A Short History of Drug Development

A personal ramble by Dr Peter Tooley
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Overview

- Early days
- The real beginning
- Some highlights
- Historical trade
- Early manufacture in England
- Today
- ..... and some problems.
- The future - what do we want?
- Do drugs prolong life?
- Discussion
The beginning?

- Drugs/medicines are not new!

Definition

- a medicine or other substance which has a physiological effect when ingested or otherwise introduced into the body
This Minoan figurine (2000BC) of the female in worship stance wearing a diadem of opium poppy heads, each painted with a slit for extraction of the sap.
Gold signet ring, Knossos (1500 BC). Demeter, seated beneath the Double Axe and the World Tree, hands three poppy heads to Persephone
Sacramental vase in the National Archaeological Museum of Taranto (450 BC), depicts Demeter's son, Dionysos, wearing a crown of opium poppies.
'Ancient Siberian Princess Buried With Cannabis'
'Prehistoric Cultivated Marijuana Stash Found in China‘ (c. 700 BC)
The Merv Oasis -
religious complex that dates back to 2000 BC
Ruins at Merv Oasis
Egyptian school
~ 300 AD
School graffiti that contains ancient Greek writings on its walls, including a text about ancient drug use that references Homer's "The Odyssey"
The Pazyryk barrows, (6th-3rd centuries B.C.) - Russia:

- artefacts including saddles, riding gear, a chariot, rugs, clothing, jewellery, musical instruments, amulets, tools, and, interestingly, an "apparatus for inhaling hemp smoke"

- Travel - Also found in the tombs were fabrics from Persia and China, which the Pazyryks must have obtained on journeys covering thousands of miles.
The Pazyryk ice maiden
Was there a drug ‘trade’?

- Travel widespread
- Distribution of knowledge - Egyptians, Greeks, Romans, Europeans - round and round it went.
- Along with knowledge went drugs, medicines and customs
More examples of widespread drug use worldwide

- The Balfarg henge is a part of a larger prehistoric ceremonial complex in Fife, Scotland. Pottery found at the site dates to around 2900 BC. May have been used to hold black Henbane (Hyoscyamus niger)

- Carrowmore, Ireland. Dated about 4,600 BC, contains the remains of a passage-tomb which may be the earliest in the country - produced the remains of over 65 fragments of antler pins, including seven pieces with mushroom-shaped heads. (Opium)

- Skara Brae, Orkneys: Hallucinogenic Alcohol: 5,000 year old traces of cereal-based fermented alcohol - laced with hemlock.
Henbane (hyoscyamus niger) - The Insane Seed that Breedeth Madness (Rowan)
The Neolithic period - The new Stone age (1)

- The starting point of the Neolithic Period is much debated, but it is generally thought to have occurred sometime about 10,000 BCE.

- During that time, humans learned to raise crops and keep domestic livestock and were thus no longer dependent on hunting, fishing, and gathering wild plants. They stopped being hunter-gatherers.

- Those earliest farmers raised barley and wheat and kept sheep and goats, later supplemented by cattle and pigs. (Eating Gazelle became less common and eating sheep increased.)
Neolithic period (2)

Their innovations spread from the Middle East northward into Europe by two routes: across Turkey and Greece into central Europe, and across Egypt and North Africa and thence to Spain. Farming communities appeared in Greece as early as 7000 bce, and farming spread northward throughout the continent over the next four millennia.
Alcohol's Neolithic Origins: Brewing Up a Civilization

By Frank Thadeusz

Did our Neolithic ancestors turn to agriculture so that they could be sure of a tipple? US Archaeologist Patrick McGovern thinks so. The expert on identifying traces of alcohol in prehistoric sites reckons the thirst for a brew was enough of an incentive to start growing crops.

It turns out the fall of man probably didn't begin with an apple. More likely, it was a handful of mushy figs that first led humankind astray.
However important, alcohol is nowhere near the full story of induced Neolithic consciousness change.

