The History of

Three Ageless Cardiac Drugs

Aspirin – Digitalis – Nitroglycerine

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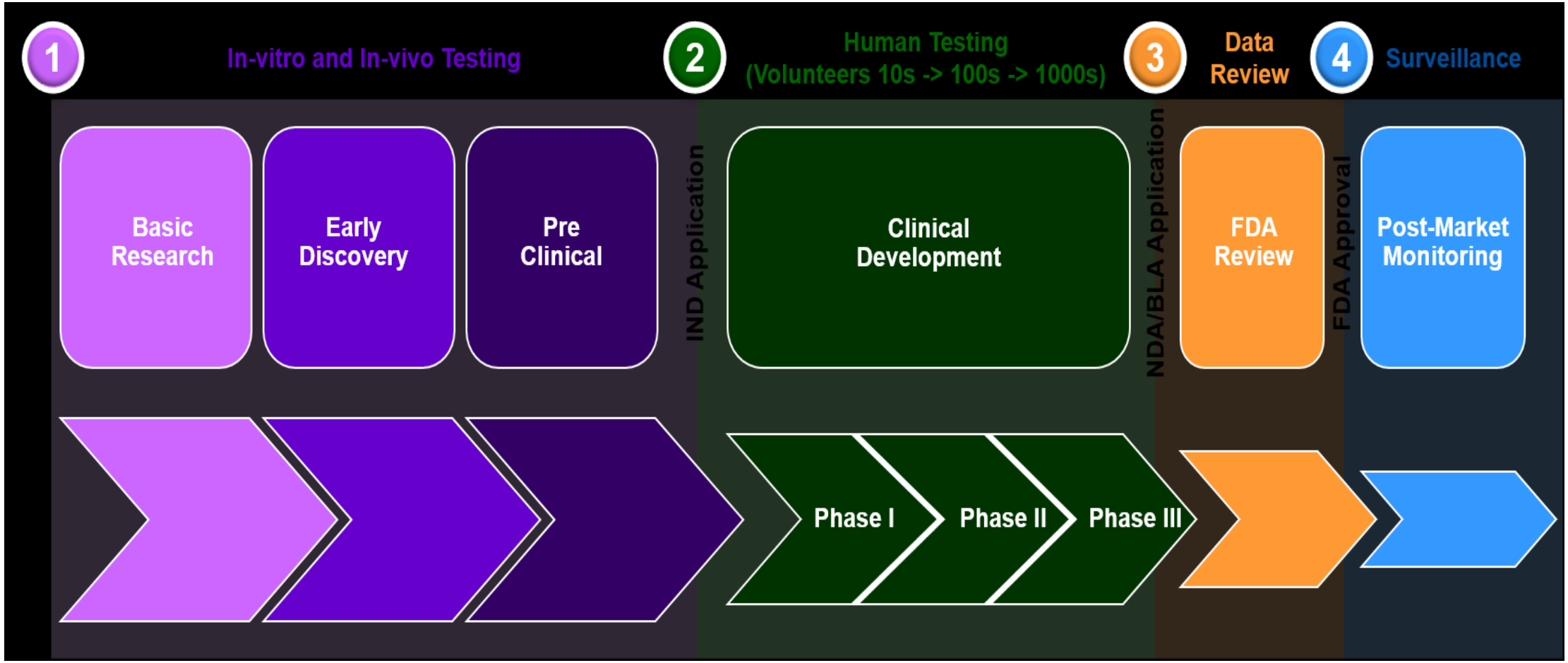
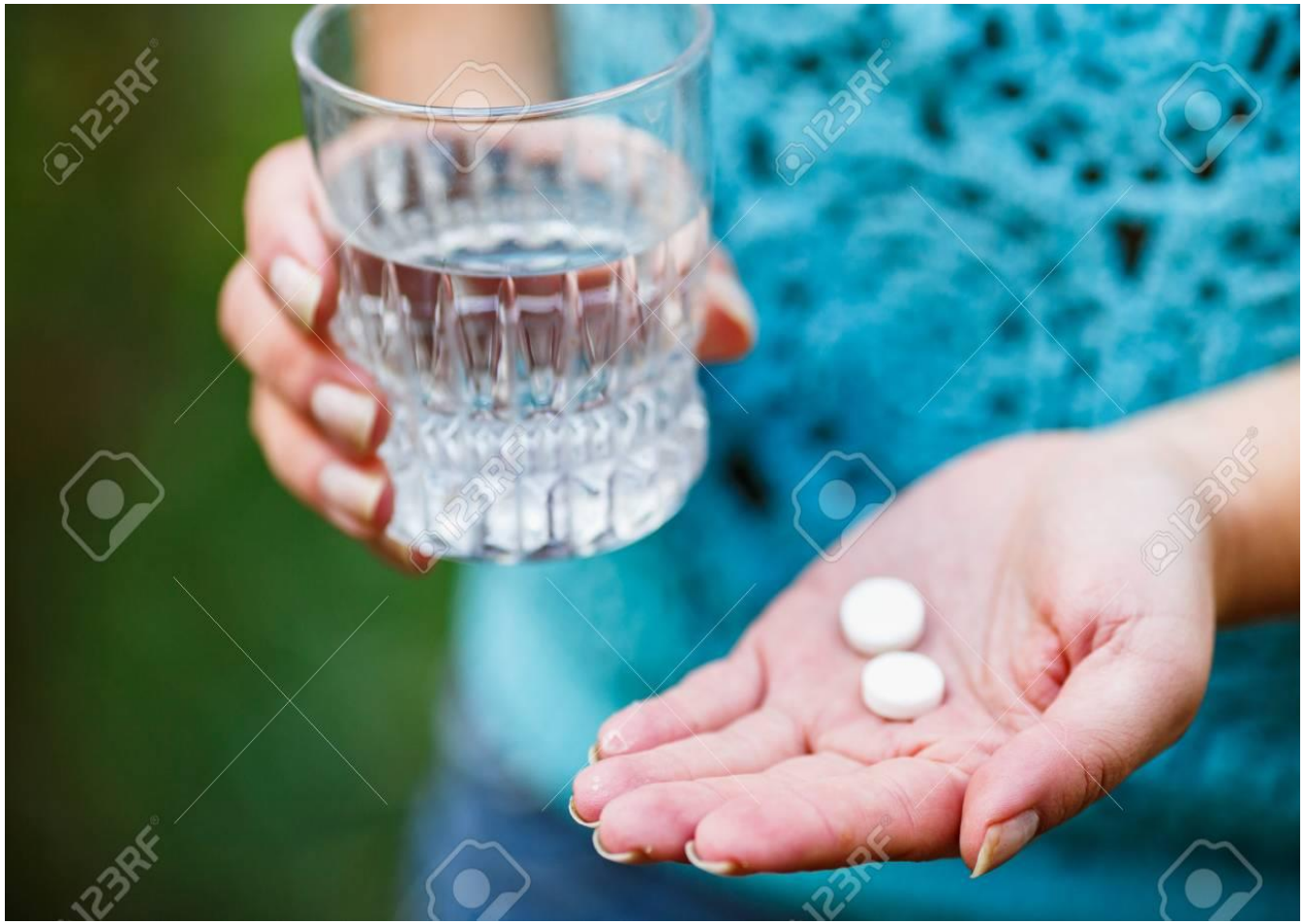
Drug Development Time

