Medical genetics – a brief history

Huw Dorkins
University of Oxford
Editor in Chief, Journal of Medical Genetics

Society of Apothecaries of London

18 February 2023

Definitions

- Medical genetics
  - the science of human biological variation as it relates to health and disease
- Clinical genetics
  - that part of medical genetics concerned with the health of individual humans and their families

(McKusick, 2007)

Key landmarks - dates

1865	Mendel's work published
1953	Watson-Crick structure of DNA
1956	Tijo and Levan publish the correct number of human chromosomes

Themes before 1956

1. Mendelism
2. Cytogenetics
3. Biochemical genetics
4. Immunogenetics
5. Statistical, Formal & Population genetics

(1) Gregor Mendel (1822 – 1884)

- Augustinian monk then abbot
- Brunn, Moravia (now Czech Republic)
- Coined the terms *dominant* and *recessive*
- Pre-dated the discovery of chromosomes

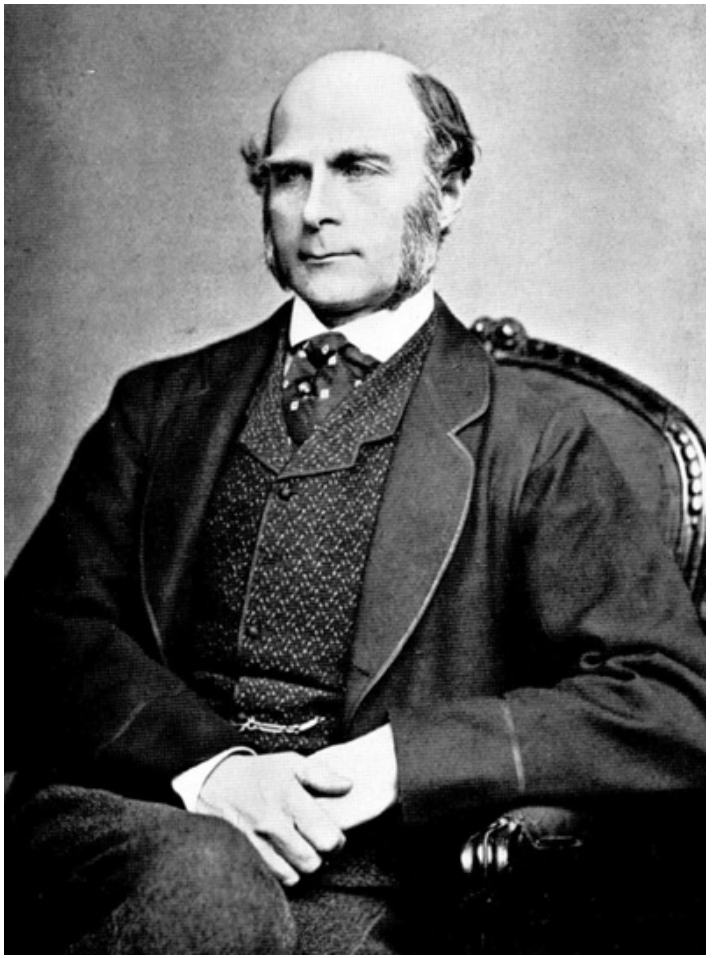
(2) Human Chromosomes

1882	First visualised by Walter Flemming, anatomist, Kiel
1888	Waldeyer introduced the term *chromosome*
1875 - 1900	Mitosis and meiosis described
1880s	Chromosome theory of inheritance Roux – deVries - Weismann
1900	Rediscovery of Mendelism

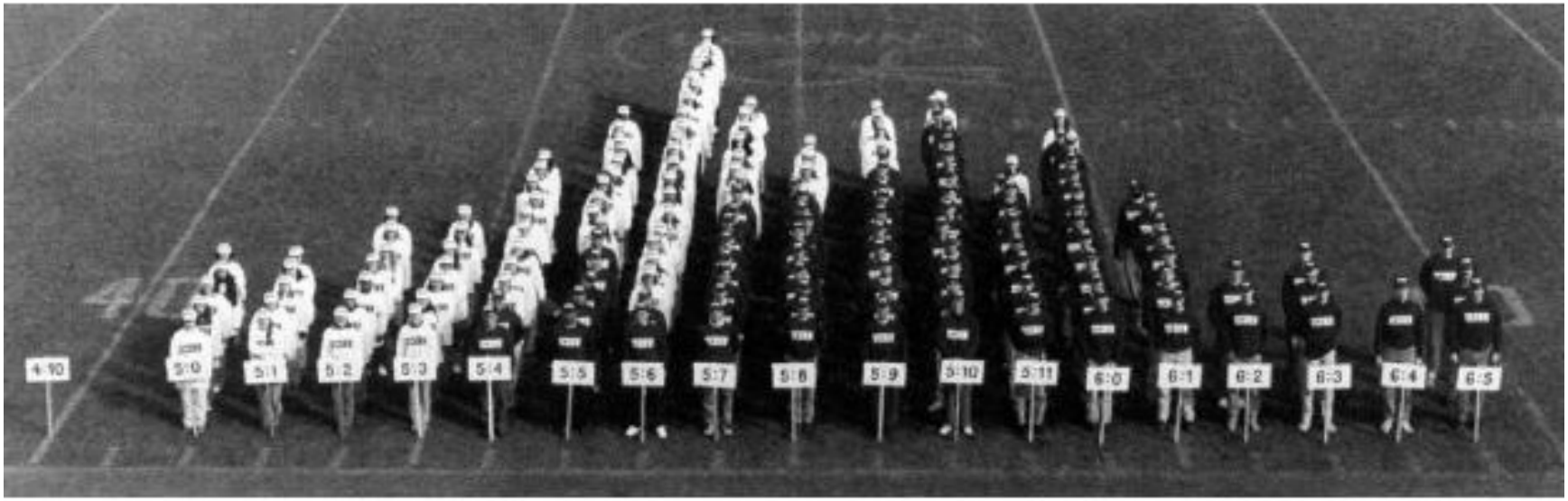
Metaphase Spread

Chromosome theory of Mendelism

1903	Theory advanced by Walter Sutton (1877 – 1916) and Theodor Boveri (1862 – 1915)
	Mendelism met with resistance from another school of thought – the biometricians. These were the disciples of Francis Galton 'Blending inheritance' - quantitative traits.
1918	Mendelian behaviour of multiple genes functioning together can explain quantitative traits R.A. Fisher



Height as a continuous variable



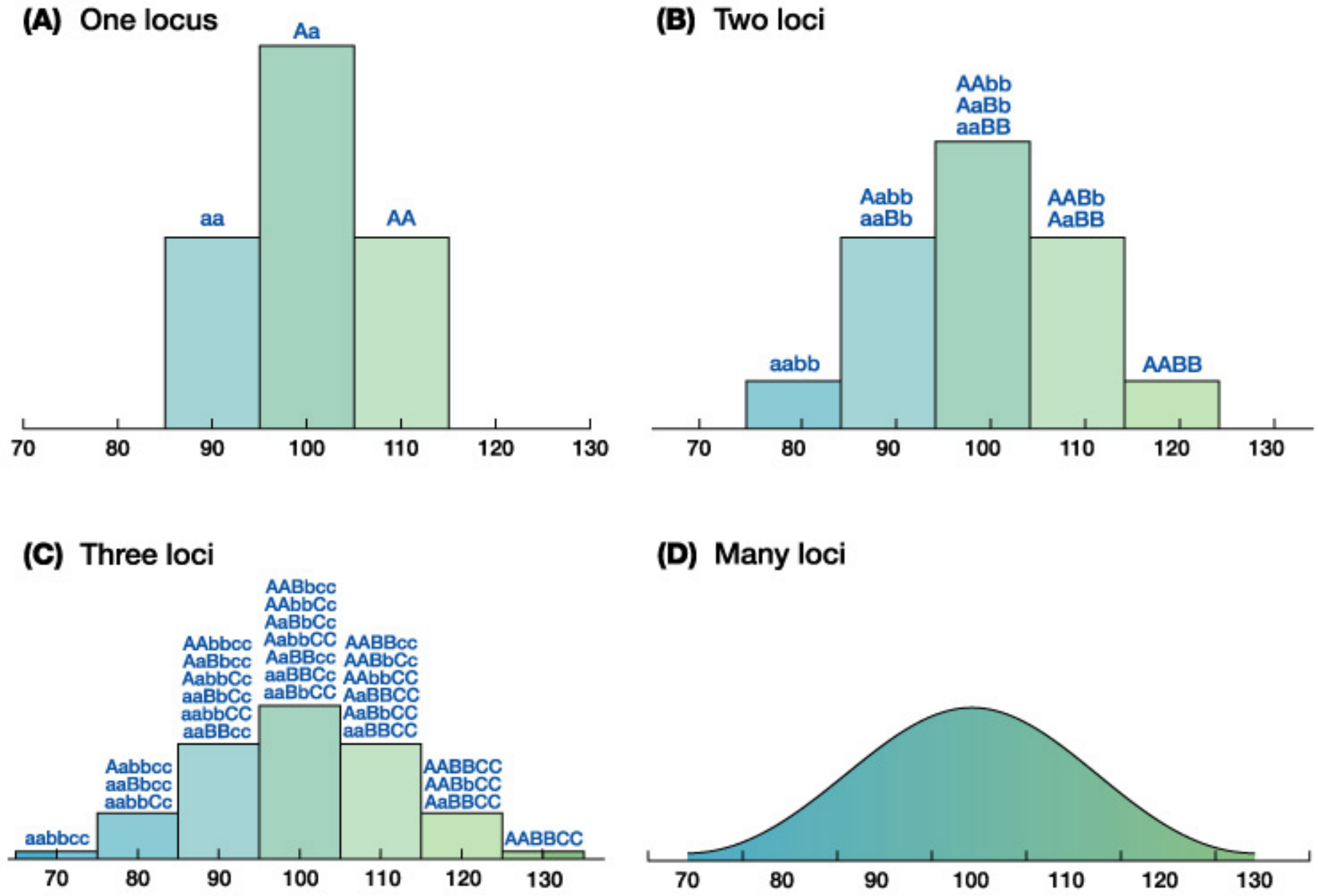


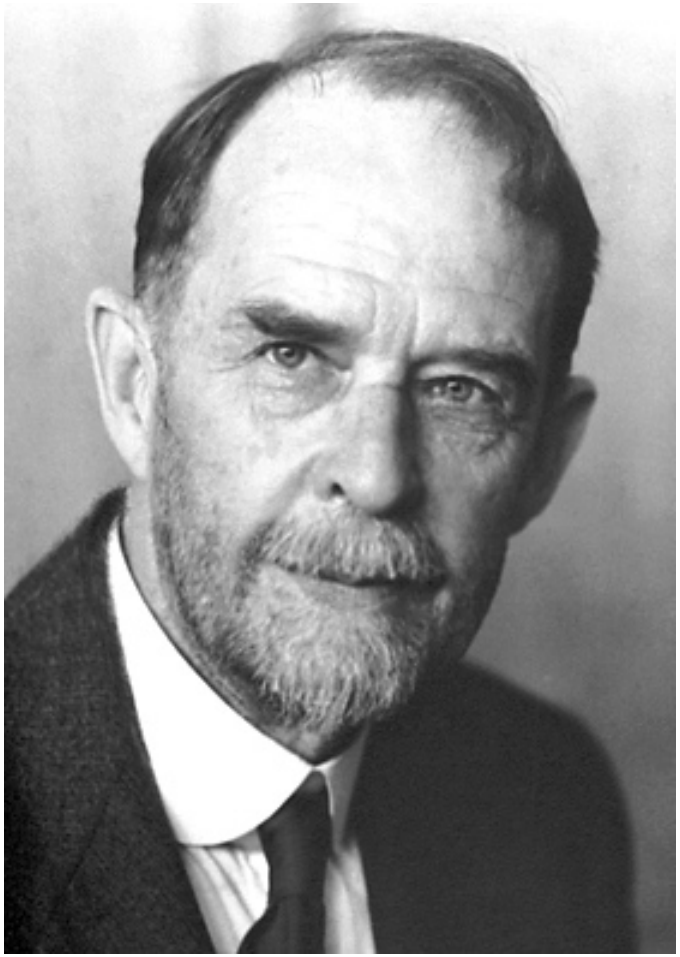
Figure 4-11 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Cytogenetics

Several attempts made to determine the chromosome number in humans	
1923	n = 48 Testicular material from a hanged criminal in Texas
1949	Barr describes Barr body: X-chromatin
1950s	Culture of cells in hypotonic medium improves visibility of chromosomes
1956	n = 46 Tijo & Levan; Ford & Hamerton

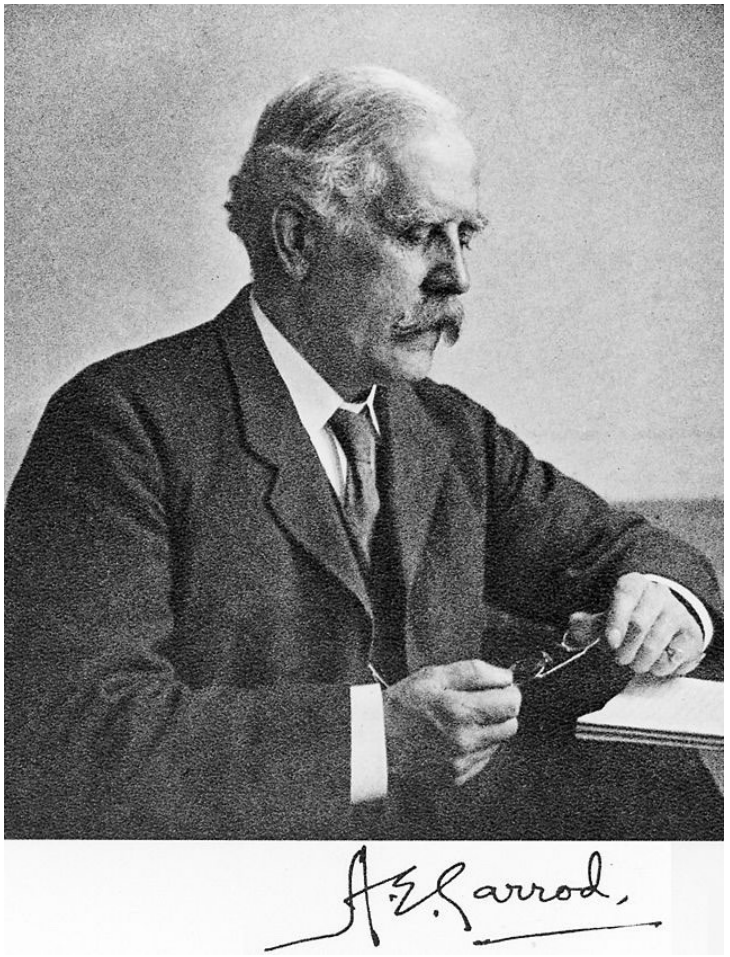
Genetic linkage

- Genes occupy positions on chromosomes
- Crossing over at meiosis shuffles alleles
- This can be applied to gene mapping
- Thomas Hunt Morgan 1866 - 1945