In many cultures, psychoactive drugs and their effects are viewed as vehicles for making contact with other worlds, in particular those of the ancestors in the context of temple-centred ceremony.

Rudgley (1999, p.137-141) has proposed cannabis and/or opium as likely candidates in the early western Neolithic and a growing body of opinion points in the same direction. (Devereux, 1997: Sherratt, 1997; Thomas, J., 1998)

The Orkney brew described above, it will be remembered, was blended with henbane and hemlock. Henbane, bearer of the trance-inducing, hallucinatory (and extremely toxic) drug Hyoscyamine, is one of what Sherratt (1996) terms “the Saturnine herbs”. Sherratt recounts how during the 1980’s henbane was recovered from carbonised Neolithic porridge, eaten from Grooved Ware pottery in the context of a mortuary structure, Balfarg/Balbirnie in Fife, Scotland. Discovery in the 1920’s of three burial chambers at the Jersey La Hougue Bie site adds weight to Sherratt’s thesis. David Keys reports that the chambers “…contained 21 pottery vessels marked with a burnt, resin-like material. Archaeologists believed that this was from drugs, possibly opium or hashish.”
Evidence of travel (1)

- German scientist Svetla Balabanova (1992)
- Found cocaine, hashish and nicotine in Egyptian mummies
- ‘Not possible’ as cocaine and nicotine were only found in the Americas. Generated great criticism (contamination, fraud, or necrobiological processes)
- NB: This was pre-Columbus
- Nerlich et al (1995), in a study evaluating the tissue pathology of an Egyptian mummy dating from approximately 950 B.C., found the compounds in several of the mummy's organs.
- Parsche and Nerlich (1995) confirmed findings in another study
Evidence of travel (2)

- c. 700-800AD: China and India: Opium poppy introduced by Arabs.
- c. 1000AD: China: Medicinal use of opium widespread and in India opium is cultivated, eaten, and drunk by all classes as a household remedy; it is used by rulers as an indulgence, and given to soldiers to increase their courage.
- c. 1250AD: Europe: distillation discovered in Europe, producing more potent and convenient alcoholic beverages. Mainly wine based. Credited with extraordinary healing powers, their common name is aqua vitae, "water of life."
Snuffing tablet - Chile
Modern side-thought -

- Recent research indicates that henbane has been shown to stimulate the manufacture of beta cells in the pancreas and therefore be a ‘cure’ for diabetes.
c. 1300 – 1500AD

- Cocaine found throughout the Inca regions
- Coffee developed in Arabia where the technique of roasting is developed.
- c. 1500AD: Widespread exploration starts to distribute active substances widely. Psychoactive drug use becomes diverse.
- Tobacco, coca, cocoa (from the New World), coffee from Arabia and Turkey, and tea from China. Many social changes mean that society become more ‘free’ and secular use rather than religious use of these substances spreads.
- The problem of uncontrolled alcohol including distilled spirits starts to appear. Luther, Calvin and others urge the need for temperance. Opiates are now established and native opium is manufactured. Recreational use is still limited. At this time Columbus lands in the New World and tobacco use is observed.
- Over the next century (1500 - 1600) not a great deal changes with regard to drugs used although use becomes more widespread.
Effects of widespread drug use

- 1575-1600: Arabia/Turkey: The Sultan orders coffee shops to close of religious grounds - no-one takes any notice. Later revoked in the Ottoman Empire.

- Smoking becomes common as a medicine but remains controversial as a social pastime. When Sir Walter Raleigh introduced tobacco to England, smoking becomes the "duty" of every man of fashion; tobacco was worth its weight in silver.
Alcohol (again!)

- 1600-1625: In America, following the founding of the English colonies, drunkenness is prominent but it is not considered a major problem. Abuse is condemned and temperance is advocated, but alcohol itself is highly esteemed as in England as the Good Creature of God, a beneficial gift to man.

- In England during the reign of James I, widespread drunkenness from beer and wine described.

