Clinical Research

Past, Present and Future

Module 1 Topic 2

The Need

The need for clinical research is closely linked to the need for new drugs. Despite the tremendous medical advance over the last few decades, we need new drugs, because the existing ones have numerous drawbacks, related to efficacy, safety and cost.

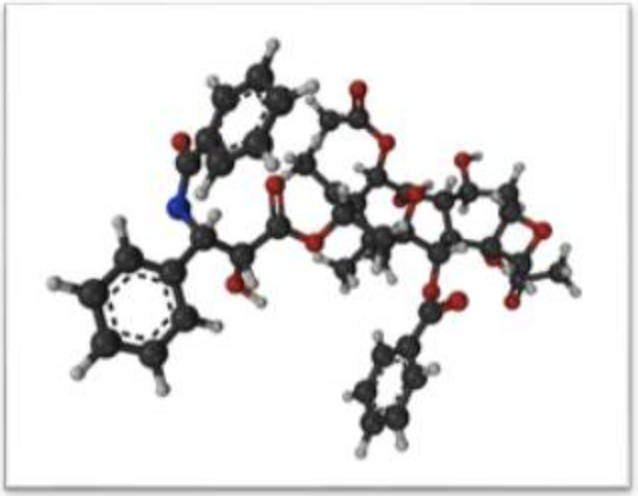
We have safe and effective drugs; unfortunately those that are safe are not effective, and those that are effective are not safe.

Lack of drugs for some diseases

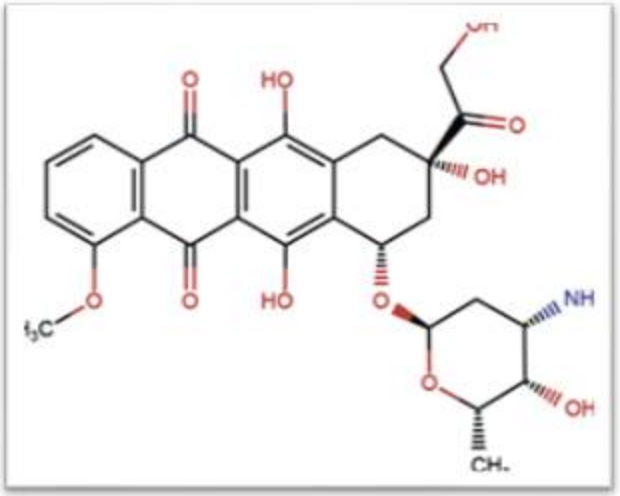
Leukoderma

Amyotrophic Lateral Sclerosis (ALS)

Toxic Drugs



Paclitaxel

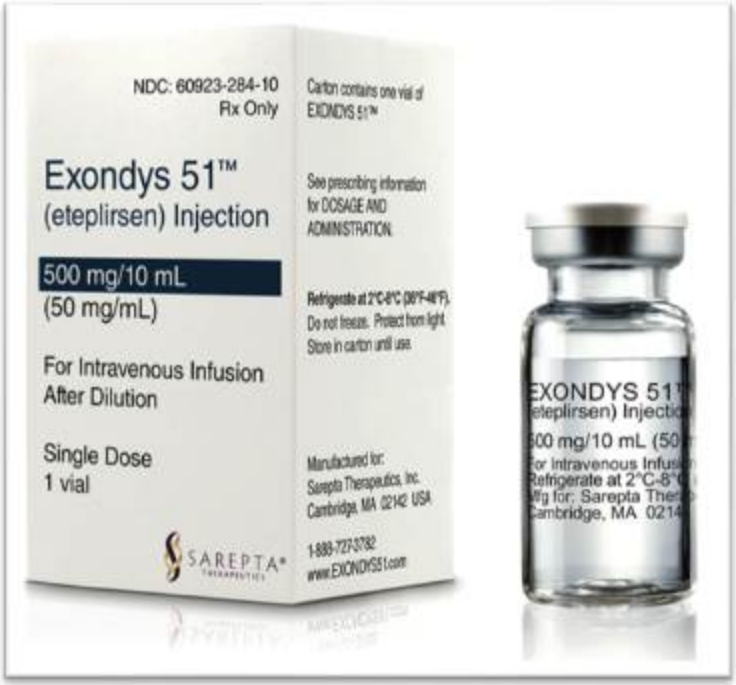


Doxorubicin

Drugs with low efficacy

Effective only in a few types of solid Tumors.