12 – 15 years





Aspirin

Black Willow Tree

Salix Nigra

Black Willow Tree

Salix Nigra

Aspirin

Ancient Era

4000 BC – Mespotamia, Sumeria
3500 – 2000 BC Assyria
1300 BC - Egypt
600 – 650 BC – Babylonia
460 – 370 BC – Hippocrates in Greece, China
100 AD and later – Rome

Modern Era

1763 – The Reverend Edward Stone – letter to
The Royal Society

Powdered Willow Bark in a dram of water

XXXII. *An Account of the Succeſs of the Bark of the Willow in the Cure of Agues. In a Letter to the Right Honourable* George *Earl of* Macclesfield, *Preſident of R. S. from the Rev. Mr.* Edmund Stone, *of* Chipping-Norton *in* Oxfordſhire.

My Lord,

Read June 2d, 1763. AMong the many uſeful diſcoveries, which this age hath made, there are very few which, better deſerve the attention of the public than what I am going to lay before your Lordſhip.

There is a bark of an Engliſh tree, which I have found by experience to be a powerful aſtringent, and very efficacious in curing aguiſh and intermitting diſorders.

About ſix years ago, I accidentally taſted it, and was ſurpriſed at its extraordinary bitterneſs; which immediately raiſed me a ſuſpicion of its having the properties of the Peruvian bark. As this tree delights in a moiſt or wet ſoil, where agues chiefly abound, the general maxim, that many natural maladies carry their cures along with them, or that their remedies lie not far from their cauſes, was ſo very appoſite to this particular caſe, that I could not help applying it; and that this might be the intention of Providence here, I muſt own had ſome little weight with me.

The exceſſive plenty of this bark furniſhed me, in my ſpeculative diſquiſitions upon it, with an

Page 1 of the letter from Rev. Edmund Stone to the Royal Society April 1763

50 patients over 5 years

Aspirin

Development

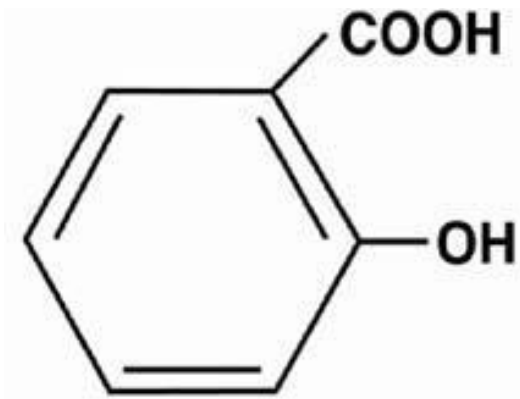
1828 – Buchner at University of Munich – separated active substance – called it Salicin (after the tree)

1829 – Leroux – French pharmacist – crystallized the substance

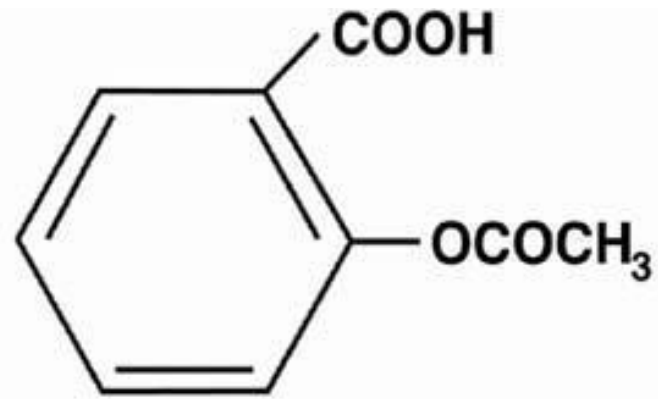
1860 – Kolb and Lauterman – chemical synthesis led to small scale and then commercial production by Heyden Chemical Company in Germany – sold to relieve pain and fever.

1895 – Salicylic Acid now produced by the Bayer Company

1897 – Bayer tries to modify the drug for a drug with fewer side effects – Acetylation



Salicylic Acid



Acetylsalicylic Acid (aspirin)

Aspirin

Discovery

1934 – Bayer Company publishes history of Aspirin discovery
Felix Hoffmann – chemist at Bayer – asked to formulate a related compound with fewer side effects. Assigned the task to
Heinrich Dreser – investigated several derivatives (including acetyl) then set the project aside for 18 months
1898 – promising clinical experience
1899 – Bayer names the drug Aspirin and markets it as a powder
1900 – Aspirin tablets

1949 – Arthur Eichengrün – former head of chemical research at Bayer and colleague of Hoffman now claims credit for development of Aspirin
1944 – Nazis take over his business and send him to a concentration camp at age 76.

Bayer Aspirin Bottle
1899

Aspirin

Modern Era

1950's – Lawrence Craven M.D. family practice – Glendale, California
published 3 articles in minor journals recommending aspirin to prevent heart attacks – got little notice

1960's – Aspirin interfered with the clotting mechanism and suppressed inflammation – both features of atherosclerosis.

