CHAPTER 2

A HISTORICAL PERSPECTIVE OF INFECTIOUS DISEASES WITH REFERENCE TO CRIMEAN-CONGO HEMORRHAGIC FEVER

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2.1. HISTORICAL PROCESS OF THE DISEASE CONCEPT

In studying the evolution of the concept of disease, Kraupl Taylor argues that the term "disease" emphasizes more the pathological side of the disease itself, while the term "illness" corresponds to clinical signs [13]. From the perspective of the history of medicine, the term "disease" should be used in its widest meaning, because if the label of "disease" is used in the sense of its definitions made by contemporary medical scientists, many disease definitions in the medical history will have to remain unmentioned. However, despite their great differences from their definitions today, the smallpox disease defined by Galen in the 3rd century is a "disease" as is the smallpox defined by Rhazes (Fig. 2-1) in the 10th century. Similarly, in the 1700s, the smallpox disease defined by Jenner is also a "disease". Remarkably, way back in history, the signs of a disease, considered only a symptom today, were regarded as a disease on their own. Hence, symptoms such as abdominal pain, hemorrhage, diarrhea, vomiting, and fever were cited as diseases in the Hippocratic era, Galen, and/or Razi and Avicenna, the distinguished representatives of the Eastern world [8]. This approach has cultural and in fact, mythological bases, which can be embodied by the example of Febris, the goddess of fever and malaria. She represents fever and febrile diseases. In antiquity, unlike in our times, not much was known about the mechanism of fever in disease and therefore was considered a disease on its own. In periods of medicine with mystical explanations, supernatural forces were blamed. Consequently, it is not surprising that the goddess Febris was held responsible for fever.

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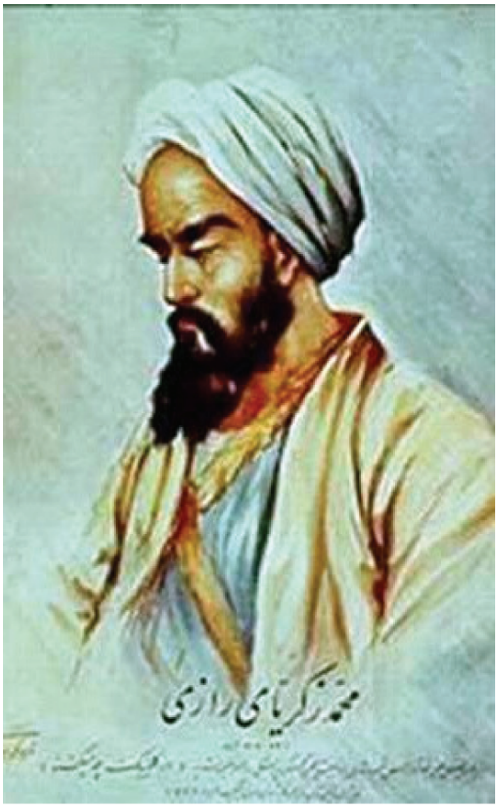

Fig. 2-1. Abū Bakr al-Rāzī (854–932), "Rhazes", eminent physician of the eastern medieval world.

In the medical paradigm of our times, the term "disease" ("antite morbide") is used in its most specific meaning [2]. To label a clinical picture with this term, a through knowledge of all its characteristics is the primary requirement. A clinical picture described under the heading of "X disease" in any textbook is explained in subtitles covering its nosological and symptomatological characteristics, and progression and process. Its etiology and pathogenesis as well as "anatomopathology" and "histopathology" are also provided. Similarly, the treatment is defined under the same heading. In this book, the same scheme has been used for Crimean-Congo hemorrhagic fever (CCHF). If there is a lack of information associated with the disease, particularly with etiology and pathogenesis, the clinical picture will often be labeled as a "syndrome."

