

## History of Medicine in Iran

# A Historical Profile of Diphtheria in Iran during the 19th and 20th Centuries

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## Abstract

Diphtheria is a contagious and life-threatening disease historically regarded as a major cause of mortality, particularly in children. Over the past centuries, frequent diphtheria outbreaks have occurred. Herein, after a quick look at the history of diphtheria throughout the world, a historical account of this lethal disease in Iran during the 19th and 20th centuries is presented.

**Keywords:** Diphtheria, history, Iran

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## Introduction

The term 'diphtheria' is derived from a Greek word which means 'leather'.<sup>1</sup> It describes the leathery appearance of a tightly adhering diphtheritic membrane, known as a pseudomembrane, that covers the mucosa of the upper respiratory tract. Diphtheria is an infectious disease caused by *Corynebacterium diphtheriae* which are facultative anaerobic gram-positive bacilli. It has two forms: non-virulent (non-toxigenic) and virulent (toxigenic). The virulent type may be deadly due to the production of a potent exotoxin by the bacilli which affects myocardial and neural tissues. The fatal dose of diphtheria exotoxin is 0.1 µg per kilogram of bodyweight.<sup>2</sup> Diphtheria affects mainly the palatine tonsils, uvula, soft palate, pharyngeal wall, nasopharynx, and larynx. Attack by its bacilli leads to severe inflammation.<sup>3</sup> Laryngeal diphtheria is potentially lethal and untreated cases may result in suffocation and death. Diphtheria presents with low grade fever, sore throat, and cervical lymphadenopathy. It may lead to the characteristic swollen neck, known as a 'bull neck'.<sup>4</sup> In children, the affected child appears very toxic.<sup>5</sup>

In the 20<sup>th</sup> century, the incidence of diphtheria has greatly decreased, however it is not totally eradicated. According to the World Health Organization (WHO), the best preventive approach is widespread mass immunization of the entire population.<sup>6</sup>

## Diphtheria timelines

The history of diphtheria dates to ancient times. Between the 16<sup>th</sup> and 19<sup>th</sup> centuries, recurrent diphtheria epidemics have occurred in Europe.<sup>7</sup> In 1826, the French physician Pierre Bretonneau (1778 – 1862) called it 'diphtherite'.<sup>8</sup> Diphtheria, regarded as a dreaded disease throughout history was also called 'strangling angel of children'.<sup>9</sup> In 1880, the American physician Joseph O' Dwyer (1841 – 1898) invented a specific endotracheal tube to

overcome airway obstruction in affected children.<sup>10</sup>

Finally, in 1884 the causative agent (*Corynebacterium diphtheriae*, also known as Klebs-Löffler bacilli) was discovered by two German bacteriologists: Edwin Klebs (1834 – 1912) and Friedrich Loeffler (1852 – 1915). This discovery was a great scientific achievement.<sup>11</sup> Diagnosis of diphtheria has been based on clinical findings and laboratory data, of which laboratory diagnosis of diphtheria has been possible since the 1890s.<sup>12</sup>

Diphtheria may affect the skin and kidneys. Cutaneous diphtheria is the major source for acquisition of this infection in tropical countries.<sup>13</sup> Acute interstitial nephritis which is usually associated with sudden renal dysfunction may be seen in cases of diphtheria and was initially described by an American pathologist, W. T. Councilman (1854 – 1933).<sup>14</sup> The Schick test was invented in 1920 to detect individual susceptibility to diphtheria.<sup>15</sup> This test was developed by Béla Schick (1877 – 1967), a Hungarian-born American pediatrician.<sup>16</sup>

For centuries, various infectious diseases were the leading cause of mortality and morbidity among children,<sup>17</sup> of which diphtheria was a major challenge for physicians. In 1892, around 1% of all published medical papers recorded in Index Medicus were devoted to diphtheria. However, due to improvements in sanitation and mass immunizations, nowadays it is rarely seen except among unvaccinated populations.<sup>18</sup>

In 1913, the German physician Emil von Behring (1854 – 1917) introduced a mixture of toxin-antitoxin for protection against diphtheria.<sup>19</sup> Later, more effective and safer antitoxins and vaccines have been produced. To treat patients, both antitoxin and antibiotics are needed. The released diphtheria exotoxin is neutralized by the antitoxin and antibiotics prevent further production and spread of the bacillus.<sup>20</sup>