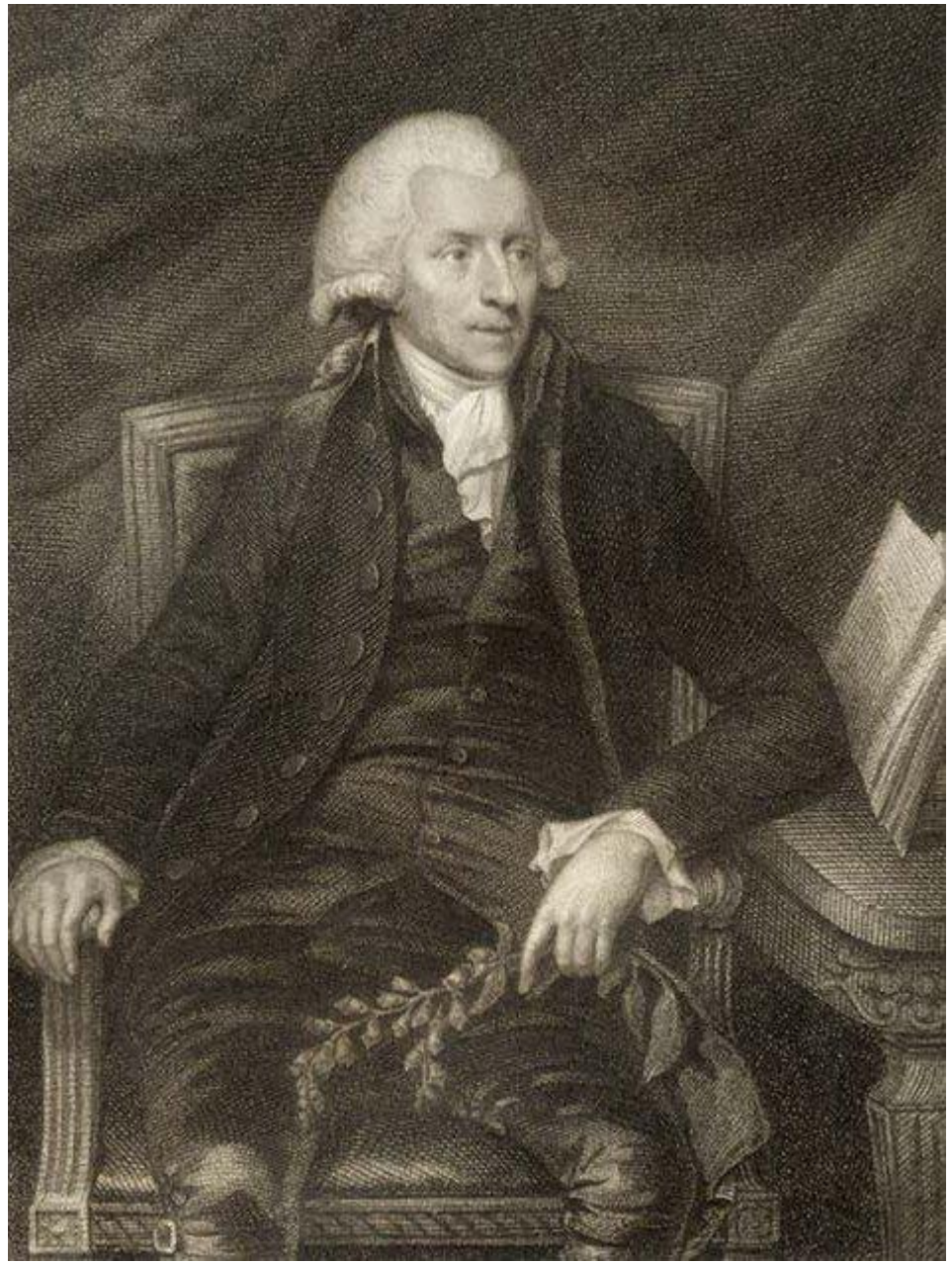
1970's – Explanation of how Aspirin relieved pain and fever – led to development of NSAIDs
Sir John Vane (and others) wins Nobel Prize

1980's – Clinical trials in thousands of patients showing benefits in the treatment and prevention of coronary heart disease.

Summary

Digitalis

(Digoxin)



William Withering
1741 - 1799

Digitalis

1. William Withering
   born 1741 in Wellington, Shropshire, England.
   Worked for his father – an apothecary
   Two physician uncles – encouraged him to go medical school
   Graduated from University of Edinburgh -1766
   Opened a practice in Stafford – Stafford Infirmary – 8 years
   Practice slow - spare time – expert in Botany

2. New unexpected practice opportunity in Birmingham
   Offered by Erasmus Darwin (Grandfather of Charles Darwin)
   Busy, lucrative practice – one of the richest in England
   One day per week in Free Clinic for the poor – General Hospital at Birmingham

