Asthma: A brief history

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Abstract: Asthma is a chronic inflammatory disease of the airways characterized by reversible airway obstruction, Inflammation and hyper responsiveness of the airways. The actual term asthma is derived from Greek word verb aazein, meaning to exhale with open mouth, to pant. In Unani system of Medicine it is known by various names like Buhr, Rabu, Zeequn Nafas, Dama and Intesabun Nafas. In this paper an attempt is made to do the historical review of asthma in brief including Unani description.

Key words: Asthma, Buhr, Rabu, Zeequn Nafas, Dama and Intesabun Nafas

INTRODUCTION

World Health Organization (WHO) defines asthma as

It is a disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. This condition is due to inflammation of the air passages in the lungs and affects the sensitivity of the nerve endings in the airways so they become easily irritated. In an attack, the lining of the passages swell causing the airways to narrow, thus reducing the flow of air in and out of the lungs.[1] The actual term asthma is a Greek word that is derived from the verb aazein, meaning to exhale with open mouth, to pant[5.] Asthma is a common chronic disease worldwide, with an estimated 300 million affected individuals. It appears that global prevalence of asthma ranges from 1% to 18 % of the population in different countries.[2,3] It is very well documented from the ancient times.

HISTORICAL REVIEW

Asthma is known since the time of yore where the symptoms of asthma were described. This disease has apparently beleaguered man for a very long time and the writings from the earliest civilizations and it is thought that the history of medicine began with the Greeks and before the time of *Buqrat* (460 B.C) ancient Egypt (Misri) was the first civilization known to have an extensive study of medicine and to have left over written records of its practices and procedures. It has been substantiated well by the discovery of the Ebers papyrus in the graves of Thabes by famous German Egyptologist "Georg Ebers" in 1862 A.D. The Ebers papyrus written about 1550 B.C is one of the most well-known manuscripts relating to the ancient practices of medicine. It contains descriptions of various diseases.[4] The expression asthma appeared for the first time in the Iliad by Homer, with the meaning of a short-drawn breath, but the earliest text where the word is found as a medical term is the *Corpus Hippocraticum*. However it is difficult to determine whether in referring to "Asthma," Hippocrates and his school (460-360 B.C.) meant an autonomous clinical entity or simply a symptom.[5] Hippocrates described panting, which he termed as asthma. In his writings, he noted such persons as become hunch-backed from asthma or cough, before puberty die. Hippocrates is also believed to be one of the first physicians to understand the relationship between the environment and respiratory ailments. [6]

The Roman encyclopaedist Aulus Aurelius Cornelius Celsus (first century BC), the first medical historian, described Asthma in Book Four of his *De Medicina* as the inability to breathe without making noise and gasping. As treatment, Celsus suggested bleeding, purgatives, hot wet compresses, emetics and diuretics. [6]

Aretaeus of Cappadocia, a Greek physician, who studied in Alexandria and practiced in Rome probably in the second century CE, is credited with the first accurate description of asthma, as we know it today. Aretaeus is considered one of the most valuable medical writers of antiquity, an original observer that included in his work his personal experience and also the achievements of anatomy and physiology. His prevailing but incomplete treatises are: *De Causis et Signis Morborum Acutorum et Diuturnorum* (On the Causes and Symptoms of Acute and Chronic Diseases), in four books, and *De Curatione Morborum Acutorum et Diuturnorum* (On the Cure of Acute and Chronic Diseases), also in four books. In Chapter XI of his essay On the Causes and Symptoms, entitled on Asthma, Aretaeus defined the disease, emphasizing the association with exercise: "If from running, gymnastic exercises or from any other work, the breathing becomes difficult, it is called asthma". [7]

The numerous mentions of "Asthma" in the extensive writings of Galen (130-200 A.D.) appear to be in general agreement with the Hippocratic texts and to some extent with the statement of Aretaeus. [5]

Pliny the Elder (Gaius Plinius Secundus), acknowledged pollen, which he knew had a role in plant fertilization, as a source of respiratory distress, and he recommended the use of ephedra (called anabis) in red wine as a remedy for Asthma. [6,8]