(3) Biochemical genetics

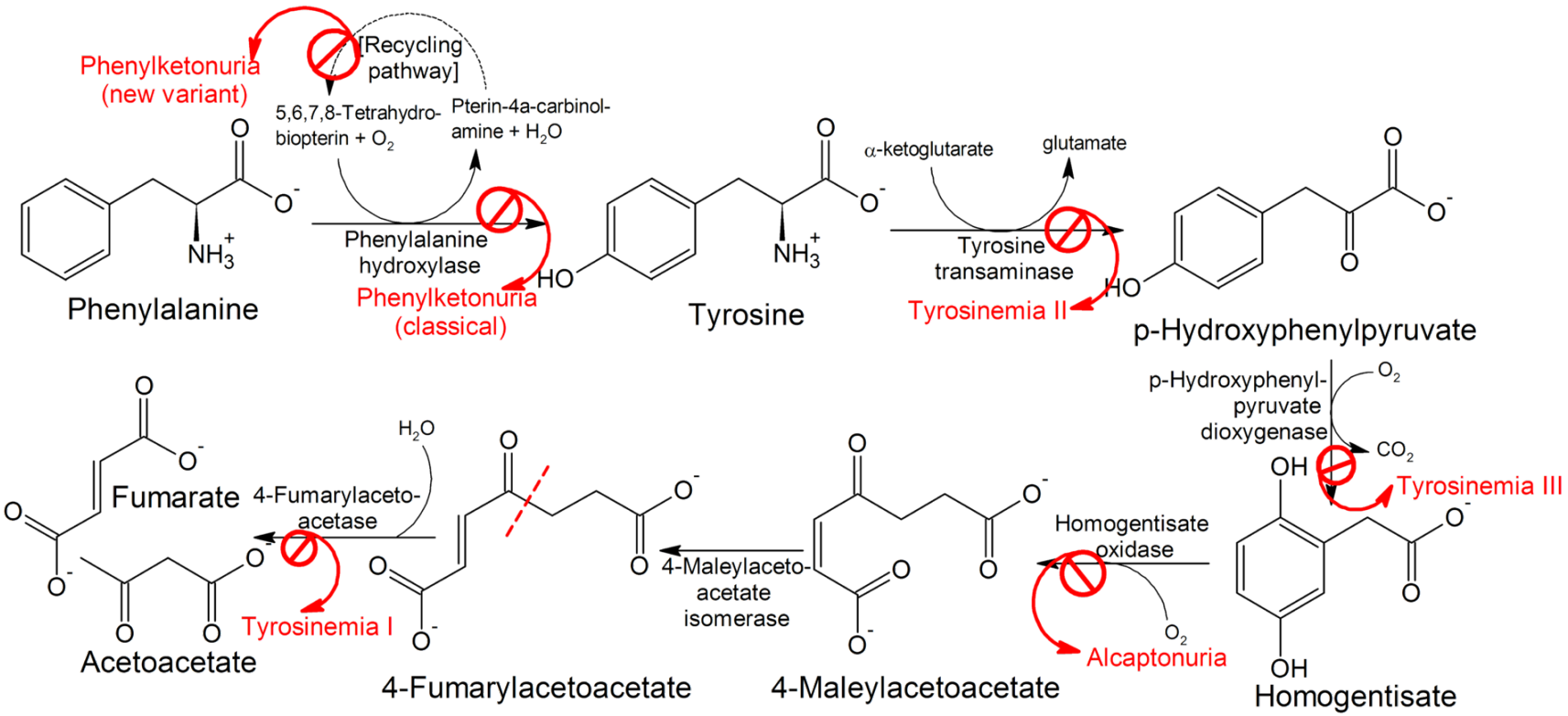
- Archibald Garrod (1858 – 1936)
- Inborn errors of metabolism
  - Alkaptonuria
  - Pentosuria
  - Albinism
  - Cystinuria



Alkaptonuria

- Seen in both male and female children of normal parents
- Inferred that inheritance pattern was (autosomal) recessive

Metabolic block in Alcaptonuria

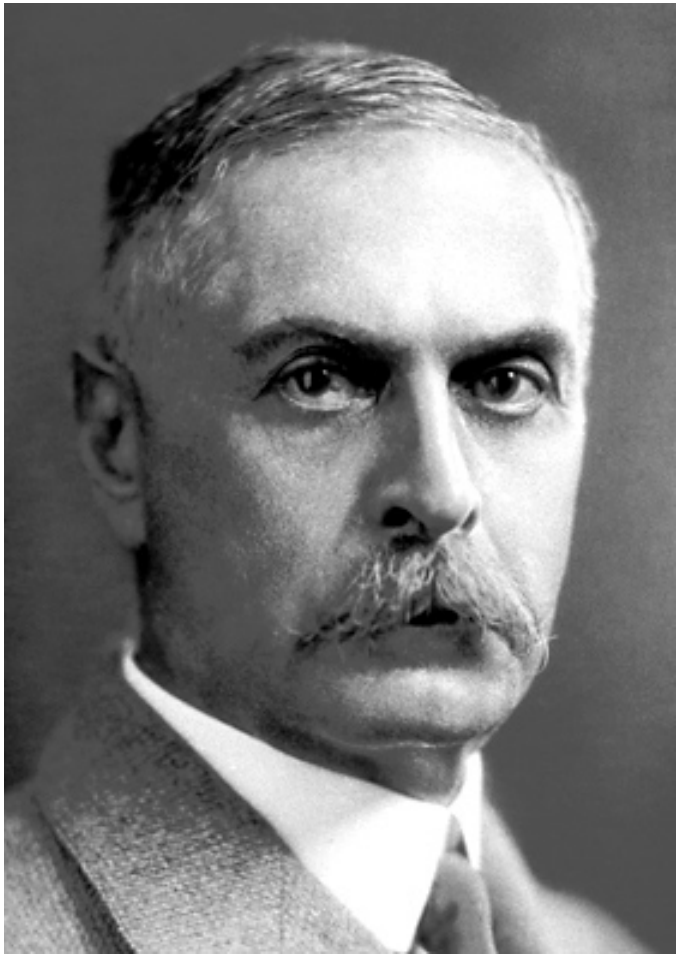


Other inherited biochemical disorders

1952	Glycogen storage disease I
1953	Phenylketonuria (enzyme deficiency demonstrated; disease described in 1934)
1956/7	Description of single amino acid change in sickle globin

(4) Immunogenetics

1901	Karl Landsteiner demonstrated ABO blood group system
1920	Multiple allele, one locus explanation for ABO advanced by Bernstein
1927	MN group (Landsteiner and Levine)
1939	Rhesus



(5) Statistical & Population Genetics

- Hardy-Weinberg principle 1908
  - G.H. Hardy Cambridge
  - W. Weinberg Stuttgart
- Population genetics
  - R.A. Fisher
  - J.B.S. Haldane (linkage of colour blindness and haemophilia)
  - Sewall Wright (random genetic drift)

1956 onwards

Convergence of the above strands and the emergence of specific methodologies

- Chromosomolgy
- Somatic cell genetics
- Molecular genetics

Later, these were joined with

- Gene transfer/knockout technologies
- Bioinformatics
- Array technologies

Chromosomology

- Lejeune 1959: extra small chromosome in mongoloid idiocy
- Advances in banding techniques permitted the identification of individual human chromosomes
- Convergence of molecular genetic methods and cytogenetics
- Fluorescent in situ hybridisation (FISH)
- Chromosome deletions and rearrangements in cancer

Somatic cell genetics

- Fusion of cells from different species and the subsequent loss of chromosomes permitted mapping of genes
- Mixture of cells from different patients permitted determination of complementation groups (e.g. in XP)
- Detailed study of biochemical defects in inborn errors of metabolism
- Cancer

HeLa cells

- Henrietta Lacks
- Adenosquamous Ca cervix age 31 in 1951
- Henrietta's G6PD heterozygosity (cf. deficiency in HeLa cell line) suggested monoclonal origin of the latter

Cell culture

Fibroblasts

- Wide biochemical repertoire
- Invaluable in defining biochemical defects in
- Galactosaemia
- Lesch-Nyhan syndrome (HPRT)
- Familial hypercholesterolaemia (FH)

Amniocytes

- Biochemical repertoire similar to that of other cells
- Cells of fetal origin obtained by amniocentesis
- Useful in prenatal biochemical diagnosis of inherited metabolic disorders

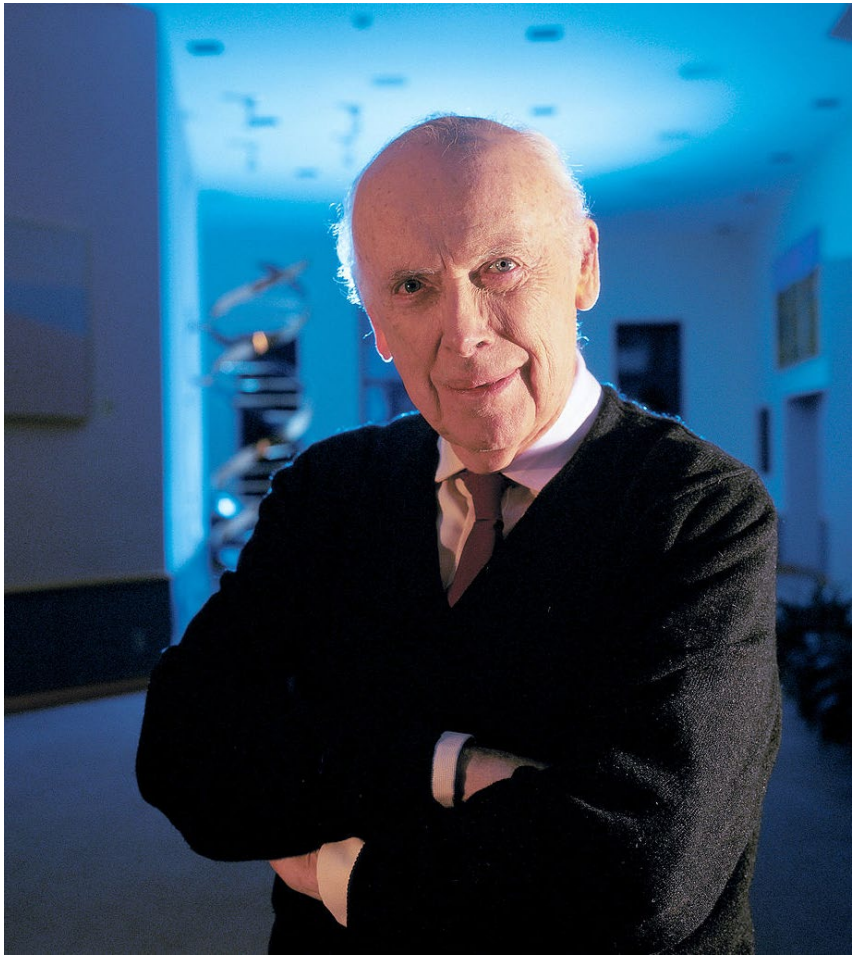
Cell Fusion

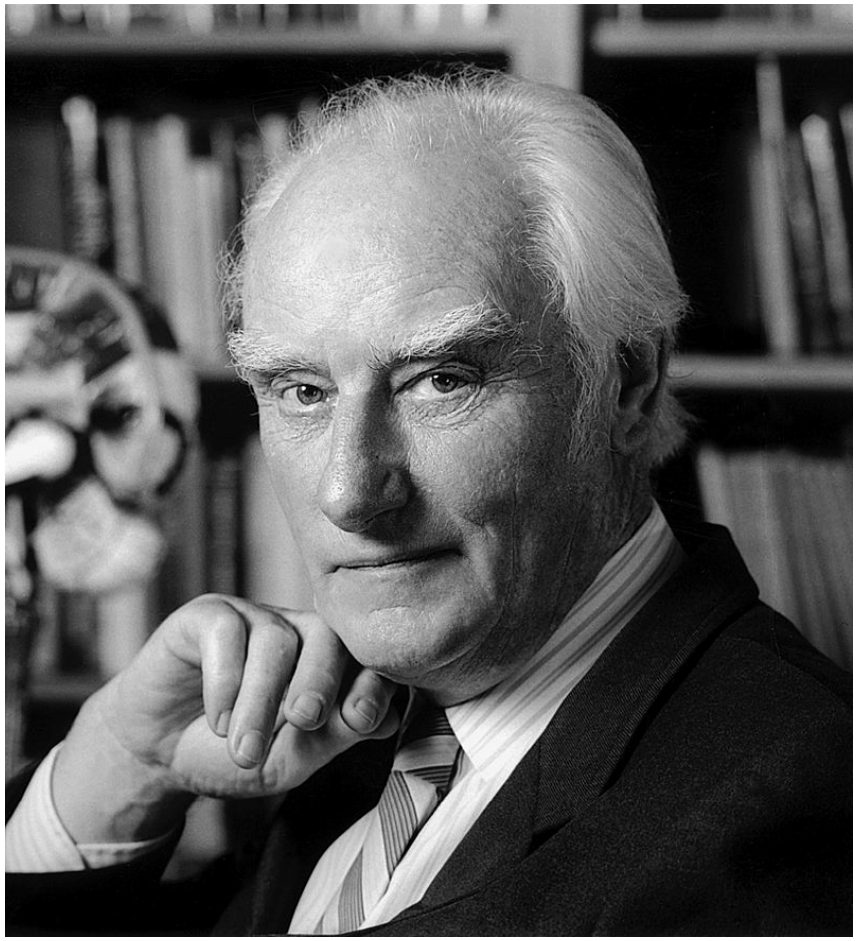
- Human and mouse cells can fuse if treated appropriately:
- Sendai virus 1958
- Polyethylene glycol 1975
- Applied to localisation of genes to individual chromosomes

