# ***Pathophysiology***

***Dr. Yasser Mufid***

**Lecture 12**

# II. Disorders of Respiratory system

## IV. Bronchial Asthma

A *chronic disorder characterized by widespread and largely reversible reduction in the caliber of bronchi and bronchioles, due in varying degrees to smooth muscle spasm, mucosal edema, and excessive mucus in the lumens of airways.*

**Cardinal symptoms**

1. Dyspnea,
2. Wheezing, and
3. Cough.

**Pathophysiology of Bronchial Asthma**

Based on the stimuli initiating bronchial asthma, two broad etiologic types are traditionally described:

1. **Extrinsic (allergic, atopic).**
2. **Intrinsic(idiosyncratic, non-atopic) asthma**.
3. A third type is **a mixed pattern** in which the features do not fit clearly into either of the two main types.

**1. Extrinsic (atopic, allergic) asthma** This is the most common type of asthma. It usually begins in childhood or in early adult life. Most patients of this type of asthma have personal and/or family history of preceding allergic diseases such as rhinitis, urticaria or infantile eczema. Hyper sensitivity to various extrinsic antigenic substances or 'allergens' is usually present in these cases. Most of these allergens cause ill effects by inhalation e.g. house dust, pollens, animal dander, molds etc. Occupational asthma stimulated by fumes, gases and organic and chemical dusts is a variant of extrinsic asthma .

There is increased level of IgE in the serum and positive skin test with the specific off ending inhaled antigen representing an IgE-mediated type I hypersensitivity reaction which includes an 'acute immediate response' and a 'late phase reaction':

A. **Acute immediate response** is initiated by IgE-sensitized mast cells (tissue counterparts of circulating basophils) on the mucosal surface. **Mast cells** on degranulation release mediators like histamine, leukotrienes, prostaglandins, platelet activating factor and chemotactic factors for eosinophils and neutrophils. Th e net effects of these mediators are bronchoconstriction, oedema, mucus hypersecretion and accumulation of eosinophils and neutrophils.

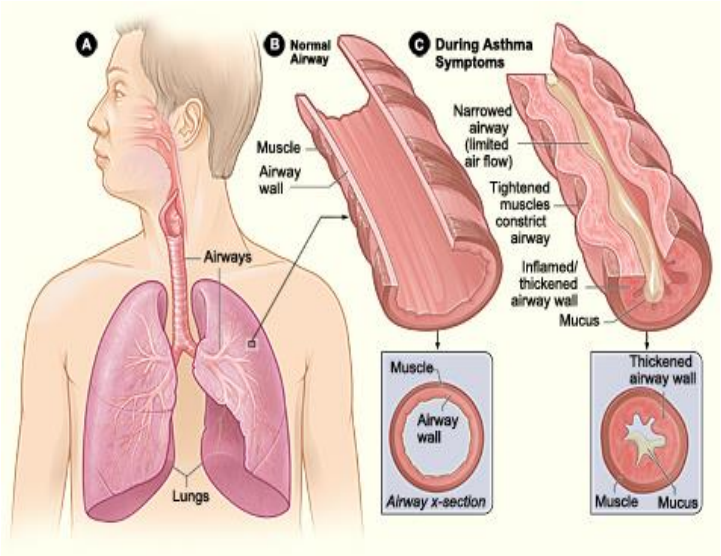
B. **Late phase reaction** follows the acute immediate response and is responsible for the prolonged manifestations of asthma. It is caused by excessive mobilization of blood leucocytes that include **basophils** besides **eosinophils and neutrophils**. These result in further release of mediators which accentuate the above-mentioned effects. In addition, inflammatory injury is caused by neutrophils and by major basic protein (MBP) of eosinophils.

