

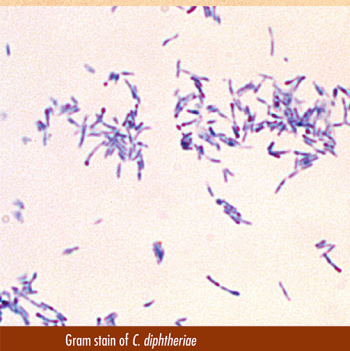
Diphtheria: from Klebs to Elek

Edwin Klebs (1834–1913)

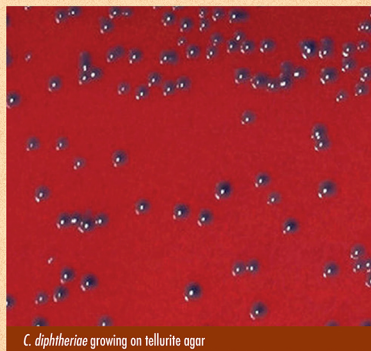
Diphtheria was probably present in antiquity, although it was not distinguishable from other throat diseases at the time. Deadly epidemics were recognised in the Middle Ages and up to the present century. Although vaccine programmes have made the disease a rarity in the modern era, it persists in countries where circumstances cause a failure of vaccine programmes and where anti-vaccination groups are active. Diphtheria still occurs occasionally in the UK, and laboratories must be able to recover the organism from patients suffering from this serious and still life-threatening disease.

Ancient world

- Classical medical writings refer to severe sore throat ending in death, termed *Kynache* (Greek) or *angina* (Latin).
- Descriptions record an acute inflammatory infection of the throat and larynx with difficulty in swallowing and breathing, sometimes resulting in death.
- First clear descriptions by Aretaeus of Cappadocia in the second century CE, Coelius Aurelianus in the fifth century CE and Aetius of Amida in the sixth century CE.
- Sanskrit writings in India describe a disease that may have been diphtheria.
- Similar descriptions are found in The Chronicle of St Denis (580s CE) and the Ecclesiastical Annals of Baronius describing a plague of "mortal throat disease".
- Classical synonyms: *Kynache trachealis*, *angina*, *maligna contagiosa*, *angina suffocative*, *el garotillo*, *morbus suffocans*.



Gram stain of *C. diphtheriae*



C. diphtheriae growing on tellurite agar

Mediaeval world

- No real medical evidence on actual diphtheria but extant chronicles hint that the disease was present and active.
- 1039 CE: The Byzantine chronicler Cedrenus records an outbreak of *Kynache*.
- 1389 CE: William Short records an outbreak of *Angina* in England killing many children.
- 1492: Hartmann Schedel (city physician in Nuremberg) describes a disease that was probably diphtheria.

Diphtheria and early medical science

- Pierre Fidele Bretonneau coins the word "diphtherie" from the Greek for leather, referring to the leathery choking mucous tissue developing in the throat. He has the experience of 60 autopsies, and establishes diphtheria as a single specific disease.
- Edwin Klebs reports at The Congress for Internal Medicine in Weisbaden a rod-shaped bacterium varying in size and clubbed in morphology in diphtheria membranes. The bacillus did not appear in the blood or internal organs.
- Friedrich Loeffler confirms Klebs' findings. He isolates the bacterium in culture. He discovers the bacillus in a healthy child, raising the fundamental issue of the healthy carrier.

Immunisation and control

- A series of brilliant laboratory investigations by Emile Roux, Alexandre Yersin, Karl Frankel and Emile Behring (supported by his colleague Shibusaburo Kitasato) evaluate the mechanism of disease.
- Roux and Yersin show that the bacterium produces a poison (exotoxin) which they separated from the organism and injected into animals to produce diphtheria symptoms, thus permitting definitive diagnosis.
- Frankel, Behring and Kitasato perform immunological studies, resolving the problem of diphtheria protection and control. Attenuated cultures produce immunity to diphtheria in guinea pigs.
- Diphtheria antitoxin raised in horses.
- Behring treats toxin with antitoxin to produce immunity.
- G Roman treats toxin with formalin to produce toxoid, with much improvement over antitoxin treatment and is less likely to produce severe reactions.
- Further improvements by developing alum-precipitated toxoid.
- Large-scale immunisation programmes are instituted.