Among Arab physicians, *Ali bin Rabban Tabri* (810-895 AD) was the first physician who described different type of Asthma in his famous book "*Firdausul-Hikmat*" and thus he gave classification of Asthma for the first time.[9]

Razi gave the first description of status asthamaticus. [9]

Moses Maimonides (1135-1204 AD), the rabbi and philosopher who lived in Andalucía (Spain), Morocco and Egypt, was also a physician who practiced medicine in the court of Sultan Saladin of Egypt and Syria. Among many medical texts, Maimonides wrote Treatise of Asthma for Prince Al-Afdal, a patient of his. Maimonides revealed that his patient's symptoms often started as a common cold during the wet months. Eventually the patient gasped for air and coughed until phlegm was expelled. He noted that the dry months of Egypt helped asthma sufferers. Maimonides also suggested avoidance of strong medication, plenty of sleep, fluids, moderation of sexual activity, and chicken soup.[10]

Jean Baptiste Van Helmont (1579-1644 AD), a physician, chemist and physiologist from Belgium, said that Asthma originates in the pipes of the lungs. [10]

Bernardino Ramazzini (1633-1714 AD), known to some as the father of sports medicine, detected a link between Asthma and organic dust. He also recognized exercise-induced Asthma.[10]
Sir John Floyer in 1698, in his treatise of Asthma wrote, the bronchia are contracted.[6] 14
Familial aggregation of asthma was probably first described by Sennertus in 1650.[11]
In 1903 the Austrian pediatrician Baron Clemens von Pirquet coined the terms allergy and allergen after observing 'altered responses' of his patients to certain substances.[12]
Histamine was discovered in 1910 by a British scientist named Henry Dale. [13]
Bronchial responsiveness in asthmatics was first reported by Alexander and Paddock in 1921. [14]
The term "atopy" was coined by Coca and Cooke who in 1923 attempted to develop a classification for "hypersensitiveness", an abnormal level of sensitiveness for which the mechanism was not known.[15]
Leukotrienes were discovered in 1938 and proved to be a major cause of airway constriction during an allergy attack.[13]
In 1940 Rackeman, introduced the term "intrinsic" asthma in order to emphasize that this type is distinct from allergic extrinsic asthma with respect to the absence of an obvious precipitating exogenous cause. [16]
In 1960, Dunhill reported that mucus obstruction of peripheral airways is an important pathological finding in fatal asthma. [17]
In 1966 Ishizaka and coworkers identified IgE antibodies as the cause of immediate allergic reactions.[17]
In 1967, Immunoglobulin E antibodies (IgE) were discovered. It was later learned IgE has a significant role in an allergic response. Xolair was approved by the FDA in 2003 as the first drug to block the effects of IgE.[13]
In the 1970s, Turner-Warwick described subgroups of patients with asthma characterized by differing patterns of airflow obstruction including 'brittle asthma', 'irreversible asthma' and 'the morning dipper'.[18]
Okumura et al [1971] were the first workers to show that IgE production is dependent on and is regulated by the presence of T-cells. These are mainly helper T (TH) cells (CD3+, CD4+), which express the low affinity IgE receptor (FceRII or CD23), and produce a variety of substances such as IgE binding factors (which include soluble fragments of the FceRII molecule), and lymphokines that can suppress or increase IgE production by B lymphocytes and plasma cells.[19]
The hygiene hypothesis introduced by Strahan in 1989 remains the strongest one to date. It is based on his observation that with decreasing family size and improved living conditions allergic conditions increase. [12,20]
Ernst et al. and Surdu et al. stated that exposure to allergens, particularly house dust mites is a risk factor of asthma development and exacerbation. [21]
With the use of sensitive RT-PCR methods, Friedlander and Busse detected respiratory viruses in approximately 80% of wheezing episodes in children and in approximately one half of such episodes in adults. Rhino viruses was a major cause of asthma exacerbation.[22]
O' Byrne et al reported that severe asthma exacerbations are associated with a more rapid decline in lung function and treatment with low doses of inhaled corticosteroid is associated with an attenuation of the decline.[23]
In children with an anthroposophic lifestyle, Wickens et al found a higher risk of asthma when antibiotics were applied in infancy.[24]
Researchers at Imperial College London found that children with severe asthma with a parent who smokes at home have lower levels of the enzyme HDAC2 compared with those whose parents don't smoke. HDAC2 is required for steroids to exert their beneficial anti-inflammatory effects in asthma.[25]
Bouzigon et al reported that polymorphisms in 17q21 confer higher risk in early onset asthma and the risk increases further when there is exposure to environmental tobacco smoke in early life. [11]
Angela et al supported the hypothesis that ADAM33 polymorphisms influence lung function in early life and epithelial-mesenchymal dysfunction in the airways may predispose individuals toward asthma, being present in early childhood before asthma becomes clinically expressed.[11]
Empey and colleagues showed that respiratory infections increased airway hyper responsiveness; this observation raised the possibility that respiratory viruses affect airway responsiveness and accomplish this by causing or enhancing bronchial inflammation.[17]
Chiang et al established that polymorphism in the promoter of the IL-4 is associated with asthma and is a disease modifier in terms of the severity of airway hyper-responsiveness (AHR). [11]
Koskela et al found that facial cooling during cold air challenge induces a cutaneous reflex mechanism, which results in marked bronchoconstriction in patients with asthma and chronic obstructive pulmonary disease.[26]
The first study which showed linkage between IgE responses underlying asthma and atopy and chromosome 11q was presented by Cookson et al. [27]