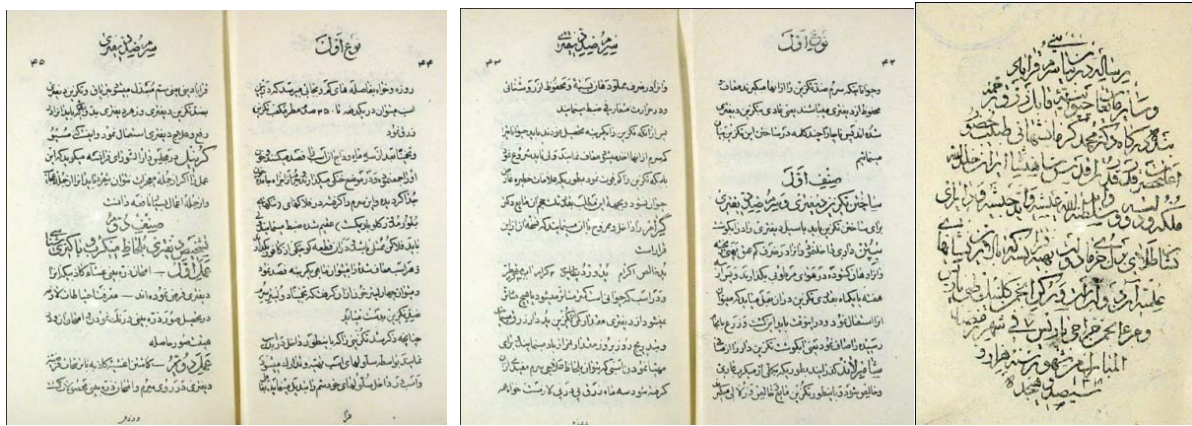
Until the first decades of the 20<sup>th</sup> century, no antibiotics were available. Penicillin was discovered in 1928 by the Scottish bacteriologist Alexander Fleming (1881 – 1955); however, he was unsuccessful in its isolation and purification. During World War II (WWII), sulphonamide and penicillin were used for the treatment of wounded patients and since 1944, penicillin has been used to treat bacterial infections.<sup>21</sup> The response of *Corynebacterium diphtheriae* to proper antibiotics is favorable and after 24 hours of antibiotic therapy, patients could usually be considered non-

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**Figure 1.** 'Resale dar Bayan-e Serom-e Qarabādini wa Sayer-e Mayeaat-e Haywaniya-ye Qabel-e Tazriq' published in 1900 as a lithographic edition was written by Dr. Mohammad Kermanshahi. The first page of the book (right). Four additional pages described antitoxin production and microbiological diagnosis of diphtheria. (Courtesy of Mr. Ali Akbar Vatan–Parast.)

contagious.<sup>6</sup>

During the 1940s and 50s, diphtheria was endemic in most countries and mostly appeared in preschool children, but it was infrequent in children less than one year of age.<sup>22</sup> Before mass vaccinations, the rate of vaccination coverage in children for prevention of common infectious diseases was less than 5%.<sup>23</sup> However, after mass vaccination between the 1980s and 1990s, diphtheria was almost eliminated in developed countries.<sup>24</sup> The worldwide vaccination program against diphtheria was conducted by WHO in 1974, which led to a substantial decline in the incidence of diphtheria.<sup>25</sup>

### Historical background of diphtheria in Iran

In Persian traditional medicine, diphtheria was known as “*Khonaq*”. For instance, this term was used by Ismail Jorjani (1040 – 1136 CE) in his Persian medical text ‘*Zakhireh-ye Kharazmshahi*’ (Treasure of Kharazm Shah).<sup>26</sup>

Little information is available on diphtheria mortality rates in Iran in the past centuries; nonetheless, its historical profile between the 19<sup>th</sup> and 20<sup>th</sup> centuries was more informative. According to W. Floor, the historian of the Qajar period (1785 – 1925), diphtheria appeared in Iran in the 1850s and became virulent in 1876, when an outbreak of diphtheria occurred in a few cities, including Tehran. At that time, diphtheria was responsible for 20% to 30% of all mortalities.<sup>27</sup>

Early efforts for the promotion of public health measures and prevention of communicable diseases such as diphtheria in Iran began in the second half of the 19<sup>th</sup> century. Dar al-Fonun School (House of Techniques) was the first modern higher educational institute founded in 1851 as a result of Amir Kabir’s endeavors who was the Prime Minister. This school had a significant impact on the introduction of modern medicine in Iran.

