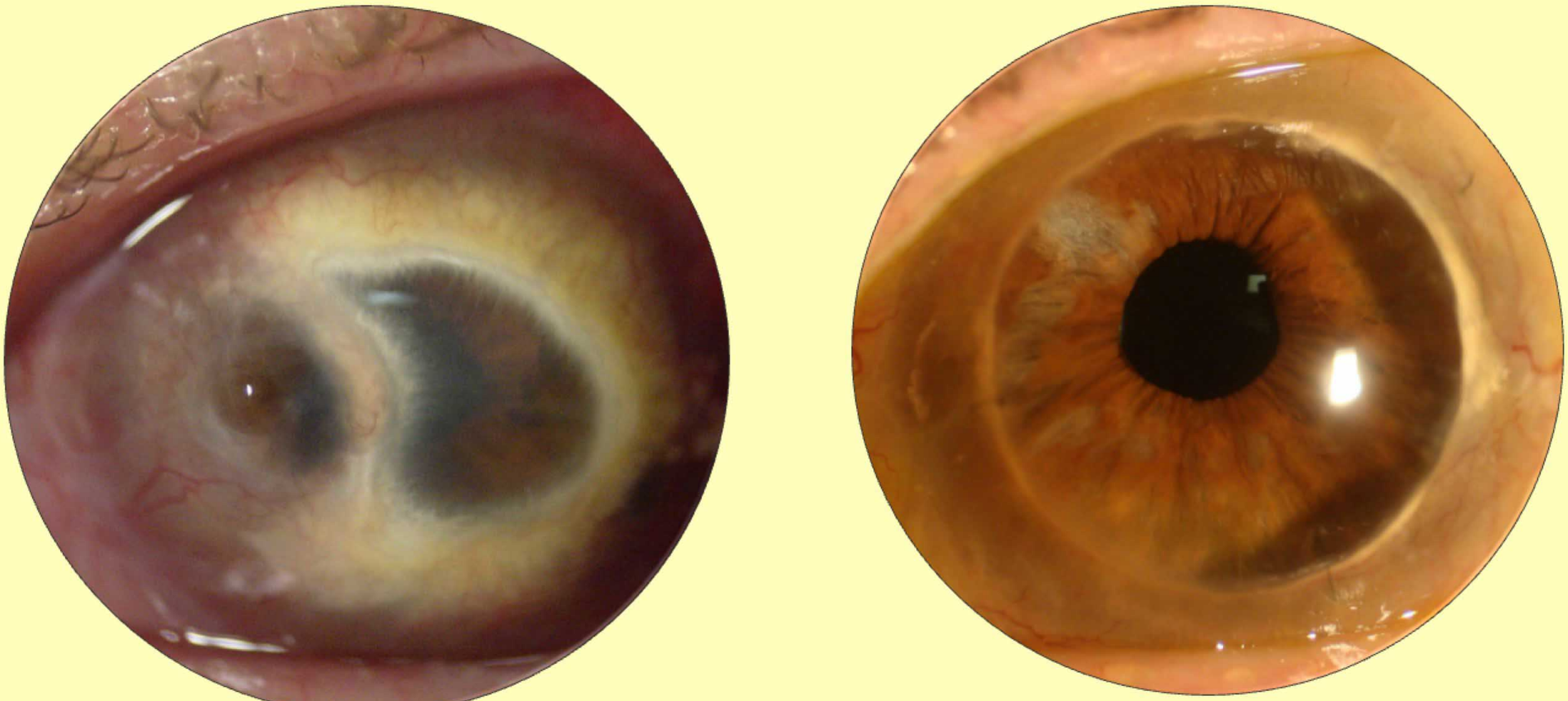
Transplantation and the eye

From darkness to light



William Ayliffe
Gresham College and The Lister Hospital
London

27 Nov 2013

Free grafts

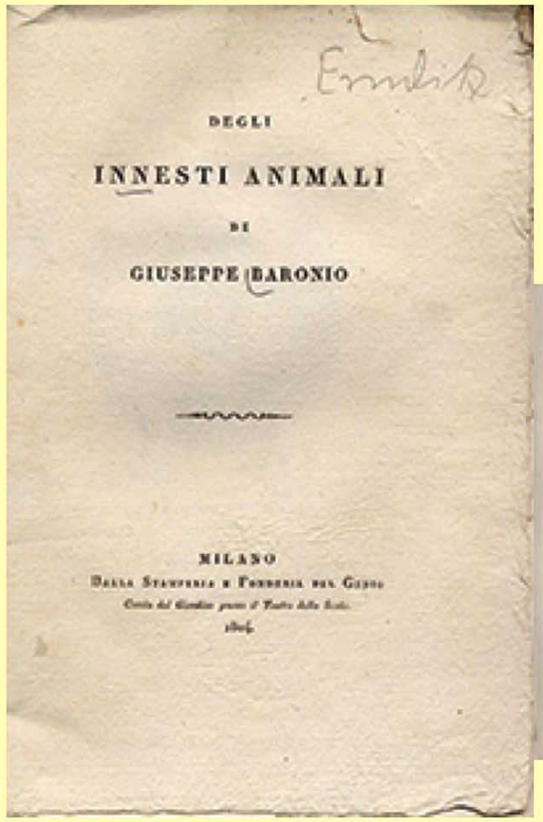
Giuseppe Baronio (1759-1811),

Experimental skin transplantation

1804: "Degli innesti animali" ("Concerning the transplantations in animals")

excised two pieces of skin, swapping their site. ointment & compresses for 8 days, Complete success

12.5 by 7.5 cm, replaced them 80 minutes after excision, the skin survived.