The study by Nimmagadda et al suggests that patients with poorly controlled asthma and steroid resistant asthma are the ones who would benefit most from allergen reduction. [28]
Schwartz et al. first reported the observation of apparent glucocorticoid resistance in asthma management. They recognized a reduced eosinopenic response and accelerated plasma cortisol clearance in glucocorticoid resistant asthmatic patients as compared to a control population.[29]
In smokers, oxidative stress results in reduced levels of histone deacetylase-2. Stress may induce steroid resistance via multiple mechanisms, including the chronic elevation of the stress hormone, cortisol, which down regulates expression of the GR.[30]
According to Halonen et al (1982), a significant relationship exists between serum IgE levels and eosinophilia in populations presumed to be free of parasites where IgE levels presumably provide a better clue to atopy than do skin tests. [31]
Di Lorenzo et al (1997) reported that there is an interrelationship of the allergen type, total serum IgE, eosinophil and bronchial hyper responsiveness suggesting that all three may play a role in the development of bronchial asthma in rhinitis patients. [31]
Fahy (2000) stated that IgE secretion by lymphocytes defines the allergic state and nearly all asthmatics have a higher IgE levels in serum than normal, following adjustment with age and sex. [31]
Markers of oxidative stress such as 8-isoprostane is elevated in severe asthma. Cigarette smoking and poor dietary anti-oxidant intake are potential sources of oxidative stress, and it has been shown that asthmatics who smoke are clinically more resistant to glucocorticoid therapy.[32]

Bruzzese and colleagues (2009) reported that computerized games, web-based programmes, and peer education lead to improved asthma outcomes for adolescents.[33]

In a prospective study conducted on 92 patients in Finland, sECP was found to be specifically high in acute attacks of wheezing. [34]

Amin et al. demonstrated that no differences existed between atopic and non-atopic patients in terms of lung function, symptomatic scores, or PC20, but differences were observed in the pathologic characteristics.[35]

In 2010, in Italy, the sECP levels of 441 cases of respiratory tract diseases were investigated retrospectively and compared to 33 healthy infants. The sECP levels were found to be significantly higher in cases with asthma. However, the sECP levels were not found to be high in respiratory tract diseases other than asthma.[34]

Patients hospitalized for RSV and rhinovirus bronchiolitis at <24 months of age had an increased asthma risk at 15-18 years of age as compared with population controls.[36]

Contoli et al reported deficits in IFN-λ responses and increased viral shedding by rhinovirus infected bronchial epithelial cells obtained from subjects with asthma who had mild baseline airflow limitation. These results thus suggested that deficits in several innate inflammatory responses might facilitate virus replication and cytolysis, with increased infection of neighboring airway cells, thus inducing exaggerated secondary responses, which in turn may activate remodeling and abnormal repair mechanisms.[37]

A study by Gauvreau et al found that IL-13 has a role in allergen-induced airway responses.[38]