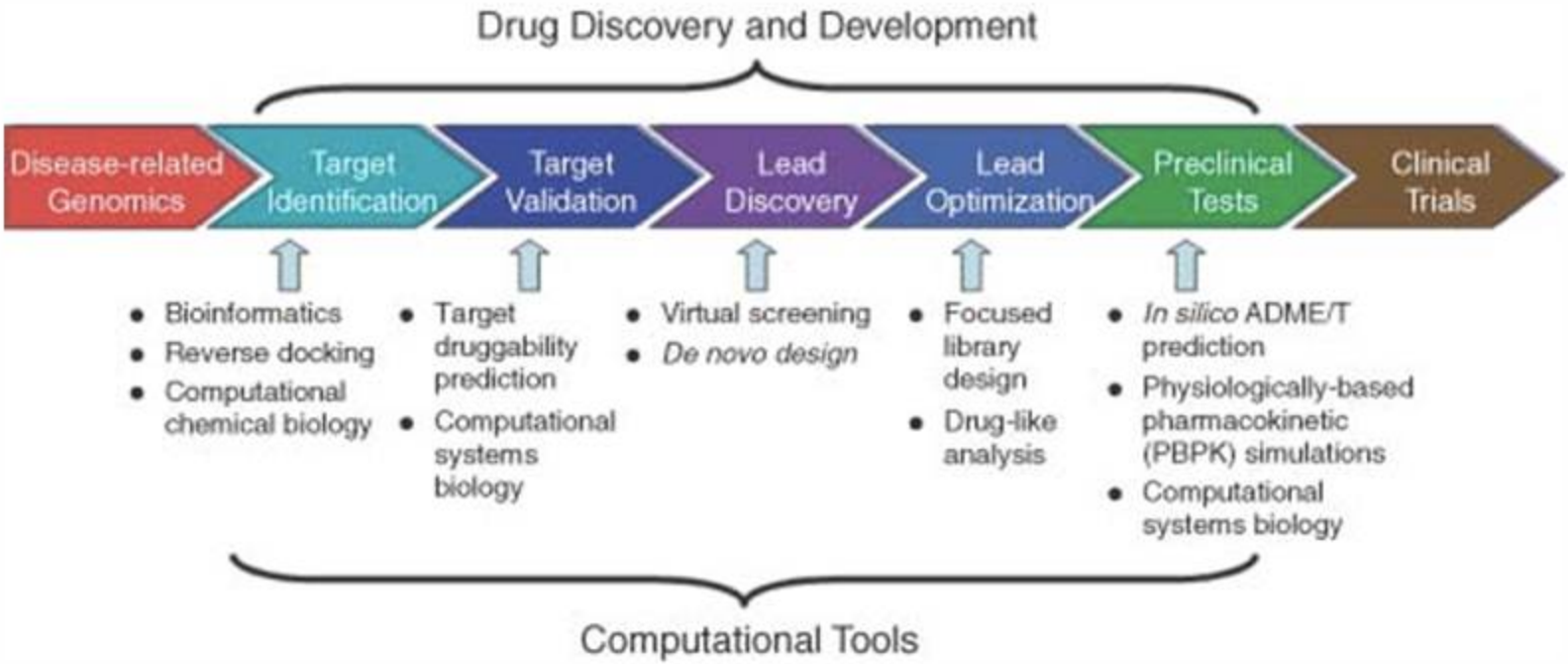
Expensive Drugs



Cleared by FDA in 2016 EXONDYS 51 is indicated for the treatment of Duchenne's Muscular Dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Reported annual cost of treatment is Rs. 1.95 crores.