3. Lunar Society membership
   Erasmus Darwin
   James Watt (inventor of the steam engine)
   Josiah Wedgewood (pottery)
   Joseph Priestly (isolator of oxygen)

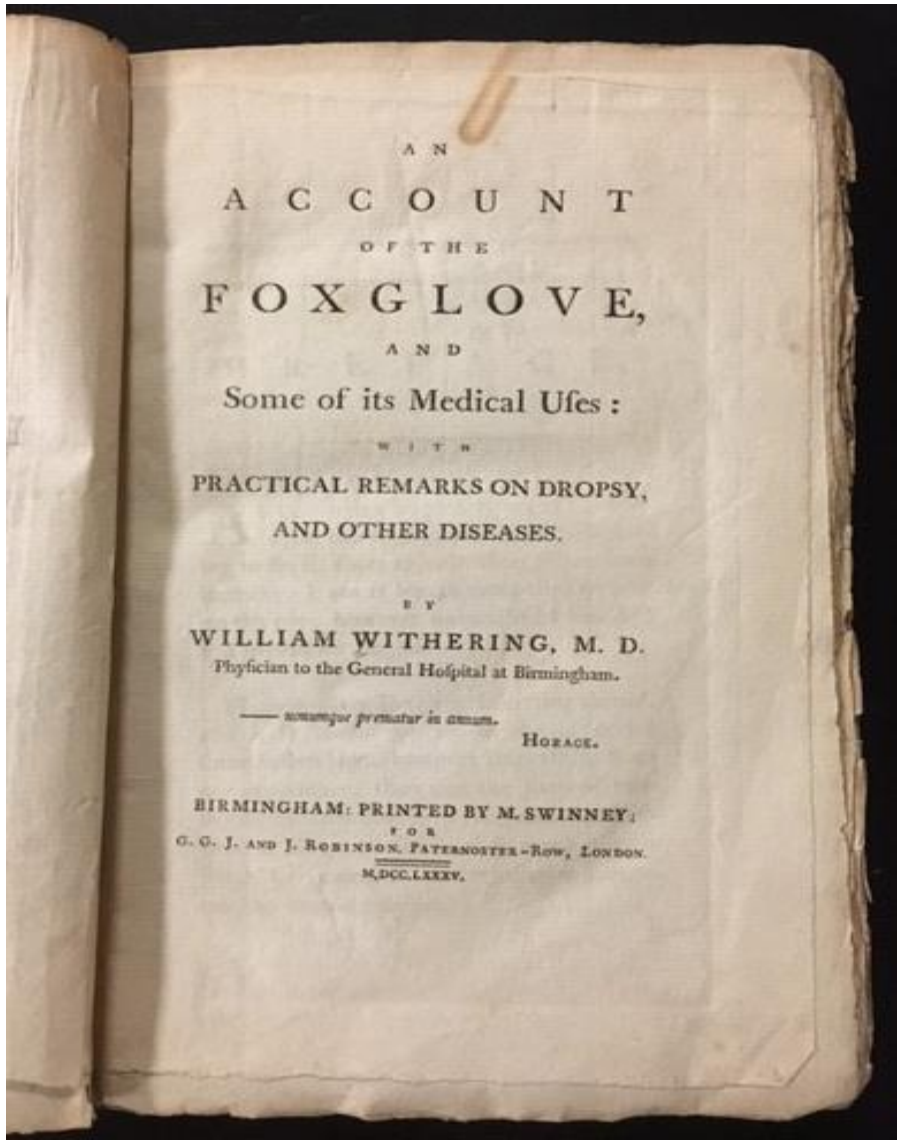
Digitalis

1. <u>Dropsy</u>
   One of the chief causes of death
   Swelling (edema) of the feet, abdomen
   No effective treatment known at the time.

2. Where physicians had failed, including himself, Withering learned of an old woman who had successfully treated dropsy with a home brewed tea.
   After some persuasion, Withering convinced her to disclose the contents

3. Withering's written description of the events.
   " In the year 1775 my opinion was asked concerning a family receipt for the cure of the Dropsy. I was told that it had long been kept secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed……This medicine was composed of 20 more different herbs: but it was not very difficult for one conversant in these subjects to perceive, that the active herb could be no other than the Foxglove."

Digitalis Purpurea
(Foxglove)



AN

ACCOUNT

OF THE

FOXGLOVE,

AND

Some of its Medical Uſes:

WITH

PRACTICAL REMARKS ON DROPSY,

AND OTHER DISEASES.