A study by Cottrell et al explored the relationship between asthma, obesity and abnormal lipid and glucose metabolism. The study found that community based data linked asthma, body mass and metabolic variables in children. Specifically, these findings described a statistically significant association between asthma and abnormal lipid and glucose metabolism beyond body mass association. [38]

A study by Beasley et al demonstrated some epidemiological evidence that exposure to acetaminophen is associated with an increased risk of asthma.[38]

Mai et al. studied the association between serum leptin levels and asthma in overweight and non-overweight children in Sweden. They found that serum leptin levels were twice as high in overweight children with asthma as in overweight children without asthma.[39]

Rastogi et al. demonstrated that obese children with asthma had lower FEV_1/FVC ratios than did non-obese children with asthma and children without asthma, and that the FEV_1/FVC ratio was negatively correlated with serum IFN-γ levels.[39]

Macgregor and Greenberg in Australia described strong evidence of reversibility in their weight loss study. In a subset of five patients with asthma who had bariatric surgery, asthma symptoms improved following weight loss. The symptoms worsened after subjects regained some of their weight.[40]

In a study done by Nagel and Linseisen in 2005, they found no association between fat intake, saturated fatty acids, monosaturated fatty acids or n6/n3 PUFA ratio and asthma, or between BMI and asthma.[40]

The study by Stokes et al. hypothesized that Cannabis might be clinically important allergen especially in patients complaining of asthma and/or rhinitis symptoms.[30]

In another prospective study of subjects suffering from asthma and rhinitis, IT showed significant improvement in the symptom score, forced expiratory volume in first second, and immunological parameters.[41]

Camargo et al found that continuous administration of nebulized beta agonist improved lung function, reduced the need for hospitalization and was generally well tolerated.[42]

Corbo et al found high concordance between arterial blood gas values and end-tidal carbon dioxide levels in patients with acute asthma.[42]

Studies of adult-onset asthma have identified an increased risk associated with ozone exposure, although this effect was restricted to male individuals.[42]

The first comprehensive GWAS (genome-wide association studies) in asthma was reported by Moffatt and colleagues in 2007 and they identified a novel locus on 17q21 containing several genes. This study revealed the potential for GWAS to be used to uncover novel susceptibility genes and thus to identify previously unknown biological processes involved in asthma susceptibility. 17q21 has been the most consistently identified locus associated with asthma in subsequent GWAS.[43]

In addition, a post hoc analysis of the Inhaled Steroid Treatment as Regular Therapy Trial by O'Byrne and colleagues reported that patients with newly diagnosed mild asthma who smoked did show significant improvements in post bronchodilator FEV1 measurements after 3 years of treatment with inhaled budesonide 400 µg daily. (71.5 ml in smokers vs 46.5 ml in nonsmokers).[44]

Observational studies in both adults and children have also consistently shown that a high intake of fresh fruit and vegetable is associated with less asthma and better pulmonary function.[45]

Observational studies have reported that low vitamin C, vitamin E and selenium intakes are associated with a higher prevalence of asthma.[45]

In vitro studies suggest that supplementing the diet with omega n-3 fatty acids, which are most commonly found in fish oils, might reduce the inflammation associated with asthma.[45]

Low magnesium intake has been associated with a higher prevalence of asthma with increasing intake resulting in reduced bronchial hyper responsiveness and higher lung function. Magnesium plays a beneficial role in the treatment of asthma through bronchial smooth muscle relaxation, leading to the use of intravenous or inhaled preparations of magnesium sulphate for acute exacerbations of asthma.[45]

A population study by Goldney et al examined the relationship between depression (as measured by the Prime-MD) and a number of symptoms known to be related to asthma severity, and found that dyspnoea, wakening at night, and morning symptoms were particularly strongly associated with depression.[46]

Krommydas et al reported that individuals with asthma and symptoms of depression (measured by the Personal Disturbance Scale) had significantly lower FEV1% than individuals with asthma who showed no symptoms of depression.[46]

Asthma is one of those diseases, which are very well described in Unani literature.

Most of the Unani physicians described asthma in detail. *Buhr, Rabu, Zeequn Nafas, Dama* and *Intesabun Nafas* [54,55,56,57,58,59] these are various names that are being used in Unani Medicine for Asthma.