KLINTEC Academy

Clinical Trials-The final frontier

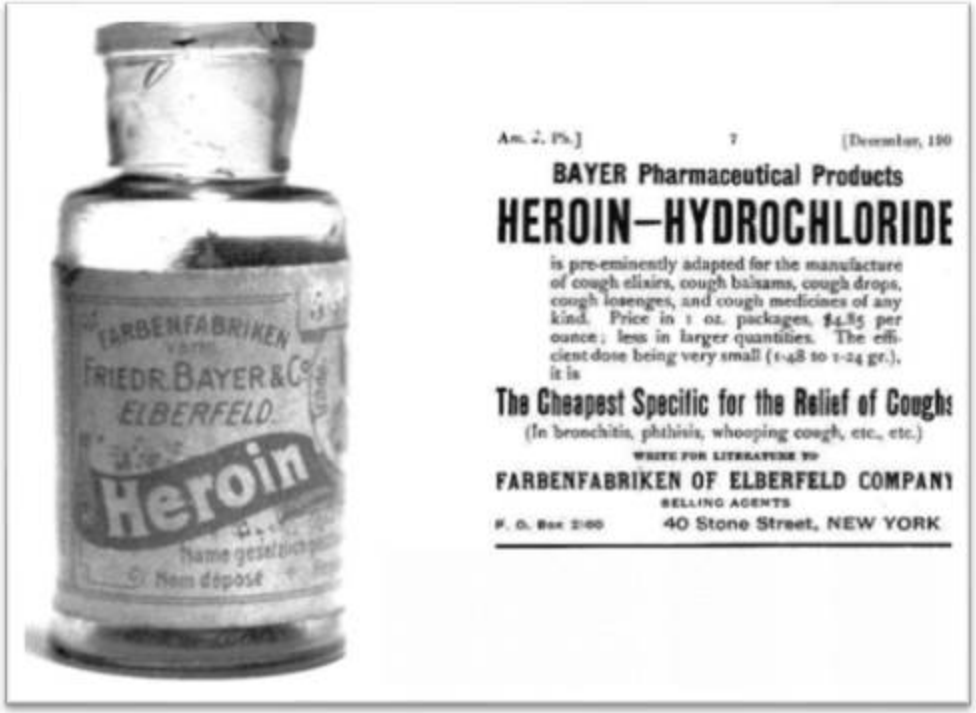


Low Hanging Fruit

Low hanging fruit gets picked first, it is more difficult to pick the fruit from higher branches. Clinical Research is facing this problem currently.

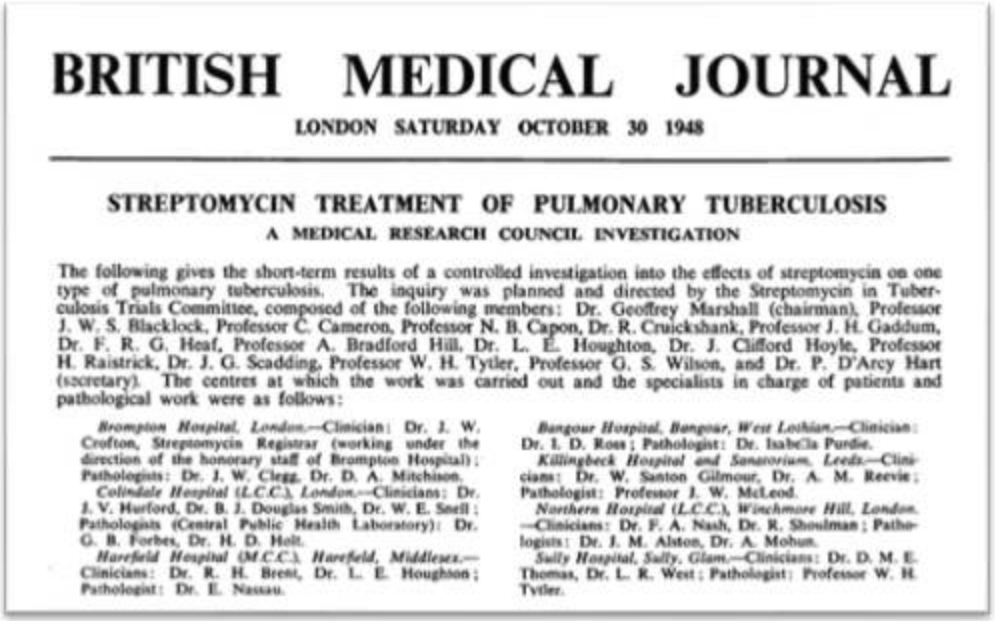
In the past there were very few effective drugs, and one with little efficacy or even high toxicity was acceptable. This no longer holds good.