DEGLI

INNESTI ANIMALI

DI

GIUSEPPE BARONIO

MILANO

FIRST SUCCESSFUL HUMAN FREE GRAFT

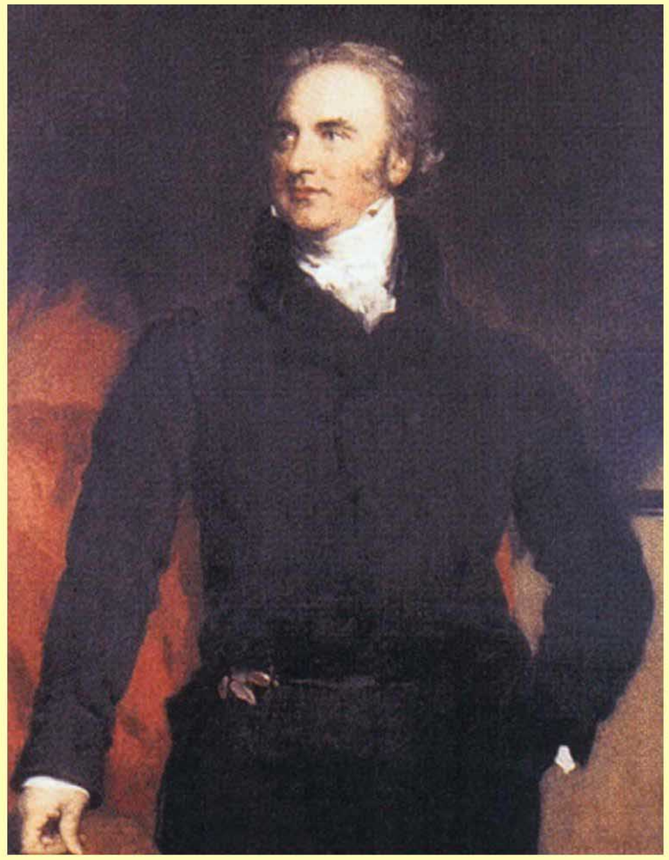
Astley Cooper: (1768-1841)

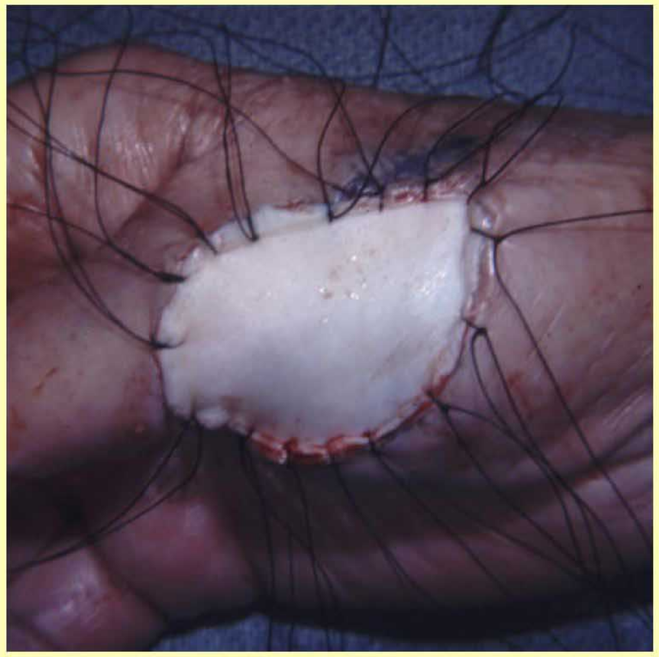
Young male admitted to Guy's hospital on 9th April, 1817, with a diseased thumb.

Amputated between phalanges.

Piece of skin from removed from thumb applied to stump adhesive slips.

The graft was completely successful, first recorded certain success of human autografts.