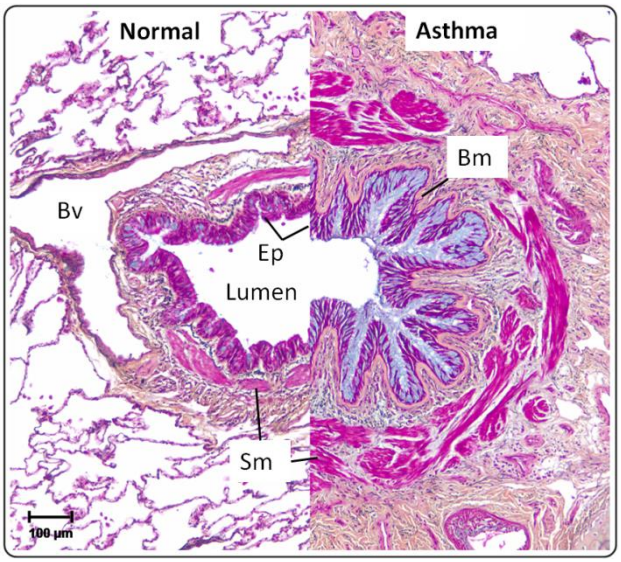
***Allergens are***

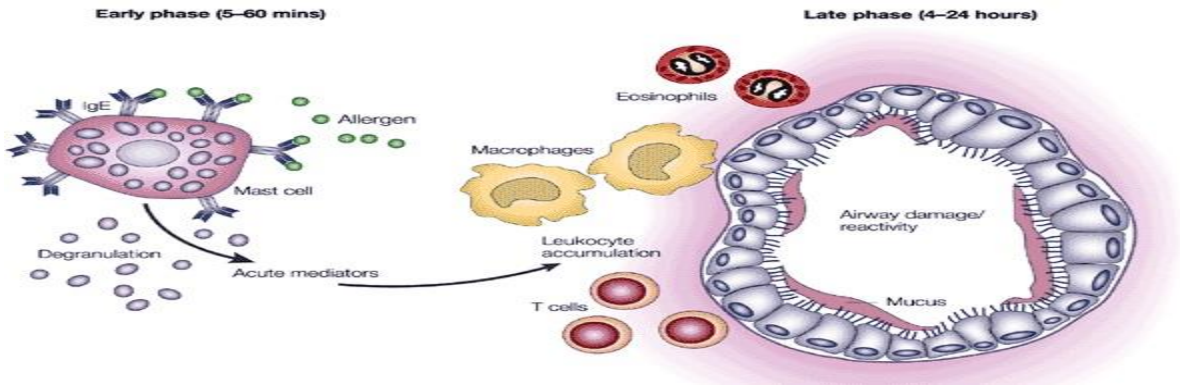
1. Airborne allergens (for example, molds, pollens, animal dander, dust mite and cockroach antigens),
2. Inhaled irritants (for example, cold air, cigarette smoke, ozone),
3. Physical exercise,
4. Respiratory infection,
5. Psychological stress, or other factors.

**2. Intrinsic (idiosyncratic, non-atopic) asthma** This type of asthma develops later in adult life with negative personal or family history of allergy, negative skin test and normal serum levels of IgE. Most of these patients develop typical symptom complex after an upper respiratory tract infection by viruses.

Associated nasal polyp and chronic bronchitis are commonly present.



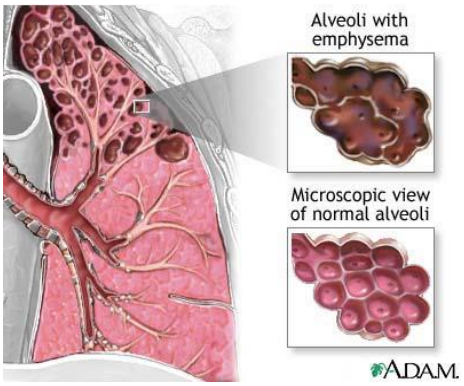



## V. Emphysema

*Emphysema is a form of Chronic Obstructive Pulmonary Disease, in which the tiny air sacs (alveoli) in the lungs become permanently damaged.*