- Alcohol use is tied to every endeavour and phase of life, a condition that continues well into the eighteenth century. (?)

- Parliament passes "The Act to Repress the Odious and Loathsome Sin of Drunkenness" (1606).
Medicine, Drugs and time ..... (at last a little history!)

- ‘Pre-history’ - witchcraft, religion, experience, luck
- Egyptians, Romans, Greeks - started to write it down
- Animal carcasses only source of anatomical info
- Injured soldiers (e.g.
- The ‘Galenic interval’
- Advances in understanding human biology - ‘enlightenment’
- Leads to more specified medicines (limited)
Digitalis purpurea
Digitalis - example of serendipity

- William Withering
- 1775
- Dropsy
- Gypsy
- ‘Analysis’
- Trial of formulations - dried powdered leaf was best
- Results very positive - he introduced this is 1785
- Historical use for ‘trial by ordeal’ in Middle Ages
- Some evidence used to treat dropsy
Drug Manufacture at Apothecaries Hall

- 1673 - Drugs produced for WSA at Chelsea Physic Garden together with training of apprentices (an example of drug ‘manufacture’ and teaching) (Note: Hall reopened after rebuild 1672)
- 1692 - An ‘elaboratory’ founded at the Hall to manufacture and sell medicines (note the shop)
- 1705 - Navy Stock founded. Drugs for naval fleets, Captain Cook’s expeditions and convict ships (Hunting p 170)
- 1776 - Obtained contract to supply East India Company
Society of Apothecaries
(cont)

- 1822 - Formation of United Stock Company (amalgamation of Laboratory and Navy Stocks). Also supplied the Army.
- During Napoleonic wars it was said we could supply an army of 30,000 men with medicaments in a space of 10 days! Supplied the Army during Crimean war and Indian Mutiny (Indian War of Independence)
- Decline of natural products use and increase of chemical drugs Physic Garden lost in 1899 and with it contracts to the army, navy and EIC.
- Manufacture and shop ceased in 1920.
Apothecaries’ Hall - manufacturing
Apothecaries’ laboratory - the grinding wheel
Beecham’s Clock Tower - St Helens - 1877
History of a ‘modern’ disease - Parkinson’s

1000 BC
Ayurvedic medicine described Parkinson’s-like symptoms

175 AD
Galen of Pergamon described Parkinson’s symptoms

1817
James Parkinson defined the syndrome

1859
Edouard Brissaud suggested involvement of the substantia nigra

1912
Lewy bodies identified by Konstantin TRETIAKOFF

1919
Frederic LEBEY identified “spherical neuronal inclusions”

1961
David Poskanzer and Robert Schwab proposed link with influenza exposure
Serendipity - apomorphine ‘development’

- 1869: Emesis, psychosis-sedative
- 1870: Sydenham’s chorea
- 1874: Expectoration
- 1877: Epilepsy
- 1884: Muscle spasm
- 1887: Abdominal pain
- 1899: Delirium tremens, alcohol & opiate addiction
- 1900: Insomnia
- 1928: Paroxysmal tachycardia
- 1934: Neurosis
- 1945: Hyperthyroid crisis
- 1947: Analgesia
- 1966: Sexual dysfunction – penile erections
DRUG DEVELOPMENT PROCESS

Out of every 10,000-15,000 new compounds identified during discovery, five are considered safe for testing in human volunteers. Only one of these compounds is typically approved as a marketed drug.

3-6 YEARS
- Drug Discovery
- Pre-clinical

6-7 YEARS
- Clinical Trials
- Phase I: 20-100 Volunteers
- Phase II: 100-500 Volunteers
- Phase III: 1,000-5,000 Volunteers

0.5-2 YEARS
- FDA Review
- Manufacturing
- Phase IV Post-Approval

PRE-IND SUBMITTED
IND SUBMITTED
NDA SUBMITTED

AVERAGE COST: $1 billion+
DURATION: 10-15 years*

*Source: ACRO

ppdi.com
New formulations of existing drugs?
Example: New formulation development - From subcutaneous to transdermal? - How long?