Graft blood supply

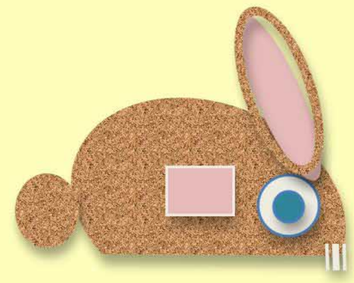
Free grafts fail if bed is too large

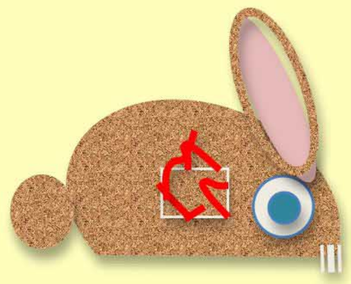
Failure of blood supply

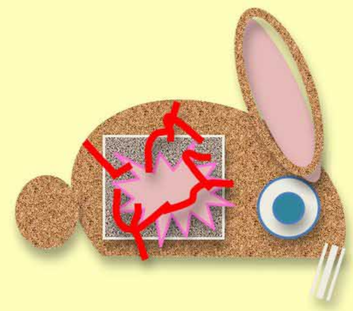
Donor site issues

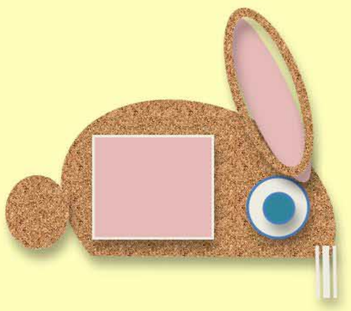
(Split skin grafts late C19th)

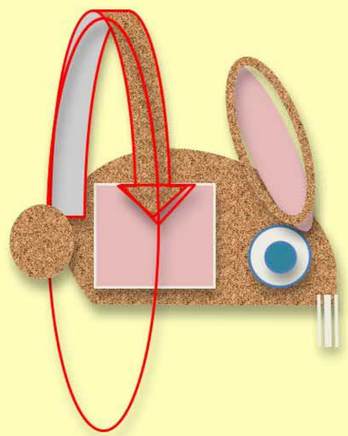
Pedicle containing blood supply

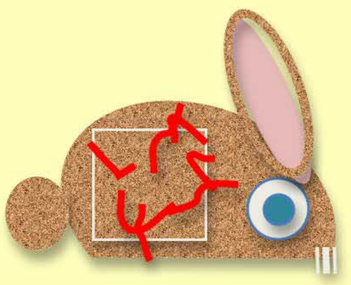












Burns

Ambroise Paré (c. 1510 –1590) barber surgeon pioneer in surgical techniques and battlefield medicine

1536: two men horribly burned by gunpowder. Asked to help Paré shook his head. Soldier cut their throats.

"Were I in such a situation, I would only pray to God for someone to do the same for me."

Replaces Hippocratean hot fat poultice

Wilhelm Fabry 1560-1634: Classification of burns by severity Describes surgery to alleviate scarring

Wife Marie: Barber, described removing metal FB from eye with a magnet

Baron Guillaume Dupuytren (1777 –1835) French military surgeon. Treating Napoleon Bonaparte's haemorrhoids,