BY

WILLIAM WITHERING, M. D.

Phyſician to the General Hoſpital at Birmingham.

—— *nonumque prematur in annum.*

HORACE.

BIRMINGHAM: PRINTED BY M. SWINNEY;

FOR

G. G. J. AND J. ROBINSON, PATERNOSTER-ROW, LONDON.

M,DCC,LXXXV.

Title Page

“An Account of the Foxglove”

by

William Withering M.D.

1785

An account of 158 treated patients

10 year experience

Successes and failures

Dose responses

Toxic effects

Digitalis

Follow-up

1. Book widely read in Europe and America and drug widely used but Ineffective in non-cardiac causes of Dropsy.
2. Cornerstone of the treatment of heart failure
3. Little research on the drug or its effects for the next 100 years
4. Identification and purification of the active substance and eventual commercial synthesis
5. Explanation of its actions led to a better understanding of the mechanisms of cardiac contraction.
6. In the last 20 to 30 years, has been edged aside by more effective agents but it is still available and plays a small clinical role.
7. Withering died in 1799 at age 58 of tuberculosis

Summary

Nitroglycerine

Ascanio Sobrero
1812 - 1888

Nitroglycerine

Ascanio Sobrero

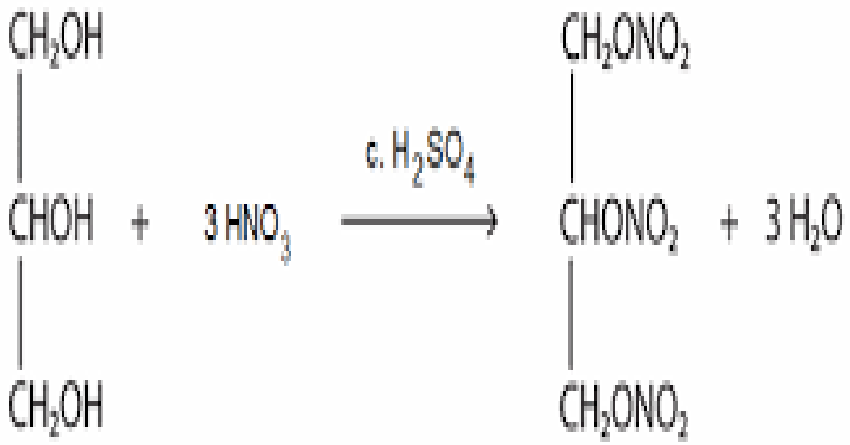
Born in 1812 in the Piedmont region of Italy

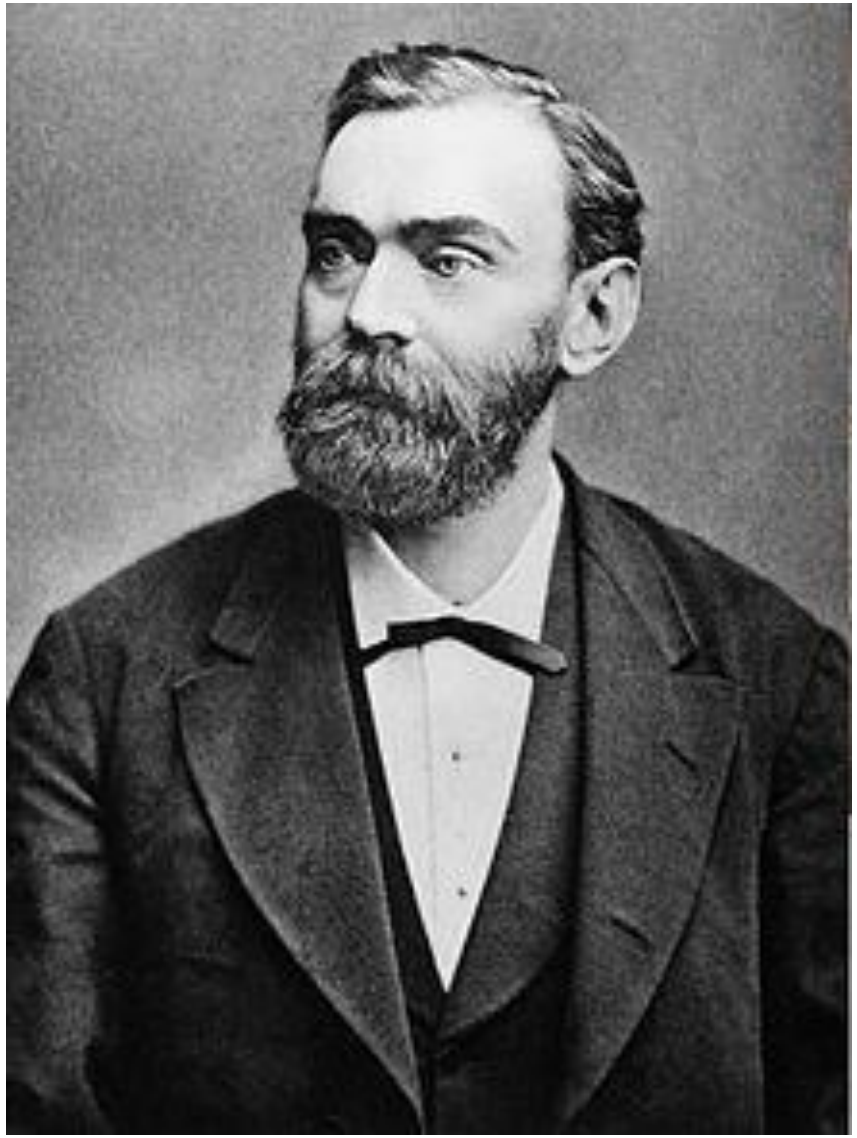
Educated in Medicine at the University of Turin in Italy and in Chemistry at the University Gießen in Germany.