In subsequent years, Iranian physicians replaced their European colleagues at the Dar al-Fonun School. Mirza Ali Doctor (Motamed-o-al Atteba ), a French-trained physician was one of these teachers who wrote a medical textbook on internal medicine entitled “*Jawaher-o-Hekma-ye Nasserii*” that was published in 1880. In his book, he pointed out that the etiology of diphtheria was unknown (diphtheria bacillus was recognized three years later) and described its clinical manifestations, prognosis, and pathologic findings. However, in the treatment section, only those medica-

tions which were popular at that time were discussed (antibiotics were popularized about seventy years later). Mirza Ali Doctor also mentioned diphtheric myocarditis, albuminuria in patients with renal involvement, and indications of tracheotomy in cases of laryngeal diphtheria.<sup>28</sup>

Dr. Mohammad Kermanshahi (1829 – 1908) was another pioneer physician and surgeon, a graduate of the Dar-al Fonun School who continued his studies in Paris and received his medical degree from the Sorbonne University in 1879. On his return to Iran in 1881, he became the Director of the Governmental Hospital (Marizhkaneh-e Dowlati, now Sina Hospital). He was also appointed as a medical teacher at the Dar al-Fonun School.<sup>29</sup> In 1900, he published two books in which diphtheria was discussed. The Persian titles were: ‘*Resale dar Bayan-e Serom-e Qarabadini wa Sayer-e Mayeaat-e Haywaniya-ye Qabel-e Tazriq*’ (translated from French) and ‘*Elaj-e Diftiri*’ (Treatment of Diphtheria) which was published in 1900 as a lithographic edition (Figure 1).<sup>30</sup>

In 1881, the Sanitary Council (Majles-e Hefz-o-Sehheh) was founded as the highest health authority of the country and reestablished in 1904. The Sanitary Council had several responsibilities, among which included the prevention of infectious diseases.<sup>31,32</sup> For instance, inspectors from the Sanitary Council in 1881 reported an outbreak of diphtheria as well as epidemics of other infectious diseases in the cities located along the Iran-Iraq border and in Bushehr Port.<sup>27</sup>

### The Pasteur Institute of Iran

According to Afkhami in the first decade of the 20<sup>th</sup> century, free anti-diphtheria vaccines were provided by the Pasteur Institute of Paris.<sup>33</sup> However, in 1910, the Second Parliament (Majles-e Dowom) passed the ‘Act of the Health Protection and Smallpox Vaccination’. A budget was allocated for the promotion of a smallpox vaccination program and preparation of anti-diphtheria serum in Iran.<sup>34</sup> Dr. Amir Aalam

(1877 – 1961), a professor at Tehran Medical School and member of Parliament played a major role in the approval of the ‘Act of the Health Protection’.<sup>35</sup>

The establishment of the Pasteur Institute of Iran in 1921 was instrumental in controlling infectious diseases, including diphtheria. The Iranian government allocated 15,000 Tomans for the establishment of this institute. In addition, Mirza Abdul-Hossein Khan



Figure 2. Dr. Aziz Rafiei (1911-1996).



Figure 3. Razi Institute (1949). From right to left: Dr. Aziz Rafiei, Dr. Louis Delpi, Dr. Gholamreza Maghami, Dr. Hossein Mirshamsi, Dr. Vali Sohrab.



Figure 4. The High Council of Tehran University (Shorai Aali Daneshgah-e Tehran) in 1952. In this picture, Dr. Aziz Rafiei is also seen.

Farmanfarma (1859 – 1939) bequeathed 10,000 square meters of his own property and 10,000 Tomans. In the bequeathal document dated in 1923, he stated his intentions for his bequest: “The establishment of the Pasteur Institute will allow the required sera and vaccines against such diseases as smallpox, plague, cholera, diphtheria, rabies and others to be manufactured at this place”.<sup>36</sup> At that time, over 57% of the reported mortalities in Tehran resulted from preventable infectious diseases, of which approximately 50% of these infections occurred in children less than four years of age. In 1923, immunization against transmissible diseases in Iran was still limited to smallpox and diphtheria mortality was high. However, vaccine manufacturing gradually started at the Pasteur Institute of Iran. In 1924, the Public Health Committee of the League of Nations send a delegation to Iran that reported on some of the activities of the Institute, which included its role in vaccine manufacturing and the vaccination program.<sup>37</sup> Subsequently, a vaccination department was established at the Pasteur Institute of Iran under the directorship of Dr. Kerandel, Director of the Institute between 1926 and 1934. Later, various vaccines and sera were produced at the Institute.<sup>38,39</sup> In addition, the Institute had two other responsibilities that included the conduction of scientific research on human and animal infectious diseases and the provision of required diagnostic services.<sup>40</sup>