There is in fact a historical dimension to the labeling of "syndrome." We are all aware of the importance of scrutinizing a patient's symptoms for the development of a differential diagnosis of diseases. In times when symptoms were considered a disease in their own right, the signs that accompanied each other were termed "symptom," which literally means "a friend for the road walking the same path." Thus, it can be said that the term "syndrome" was a concept

used in the medicine of antiquity. Hippocratic paradigm is also compatible: careful observation of the symptoms, follow-up of the patient, and disease as a natural result of natural reasons. In this respect, CCHF is a syndrome progressing with fever and hemorrhages. In 1937, Behçet was defined as a syndrome characterized with iris infection, ulcerative lesions of the mouth, and genital ulceration. When AIDS was defined as a new syndrome in 1981, skin eruptions, diarrhea, and accompanying symptoms associated with respiratory system directed physicians to the same point: "All of these constitute a different disease from the other diseases you have known so far."

The definition and explanation of the changes inflicted by the disease agent on the healthy organism forms the theories of pathology, which have developed parallel to various thought patterns throughout the ages. Whatever their type, all theories of disease are the products of intellectual endeavors to "understand and account for" the concept of disease. In fact, when naming and interpreting the concept of disease, the human mind has always followed this path. This notion is important in the definition and explanation of the disease entity, particularly with respect to infectious diseases. The history of medicine encompasses various theories and explanations on how a human becomes ill and the resulting effect.

2.2. CAUSE–EFFECT RELATIONSHIP AND SIMPLE EPIDEMIOLOGICAL AND CLINICAL OBSERVATIONS

Since ancient times, fighting disease and the protection of health has been one of the primary objectives of humankind. The behaviors of this kind that had initially helped form the "healing power of nature" (*vis medicatrix naturae*) with their mechanisms of protection made up of a chain of natural reactions or reflexes created "instinctive medical behaviors." Over time, certain applications that were proven to be useful through the trial and error method were regarded as acquired medical behaviors and the experiences of thousands of years constituted the content of empirical medical practice. The fact that there are social and psychological grounds to diseases, as well as a biological basis, is a result that was attained through observations of empirical medicine. It is known that civilization started at various locations on the earth including India, China, Mesopotamia, Egypt, Anatolia, and Aegean coasts of the Mediterranean. Thus, medical knowledge is a product of empirical medicine, but is also a part of our inheritance from many earlier civilizations.

The importance of agricultural reform and domestication of animals have been widely emphasized by medical historians. It is clear that ability to recreate nature and observe biological processes has improved human thought. Invention of agriculture was at the same time "cultivation" of diseases [9], of which parasites were the primary mediators. The pathogens in domesticated animals found favorable living conditions in the human organism and, thereafter, adapted themselves accordingly. Mice, rats, mosquitoes, fleas, lice, and ticks have been known to act as disease carriers since antiquity. For example,

a louse was found among the hair of a mummy dated around 3000 BC, which belongs to first royalty period of Egypt. However, it is not known whether a clinical picture similar to CCHF was ever among this group of diseases. The agents of certain infectious diseases, such as smallpox and measles, have been well adapted to humans. They were transmitted from person to person because of their highly contagious nature.

As humans began to transform nature to a living area, they also began to become more heavily infected, i.e. parasitized, by their own microorganisms. Thus, humans started to develop immunity and live with these microorganisms. This way a compromise between the assailant and human was established. Immunity is a key concept for the history of infections. Clearly, similar conditions occur genetically in some diseases. In falciparum malaria, for example, persons with sickle cell anemia are more resistant to infection by *Plasmodium falciparum*. These types of examples show that when exposed to a certain pathogen for a given amount of time, we learn the ways to overcome the disease provoked by this pathogen.