With the influence of family and friends was accepted to study further in the laboratory of famous chemist Theophile-Jules Pelouze in Paris. 1840

Accomplished the nitration of glycerine in 1846

Detonated a small amount at an important lecture at the Academy of Science in Torino 1847.


CH2OH
CHOH
CH2OH
+
3 HNO3
c. H2SO4
CH2ONO2
CHONO2
CH2ONO2
+ 3 H2O
Glycerol
Nitroglycerine



Alfred B. Nobel
1833 - 1896

Nitroglycerine

(Explosive)

Alfred B. Nobel

Born in Stockhlolm – 1833

Father moved his failing business to St. Petersburg, Russia – making munitions and military equipment for the Czar – Crimean War.

Business initially successful – Alfred sent to Paris to study chemistry and explosives in laboratory of Pelouze (1850).

Meets Sobrero and after one year, takes NTG back to Stockholm to improve its stability – 1860's

Multiple explosions – one kills younger brother.

Two most important patents – blasting cap and dynamite.

Leaves most of his fortune to fund 5 Nobel Prizes – Chemistry, Physics, Physiology or Medicine, Literature and Peace.

Nitroglycerine

(Medication)

Amyl Nitrite

A volatile liquid discovered by French chemist Antoine Balard in 1844.

When sniffed produced a brief flushing of the face, racing of the pulse, headache and a fall in blood pressure.

Thomas L. Brunton – Scottish physician (pharmacologist) described its use in the relief of angina pectoris in the Lancet – 1867 – sought a more convenient and longer lasting remedy.

Nitroglycerine

Similarity to amyl nitrite – later onset, longer duration

William Murrell – a London physician – began using liquid NTG for angina pectoris. published his findings in Lancet – 1879.

William Martindale – British chemist – prepared a solid form imbedded in chocolate. "is stable, non-volatile….and perfectly inexplosive – it cannot be detonated".

Within 4 years, reports of the benefit of NTG had spread widely and described in the Boston Medical and Surgical Journal.

Manufactured by Parke-Davis in 5 different strengths.

Sublingual Nitroglycerine Tablets

Nitroglycerine

Follow-Up

1. Mechanism of action of nitroglycerine not explained for over 80 years.
2. Involved with the function of the inner lining of blood vessels.
3. Fundamental understanding of the circulation and awarding of the Nobel Prize in Physiology or Medicine to the involved scientists.
4. Still widely use for the relief of angina and the treatment of heart failure inexpensive. With “Free Coupon” at a local pharmacy – 25 tablets for $14.00.
5. Dynamite still used for blasting, roads etc. but has been replaced by TNT for most military purposes.
6. Alfred Nobel died of heart disease in 1896, but refused to take NTG for angina.

Summary