At that time, diphtheria was a deadly disease, particularly in children. According to a report of the Public Health Department of the League of Nations (June-September, 1924), between 1922 and 1924 there were 25 patients who died of diphtheria in Tehran.<sup>37</sup> In addition, there were frequent diphtheria epidemics. For

instance, in 1930 a public announcement in the main daily newspaper (Ettelaat) declared an outbreak of diphtheria near Tehran, in Firoozkooh.<sup>41</sup>

With the propagation of modern medicine in Iran, Persian physicians gradually became more familiar with up-to-date concepts on infectious diseases such as diphtheria, and they wrote several papers regarding these diseases. In 1935, in an issue of a medical journal, ‘Sehhat Nemay-e Iran’ (Health Mirror in Iran) published by Dr. Mohammad-Ali Totiya, diphtheria was discussed as a communicable and fatal, yet preventable disease. In this paper, it was written that diphtheria serum was prepared from horse serum after repeated injections of diphtheria toxin.<sup>42</sup>

### Razi Serum Manufacturing Institute

In 1930, a laboratory for the diagnosis of animal diseases, known as the ‘Dar-a-Tajzih-e Amraz-e Haywani’ (Diagnostic Laboratory of Animal Diseases) was founded in Hesarak-e Karaj, located around 40 kilometers from Tehran. The director was Dr. Louis Delpi, an expert veterinarian from France.<sup>44</sup> Initially, the laboratory’s activities were limited; however it expanded and in 1931 an, Bongah-e Serom Sazi Hesarak (Serum Manufacturing Institute of Hesarak) was established as a sister-institution of Pasteur Institute.<sup>44</sup>

In 1935 Iranian experts, including Dr. Aziz Rafiei (1911 – 1996) a veterinarian from France (Figure 2) who completed his studies in parasitology, joined this newly established institute. After Dr.



Delpi, he was appointed as its Director from 1949 to 1964 (Figure 3). As a result of his efforts, the Serum Manufacturing Institute of Hesarak expanded with the establishment of a Serotherapy Department and new laboratories.<sup>45</sup> In 1964, Dr. Rafiei became the Dean and Professor of the Veterinary School of Tehran University and he left the Hesarak Institute. (Figure 4).<sup>43</sup>

In 1936 Dr. R. Legroux, a French professor of microbiology from the Pasteur Institute of Paris came to Iran and he began his studies on 'glanders' and the manufacture of its antiserum at Pasteur Institute of Iran. His co-worker was Dr. Reza Rastegar, a French-trained veterinarian who returned to Iran in 1934, and he initially worked at the Pasteur Institute of Iran. Subsequently he transferred to Hesarak Institute, where he began manufacturing various human vaccines and biologic products, which included diphtheria and tetanus antitoxins.<sup>46</sup> Dr. Rastegar left the Institute in 1942 and joined the faculty of Tehran University.<sup>43</sup>

In 1942, there was a shortage of diphtheria anti-serum in Iran due to WWII. Dr. Mohammad Gharib (1910 – 1975), a professor of pediatrics at Tehran Medical School and his two colleagues visited Hesarak Institute and they encouraged the Institute's authorities to manufacture diphtheria anti-serum. During that time, over an eight month period, more than 2000 children died of diphtheria.<sup>43</sup> Finally, in 1943, the 'Public Mandatory Vaccination' law was approved by Parliament.<sup>34</sup>

In 1943 Professor Charles Oberling (1895 – 1960), the renowned French pathologist who was the Dean and Faculty of Tehran School of Medicine, recommended the health authorities to carry out a nationwide pediatric vaccination program in order to control diphtheria. He also pointed out that enough vaccine and antitoxin must be manufactured at the Hesarak Institute.<sup>47</sup> Thus, during WWII, Hesarak Institute manufactured diphtheria vaccine and antitoxin. Dr. Hassan Tadjbakhsh, Professor of Microbiology and Immunology at the College of Veterinary Medicine of Tehran University stated: "What I personally heard from the late Mirshamsi regarding production details of serum and vaccines with human uses was that around 1944 – 1945 due to WWII, the diphtheria vaccine was not imported to Iran and from this aspect the country was in distress. The Minister of Public Health requested Louis Delpi (a Frenchman) who was Head of the Razi Institute at the time, to pursue this matter at Hesarak Institute. Dr. Delpi appointed Dr. Mirshamsi to this assignment and provided him with the basic supplies. Dr. Mirshamsi accomplished this task".<sup>48</sup> In 1946, the name of "Hesarak Serum Manufacturing Institute" was changed, and it was called the "Razi Vaccine and Serum Research Institute".<sup>49</sup>