Research on burn patients in the hospital Ho□tel-Dieu

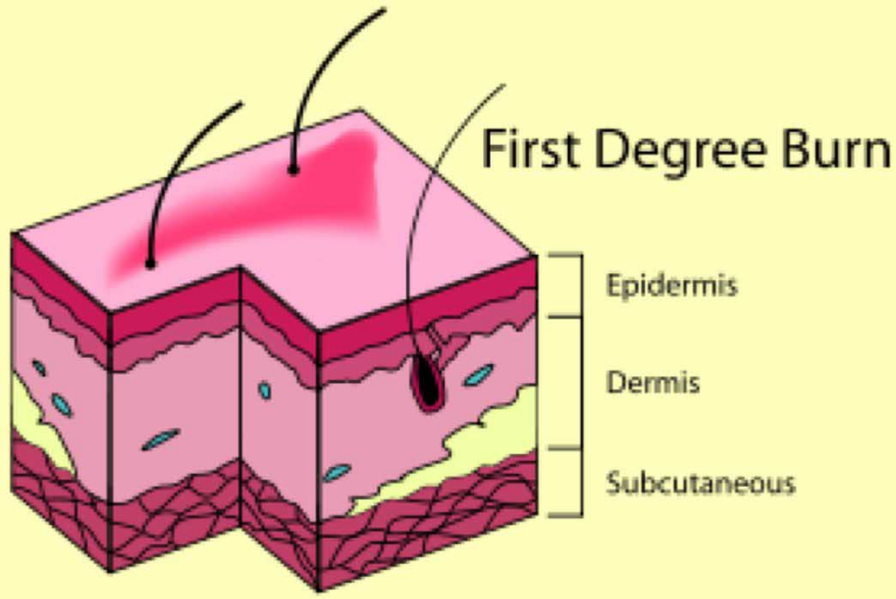
7 grades depending on the depth

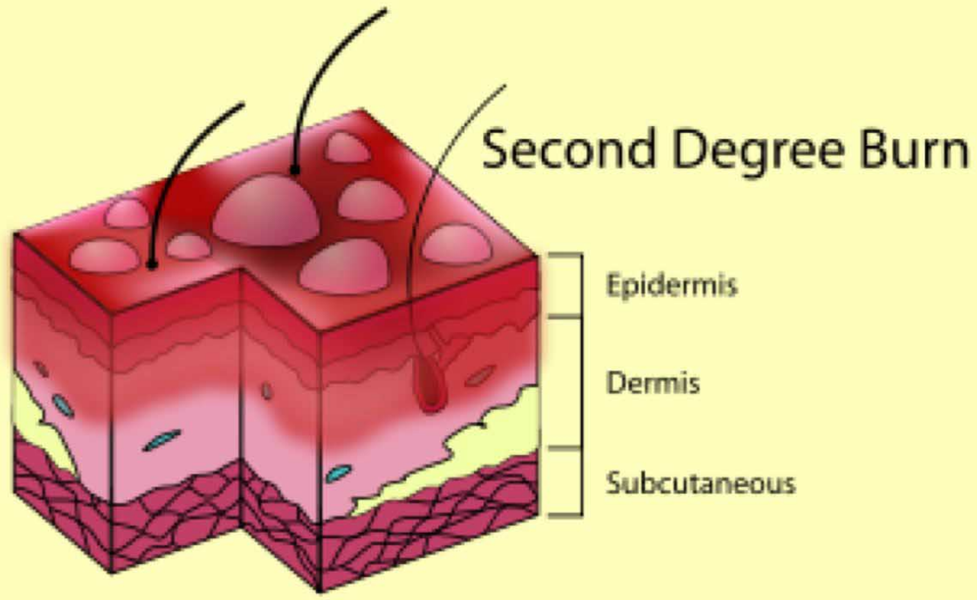
4 different physiologic patterns of bodily reaction, irritation, inflammation, suppuration and exhaustion.