DNA

1867	Miescher extracts DNA from pus in bandages
1944	‘The transforming factor’ O.T. Avery, C. Macleod and M. McCarty
1953	James Watson and Francis Crick, Maurice Wilkins and Rosalind Franklin – Double helical structure of DNA
1961 - 6	Elucidation of the genetic code
1970	Identification of restriction enzymes (Hamilton Smith et al)
1975	DNA blotting (Ed Southern)
1973	Bacterial plasmids constructed *in vitro* – the start of molecular cloning (Cohen)
1986	Polymerase chain reaction (Mullis et al)

James Watson & Francis Crick



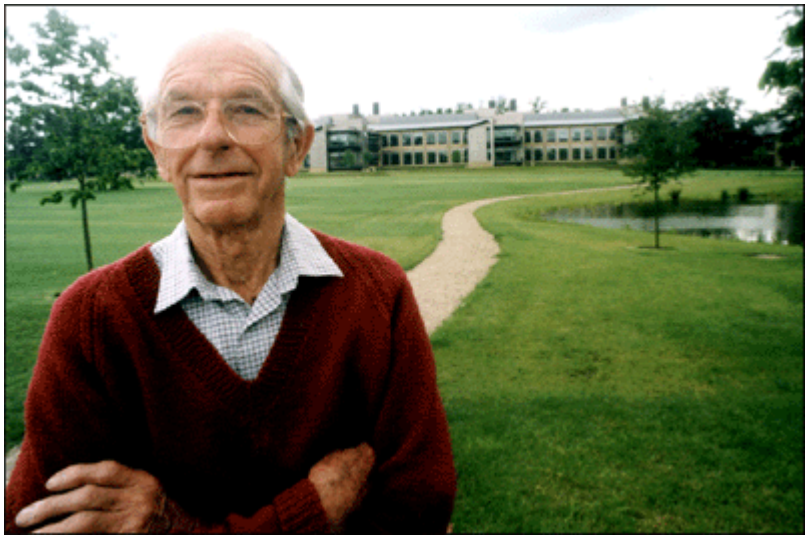


Gene cloning technology

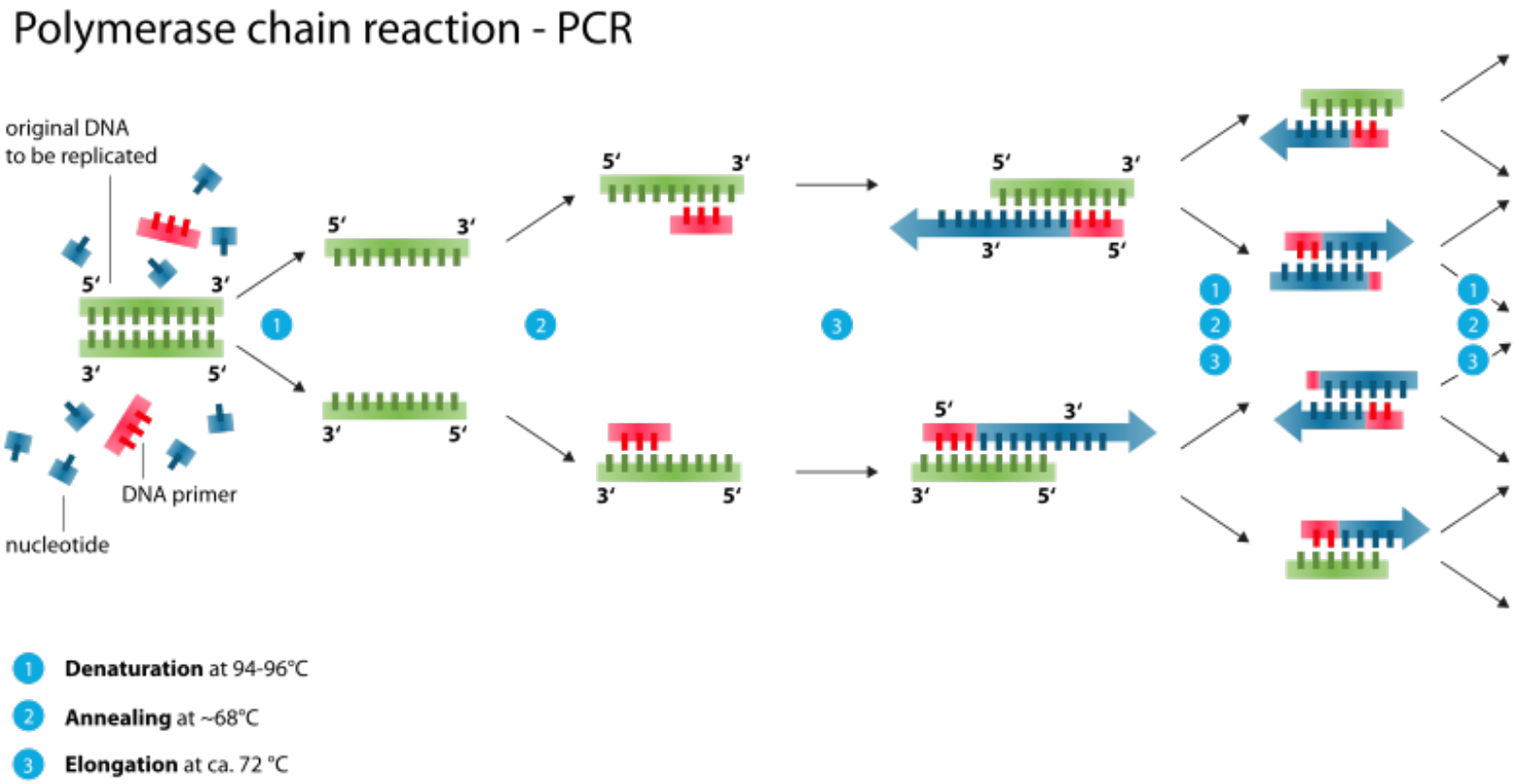
1977	First human gene cloned – chorionic somatomammotrophin - Shine et al
	α – globin and β – globin - Maniatis
1970	Reverse transcriptase discovered (converts RNA in to cDNA) Temin, Baltimore
1977	Discovery of introns - ‘junk’ DNA Roberts
1977	DNA sequencing invented – Sanger, Gilbert
1987	High capacity cloning vectors (Yeast artificial chromosomes) invented - Olson

DNA sequencing

- Chain termination method aka Sanger sequencing, after its inventor
- Fred Sanger (1918 – 2013)
- Nobel Prize in Chemistry 1958 and 1980
- Based on action of DNA polymerase
  - Adds nucleotides to complementary strand
- Requires template DNA and primer

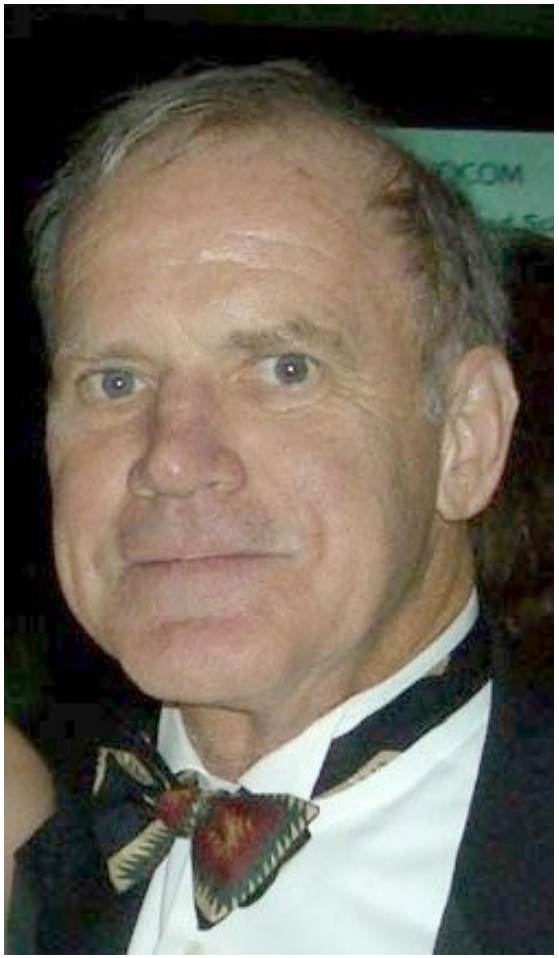


PCR


Polymerase chain reaction - PCR
original DNA
to be replicated
5′
3′
3′
5′
DNA primer
nucleotide
1
2
3
1 Denaturation at 94-96°C
2 Annealing at ~68°C
3 Elongation at ca. 72 °C

PCR

- Invented by Kary Mullis (1944 – 2019) in 1983
- Nobel Prize in Chemistry 1993
- Mullis claimed to have had the idea for PCR while under the influence of LSD



Mapping genes – colour blindness

1790s	John Dalton describes his own colour blindness
	Horner describes pedigree patterns suggestive of X-linked (sex-linked) inheritance of CB
1896	E.B. Wilson suggests CB is on the X-chromosome
1937, 1947	Genetic linkage between CB and haemophilia Haldane, Bell, revised Smith

Why map genes?

- Important diseases were recognised to be inherited, but there was no understanding of their biochemical nature
  - Duchenne muscular dystrophy
  - Cystic fibrosis
  - Huntington's disease
- 'Reverse genetics' – identify the gene underlying a Mendelian disorder by finding it on a genetic map

Gene mapping

- Relies on the phenomenon of ‘genetic linkage’
- Genetic markers close to a disease gene will be co-inherited with the latter
- Meiotic recombination will separate marker alleles from disease alleles
- The further away the marker is from the disease gene the more often crossing over at meiosis will separate the two

Meiotic crossing over

- Morgan's illustration of crossing over, from his 1916 *A Critique of the Theory of Evolution*

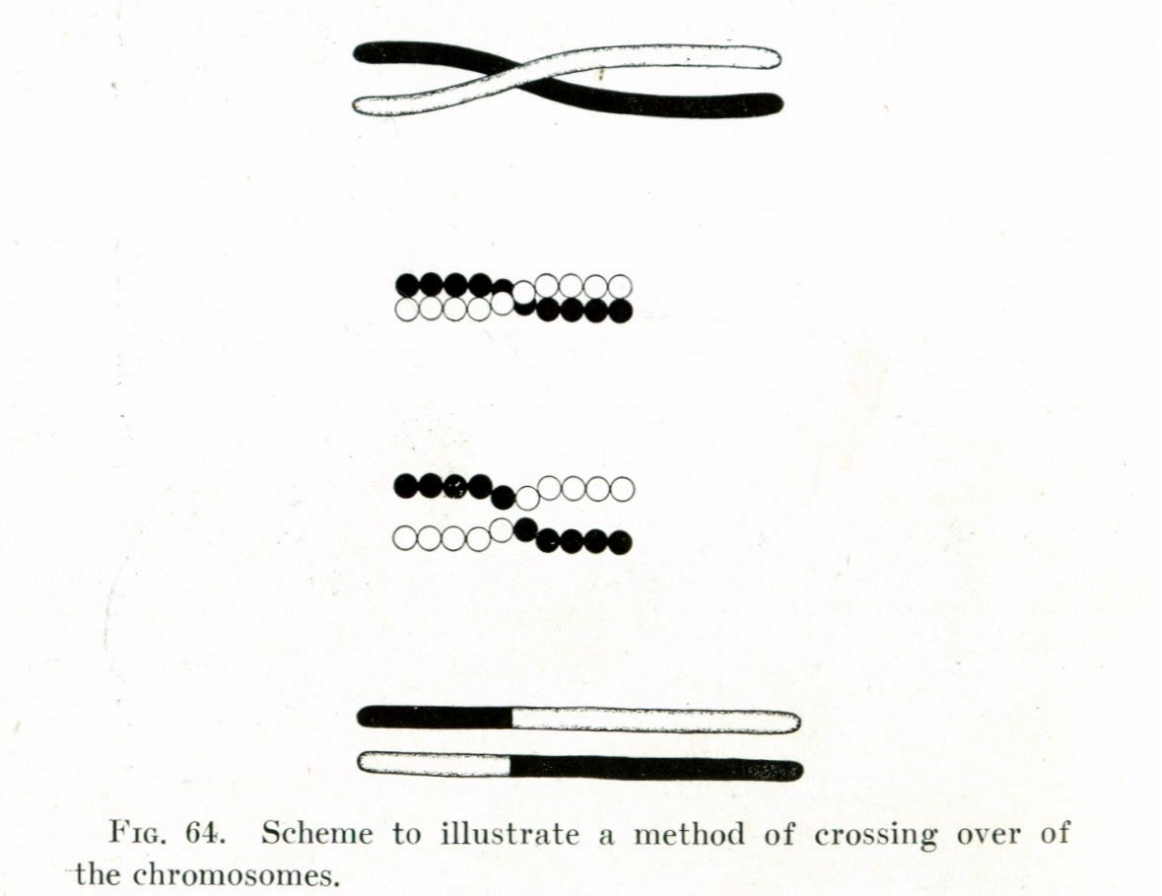
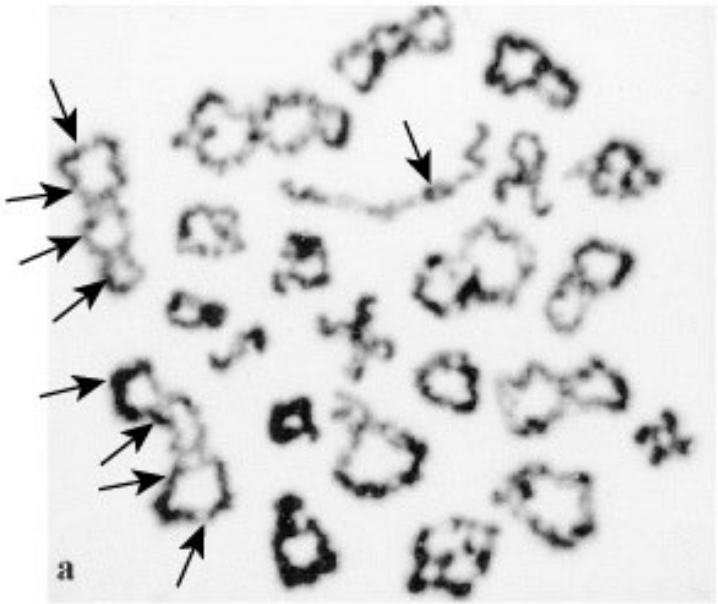


FIG. 64. Scheme to illustrate a method of crossing over of the chromosomes.