The WHO has defined pulmonary emphysema as combination of permanent dilatation of air spaces distal to the terminal bronchioles and the destruction of the walls of dilated air spaces. Thus, emphysema is defined morphologically,

Normal, healthy lungs look like upside down branches of a tree with many thousands of these tiny air sacs at the ends of those branches. **Lungs with emphysema have fewer, larger air sacs.**




**The 3 described morphological types of emphysema**

*are centriacinar, panacinar, and paraseptal.*

1- ***Centriacinar emphysema***

**Begins in the respiratory bronchioles and spreads peripherally.**

Also termed **centrilobular emphysema**, this form is associated with **long-standing cigarette smoking** and predominantly involves the **upper half of the lungs**.

2- ***Panacinar emphysema***

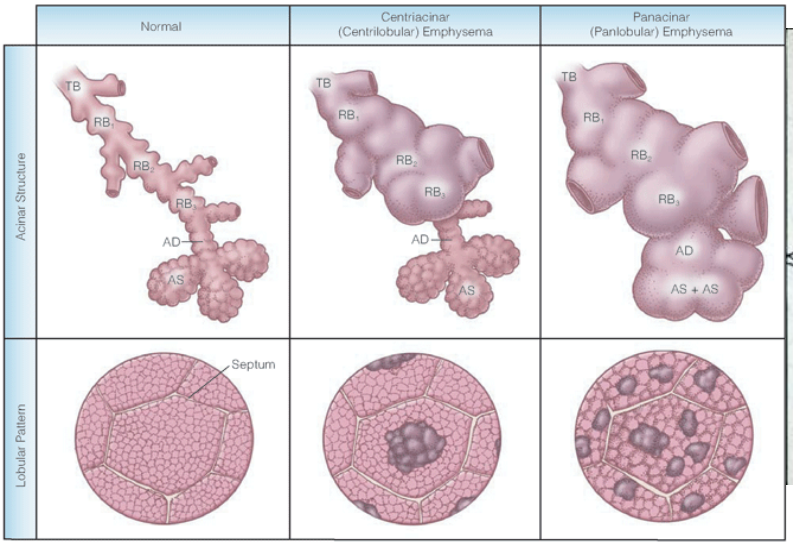
**Destroys the entire alveolus uniformly.**

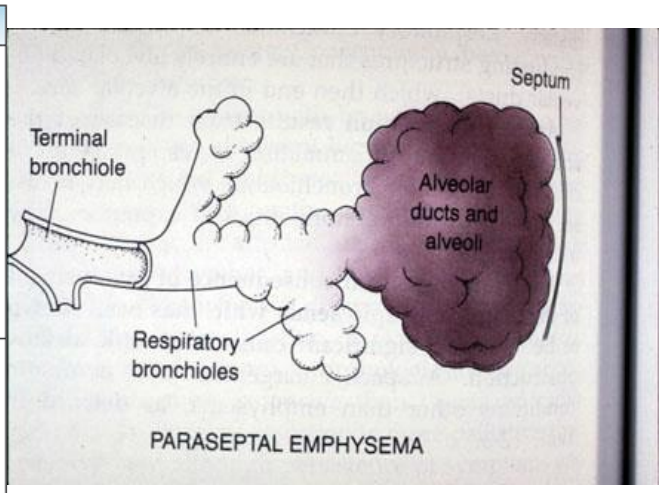
Predominant in the **lower half of the lungs.** Panacinar emphysema generally is observed in patients with **homozygous alpha1-antitrypsin (AAT) deficiency.**

In people who smoke, focal panacinar emphysema at the lung bases may accompany centriacinar emphysema.

3- ***Paraseptal emphysema***, also known as **distal acinar emphysema**, preferentially **involves the distal airway structures, alveolar ducts, and alveolar sacs.**

The process is localized around the **septae of the lungs or pleura**. Although airflow frequently is preserved, the apical bullae **may lead to spontaneous pneumothorax**. Giant bullae occasionally cause severe compression of adjacent lung tissue.