Dr. Hossein Mirshamsi (1917 – 2008; Figure 4) played a great role in the production of various human vaccines in Iran. He worked at the Razi Vaccine and Serum Research Institute in Hesarak for over five decades. He was born in Isfahan and after completing high school, he enrolled in the Veterinary Medical School of Tehran University in 1935. In 1950, Dr. Mirshamsi continued his studies in microbiology and immunology at the Pasteur Institute of Paris. Upon his return to Iran, he was appointed as Technical Vice-Chancellor at Razi Institute and in 1955, he oversaw vaccine production at Razi Institute. Since 1972, Dr. Mirshamsi was the consultant to WHO in the Middle and Far East.<sup>50</sup> He received the A.T. Shousha Award in 2002, which was given by WHO. (Figure 5).



Figure 5. Dr. Hossein Mirshamsi (1917 – 2008).

In 1954, when the second author (Moslem Bahadori) was trained as an intern at the pediatric ward of the former Pahlavi Hospital (Imam Khomeini Hospital) affiliated with Tehran School of Medicine, there were still many cases of diphtheria with high mortality in children. These patients frequently needed tracheotomies.

Vaccination against diphtheria, tetanus, and pertussis (DTP vaccination) began in Iran in the 1950s by using vaccines manufactured at Razi Institute.<sup>52</sup> After mass vaccination, the diphtheria mortality rate markedly decreased.<sup>53</sup> According to Faghhih, in 1976, the vaccination coverage of communicable diseases reached an annual rate of five million children.<sup>54</sup>

From the 1940s onwards, the following academic physicians played important roles in teaching medical students of Tehran Medical School the concepts of microbiology, which included diphtheria as well the treatment of diphtheria patients:<sup>55</sup>

- Dr. Hassan Mirdamadi who was born in Isfahan in 1901 and graduated from Tehran Medical School. He continued his training on serology in France and in 1940 he was appointed as a professor at Tehran School of Medicine. He wrote two books on microbiology and serology.
- Dr. Hossein Sohrab who was born in Isfahan in 1902 and graduated from the Paris Medical School in 1938. Upon his return to Iran, he was appointed as professor of microbiology. Dr. Sohrab published a textbook on microbiology in 1942.
- Dr. Mehdi Azar (1903 – 1993) went to France in 1928 where he became an internist. He returned to Iran in 1934. He was appointed as the Director of Razi Teaching Hospital, affiliated with Tehran Medical School and in 1940 he became a full professor of clinical medicine. Razi Hospital had an Infectious Diseases Department.
- Dr. Mohammad Gharib (1910 – 1975) was born in Tehran in 1910 and went to France in 1932 and he received his MD degree from Paris Medical School, after which he continued his training in pediatrics. He returned to Iran in 1939 and was initially employed at the Department of Pediatrics of Razi Hospital. Later, Dr. Gharib became Chair of the Departments of Pediatrics at Razi and Hezar Takhte-Khabi Hospitals (now called Imam Khomeini Hospital). Dr. Gharib and Dr. Hassan Ahari were among the pioneers who established the Children's Medical Center.

### Current state of diphtheria in Iran

According to Zamiri and his colleague the program of mass immunization in Iran was initiated in 1965. Between 1965 and 1968 more than seven million people, particularly in rural areas, were

vaccinated. In 1969 the incidence of diphtheria during the peak months of January and February declined to one-seventh as compared to the same months before public vaccination.<sup>56</sup>

At the present time, diphtheria is rarely seen in Iran. According to a WHO report, the total number of approved reported cases of DPT in Iran in 2005 was 15 (diphtheria), 8 (tetanus), and 125 (pertussis) cases and in 2006, it was 26 (diphtheria), 11 (tetanus), and 89 (pertussis).<sup>57</sup> At present, the Razi Vaccine and Serum Research Institute manufactures annually 3.5 billion doses of over 60 types of biologic products, including human vaccines, veterinary vaccines, diagnostic products, and therapeutics sera.<sup>58</sup> The Eastern Mediterranean Regional Office of WHO reports that from 1997, the DPT vaccination coverage in Iran has been nearly 100%.<sup>59</sup>

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