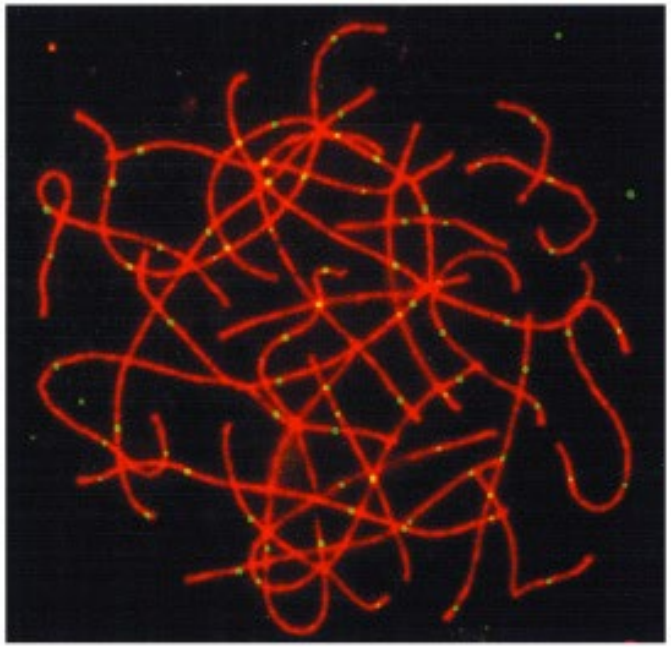


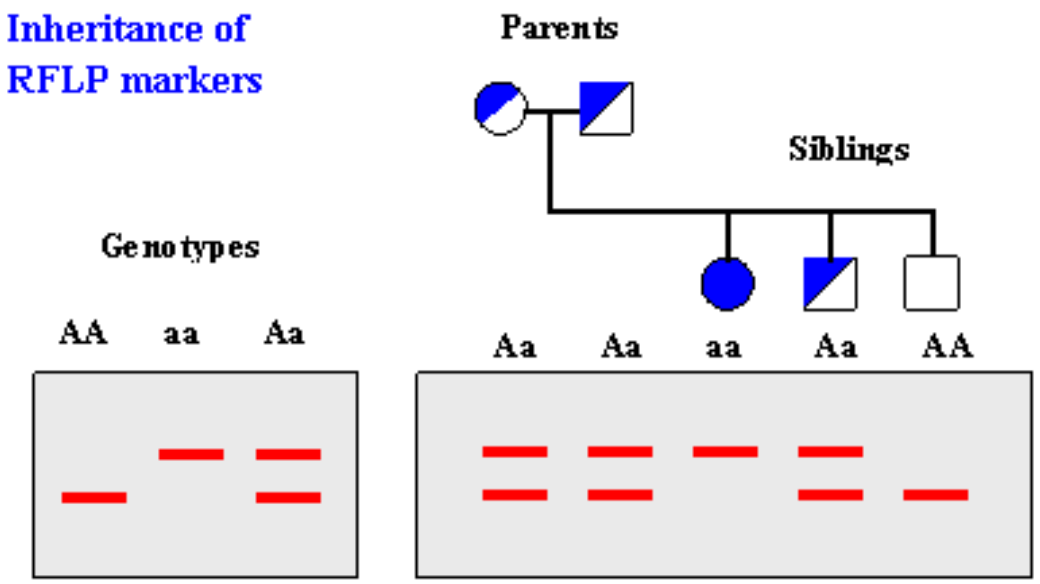
Figure 13-3 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Gene mapping – the problem

- Not enough markers
- Protein polymorphic markers (enzymes, blood groups) are rare
- Some successes, but very limited
  - Lutheran blood group and Secretor factor (Mohr 1954) First autosomal linkage
  - Elliptocytosis and Rh blood group (Morton 1956)
  - ABO and Nail patella syndrome (Renwick)

Genetic markers

- Restriction fragment length polymorphisms (RFLPs) - Botstein, White et al. (1980).
- Variable number tandem repeats (VNTRs) – Jeffreys (1985)
- CA repeats – Weber and Litt



Gene mapping successes

Localising disease genes	
1983	Huntington's Disease localised to short arm of chromosome 4 through linkage to DNA marker G8 Gusella et al
	Localisation of Duchenne muscular dystrophy to short arm of X-chromosome
	Cystic fibrosis localised to Chromosome 7
Characterising disease genes	
1985 - 6	Duchenne muscular dystrophy (Kunkel et al)
1993	Huntington's disease (IT15)
1989	Cystic fibrosis

Human Genome Project

Aim	Sequencing of the entire human genome and mapping of all human genes
1985 - 6	Walter Gilbert and colleagues (molecular biologists not medical geneticists) suggest a sequencing project
1985 - 1990	Period of objections to HGP on two grounds: •'mindless sequencing' – no biological understanding •projected cost $3bn
1990	US Federal funding for HGP
	US NIH project led by James Watson
	Major genome projects in UK, Japan and France
1987	HGP planned to complete 2005
	Technical advances accelerated progress: •PCR •Shotgun sequencing

HGP success

- ‘Draft’ human genome published February 2001, *Nature* and *Science*
- Follow up on ‘completed’ sequence in 2003, 50 years after Watson-Crick DNA structural model

Gene mapping applied

- Gene ‘tracking’
- Permitted prenatal diagnosis and carrier detection without knowledge of underlying molecular pathology
- Relies upon linkage between genetic markers and the genetic locus for the relevant disease

Genetics in the clinic

Pre-Mendelian ‘pedigree genetics’	
1750s	Early recognition of inheritance patterns consistent with autosomal dominant and autosomal recessive inheritance
1790s	X-linked recessive inheritance of haemophilia noted in a newspaper article
1803, 1813	Medical reports of haemophilia inheritance pattern
1876	X-linked recessive inheritance of colour blindness
1857	Consanguinity related to increased frequency of genetic disorders

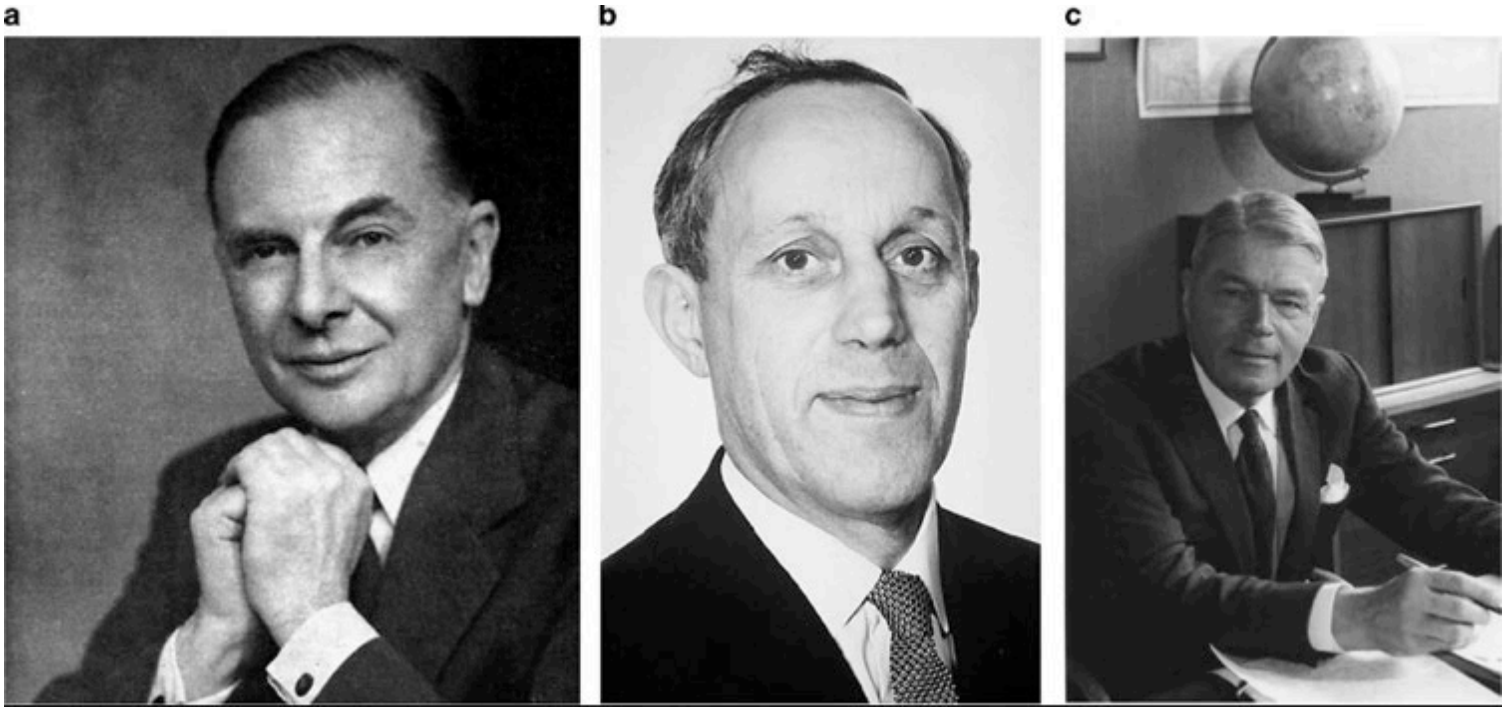
Genetics in the clinic II

- What is wrong? (Δ)
- What will happen? (prognosis)
- What can be done? (Rx)
- Why did it happen? (aetiology and pathogenesis)
- Will it happen again?(recurrence risk)

Genetics as a clinical specialty

United States	
1940 - 1955	U.S. Heredity clinics *Outside* conventional medical organisations Often university based; some run by clinicians, others by basic scientists
1955 – 1975	Three major North American centres Montreal (Fraser) Baltimore (McKusick) Seattle (Motulsky)
United Kingdom	
1946	Fraser Roberts started first genetic counselling clinic at GOSH
1960	First comprehensive medical genetics department established at Guy's Hospital (Polani)
1963	Nuffield Institute of Medical Genetics, Liverpool (Cyril Clarke)

Pioneers of UK medical genetics

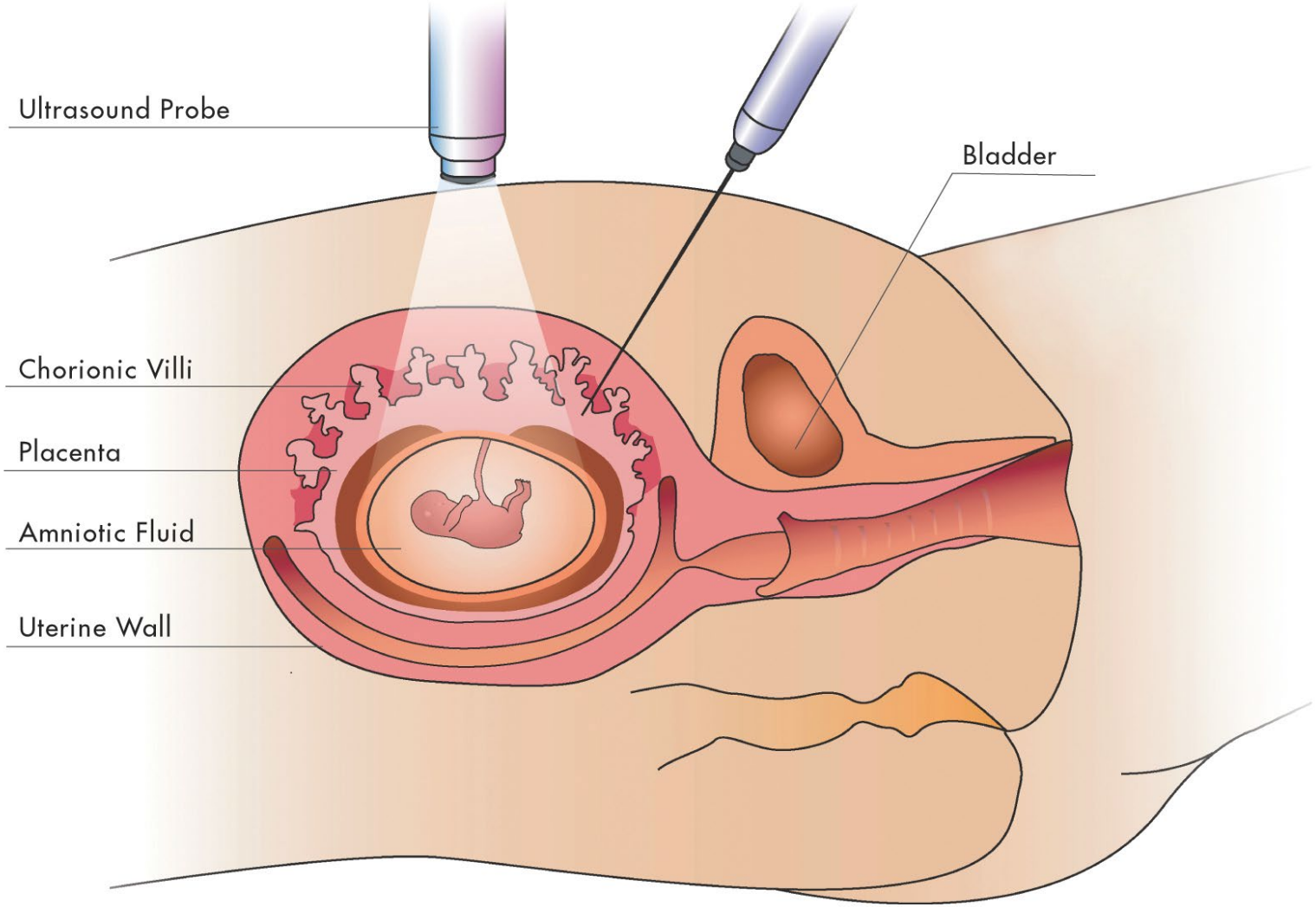


(a) John Fraser Roberts, London, (1899–1987)
(b) Cedric Carter, London (1917–1984)
(c) Cyril Clarke, Liverpool (1907–2000)

