrics, noting that the child's body differs from the adult not only in size but also in its peculiarities. In neurology, Avicenna was the first physician to provide the clinical manifestation of sarsām-e sard or lethargic "Economo's encephalitis" [8], more than 1000 years ago before Constantin von Economo [62] [63]. In mental health, Avicenna considered exhaustion, abuse of drugs, as well as infectious diseases, congenital factors, constitutional anomalies, moral failures, and sexual deviations, to be causes of mental disorders. Avicenna is likely the first physician who used an animal model to demonstrate the negative effects of stress on health. He is known for his experiment where he kept two lambs in the same environment, except that one of them faced a wolf whilst the other could not see the wolf. Both lambs were looked after equally, but the lamb that directly faced the wolf died after a while, whilst the other survived. He was the first to connect various mental activities and disorders with certain parts of the brain. He confirmed that mental illnesses are no different in origin from somatic ones and rejected the belief that evil spirits were the cause of mental illness. He was well experienced in psychosomatics, claiming that there was an "invisible" connection between the soul and the body; something like a bridge over a river, where if there is a change on one bank, the other will be affected similarly. In the treatment of mental disorders, in addition to medication, Avicenna recommended ergo therapy, music therapy, and physical exercise [8]. Avicenna classified mental disorders under the followings categories: 1) sleeping disorder, including both hypersomnia (*sobāt*) and insomnia, 2) acute and transient

brain dysfunctions, including transient memory disorders, disorganised behaviours, and perceptual disorders; 3) *hazyân* (delirium), 4) *ru'unat wa hamāqhat* (mental retardation), 5) *Fasâd-e-zehn* (dementia), 6) *fasâd-e-takhayyol* (corruption of imagination), 7) *mâniâ*, and *dâ-al-kalb* ("dog's disease", a mixed psychosis fluctuating between calmness and hostility), 8) *malīkholyâ* (melancholy), 9) *qhutrub*, 10) *eshqh* (love) disorder; and 11) *ikhtenāq-ul-rahm* (uterine suppression or hysteria). As far as melancholy is concerned, Avicenna recognised five forms of melancholia: a) sanguinolent melancholy described as a form of illness, which presented with "laughing and happy imaginations", b) melancholic melancholy, associated with "lachrymosity and suicidal ideations", c) "cerebellar" melancholy, characterised by symptoms of "deep thinking, prolonged and excessive obsessive thoughts, poor eye contact, etc." d) "splenic" melancholy, associated with "anorexia and fever", and e) "ventricular" melancholy. In terms of mania, Avicenna recognised two types of mania; *sobārī* or agitated, psychotic mania, and *hārī* or inhibited mania without psychomotor agitation. With regards to the treatment of mental disorders, Avicenna provided several treatment alternatives, including medications and bloodletting. However, he suggested that if patients are extremely agitated or at risk of suicide, they should be "securely placed in a cage and hung from the ceiling". He also recommended that if patients were agitated or aggressive and medications ineffective, "one could hit the patient on the head or slap them or burn their head" [64].

Abu al-Qāsim Khalāf ibn al-Abbās al-Zahrāwī, Latinised **Abulcasis** (936-1013 A.D.), was born in Zahra, northwest of Cordoba and because of exceptional skill in pharmacology and surgery, he was also known as the "Pharmacist Surgeon". Al-Zahrāwī is the author of *Kitāb al-Tasrīf*, a thirty-volume encyclopaedia of medical practice [65]. He invented numerous surgical instruments, including the use of catgut, the ligature, the surgical needle, the retractor, and the surgical rod [66].

Of **Abu Rayhān Muhammad ibn Ahmad al-Bīrūnī** (362 A.H./973 A.D.-440 A.H./1048 A.D.), there is little information regarding his origin; Bīrūnī lived most of his life in Afghanistan and India under the rule of Ghaznavid sultans of Afghanistan [18] [46]. Al-Bīrūnī was a polymath universal scientist, who is described as one of the "greatest men science has produced", and as "a phenomenon in the history of Islamic learning and literature" [20]. Al-Bīrūnī wrote hundreds of works, including his masterpiece *Al Ātharu'l Bāqiya an'l Qurūni'l Khāliya* (Chronology of Ancient Nations) in the field of history [67], and *Kitāb-al Sidana fi al-Tib* (The Book of Pharmacy in Medicine), which details more than 1000 drugs of various origins [8].