**Pathophysiology**

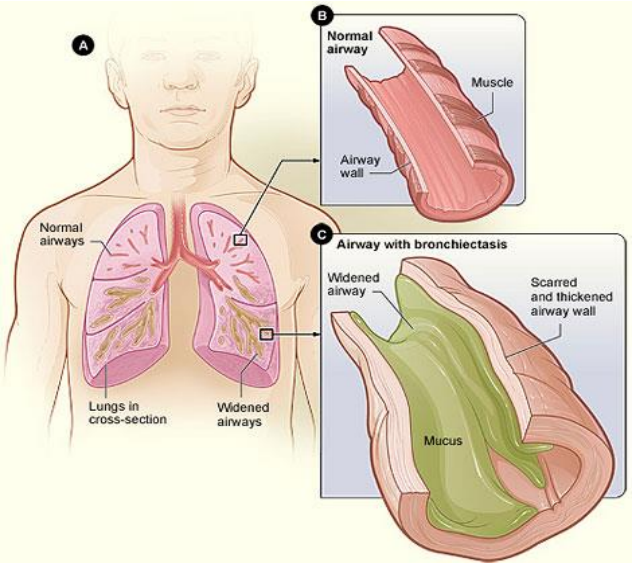
1) **Inhalation** of cigarette smoke or certain other **irritants**, **noxious stimuli**.
2) The cellular composition of airway inflammation is predominantly mediated by **neutrophils, macrophages, and lymphocytes**.
3) These cells release chemotactic factors to recruit more cells (proinflammatory cytokines that amplify the inflammation) and growth factors that promote structural change.
4) The inflammation is further amplified by **oxidative stress** and **protease production**.
5) Oxidants are produced from cigarette smoke and released from inflammatory cells.
6) Proteases are produced by inflammatory and epithelial cells.
7) This leads to a **protease-antiprotease imbalance** that leads to destruction of **elastin and other structural elements**.
8) But the body normally inhibits such action with the release of **antioxidants**.
9) In smokers and those with the inherited defect, however, **no such prevention occurs and the lung tissue is damaged in such a way that it loses its elasticity**.
10) The small passageways (bronchioles) leading to the alveoli collapse, trapping air within the alveoli.
11) The alveoli, **unable to recoil efficiently** and move the air out,
12) Leading to over expand and rupture.
13) As the disease progresses, coughing and shortness of breath occur.
14) **In the later stages**, the lungs cannot supply **enough oxygen to the blood**. Emphysema often occurs with other respiratory diseases, particularly **chronic bronchitis**. These two diseases are often referred to as one disorder called **Chronic Obstructive Pulmonary Disease (COPD).**

## VI. Bronchiectasis

***P****ermanent abnormal widening of the* ***bronchi*** *(air tubes that branch deep into the lungs)* ***caused by destruction of the muscle and elastic tissue.***

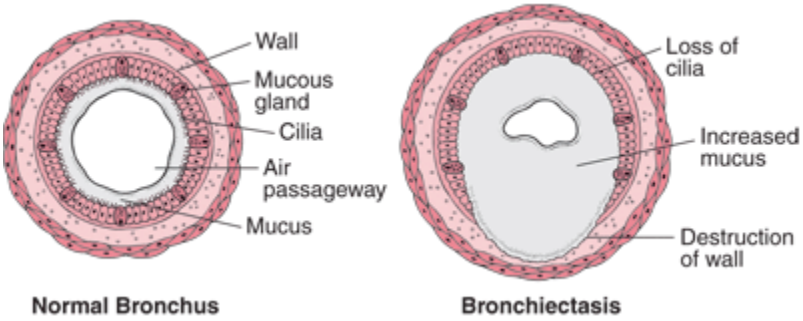
Bronchiectasis can cause:

1) Recurrent lung infections,
2) A disabling cough,
3) Shortness of breath, and
4) Coughing up blood (hemoptysis).
5) It is classified as an **obstructive lung disease, along with emphysema, bronchitis, asthma, and cystic fibrosis.**
6) The clinical course of the disease is chronic and progressive and in most cases, causes **lung damage over many years.**




There is usually an initial event, which causes **impairment of mucociliary clearance** of the bronchial tree.