After the era when mystical explanations were given for healing, humanity developed a long-standing disease theory: "four elements or humoral pathology theory." The basis of this theory rests on the beliefs rooted in ancient times. Based on the civilizations of the Far East, humans have been thought to be a small model of the universe. Accordingly, the factors constituting the universe (macrocosmos) and human (microcosmos) are similar. The four elements in nature "fire," "air," "water," and "soil" correspond to "yellow bile," "blood," "phlegm," and "black bile," respectively. Based on the humoral pathology theory of the Hippocratic School, disease is the disturbance of the balance of these four elements. To regain health, the balance had to be reestablished. It is possible to see the initial traces of homeostasis theory of 20th century based on simple observation in this theory of pathology. Humoral pathology observed by Avicenna in the Eastern world has been effective for ages. However, it was replaced by "cellular pathology" by the work of Rudolph Virchow in 19th century [6, 12].

Definition of microorganisms, description of their transmission mechanisms, and prevention of contamination have contributed significantly in gaining the desired medical outcomes. The dissolution of "self reproduction" (spontaneous generation) theory and reproduction of bacilli under laboratory conditions paved the way for the development of vaccines and antimicrobial treatments, a turning point in the history of infectious diseases. Thus, many new developments in microbiology and infectious diseases were seen during the 20th century; however, this is also an age when threats of bioterrorism are realized [10].

2.3. RESEARCH INTO THE HISTORY WITH THE DEFINITIONS OF TODAY

In our times, CCHF is a medically and scientifically defined tick-borne arboviral disease [14]. This definition means that the etiology, pathogenesis, and symptomology are largely known. Starting from the case definition and symptoms of

CCHF, we studied the written documents of some of the civilizations of the past that had settled in the geography known to be endemic for CCHF.

Of course, it is very difficult to determine when a disease, as is defined today, first appeared in terms of the evolutionary development of medicine. Thus, in retrospective evaluations of diseases, it is necessary to be cautious and be aware that the name of a particular disease may also refer to many other diseases with similar symptoms. Medical historians, while researching the history of certain infectious diseases, agree that it is not possible to accurately go beyond 3000 BC.

It might be predicted that the smallpox virus was transmitted by cattle. The statues of Gods erected in the name of this disease in the temples of Indian civilizations are concrete evidence for the prevalence of this virus in Southern Asia [9]. Identification of plague in many different periods, in fact encompassing a wide array of diseases under the same name, is an interesting, if not inevitable, incident. Certain documents show that plague first appeared in Egypt and caused a widespread epidemic in 1347; thus, the entire world learned about this disease. However, it is not surprising that many diseases such as typhoid, paratyphoid, cholera, and typhus were described under the name of "plague." It was not until the late 19th century, when the specific causative agents of many of these diseases were identified, that they were no longer simply labeled as "plague." Consequently, "plague" has been a label representing lethality and destruction. It was referred to as "ta'un" in the Ottoman language. Similarly, research into today's terminology corresponding with the names of many fevers used by Thomas Sydenham in his book, "The Method of Treating Fevers" in 1666 is interesting as to the classification and shifts in the meanings of these terms throughout medical history. For example, a few of the terms used in this book in order to refer to various diseases are "goal fever," "hospital fever," "yellow fever," "malaria fever," "scarlet fever," "puerperal fever," "Malta fever," and "typhoid fever" [3]. Likewise, as for CCHF, a descriptive term taking the most dominant symptoms and its geographical location into consideration has been used, as is often the case for various viral diseases.

Having established a glorious civilization in Anatolia, the Hittites were dominant around 1650–1200 BC. Hittite culture was based on tolerance rather than violence and "an eye for an eye" notion. They believed diseases to be associated with supernatural forces. Accordingly, diseases were the result of the negligence of humans towards Gods, crimes against Gods, sins, disturbance of the dead, black magic, and/or the breaking of oaths or agreements. Ishara was the God of disease and Kamrusepas was the God of health. Yarris, on the other hand, was the God that protected the people and the kings from communicable diseases in the war arenas. The tablets with cuneiform scripts found among royal archive in Çorum Boğazkale (Hattusas), the capital of the Hittite Empire, provide information on the lifestyle of this great civilization. They indicate that the Hittites respected female physicians with the names of Makiya, Mammitum-um-mi, and Azzari. The Hittites are also known for their hygiene. They used to associate contamination with diseases. Punishment of those polluting the public water sources, isolation of the patients in case of epidemics,

thus, starting a quarantine practice are among the medical practices attributed to this civilization.