Heroin



In the 1890s, German pharmaceutical company Bayer marketed heroin as a morphine substitute and cough suppressant. Bayer promoted heroin for use in children suffering from coughs and colds.

Clinical Trials- The Past



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

- 1909 Paul Ehrlich trial of Arsephenmine
- 1935 Gerhardt Domagk trial of sulfonamide
- 1941 Alexander Fleming trial of Penicillin
- 1948 Medical Research Council Trial of Streptomycin

KLINTEC Academy

Poor Ethical Standards

Tuskegee Study 1932-72

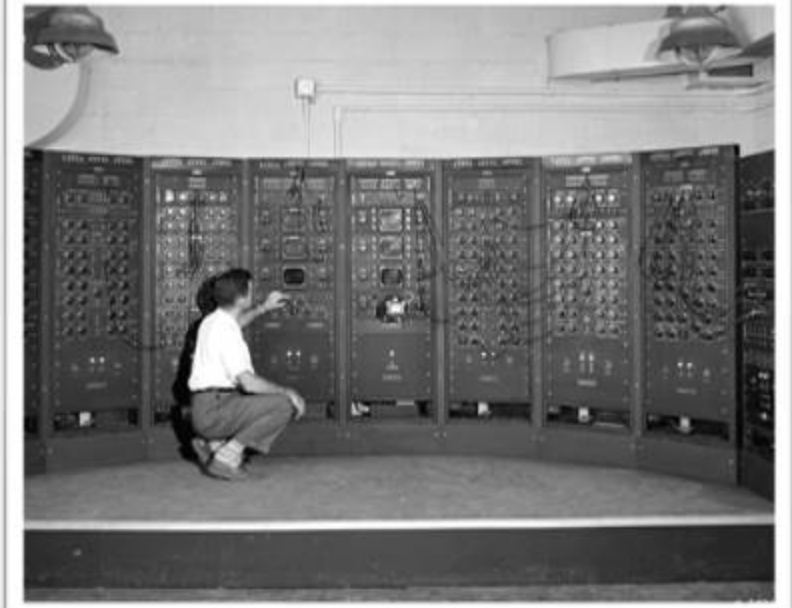
- Questionable rationale
- Absence of informed consents
- Deception
- Absence of Protocol
- Poor quality standards
- No option to opt out
- No rescue medication
- Racial discrimination

Data Submission

FDA Archives

GD Searle filed an application for Enovid to US FDA in 1957 for the treatment of menstrual disorders. The company filed a supplementary Application in 1959 as an oral contraceptive. It is reported that the application was carried in three trucks.

Data Analysis



- Mostly by hand or by computers.
- Data entry done on paper and then fed into computers using special programs:
  - 1957 Fortran
  - 1959 Cobol
  - 1964 Basic
  - 1970 Pascal
  - 1978 SQL

Clinical Trials Today

- Multicentric
- Double blind
- Standard Controlled
- Randomized
- Electronic data capture
- Regulatory approval
- Ethical approval

Multinational Trials

Trials are conducted across many countries for a variety of reasons: Multiracial subject selection reveals effects of drugs and risks to genetically diverse populations. These studies can be completed faster due to a larger patient pool to choose from.

Double Blind Trials

- Minimize potential patients' bias
- Minimize potential observers' bias
- Presently double blinding is an essential factor that drives acceptance of clinical studies.

Standard Control

- Use of placebos is discouraged, even considered unethical, unless there is no standard drug for comparison, or is a scientific necessity.
- New drugs should be compared with the best available standard therapy

Randomization

- Randomization minimizes allocation bias. Bias occurs when a **trial's** results are affected by human choices or other factors not related to the treatment being tested.
- It may be static or dynamic, usually Interactive Voice Response Technology is used for randomization

Electronic Data Capture

- An **electronic data capture** (EDC) system is a computerized system designed for the collection of clinical **data** in **electronic** format for use mainly in human clinical trials.
- The system eliminates the use of paper for recording data, thus reducing errors in transcription

Data Storage

- A single CD holds 300,000 typed pages of data
- A single DVD holds about 2,100,000 typed pages of data
- A 64 GB pen drive holds about 25,00,000 typed pages

Regulatory Approval

- No drug trial can be initiated without the approval of the Central Drugs Control and Standard Organization headed by the Drugs Controller General (India).
- New Drug trials are approved as per Schedule Y of the Drugs and Cosmetics Rules 1945.