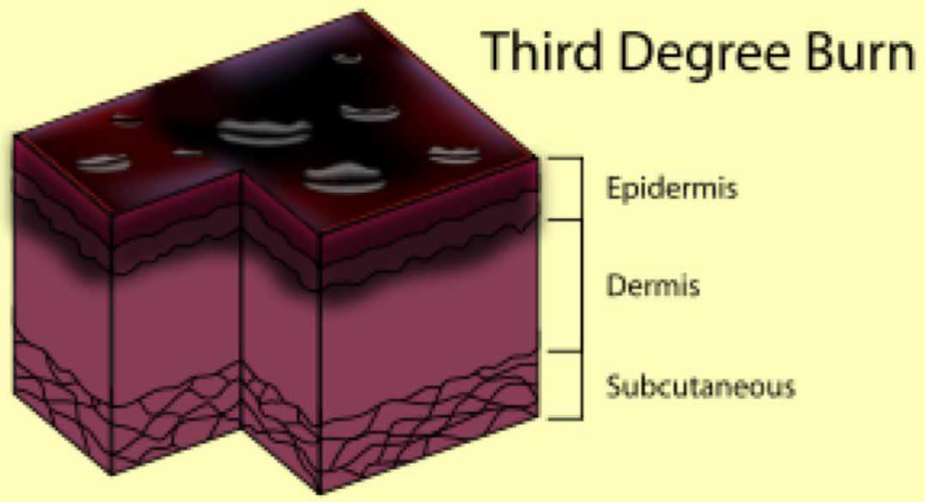
Blood letting avoided

Chances of survival correlated to area of burn

Need for replacing skin for large defects



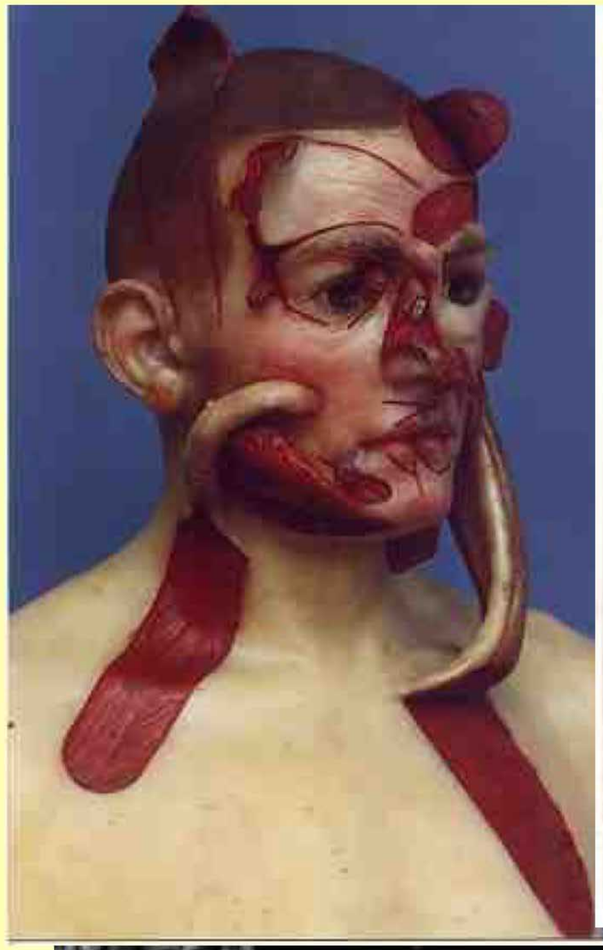


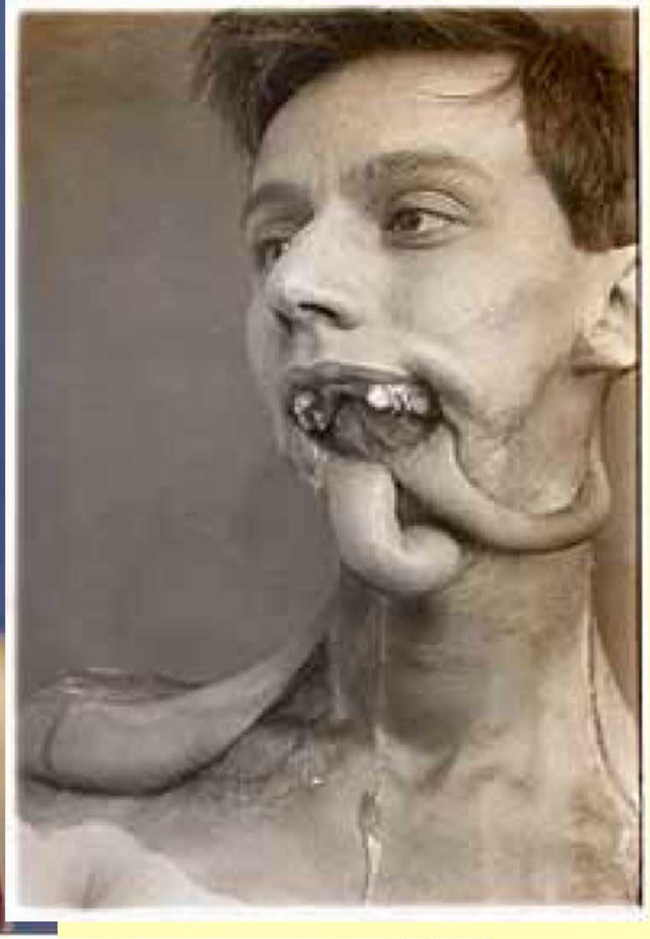


‘tubed pedical’ skin grafting.

Allows larger grafts to have blood supply and survive

Tubes no raw areas so reduces infection





Second Lieutenant Henry Lumley

b. 1892, son of barrister (and playwright) Ralph Robert Lumley d.1900

Christ's Hospital (the Bluecoat School).

August 1915. 'attested' under the Derby Scheme

April 1916, Christ Church College, Oxford, flying training.

July, 14th. Flying BE12 Central Flying School at Upavon
Crashed major burns to his face

Oct 1917: Admitted to QMH

Impossible to make a successful skin graft to cover the burns.

Gillies: scar tissue removed, huge skin graft from chest. Tubed pedicles provided further available skin.

24 October 1917, chest graft and tubed pedicles at the neck.

15 February 1918. Scar tissue excised, removing 'old' face, and the graft was stitched into place.

Large graft did not take: died of heart failure on 11 March 1918, a few days before his 26th birthday.

The **B.E.12:** A B.E.2c "Fokker Fodder"with the front (observer's) cockpit replaced by a large fuel tank, and new 150 hp RAF 4.
a failed attempt to create a fighter aircraft based on the B.E.2
Improvised rushed into service to meet the Fokker threat

Need to understand transplant rejection

Stanley Baldwin: famously predicted, "The bomber will always get through. The only defense is offense, which means that you have to kill more women and children more quickly than the enemy [does] if you want to save yourself."

Airmen burned

Bombing of cities incendiaries

1943 Operation Gomorrah: July 28 firestorm that killed more than 40,000 in Hamburg.

Albert Speer: "Hamburg had suffered the fate Hitler and Goering conceived for London in 1940."

War Wounds Committee assigned **Peter Medawar** to investigate allograft rejection.

Thomas Gibson Burn Unit Glasgow Infirmary.

Attempts to replace damaged skin on burn patients from unrelated donors unsuccessful.

Between 1 to 2 weeks, transplanted skin necrosis and fell off.

1943, report, "The Fate of Skin Homografts in Man," on a single burn victim with multiple "pinch grafts" of skin.

analysis of serial biopsies conclusions:

- Autografts succeed, but allografts fail after an initial take
- "Second-set" grafts undergo accelerated rejection
- The destruction of the foreign epidermis is brought about by a mechanism of active immunization

Guinea pig club

"Airman's burn."

Before WW2, most patients with severe burns Scalds, cooking, Industrial, Train crashes, died within 24 hours.

Dehydration, shock of losing massive amounts of serum and protein at the burn sites.

Treatment morphine, and wait for death.