In Hittite period Anatolia, certain communicable diseases named "henkan" were observed. In the 1300s BC, during the wars when the Hittites conquered the land of Egypt in Syria, several epidemics were recorded as evidenced by the prayer of "disease" by King Mursilis II (Fig. 2-2) [5].

It is possible that henkan describes an extremely wide range of diseases with skin eruptions, high fever, and diarrhea. During the time of this civilization, which lived in middle and southeast Anatolia, CCHF cases too, if ever existed, were probably considered under the name "henkan." However, in order to prove this hypothesis, a reference made to a case in the tablets that will not leave any doubts, accompanied by a definition of the disease, is needed. Furthermore, the disease should also be traced in the following civilizations located within the same geographical area [4].

Fig. 2-2. The praying verses of Mursilis II for defeating plague on a tablet (1321–1295 or 1340–1310 BC). Text belongs to the Hittite Catalogue CTH 378/I version A: Ankara Anatolian Civilization Museum, Tablet Archive, No. Bo 2801.

(*Continued*)

Fig. 2-2. cont'd. This text has approximately ten broken fragments of the tablet which obtained different excavation periods and after that philological studies all of these are joined. The all text has been published by René Lebrun; Hymnes et Prières Hittites, *Homo Religiosus* 4, Louvain-La-Neuve (1980) 193–203. Tablets have taken photographed from the museum with special permission by Professor Cem Karasu, the chairperson of Hittitology Department in Ankara University.

2.4. HISTORICAL DEFINITIONS TO DATE

Abū Bakr al-Rāzī (854–932), known as Rhazes (Fig. 2-1) in the Western world, a distinguished physician of the Eastern world, was born in the city of Rayy. He learned medicine in a relatively late period of his life. Rhazes, who valued patient follow-up, is believed to have synthesized Hippocratic and Galen medicine. Among his books on medicine, philosophy, and mathematics, his most important work was *Kitāb al-Hāwī* (*Continens*), related to the treatment of diseases. Avoiding prescribing numerous drugs to his patients, one of his greatest contributions to medicine was the differential diagnosis of smallpox and measles. Strikingly, three cases defined by Rhazes bear similarities to CCHF in

today's definition [1]; thus, they provide important information as to the earliest definitions of the disease:

Case 1:

A woman had had fever and diarrhea called hulife; later, something like black blood had started to leak from her. The master asked if that black thing boils on earth. They said it did not. The master said if it did, it would be considered black bile because the one not boils is considered burned blood trapped in the liver. Now, couple of bowls are made red-hot on fire and then dropped in ayran (yoghurt drink) of cattle and extinguished; later the patient drank the ayran. With the permission of Allah, that blood was stopped, and the patient achieved full recovery.

Case 2:

A young person had headache, high fever, and redness in the eyes, and his urine color was red too. The master ordered him to use violet lozenges and then barley extract (juice), to put şiyaf-i şakika (headache drops) to the ear on his painful side, vinegar and rose extract (juice), and rose oil on his hand, and ordered him to eat tafşil (a meal cooked with meat, husked lentils, and vinegar) and hallü zeyt (vinegar and olive oil).

Case 3:

One person had fever and bleeding from below, also palpitation. The master ordered him to use sumac extract (juice) and copal lozenges and commended him to eat meals cooked with sumac.

Various references made to Rhazes as "the master" and reference made to the other books of Rhazes, such as the *Kitāb al-Mansūrī* (*Liber Almansoris*) while talking about the treatment [1], confirms that the cases were quoted from *al-Hāwī* (*Continens*). The detailed description of the first case is suggestive of a CCHF-like disease (Fig. 2-3). Likewise, complete recovery within a few days is suggestive of a "viral" disease.