The respiratory tract becomes colonized by **bacteria** that **inhibit the ciliary** function and promote further lung damage. **The hallmark of bronchiectasis, is a chronic cough with mucopurulent or purulent sputum, lasting for months to years and may progress to chronic respiratory failure.** Diagnosis of bronchiectasis is suspected on the basis of clinical manifestations.



**Etiology**

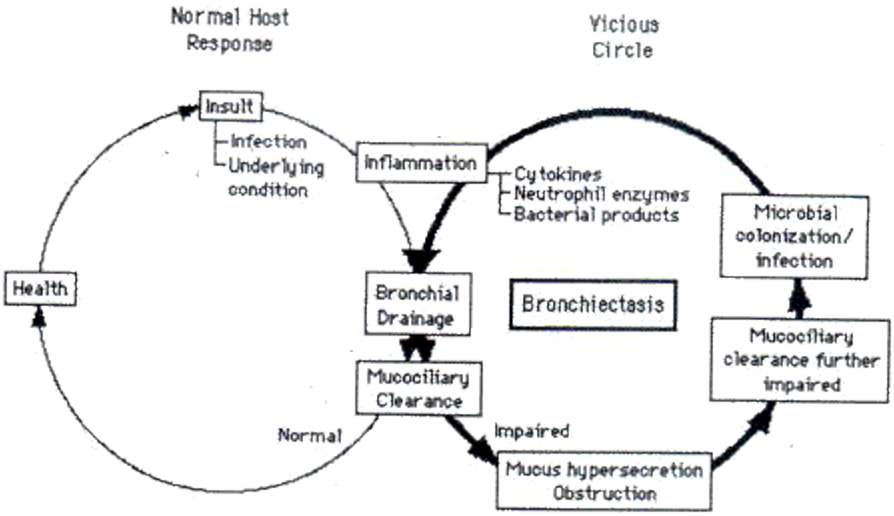
The major causes of bronchiectasis include the following:

A. Primary infections.
B. Bronchial obstruction.
C. Aspiration.
D. Cystic fibrosis & Alpha1-antitrypsin (AAT) deficiency.
E. Primary ciliary dyskinesia.

**Pathophysiology**

The **dilation and thickening of the bronchi** seen in bronchiectasis are due to

1. **Chronic inflammation** elicited by the host response to micro-organisms colonizing the airways.
2. This persistent airway inflammation leads to the subsequent development of **bronchial wall oedema and increased mucus production.**
3. Several inflammatory cells including **neutrophils, T lymphocytes**, and other immune effector cells are recruited to the airways and
4. Subsequently release inflammatory **cytokines, proteases, and reactive oxygen mediators** implicated in the progressive destruction of the airways.
5. This initial insult to the airways by the primary infection leads to increased inflammation, resulting in bronchial damage, and serves as a nidus for **subsequent colonization of the airways.**
6. As a result, **a vicious cycle** ensues that predisposes to persistent bacterial colonization and to a subsequent chronic inflammatory reaction that eventually leads to **progressive airway damage and recurrent infections.**