In famous book "*Alqanoon Fil-Tib*", *Ibn-e-Sena* (980-1037 AD) wrote about asthma as

It is difficulty in exchange of air from coming in and out of the lungs due to spasm in air passage. It is called *Zeequn Nafas*."[47]

The famous Arab physician, *Abul Hasan Ali bin Rabban Tabri* (700-780 AD), described in his book *Firdaus al Hikmat*, the cause of *Rabu* is accumulation of diseased humor in the lung due to which inflammation (*waram har*) occurs and sometimes it occurs due to *Insebab e Nazla* from head towards lungs. He has also described different clinical types of *Rabu*.[48]

The most authentic and complete description of Asthma was put forward by *Razi* (860 – 932 AD) in his book *Al-Hawi-Fit-Tib*. He appears to be in general agreement with *Tabri*. According to him *Intasabun-Nafas* is the most severe form of Asthma that is very much similar to Status Asthmaticus.[49]

He stated when there is sudden breathlessness and tightness in chest, it occurs due to *Insebab e nazla* from head towards lung in large quantity.

As he wrote further "When attack of breathlessness occurs continuously in the absence of fever and exercise it is called *Nasful-Intesab* (*Intasabun-Nafas.* In this condition in order to respire easily patient is forced to stand up as patient feels comfortable in standing position and this condition this occurs mostly at night.[49]

Ali bin Abbas Majoosi (930-994 AD) is a very famous unani physician, according to him as he wrote in *Kamil-us-Sana*

"*Rabu, Bhur, Intasabun-Nafas, Zeequn-Nafas,* all occur due to bronchospasm, and the spasm due to which breathlessness occurs is caused by accumulation of viscid cold humor. Accumulation of viscid humor causes narrowing of airway lumen that causes breathlessness. According to him, cough occurs in the patient of Asthma to remove this accumulated viscid humor.[50]

In Unani literature allergic causes of asthma are also mentioned. Sometimes there is irritation in larynx that results in cough and this may be due to use of irritating food items, dust or any other object. Here the cough is used in the context of asthma and not due to any other respiratory disease. [50, 51]

The cause of stimulation of nervous centre i.e. dusts, fumes, and coldness also causes asthma. These causes can be included into the causes of hyper responsiveness of airways.[50]

Ismail Jurjani in his book *Zakhira khwazamshahi* has given the detailed description of Asthma including its treatment.[51]

According to *Ahmad Bin Muhammad Tabri,* as he stated in *Moalajaat-e-Buqratiya, Rabu* are those thick and viscid humors that are accumulated in trachea resulting in difficulty in exchange of air from the lungs and cause breathelessness.[52]

He has also described Asthma under three categories.

1. *Rabu haqeeqi*- narrowing of airways due to cold humors.
2. Second type- narrowing of airways due to inflammation in lungs in which the pus does not accumulates.
3. Third type- due to flaccidity and dystonia (*Istirkha*) of respiratory muscles that occurs due to the accumulation of humors from head or weakness of chest or impaired hot or cold temperament of respiratory muscles. [52]

Another well known Unani physician *Hk. Azam Khan* (1211-1320 H) has given the same classification of Asthma as described above by *Ahmad Bin Muhammad Tabri.*[53]

All other eminent scholars have given detailed description of Asthma in their literature including *Sabit bin Qarrah, Hk. Akbar Arzani* and *Hk. Kabeeruddin.*

According to Hakim Ajmal Khan as he stated in his book Haziq, "It is a dreadful and discomfortable disease whose treatment is very difficult. It is characterized by bronchospasm resulting in breathlessness. It mostly occurs in paroxsyms.[60]

He also classified Asthma into two types- 1.Dry Asthma 2.Wet Asthma

Dry Asthma- In Dry Asthma, there is constriction only in bronchi, bronchioles and in respiratory muscles that causes breathlessness. It occurs due to the dryness of lungs resulting in narrowing of air passages.

Wet Asthma- In Wet Asthma, other than constriction there is accumulation of phlegm in air passages due to cold, catarrh or cough that causes breathlessness.[60]

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