Developments in obstetrics

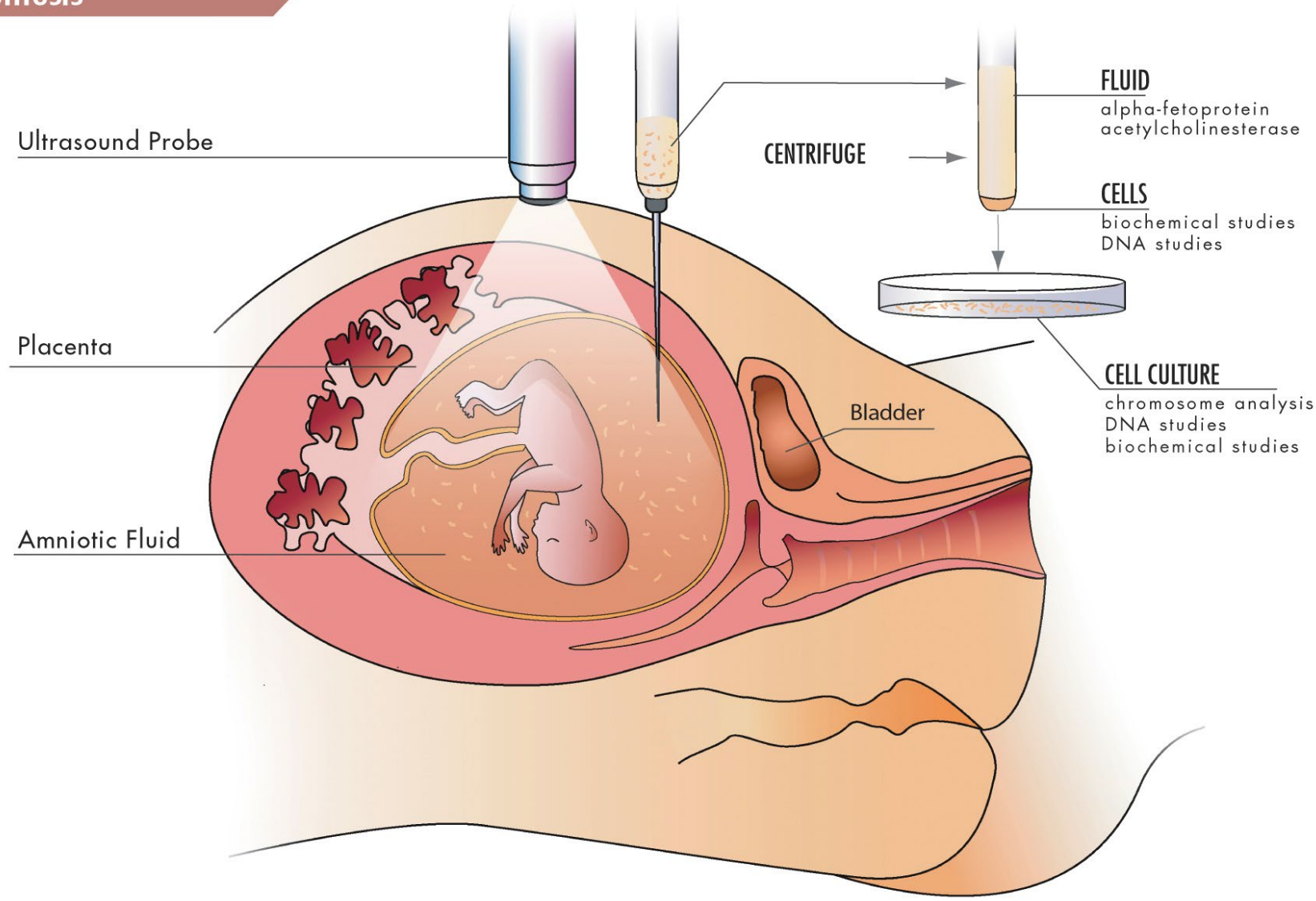
1956	Amniocentesis for fetal sexing (Fuchs and Riis)
1966	Amniocentesis for amniotic fluid cell culture and chromosome analysis (Steele and Breg)
1970	Use of ultrasound in prenatal diagnosis
1978	*In vitro* fertilisation (IVF) (Steptoe and Edwards)
1983	Chorionic villus sampling (Simoni et al)
1992	Preimplantation genetic diagnosis using IVF (Handyside et al)
1997 onwards	Non invasive prenatal diagnosis based on free fetal DNA

Transabdominal Chorionic Villus Sampling (CVS)



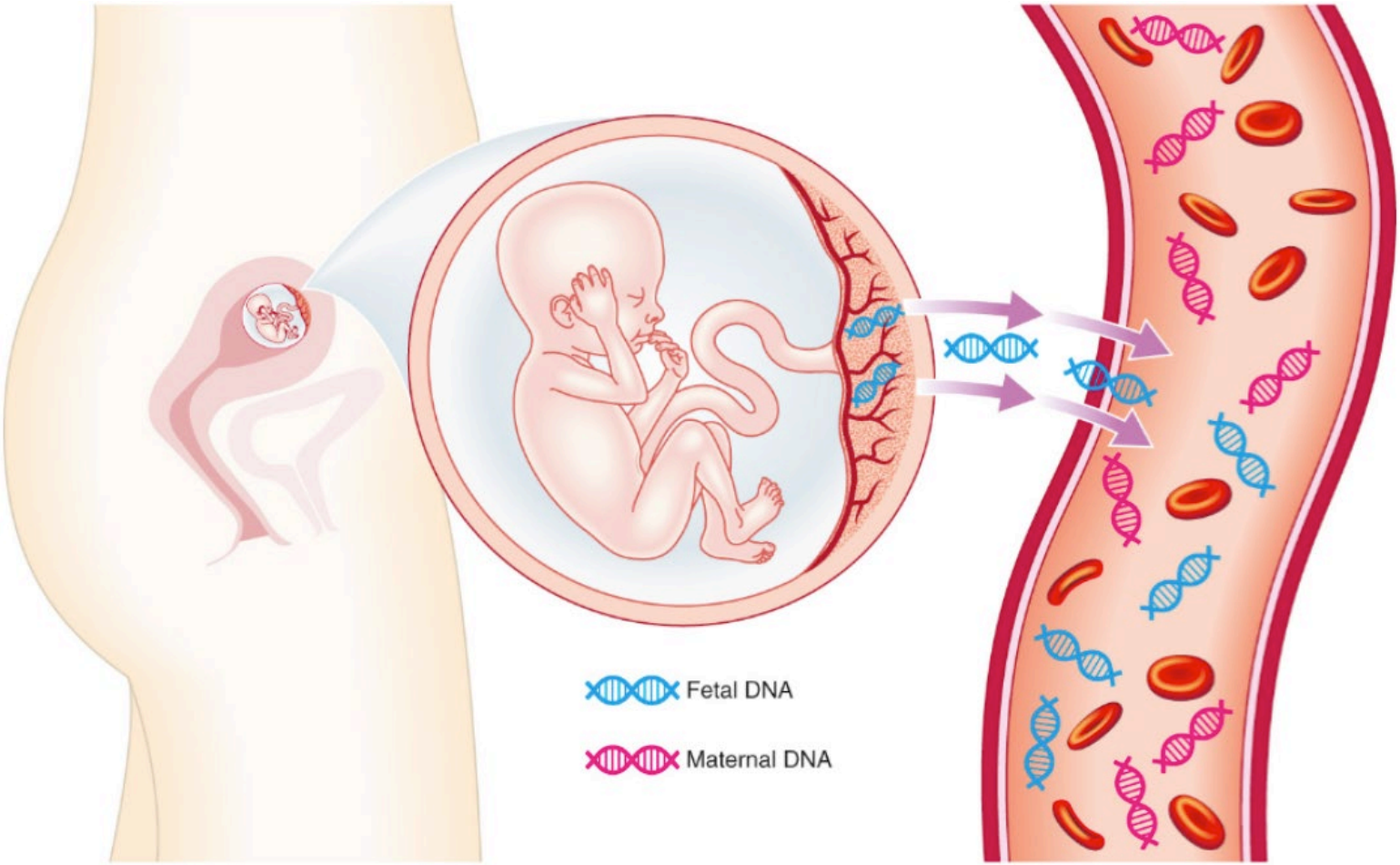
Greenwood Genetic Center

Amniocentesis



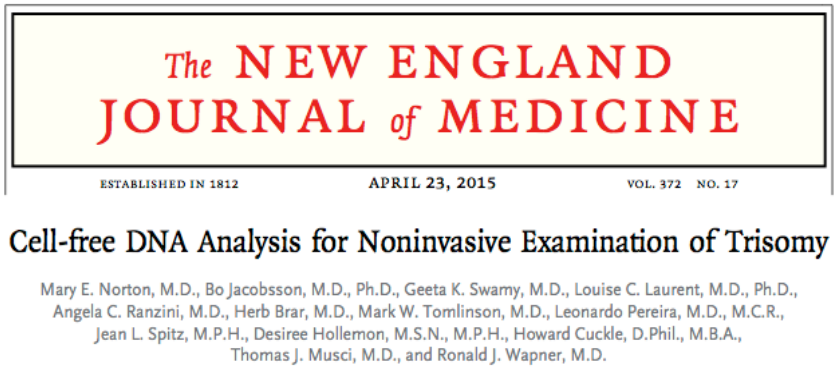
Greenwood Genetic Center

Free fetal DNA (NIPD/NIPT)



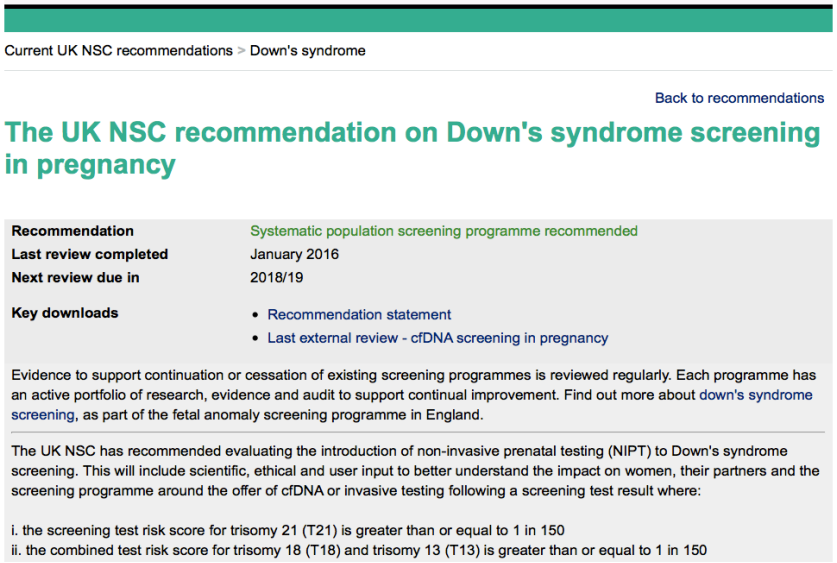
Free fetal DNA (NIPD/NIPT)

- Relatively recently in service
- Appropriate for sexing in XL disorders
- Now available for trisomies, some point mutations – likely to replace conventional approaches
- NEJM (2015) **372** (17)



Non invasive prenatal testing

- NIPT now available in the NHS
- Initially for the autosomal trisomies
  - Down's
  - Edwards
  - Patau



Current UK NSC recommendations > Down's syndrome

Back to recommendations

The UK NSC recommendation on Down's syndrome screening in pregnancy

Recommendation	Systematic population screening programme recommended
Last review completed	January 2016
Next review due in	2018/19
Key downloads	• Recommendation statement • Last external review - cfDNA screening in pregnancy

Evidence to support continuation or cessation of existing screening programmes is reviewed regularly. Each programme has an active portfolio of research, evidence and audit to support continual improvement. Find out more about down's syndrome screening, as part of the fetal anomaly screening programme in England.