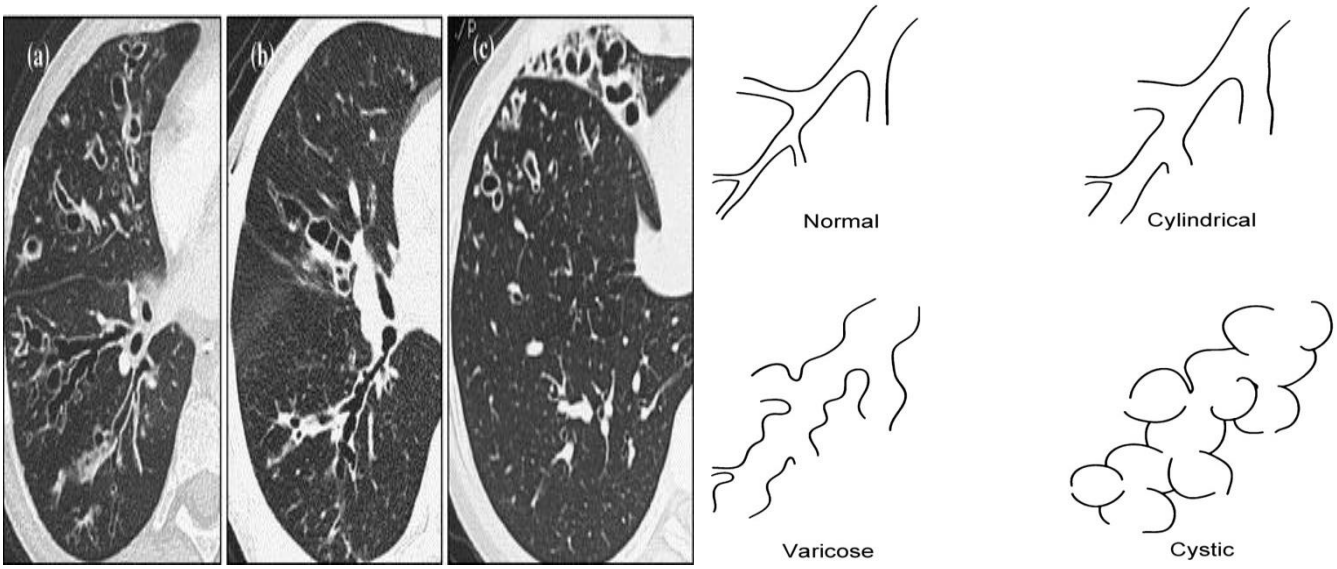

**<u>Morphological Types of Bronchiectasis</u>**

1- **Cylindrical bronchiectasis** involves **diffuse mucosal edema**, with resultant bronchi that are dilated but have straight, regular outlines that end squarely and abruptly. **(Tram-Track)**

2- **Cystic or saccular bronchiectasis** has ulceration with bronchial neovascularization. The result is a **ballooned appearance** and sometimes air-fluid levels. ***(forming a cluster of round air-filled or fluid-filled cysts).***

3- **Varicose bronchiectasis** has a **bulbous appearance** with a dilated bronchus and interspersed sites of relative constriction and, potentially, obstructive scarring.

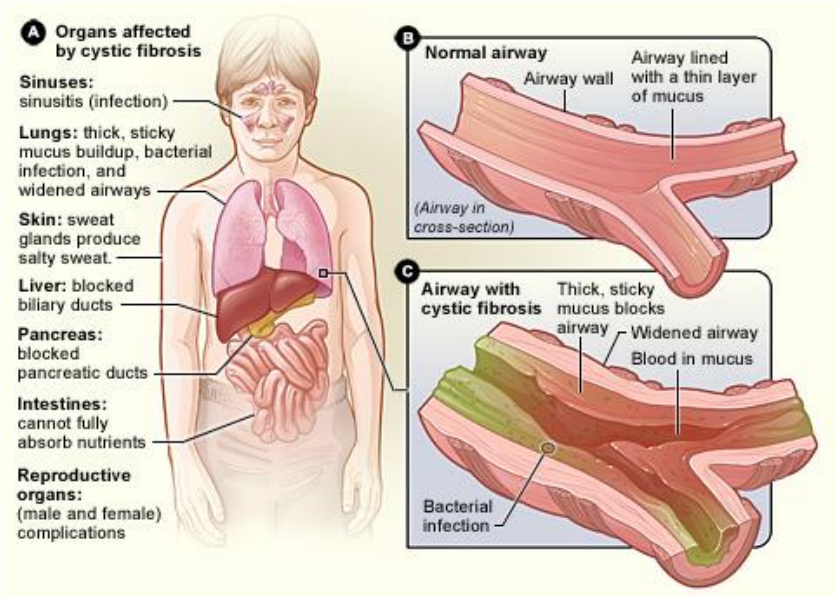
The latter may subsequently result in **postobstructive pneumonitis** and additional parenchymal damage. **(Irregular bronchi resembles varicose veins).**