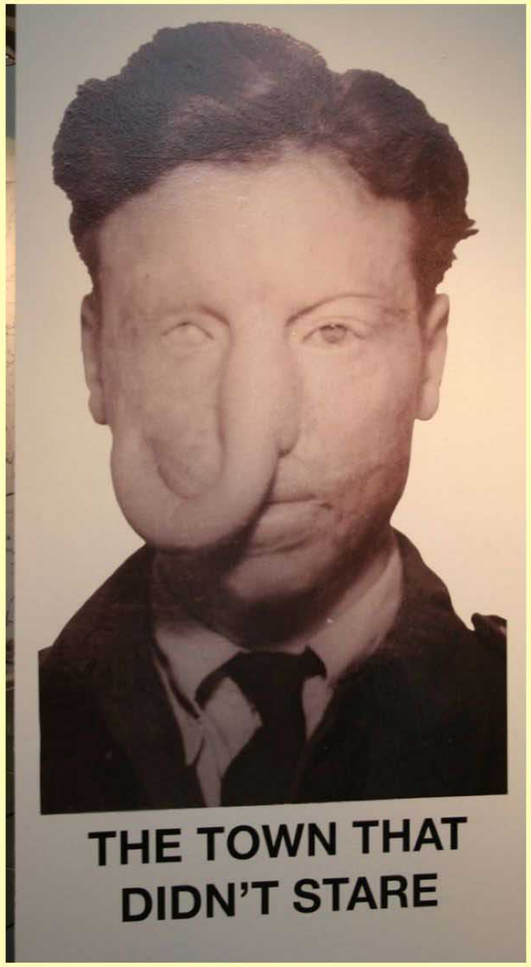
In peacetime, one or two serious burns a year.

1939-45, **McIndoe** 5,000 burn patients and 600 total facial reconstructions.”

keep the wounds open, wash with saline and regularly change the dressings.

When the burns had healed, transplantion for reconstruction

"When I looked down on the operating table and saw I had to replace a pair of burned eyelids for a boy of 21, I felt God come down my right arm."



Allografts: from another individual
Xenografts: from another species

1898: **Winston Churchill**, Sudanese war donates skin for an injured officer.

"Ye've heeard of a man being flayed aloive? Well this is it what it feels loike."

"A piece of skin and some flesh about the size of a shilling from the inside of my arm. This precious fragment was grafted to my friend's wound. It remains there to this day and did him lasting good in many ways. I for my part keep the scar as a souvenir."

1933: **Voronoy** Ukranian first human cadaveric kidney transplant. Failed

Allogeneic transplants invariably unsuccessful

NOBODY UNDERSTOOD THE REASONS FOR THE FAILURE

The charge of the 21st Lancers at Omdurman Edward Hale (1852-1924) last British cavalry charge in history, **Lieut. R. F. Molyneux** of the Blues, wounded, dismounted, disarmed, **Private Thomas Byrne** VC although wounded returned to help. Molyneux had suffered a serious sword cut on his right forearm and needed a skin graft
1945 Molyneux wrote to Churchill, : "*I never mention and always conceal it for fear people might think I was bucking*."
Churchill replies: "*Thank you so much dear Dick. I often think of those old days, and I should like to feel that you showed the bit of pelt. I have frequently shown the gap from which it was taken*."

Transplantation immunology

Transplantation: removing something from one location and introducing it in another location

Allows replacement of damaged organ or tissue

Immunology:

The science of non-self discrimination

Designed for elimination of microbes

Used although not understood in vaccination.

People who survived smallpox became immune

1715: **Lady Mary Wortley Montagu**: wife of Ambassador to Constantinople left pockmarked had son variolated on her return to London. **Danger!**

Pasteur, Koch: and others; germ theory and immunizations. Mechanism remained obscure

Exhaustion of nutrients by vaccine?

Antitoxin and Alexin (Complement)?

Ilya Metchnikoff: 1845-1916 proposed phagocytic cells basis of protection against foreign invaders.

1903: **Almroth Wright & Douglas:** St Mary's showed phagocytosis improved if organisms coated, opsonization

1796, Jenner took fluid from *Sarah Nelmes*' cowpox blister and scratched it into the skin of 8 yr old James Phipps. A single blister. inoculated the boy again, this time with smallpox matter, and no disease developed

Cells of Immune system

Derive from stem cells in bone marrow

INNATE NON-SPECIFIC IMMUNITY

The myeloid series: respond early and nonspecifically to infection.

Neutrophils engulf bacteria and send out warning signals.

Monocytes mature to macrophages in body tissues and ingest foreign material.

Eosinophils attack parasites

Basophils release granules containing histamine and other allergy-related molecules