Guillaume de Baillou (1538–1616)

Early modern world

- Severe "Angina Maligna Contagiosa" occurs in the Rhine region and in Amsterdam where Van Wiers describes it as "very destructive to children".

Modern world

- 1576 CE: Guillaume de Baillou (noted for his epidemiological studies) describes what is almost certainly a diphtheria outbreak in Paris.
- The first reliable evidence comes from Spain dealing with severe outbreaks in the Iberian peninsula, reaching a high point in the 1620s CE, called "garotillo", noting extremely high mortality.
- 1659 CE: Cotton Mather reports a "Malady of bladders in the windpipe" killing a number of children in the Massachusetts Bay Colony. He describes tracheotomy as a remedy.
- Outbreaks of diphtheria occur in Italy, the American colonies, Peru and England (especially Devon and Cornwall).
- In the American colonies the town of Hampton Falls (population 1200) suffered 210 deaths – 95% are below the age of 20 years. George Washington dies in 1799 of asphyxia from a "severely swollen throat".

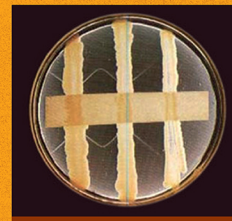
Nineteenth-century crises

- France suffers significant outbreaks.
- Large outbreaks occur in Switzerland, Germany, Scandinavia, USA and Britain.
- Diphtheria becomes pandemic in the mid-19th century.

Country	Year(s)	Number of deaths
Holland	1859–63	400
	1866–70	500
Scotland	1861	151
	1863	478
	1875	2320
New York (USA)	1866–72	1950
	1873	1151
	1874	1600
	1875	2320
China	Late 19th C	20,000

Diagnosis

- Hungarian bacteriologist Bela Schick develops the Schick test to detect the presence or absence of immunity to diphtheria.
- 1931: McLeod and colleagues describe isolation of diphtheria bacilli on blood tellurite agar and call strains from severe disease "gravis" type and those from milder cases "mitis" type. Later they describe an "intermedius" type.
- Philip Hanson His develops His's Serum Water Sugars for identification of *C. diphtheriae* (and streptococci).
- 1941: Hoyle describes another tellurite medium for culture of diphtheria and this becomes the medium for general diagnostic use.
- 1949: S D Elk invents the Elek precipitation plate test to detect the toxin of *C. diphtheriae*.
- 1994: M J Pallen publishes a PCR test for the detection of the toxin gene.
- 1997: A modified Elek test is published by Engler *et al*.
- Better diagnosis and treatment lead to a dramatic drop in diphtheria cases.



Elek plate showing diphtheria toxin:
Left, positive control; Middle, test strain;
Right, negative control

Resurgence of diphtheria

- Diphtheria resurges where vaccination programmes collapse or where anti-vaccination groups are dominant.
- Second World War sees over one million cases of diphtheria and approximately 50,000 deaths.
- Improperly manufactured aluminium phosphate toxoid leads to 68 deaths in children.
- 1990s: Large outbreak in Russia and former Russian states due to the collapse of vaccination programmes – 150,000 cases occur with mortality rates reaching 20% in the worst areas.
- Isolated cases still occur in the UK (occasional small outbreaks also occur – 11 cases in one small outbreak in a London borough).
- In England and Wales there were 14 cases in 2014 and nine cases in 2015.
- Recent outbreaks include Ethiopia (2015), Kerala in India (2016), and Venezuela (2016).

The efficient vaccination programmes and general lack of laboratory screening have led to isolated single cases of diphtheria being missed – truly forgotten but not gone.

Forgotten, but not gone:
old diseases that can still bite

Produced by members of the
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Friedrich Loeffler (1852–1915)