## VII. Cystic fibrosis

A *genetic disease that affects the exocrine glands and is characterized by the production of abnormal secretions, These secreted fluids are normally thin and slippery.*

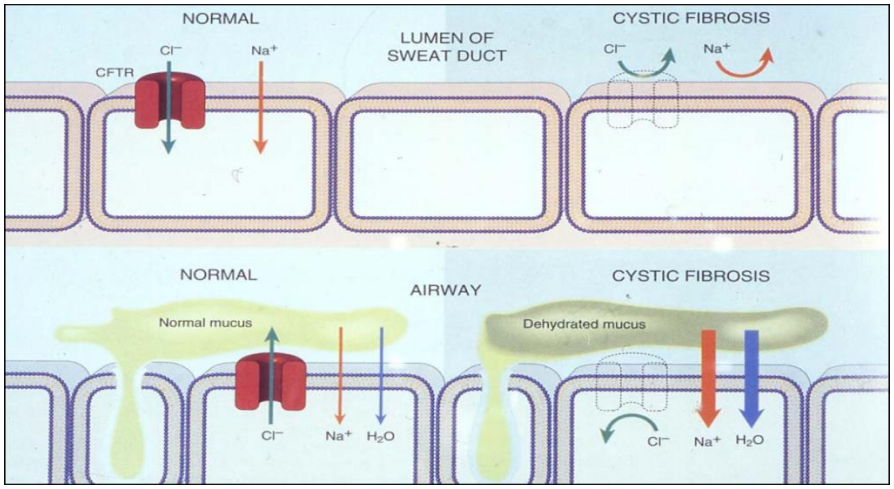
Cystic fibrosis, a defective gene causes the **secretions to become thick and sticky**. Instead of acting as a lubricant, the secretions plug up tubes, ducts and passageways, especially in the **lungs and pancreas**, leading to mucus buildup that impairs the pancreas and, **secondarily, the intestine**. Mucus buildup in lungs can impair respiration.