Ethical Approval

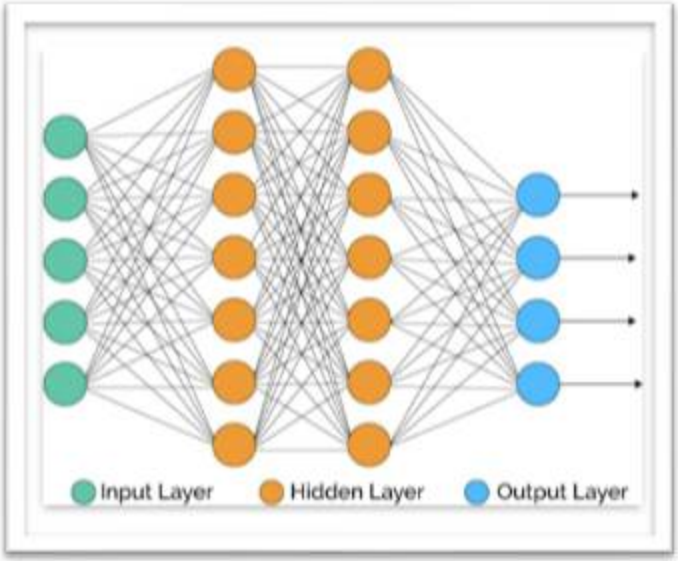
- No trial can be initiated without the written permission of the Ethics Committee. The EC shall ensure the protection of the rights and wellbeing of all study participants, with special emphasis on the protection of vulnerable subjects.

- The Nuremberg Code 1948
- Declaration of Helsinki 1964
- Belmont Report 1978
- ICH GCP Guidelines R2 2016
- ICMR Guidelines 2017

Clinical Trials Future

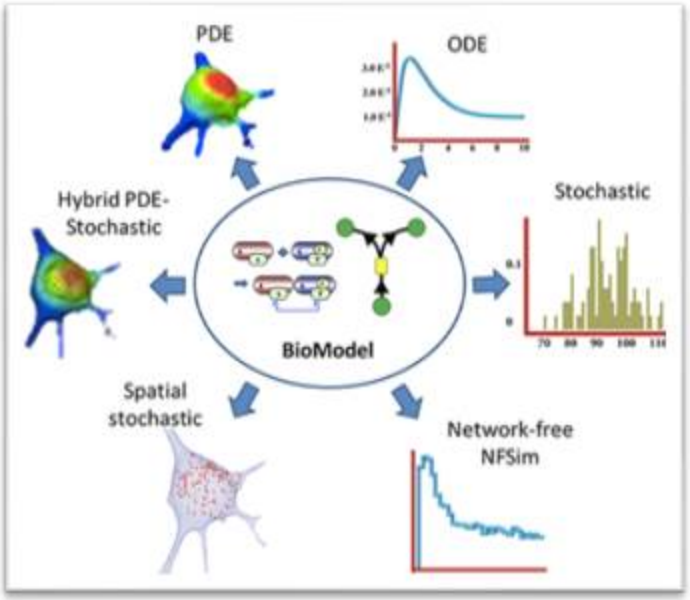
- Predicting the future in Science is hazardous
- Therapy targeted to a patients genomics could become the norm
- Editing genes could lead to eradication of disease
- Transgenic animals, organs grown in labs, virtual tissues may replace early studies
- Clinical trials may yet remain.

CNS



- The homology of the brain with neural networks is being explored.
- Artificial neural networks (ANNs) are computing systems inspired by the biological neural networks that constitute animal brains. Such systems "learn" tasks by considering examples, without task-specific programming.