Sayed Zayn al-din Ismāil bin al-Hasan, bin Mohammad, bin Mahmud, al-Husaynī, Jorjânī (434 A.H./1042 A.D.-531 A.H./1137 A.D.) was a versatile physician and the author of Zakhīraye Khwārazmshāhī (The Treasure of Kwārazmshāh) [18] [20] [29] [68] [69] which was composed at the court of Kwārazmshāh Qutbuddin Muhammad (491-522 A.H./1098-1128 A.D.) and

Al-Aghrāḍ ul tibiyah wa' al-mabāhith' ul Ala' iyah (The Aims of Medicine), dedicated to Sultan Alā' ad-Din Qīzīlarsalān Atsīz who ruled Khwarazm (a vast region consisting of most of Afghanistan, east of Iran and parts of Central Asia) between 1127 and 1256 A.D. [19] [20], both written in Farsi-Dari [45] [70]. In surgery, Jorjânī introduced different methods and instruments of surgery. He explained methods of stopping severe haemorrhages by casting them with plaster, treating the obstruction of air canals by tracheotomy, curing the difficulty in urination by catheterization, the exact method of removing apophasis, and stitching the spot after cutting and paring in polyp surgery in full detail. Moreover, he highlighted the association between exophthalmos and goitre, and the correlation between the expansion of thyroid glands and an increase in heart rate. In this way, medicine came to understand the pathologic toxic reactions of thyrotoxicosis [71]. In neuropsychiatry, Jorjani in his *Al-Aghrāḍ ul tibiyah* dedicates a full chapter on "illnesses of the head" where neuropsychiatric illnesses are listed. In terms of the psychopathology of mental disorders, Jorjani talks about the two-dimensional or two-syndrome model of mental disorders, dividing them into two categories; firstly, those that "warm and move the limbs, the humours, and the spirit, such as anger, joy, hope, and thoughts"; and secondly, those that "cool and slow down the limbs, the humours, and the spirits, such as sadness, fear, and similar things" [70]. Jorjani understood mental disorders as "the diseases of the brain substance", classifying them into 1) *malīkholyâ* or melancholy, "the person suffering from this illness is always negative-thinking, fearful, and sad", 2) *díwānagī* (madness), 3) *ghaflat* and *nasyān* (memory problems and dementia), defined as "inability of imagining and accordingly describing things and lack or decline of intellect", 4) *ahmaqhī* (mental retardation), 5) sleeping problems such as a) *sobāt* outlined as "excessive sleeping" (hypersomnia), b) "excessive lack of sleep" (insomnia), and c) *kābus*, described as a syndrome "when people in the sleep think something heavy is on their chest, pushing them to the extent they would not breathe, unable to scream or to move, and this could be a prodrome of seizure, stroke, or madness, called mania", and 6) *sar' a* (seizures). Jorjani categorises "madness" into four types, namely 1) mania, described as form of "madness" and "the person affected by this illness is mad that gets the temperament of thieves, and his gaze will look like a gaze of thieves"; 2) *dā' al kalb* (dog's disease) when the affected persons will "have the temper of dogs, sometimes behave unfriendly, on other occasions behave kindly"; 3) *sobārā*, described as "a severe form of madness associated with mania" accompanied by fever; and 4) *qhutrub*, described as an agitated form of psychosis, because "individuals affected by this madness are like qhutrub, the small mosquito-like fly (dragonfly) that moves fast and erratically over the water, will not rest" [70].

Abu-Marwan Abdel-Malik Ibn Zuhr, Latinised Avenzoar (1094-1162 A.D.), born in Damascus, Syria, the author of *Al-Taysīr fī al-Mudāwāt wa al-Tadbīr* ("On Preventive Regimen and Treatment"), is one of the first physicians to describe hydrocephalus [72] and gave the first detailed report of cancer of the co-

lon [73]. He used animal testing, and post-mortem autopsies [74].

Ala-al-Din Abu al-Hasan Ali ibn Abi-Hazm al-Qarshi al-Dimashqi known as **Ibn al-Nafis** (1210-1288 A.D.), born in Damascus, laid the foundation of physiology and was the first physician to describe the pulmonary and the coronary circulation [75] [76] [77].