The UK NSC has recommended evaluating the introduction of non-invasive prenatal testing (NIPT) to Down's syndrome screening. This will include scientific, ethical and user input to better understand the impact on women, their partners and the screening programme around the offer of cfDNA or invasive testing following a screening test result where:

i. the screening test risk score for trisomy 21 (T21) is greater than or equal to 1 in 150
ii. the combined test risk score for trisomy 18 (T18) and trisomy 13 (T13) is greater than or equal to 1 in 150

Medical genetics – some tensions

- Hope *vs* hype
- Medical benefit *vs* misapplication (eugenics)
- Reductionist *vs* holistic

The Eugenics movement

- Eugenics – attempting to improve the human race by encouraging some to breed and discouraging others
- Predates medical genetics
  - 18th century law in Sweden prohibiting the marriage of epileptics
- Galton and Pearson championed eugenic ideas – Eugenics laboratory at UCL, Eugenics Society and a journal.

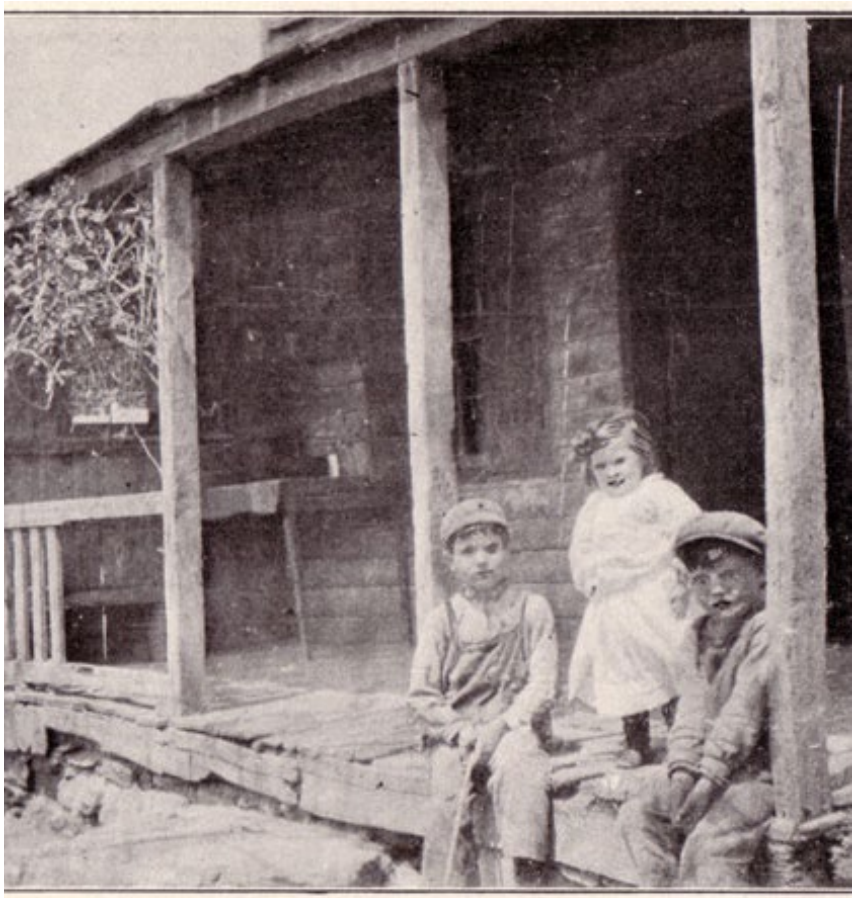
Eugenics in the USA

- Rapid spread of eugenic ideas in first decade of 20th century
- William Goddard (1912) studied the ‘Kallikak family’.
- Two branches traced back to one man – Martin Kallikak soldier in the American War of Independence
- Affair with a ‘feeble minded girl’ met in a tavern who became pregnant
- Returned home, married a girl of good family

Martin's descendants

- Goddard traced the descendants on both sides of the family
- 480 descendants of the illegitimate branch of the family – many were 'criminals, drunkards or feeble-minded'
- On the respectable side of the family – by and large 'normal, good and worthy citizens'
- Inescapable evidence for the hereditary transmission of moral traits

Kallikak family

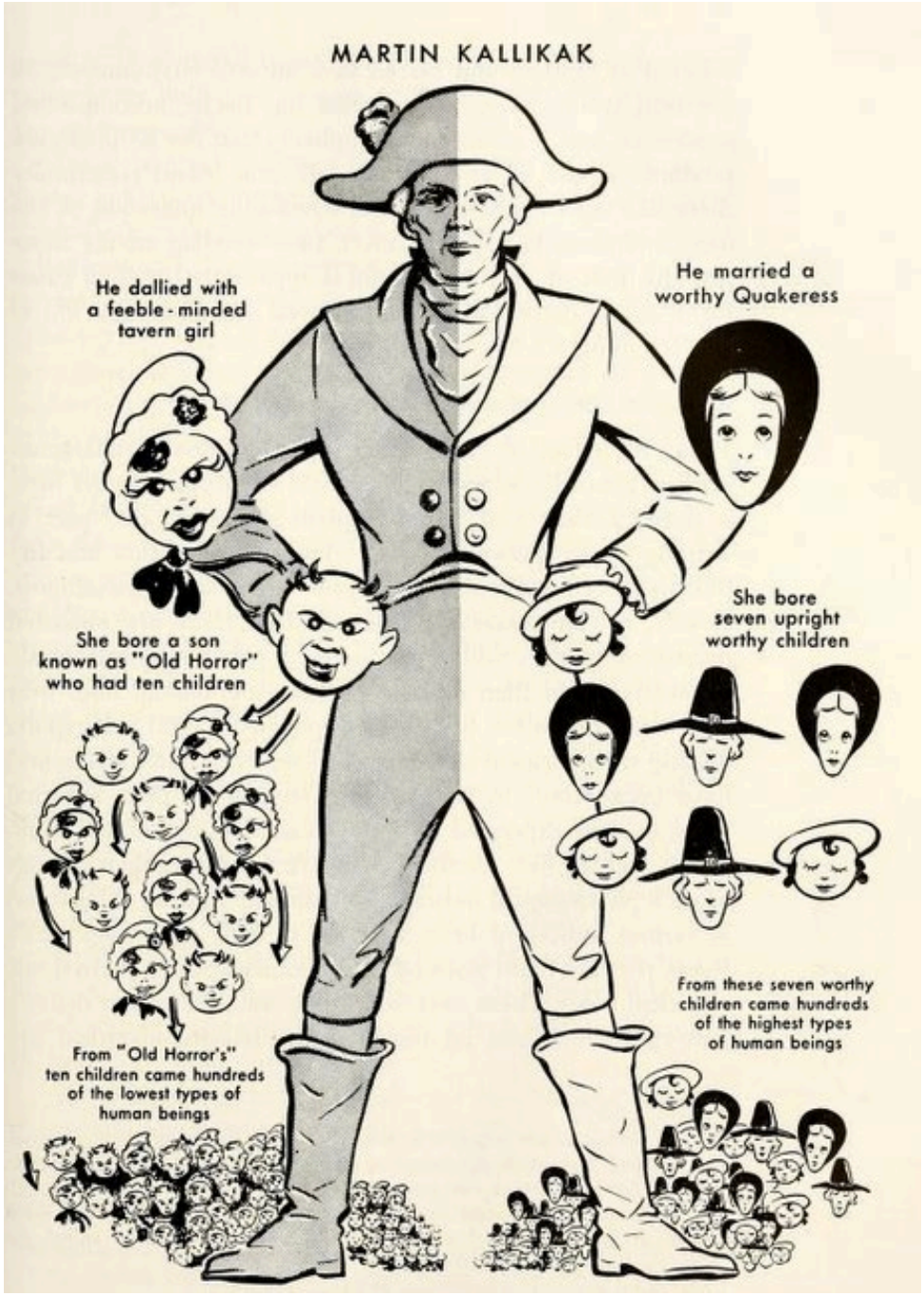


GREAT-GRANDCHILDREN OF "OLD SAL."

- A set of Kallikak children on the "feeble-minded" side of the family
- Steven Jay Gould alleged that Goddard had doctored the faces to make them look more sinister.

The Kallikak pedigree

One of the types of diagram used by the eugenicists to advance their claims

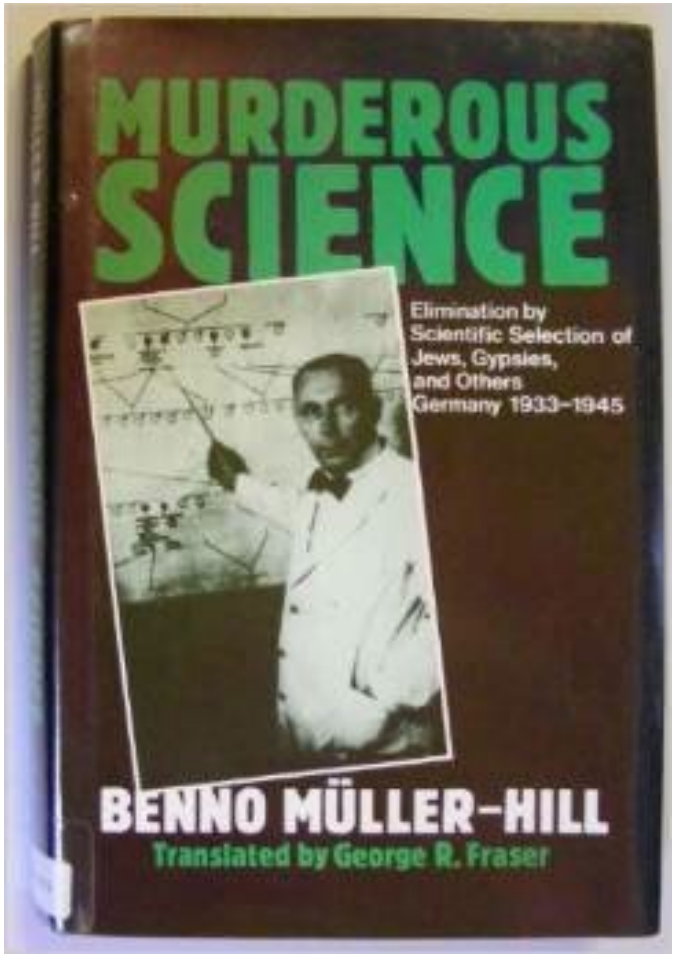


Eugenics had many supporters

- Winston Churchill
- Marie Stopes
- H.G. Wells
- Havelock Ellis
- Theodore Roosevelt
- Herbert Hoover
- George Bernard Shaw
- John Maynard Keynes
- John Harvey Kellogg
- Sidney Webb
- Linus Pauling

Genetics and the Nazis

- By the end of WWII over 250 000 people had been sterilized as mentally defective
- Over 50 000 put to death under the euthanasia law



The shadow of eugenics

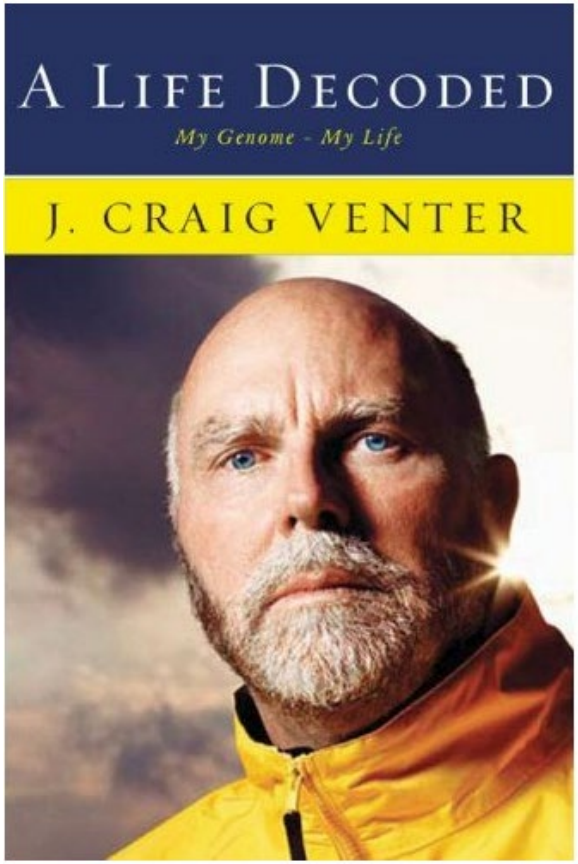
- Much opposition voiced to eugenic policies in the genetics community.

Consequences of the eugenics tragedy?