- Skin is a complex organ, primary barrier against permeation to the human body
- Two technologies available to test
- Cost €105K to evaluate technology and determine if applicable for *xyz* (*in vitro*)
The patent process

- Patent life 20 years
- Gives some protection - but ..... 
- Patent applied for at a very early stage of molecular identification (protection)
- Research may take 10 - 14 years
- Leaves 10 - 6 years to recoup costs
- 10,000 to 1
- Average cost in 2010 was 1.8 billion dollars (£1.2 billion)
- Then generics arrive
Regulatory process

- Thalidomide (~ 1961)
- Medicines Act (1968)
- Proper licensing requirements - efficacy, safety etc. Beginning of control of clinical trials
- Further developments - CSM, MHRA etc.
- Proper pharmacovigilance - Local to European to Global
- Now tighter control - inspections and high standards

- All this costs and time and money
Why are drugs so expensive?

- Time to develop new drugs (as we have seen)
- The Regulatory process (pharma industry pays)
- The licensing process (pharma industry pays)
- Vigilance and monitoring throughout (pharma industry pays)
  - A moderately minor variation will cost upwards of £10,000
- Some funds required for the next drug!
What’s happening today?
Revolutions of drug discovery

- Evolution or revolution?
- Evolution - the old way - slow - untargeted - serendipitous
- Revolution -
  - First revolution - 1950s
    - Chlorpromazine, Meprobamate, Imipramine, Diazepam
  - Second revolution - 21st Century
  - Repurposing - less onerous, existing data can be used, already established - quicker
Success?

- Are we successful in treating disease?
- Estimated to be 10,000 known diseases (and increasing)
- So far there just are 500 cures (and increasing?)
How are we doing?
FDA since 1930

FIGURE 1
FDA-approved new molecular entities. (a) The accumulation of FDA-approved new molecular entities (NMEs) over time since 1930 is indicated. Please note that the approval of two molecules, morphone and aspirin, pre-dated the creation of the FDA and its precursors. (b) The number of annual approvals since 1930 is shown, as are (c) the average annual rates of approval by decade.
The ‘omics’ revolution

- **Genomics**
  - a discipline in genetics that applies recombinant DNA, DNA sequencing methods, and bioinformatics to sequence, assemble, and analyse the function and structure of genomes

- **Proteomics**
  - the large-scale study of proteins, particularly their structures and functions

- **Metabolomics**
  - systematic study of the unique chemical fingerprints that specific cellular processes leave behind
Targeted treatments?

- Target the disease
- Target the patient
- E.g. Manipulation of T-cells for cancer treatment
- E.g. Stem cell manipulation
- E.g. Zika virus - mosquito adaptation

- Problems:
  - Time
  - Cost
  - selectivity
The future - a personal thought
Where are we going and are we going to succeed?
Drugs to prolong life?

- We are living longer - do we want to go on for longer still?
- Is it going to work?
- Why have we lengthened lives?
  - Environmental
  - Dietary
  - Prevention etc. ....
  - Drugs?
  - Genetics
- How have we done so far?
Life expectancy (white males)

- In 2016 a 65 year old man may expect to live a further 19 years.
- But what about trends, and why is this?
- Anything to do with drugs?
- At birth av. Life expectancy:
  - 1850 - 38.3 yrs (my great grandfather)
  - 1911 - 50.23 yrs (my father)
  - 1939 - 62.81 yrs (me)
  - 1969 - 67.94 yrs (my daughter)
  - 2011 - 76.3 yrs (my grandson)

- Drugs help but ‘life’ standards probably greatest contributor.
Final thoughts

- We are ‘discovering’ new diseases
  - Needing new treatments
  - But with fewer patients
  - And greater cost
  - Societal benefit therefore less
  - Niche markets unattractive
- Meanwhile we deny undeveloped populations
- An on-going socio-political-economic problem
- We may have to stop being selfish
- It won’t go away!
Thank you