Mansūr ibn Muhammad ibn Ahmad ibn Yūsuf ibn Ilyās (1380-1422 A.D.), born in Shiraz, Iran, was a physician and the author of the first colour illustrated atlas of anatomy or *Tashrīh-e Mansūrī* or The Mansur's Anatomy [78] [79].

6. Discussion

History is, in short, an art of investigation of the past, and principally, the collection of data, their organisation, and interpretation. As far as the history of medicine in Islamic territories is concerned, this task is extremely difficult. Firstly, when it comes to the collection of data it is very arduous to collect data as most of the sources have been destroyed or damaged, and those available are not easily accessible. Secondly, the interpretation of data poses a significant challenge, as during the past millennia the geography of the Islamic civilisation has significantly changed, including the names of countries. Finally, when discussing the history of Islamic medicine, one must specify whether the subject of the investigation is specifically the history of Arab medicine or the history of medicine in Islamic civilisation in general. Some interchangeably use the term "Arabic" and Islamic' as equivalent, which leads to some misinterpretation, as not all Muslims are Arabs and vice versa. Hence, we prefer the expression "Islamic" instead of "Arabic" as a more fitting term.

Evidence indicates the evolution of medicine in Islamic civilisation began millennia before the rise of Islam in the 7th century and is associated with the development of medicine in neighbouring regions, such as Mesopotamia, ancient Persia, Greece, Egypt, and India, where the medicine was highly advanced. The foundation of Islamic science was laid during the reign of caliph Mansur (754-75 A.D.) and the foundation of Baghdad as its capital in 762 A.D. The first three centuries of Abbasid rule (the eighth to eleventh centuries) saw the summit of medieval Islamic civilisation. Literature, theology, philosophy, and natural sciences (including medicine) all flourished, with fertilising influences from Persia and the Hellenistic world [80]. Further principal centres of Islamic civilisations were Bukhara, Balkh, Damascus, Ghazni, Herat, Nishapur, and Ray, where scientists of diverse religions, races, and nationalities worked and resided in harmony [8]. As in the pre-Islamic times, as well as in the post-Islamic ages, medicine was strongly influenced by Greek medicine. The influence of Greek medicine was even stronger in the post-Islamic evolution of medicine because of the translation of Greek medical literature into Arabic. In fact, early Muslim physicians, including the most prominent of all physician-philosophers Avicenna and Razi, recognise the influence of Greek medicine on their work and expressed admiration of Greek physicians such as Socrates, Galen, and Rufus, etc.

On the other hand, the advances and innovations in medical science and healthcare systems achieved during the early and medieval Islamic ages have unarguably contributed to the evolution of medicine throughout the world and to the establishment of various procedures and practices which are still relevant today. In spite of this, most Western medical textbooks rarely mention Muslim physicians, as their contribution is under-represented. Singh [81] has reported systematic bias against India in Western literature on the history of medicine. As highlighted by Kabeer & Tsai [82], the typical Western view of scientific history is distorted and incomplete. This phenomenon could be associated with selection bias of historical sources. In fact, recent evidence suggests there is a widespread prevalence of selection bias in historical sources [83]. Unfortunately, unfair accounts of the past are the result of historians' bias, of their preferring one account over others because it aligns with their interests [84]. A typical example of this bias is seen in Avicenna, whose ethnic origin is disputed by Turks, Persians, and Arabs. Whilst Turkish medical literature refers to him as Turkish [23], most Iranians refer to Avicenna as Iranian [85]. In actuality, Avicenna hailed from Balkh, Afghanistan [1] [18] [29], and neither modern Iran nor Turkey regarding his ethnicity, both Iranians and Turkish ethnic groups have lived (and still live) in Afghanistan.

7. Conclusion

The evolution of "Islamic" medicine began millennia before the rise of Islam in the 7th century. Furthermore, the history of medicine in Muslim territories is very complex and is incredibly closely related to as well as influenced by the evolution of medicine in neighbouring nations, namely Mesopotamian, Egyptian, Persian, Indian, and predominantly, Greek medicine. On the other hand, the advances and innovations in medical science and healthcare systems that were achieved during the early and medieval Islamic ages have significantly contributed to the evolution of global medicine, and to the creation of several procedures and practices which are still widely performed today. Hence, the value of comprehending the pivotal role Islamic medicine played (and indeed still plays) in the progression of medical practice across the globe cannot be overstated.

Collaborators

RM, RM-A, AO, TA-K, NS.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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