- Strongly non-directive approach in genetic counselling
- The development of medical genetics in Germany post 1945 has been particularly challenging

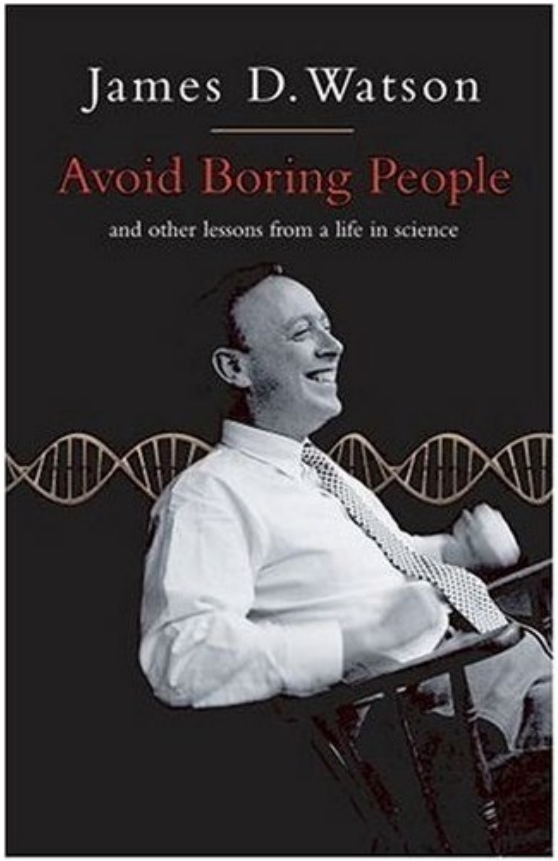
Next generation sequencing

Celebrity Genomes 1



- Craig Venter
- PLoS Biol **5** e254-286 (2007)
- Some predisposition to heart disease

Celebrity Genomes 2



- James Watson
- Nature **452**: 872-876. (2008)
- Cancer susceptibility
- Alzheimer's susceptibility gene not examined

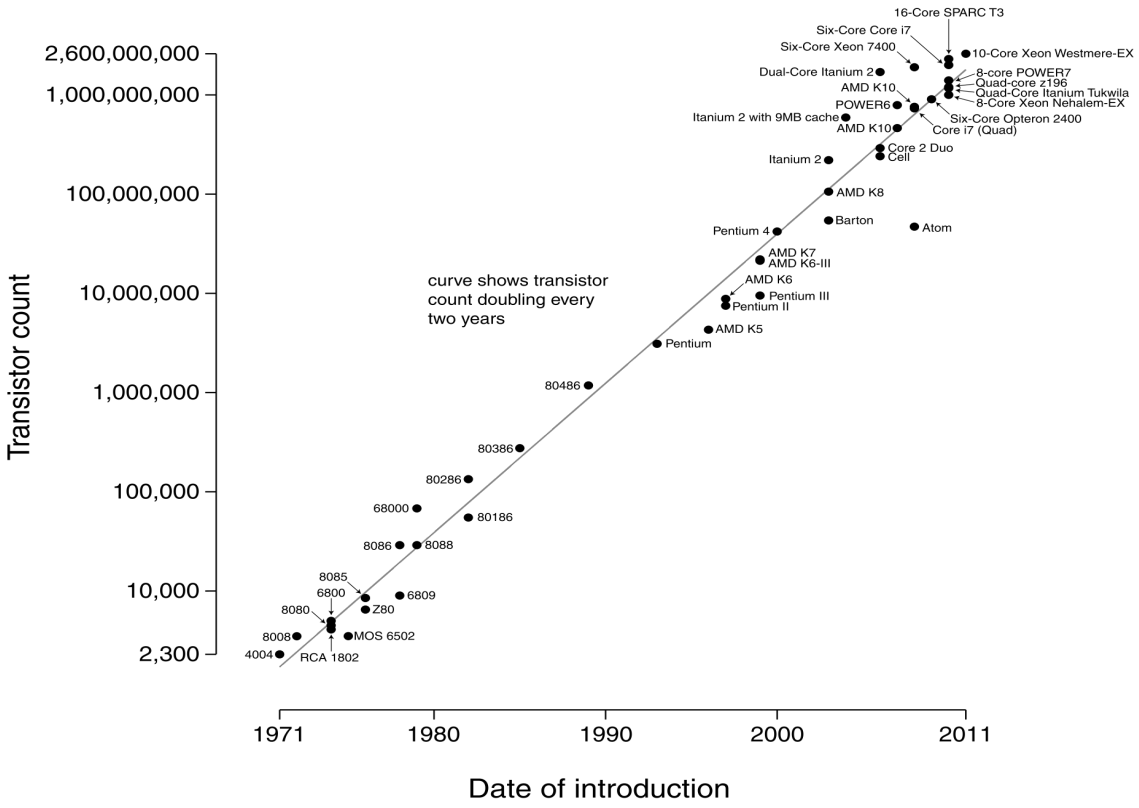
Sequencing costs fell fast

Date	Cost per base	Cost of haploid human genome
1985	10	3×10^{10}
1991	1	3×10^{9}
1993	0.10 - 0.15	3×10^{8} to 4.5×10^{8}
2007	~0.0005	9×10^{6}
2015	1.5×10^{-8}	1.4×10^{3}
2020	8×10^{-9}	7×10^{2}

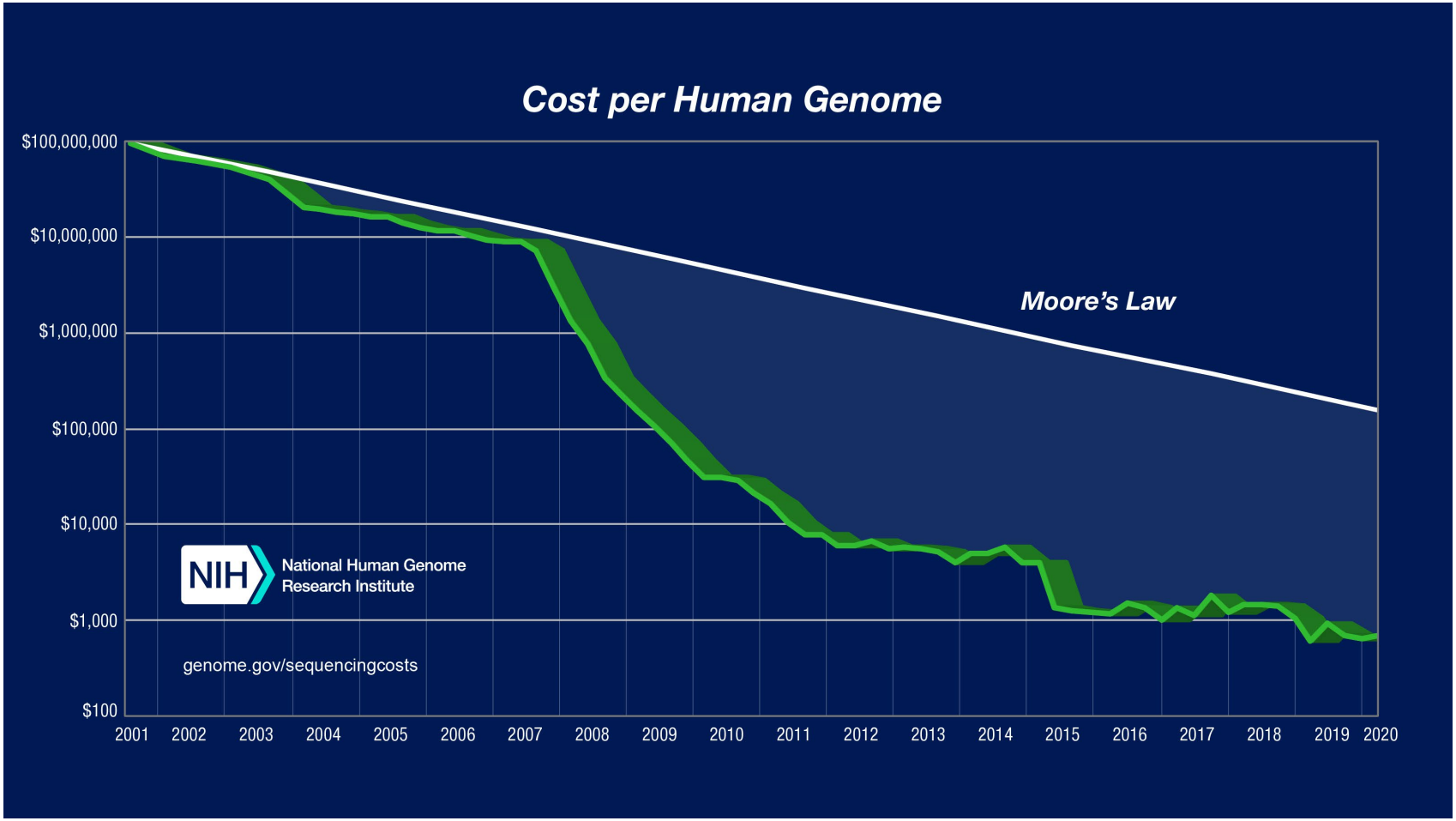
Modified from Lesk, 2007 and NHGRI, 2020. Costs in US$.

Moore's Law

Over the history of computing hardware, the number of transistors on integrated circuits doubles approximately every two years.



Sequencing costs fell faster than Moore's law

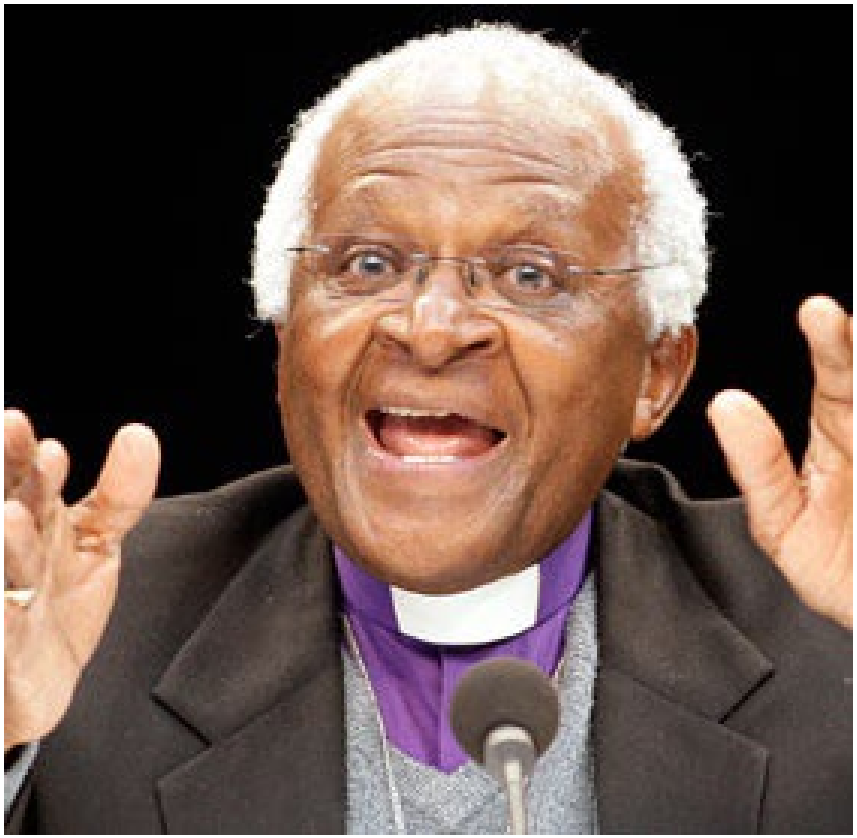


Bioinformatics

- HGP could not have succeeded without advances in information technology
- Vast amounts of DNA sequence data
- WWW crucial collaborative tool

Celebrity genomes 3

Early 2010



Late 2010

Celebrity genomes 4

Tyrolean Iceman

5,300 year old copper age individual

Nature Comm. **3** (2012)

theguardian

News | Sport | Comment | Culture | Business | Money | Life & style

Culture › Music › Ozzy Osbourne

Ozzy Osbourne genome sequenced

Genetic analysis of Black Sabbath star reveals he is more likely to experience hallucinations on marijuana and has increased risk of alcohol and cocaine addiction, researchers say

Sean Michaels
guardian.co.uk, Friday 5 November 2010 11.30 GMT
Article history

Man of visions ... Ozzy Osbourne with wife Sharon at Jon Stewart's Rally to Restore Sanity and/or Fear on Saturday. Photograph: Scott Gries/EMPICS Entertainment

In the continuing quest to understand Ozzy Osbourne, scientists have finally unravelled the singer's most microscopic mystery: his genes. Following in the footsteps of mice and mammoths, Osbourne had his full genome sequenced and analysed by American researchers, who uncovered mutations related to addiction, metabolism, and Osbourne's Neanderthal ancestors.

Identifying genes

In monogenic disorders where there is no understanding of their underlying molecular basis

1980 – 2010

Find the gene by localizing it on a chromosome

Positional cloning – 'Reverse genetics'

2010 onwards

Sequence everything – whole exome or whole genome sequencing (WES/WGS)

Try to track down the key pathogenic variant

Sequencing in the clinic

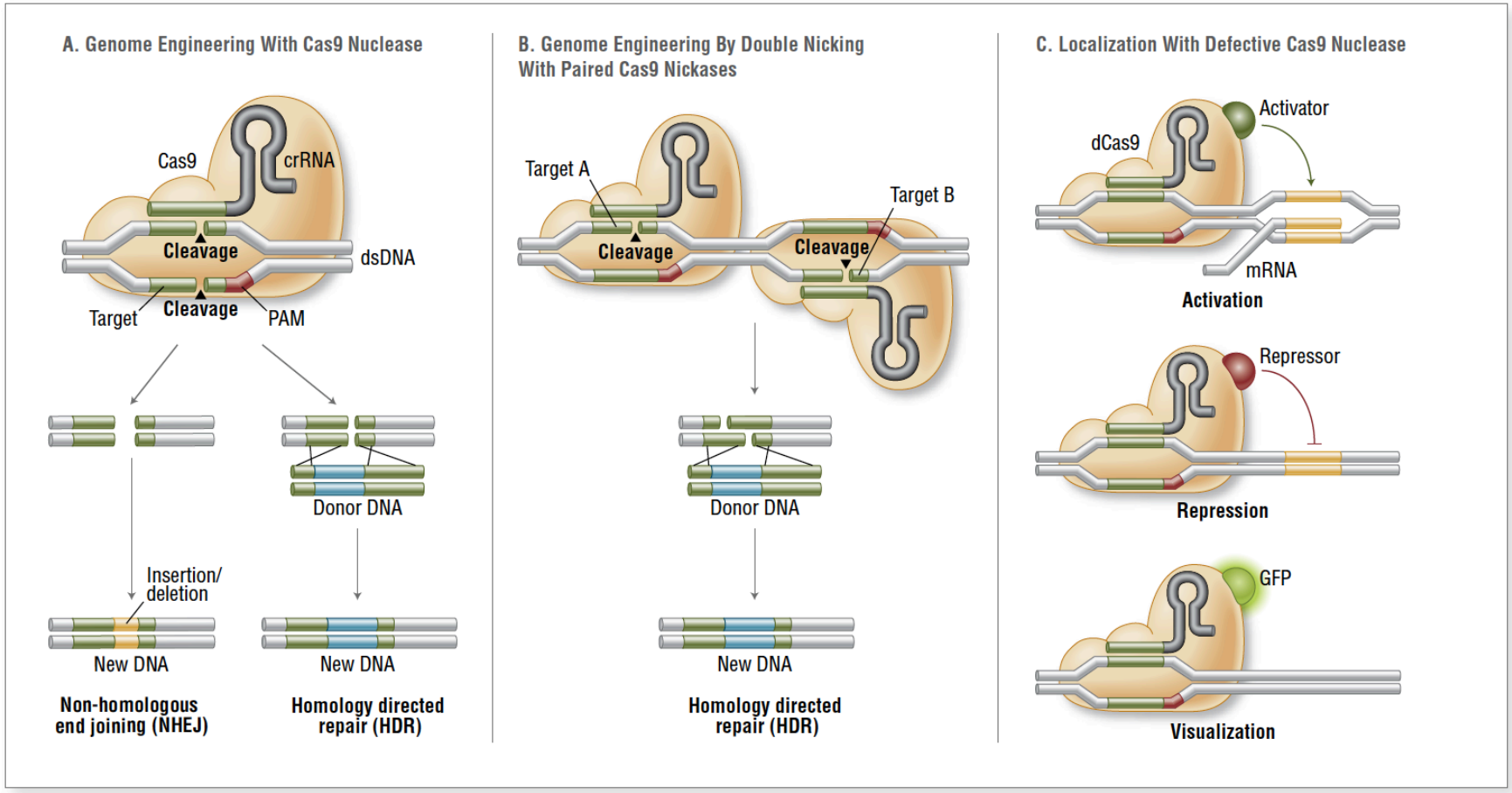
- It is now possible to undertake sequencing of whole sets of genes (genomes) for patients in a clinical setting
- Example applications
  - Rare genetic conditions: One of many possible candidate genes
    - Hereditary neuropathies, Severe paediatric epilepsies, Retinitis pigmentosa
  - Very ill newborn babies where the diagnosis is unclear
    - Inborn errors of metabolism