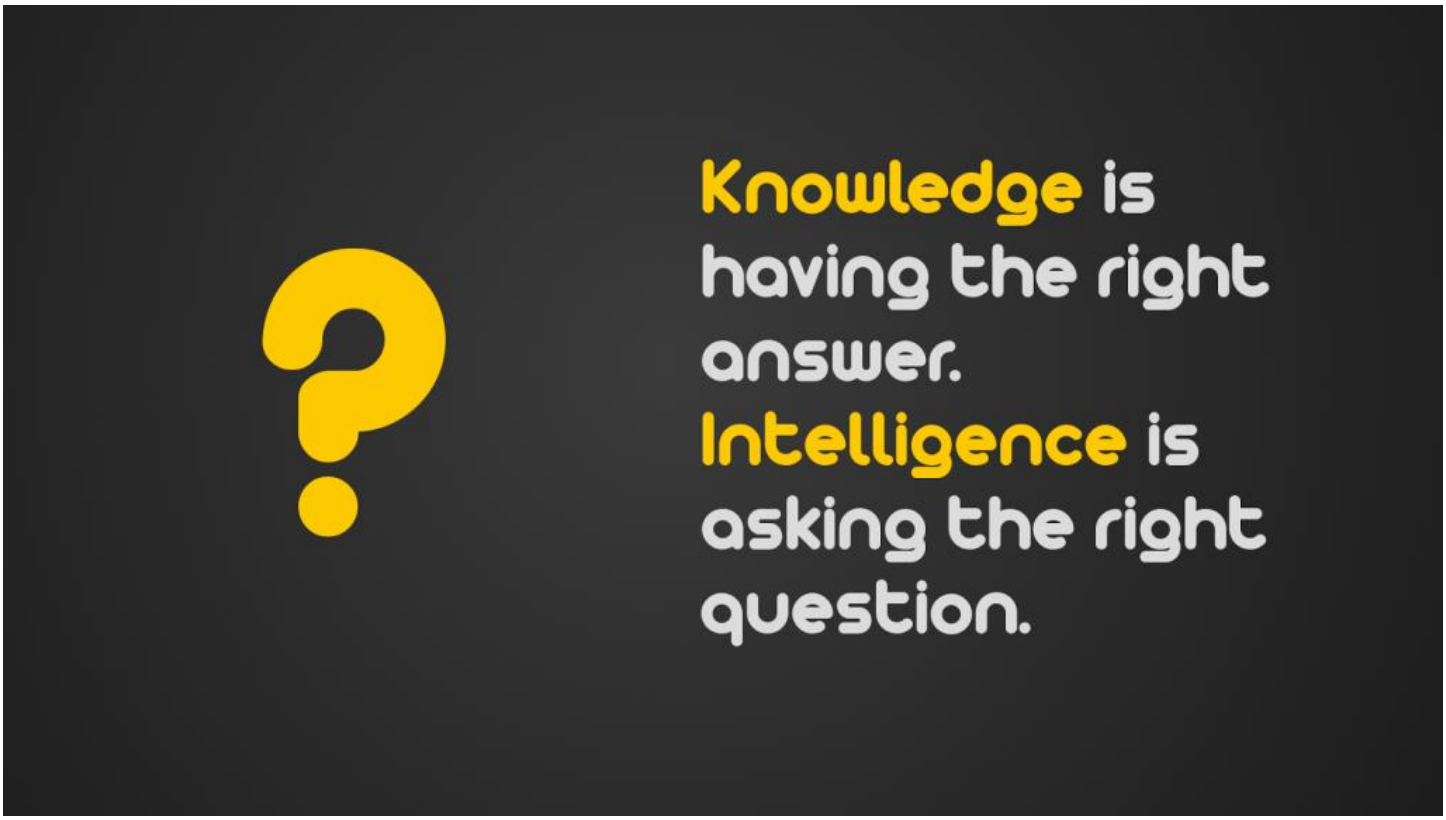

Without treatment, CF results in **death for 95 percent of affected children before age 5.**

## Etiology

Cystic fibrosis **is an autosomal recessive genetic disorder** with features that reflect mutations in the ***Cystic Fibrosis Transmembrane conductance Regulator* (CFTR) gene**. **This gene changes a protein that regulates the movement of salt in and out of cells.** The result is thick, sticky mucus in the respiratory, digestive and reproductive systems, as well as **increased salt in sweat**. CFTR controls chloride ion movement in and out of the cell.



**<u>The pathophysiology of cystic fibrosis</u>**

**Shortly after birth**, many persons with cystic fibrosis

1. **Acquire a lung infection**, leading to
2. **An inflammatory response**. Infection becomes established with a distinctive bacterial flora.
3. **A repeating cycle** of infection and Neutrophilic inflammation develops.
4. ***Cleavage of complement receptors CR1 and C3bi and immunoglobulin G (IgG) by neutrophil elastase (NE) results in failure of opsonophagocytosis***, leading to bacterial persistence.
5. Neutrophil elastase NE also causes production of the neutrophil chemoattractant interleukin 8 (IL8) from epithelial cells and **elastin degradation and acts as secretagogue**, thereby contributing to persistence of inflammation and infection, structural damage, impaired gas exchange, and, ultimately, end-stage Bronchiectasis and early death.