SPECIFIC IMMUNITY

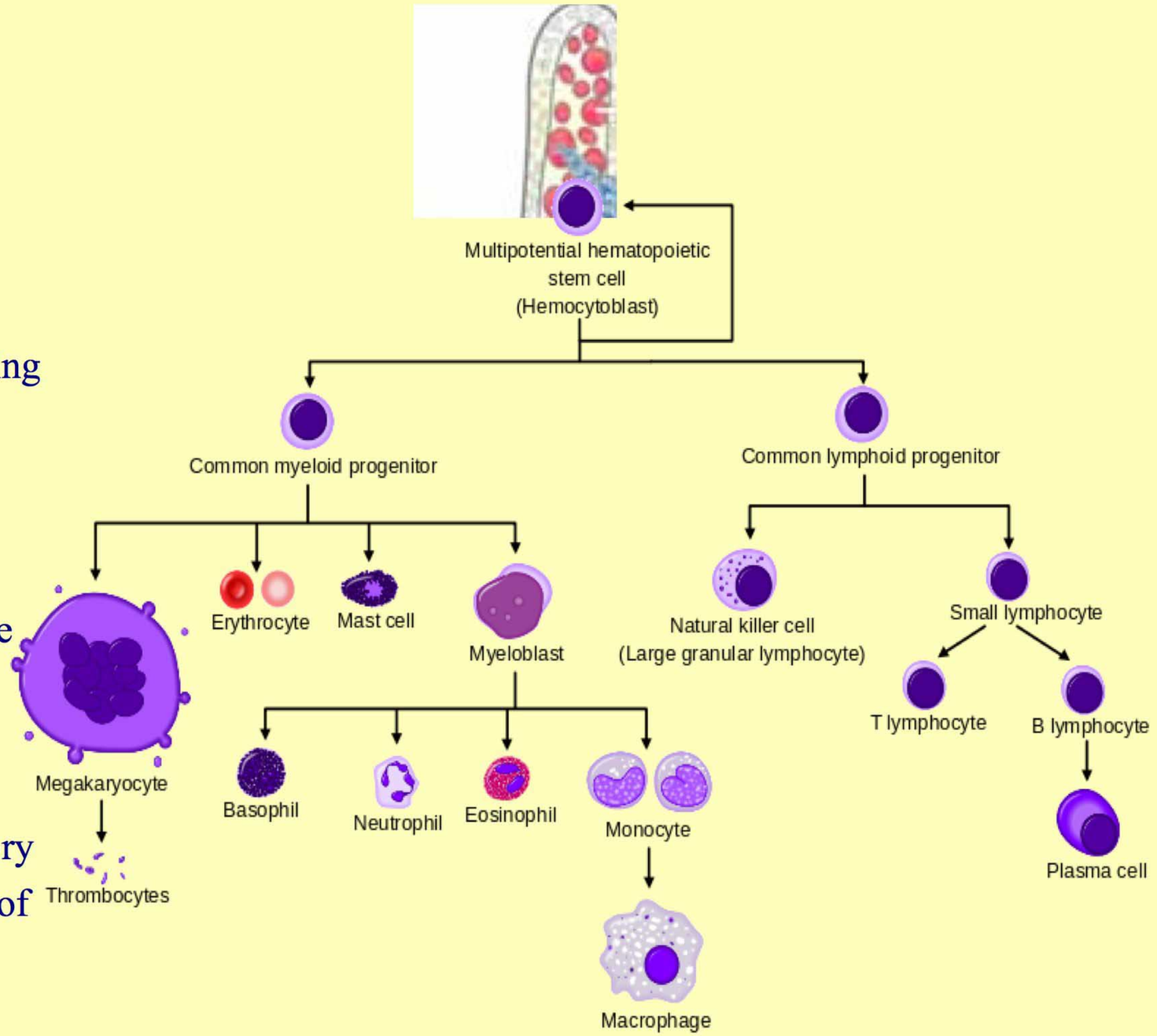
Attacks only a particular invader and has memory

Lymphocytes respond specifically to products of the invading organism called antigens

Antigen-presenting cells dendritic cells (or macrophages) process proteins and present them to the lymphocytes for recognition

B cell: becomes plasma cell that produces specific antibodies.

T cells: coordinate the immune response and eliminate the viruses hiding in infected cells.



Cornea
The first successful allo-transplant in history

Eduard Konrad Zirm (1863–1944)

Born and trains in Vienna.

Takes up post in Olomouc, Moravia

Alois Gloger: first successful cornea transplant

15 months after lime burns, corneas were white–grey opaque

right eye hand movements.