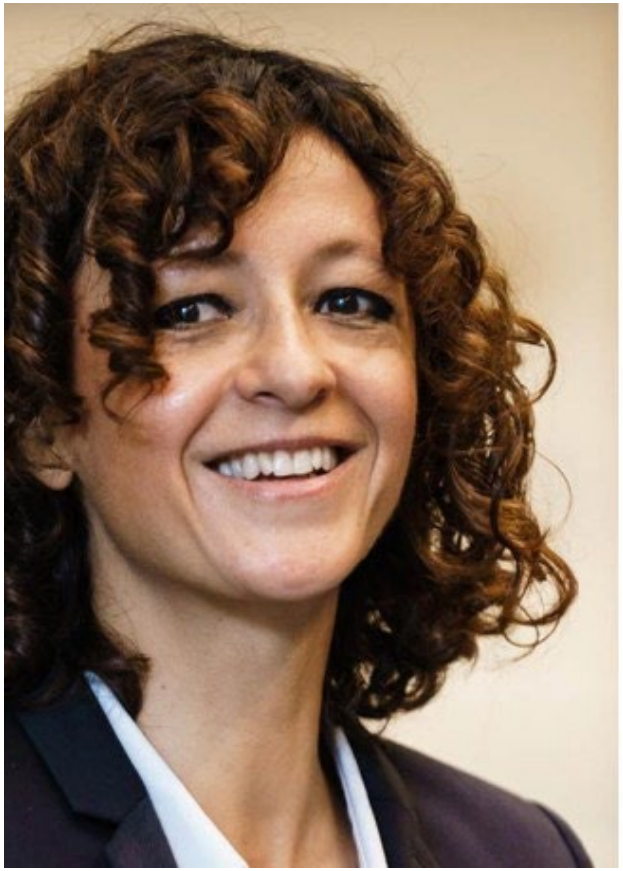
Sequencing in the clinic II

- Example applications
  - Cancers: genetic changes underlie the development of a cancer
    - Gene sequencing of the *tumour* cells and comparison with healthy body cells
    - May be useful in guiding choice of chemotherapy

Genome editing – CRISPR/Cas

- Gene editing technology developed from bacterial defence systems against viruses
- Permits efficient editing of target DNA
- Scope for use in the treatment of inherited disease
- The introduction of heritable genetic change raises major ethical issues


A. Genome Engineering With Cas9 Nuclease
Cas9
crRNA
Cleavage
dsDNA
Target
Cleavage
PAM
Donor DNA
Insertion/
deletion
New DNA
New DNA
Non-homologous
end joining (NHEJ)
Homology directed
repair (HDR)
B. Genome Engineering By Double Nicking
With Paired Cas9 Nickases
Target A
Target B
Cleavage
Cleavage
Donor DNA
New DNA
Homology directed
repair (HDR)
C. Localization With Defective Cas9 Nuclease
Activator
dCas9
mRNA
Activation
Repressor
Repression
GFP
Visualization

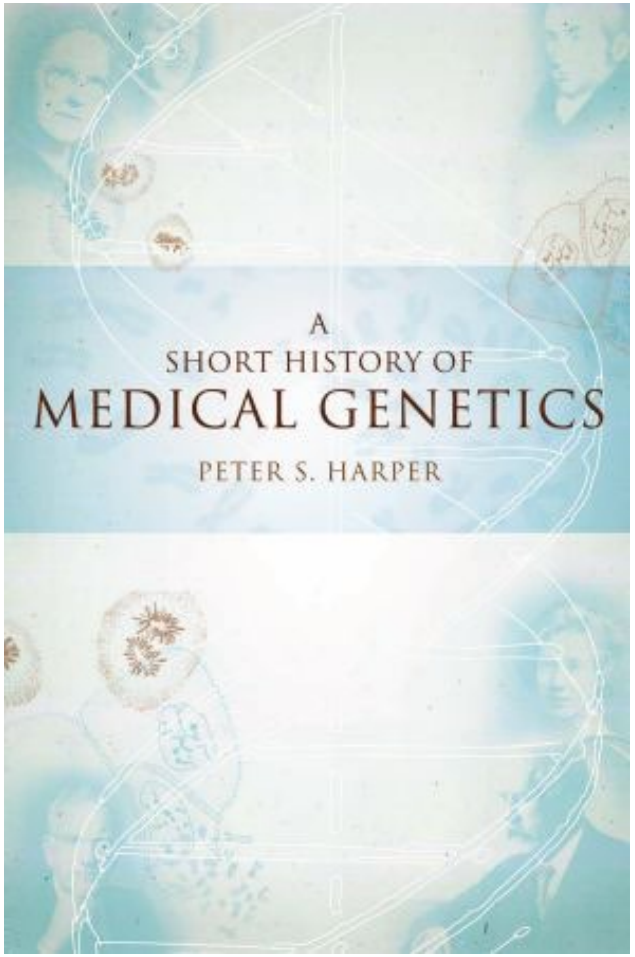


Nobel Prize in Chemistry 2020

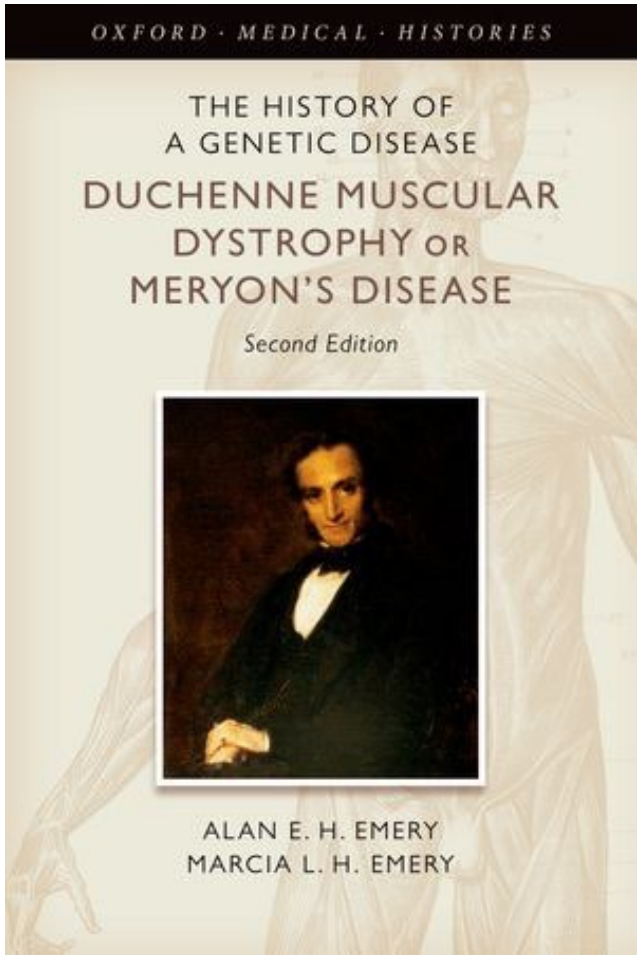
Awarded jointly to Emmanuelle Charpentier and Jennifer A. Doudna "for the development of a method for genome editing."

Further reading

- McKusick VA History of Medical Genetics in: Rimoin et al., *Emery and Rimoin's Principles and Practice of Medical Genetics* 5e. Elsevier 2007.
- Harper PS *A Short History of Medical Genetics* (Oxford Monographs on Medical Genetics 57). OUP 2008.



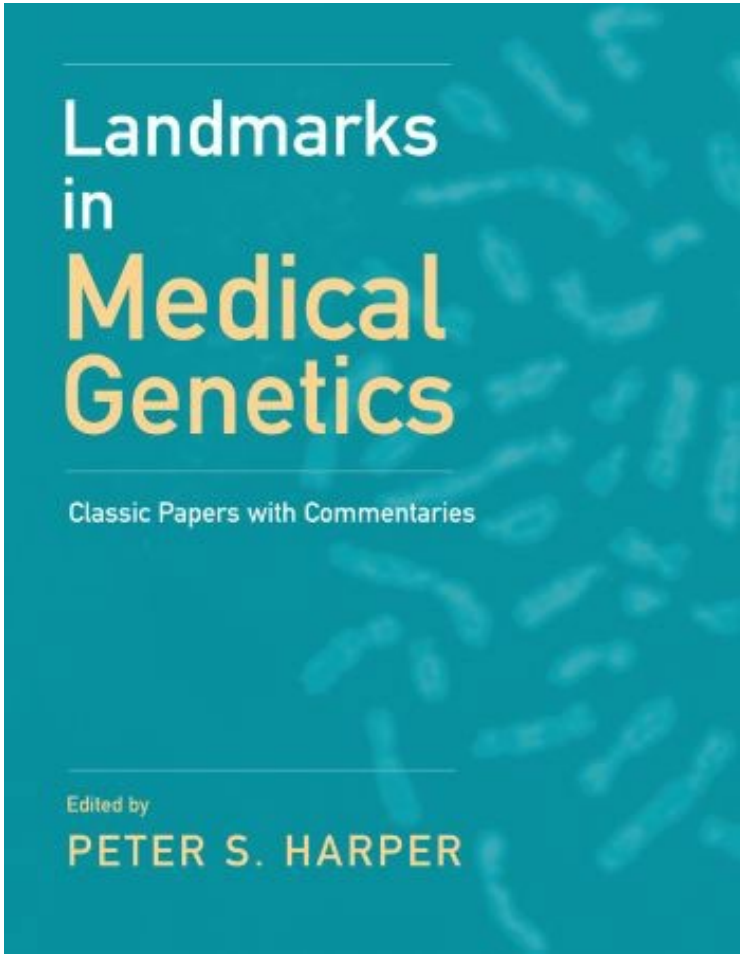
Further reading II



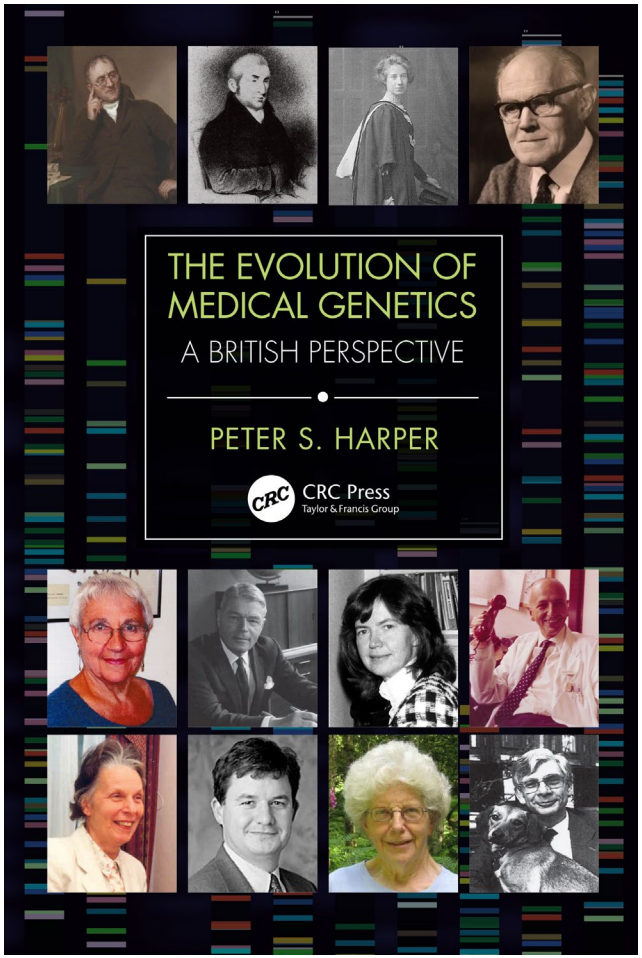
- Emery AEH and Emery MLH *The History of a Genetic Disease: Duchenne Muscular Dystrophy or Meryon's Disease* 2e, Oxford: OUP 2011

Further reading III

- Harper PS *Landmarks in medical genetics: Classic papers with commentaries* (Oxford Monographs on Medical Genetics 51). OUP 2004.



Further reading IV



- Harper PS *The evolution of medical genetics: a British perspective.* Boca Raton: CRC Press, Taylor and Francis 2020.