Virtual Cell

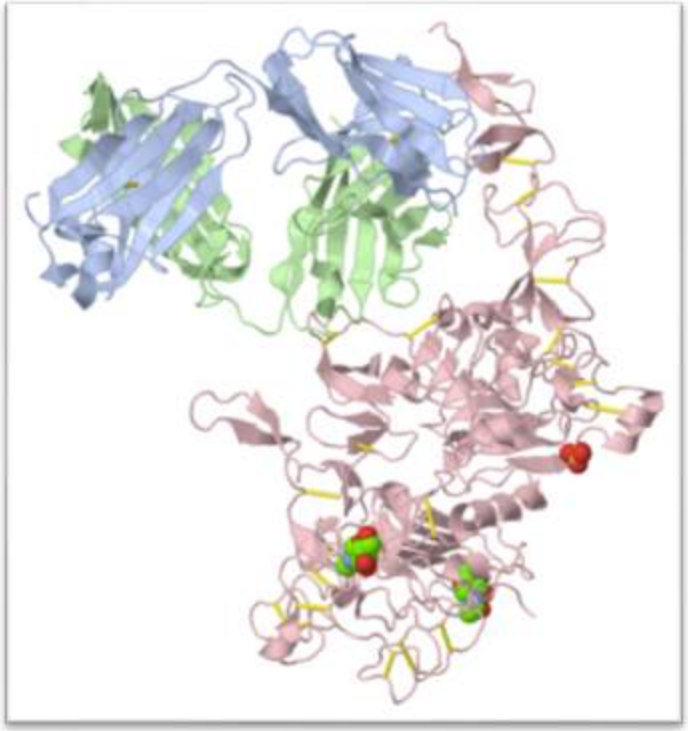


Virtual Cell (VCell) is an open-source software platform for modelling and simulation of living organisms, primarily cells. It has been designed to be a tool for a wide range of scientists, from experimental cell biologists to theoretical biophysicists.

Organs in Culture

Organ printing has already created beating cardiac **cells**, and could soon produce organs that are viable for transplant or as test systems. Muscle, cartilage and bone have been created with ease. The hottest areas in **tissue** growth are the types hardest to make: nerve, liver kidney heart and **pancreatic cells**

Targeted Therapy



Trastuzumab

- Monoclonal antibodies block a specific target on the outside of cancer cells.
- Small-molecule drugs can block the process that helps cancer cells multiply and spread.
- These drugs are available today, but they are as toxic as other anticancer drugs, safer ones are expected

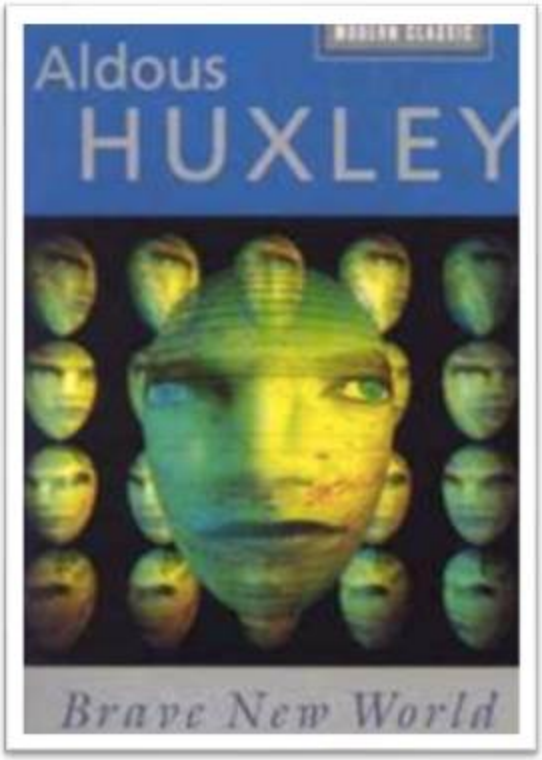
Human Cloning

- Therapeutic cloning involves cloning cells from a human for use in medicine and transplants, and is an active area of research. Two common methods of therapeutic cloning that are being researched are somatic-cell nuclear transfer and, pluripotent stem cell induction. The ethics of cloning is debatable.

Data Storage

- **Cloud storage** is a model of data storage in which the digital data is stored in logical pools, the physical storage spans multiple servers (and often locations), and the physical environment is typically owned and managed by a hosting company.
- This form of storage is already in use, it is expected to become the main model of data storage.

The Future



- Recognizing uniqueness of individual subjects
- Faster and more flexible trials
- Development of more targeted drugs
- Focus on preventive agents not merely curative ones
- Development of novel combinations, such as drug/biologic, drug/diagnostic, drug/device