Zayn al-Din Sayyed Isma'il ibn al-Husayn al-Jorjani, who lived in 12th century and died in 1136 in Merv, was a successor of Avicenna. His best-known work, *Zakhirah-i Khvarazm'Shahi* had become a widely used handbook and sustained this quality in the following centuries. It was also reported that Ibn (al-) Baytar or Baitar benefited from this book [7]. Interestingly, Hoogstraal had suggested that a disease defined in this encyclopedic book written in Persian might be CCHF. This case from the 12th century is from the Tajikistan region. The signs of the disease were blood in urine, vomit, and phlegm. It was stated that arthropods were the cause of the disease, and normally, the disease lives as a parasite in a black bird. Applying sandalwood essence and "bodzkhar" to the area of bite and feeding the patient with fresh goat milk were the treatment methods used. For centuries, similar pictures of the disease had been reported in the folk culture of Uzbekistan [7]. The relationship mentioned by Hoogstraal is one of the first simple observational examples of cause–effect relationships in

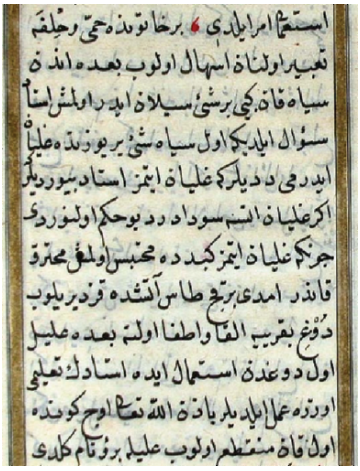

Fig. 2-3. Detailed description of CCHF-like cases. These pages belong to Razi's Hamidiye manuscript. This manuscript registered with number 1013 in İstanbul Süleymaniye Manuscript Library. It has 151 pages totally and written at the beginning of 18th century.

the 12th century. However, these determinations are highly speculative with respect to the methodology of history.

2.5. CONCLUSIONS

History is a discipline of process evaluation with retrospective data collection beginning at the present as one of its methods. Undoubtedly, tracing any disease in any society at any given time requires a comprehensive and multidisciplinary approach. Evaluation of the effects of civilizations on health and disease provides significant insight into the history of medicine, and further, the history of infectious diseases supplies many pertinent examples. While civilizations aimed to keep diseases under control, they themselves were often vectors of disease. The African continent, initially referred to as "white man's grave" because of several tropical fevers, became a site of colonization. The detection of the malaria agent and the use of quinine as an effective control also propelled imperialism. Thus, it is not surprising that Africa turned into "black man's grave" at the end of this process. Colonial medicine usually aimed at protecting the health of the colonists. Therefore, despite limited efforts of missioners, much of modern medicine of the time could not reach the local people [9, 11]. In the light of this information, in evaluating CCHF the reader should recognize that comprehension of only the technical and medical aspects of the disease will be insufficient to understand the history associated with the disease. As was detailed above, it is possible to find many traces of the history of infectious diseases. Various microorganisms can be detected through examination of historical remains, such as mummies. This facilitates the inquiries of medical historians. However, throughout biological evolution, for an infectious agent that first appeared hundreds or perhaps thousands of years ago, our words from

the perspective of medical history remain highly limited, and our claims have to be modest.

As the story of CCHF in the 20th century unfolded in the Crimean peninsula, it was only the initial stage of the act. This was a stage where humans would get to know their foe and fight against it with great vigor. Do we know in which century the story actually started? Is the disease mentioned by Jorjani in the 12th century the same as CCHF defined in the textbooks today? Or can we claim that the cases defined by Rhazes in the late 9th century and early 10th century, long before Jorjani, were CCHF? Certainly, we will continue to produce hypotheses and questions regarding our past. As we proceed forward, it is certain that history will shed light on the missing pieces of infectious diseases and the role they play in our lives.

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