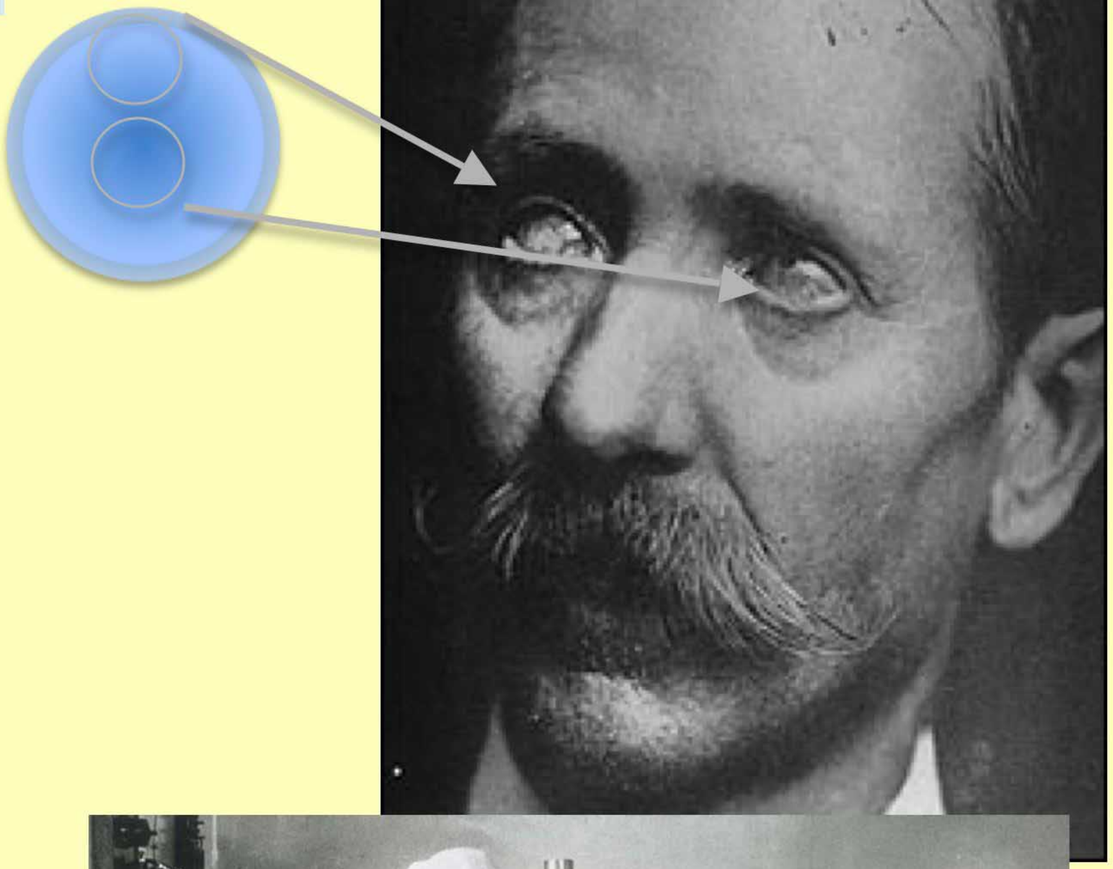
Donor: 11-year-old Karl Brauer: iron intraocular foreign body collapse of the eye enucleated; kept in warm physiological saline

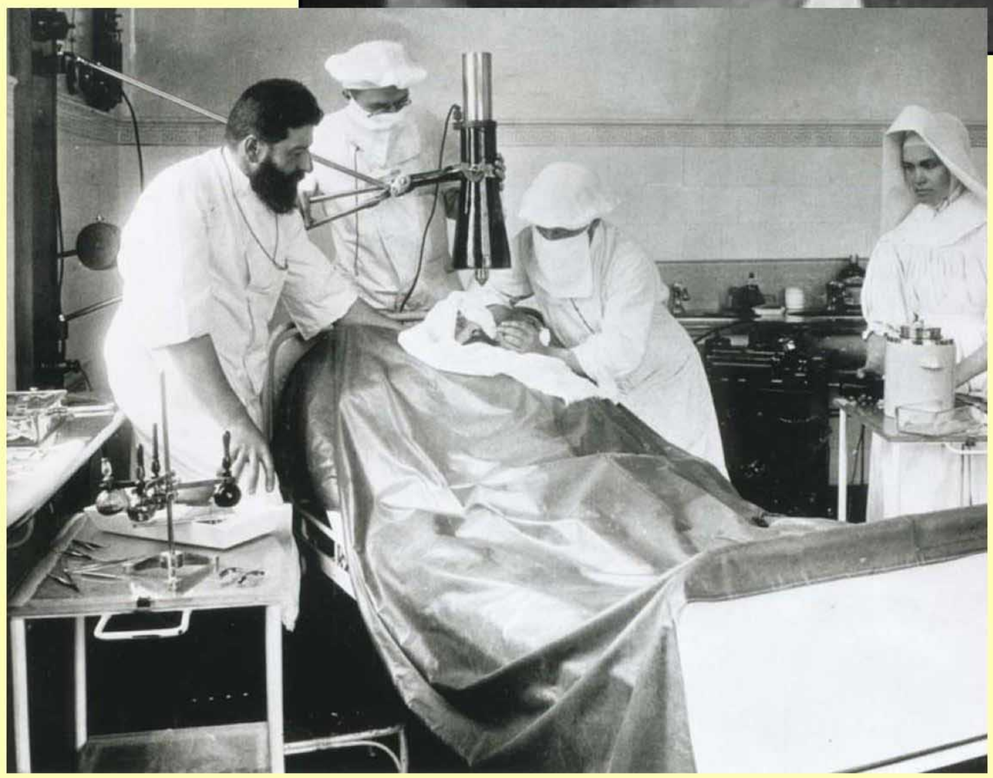
Right eye: 5-mm disc von Hippel trephine. Peripheral donor secured with conjunctival flap

After 2 weeks painful and opacifies

Left eye: Central donor and overlay suture x2

Although complications affected one eye, the other remained clear allowing Glogar to return to work



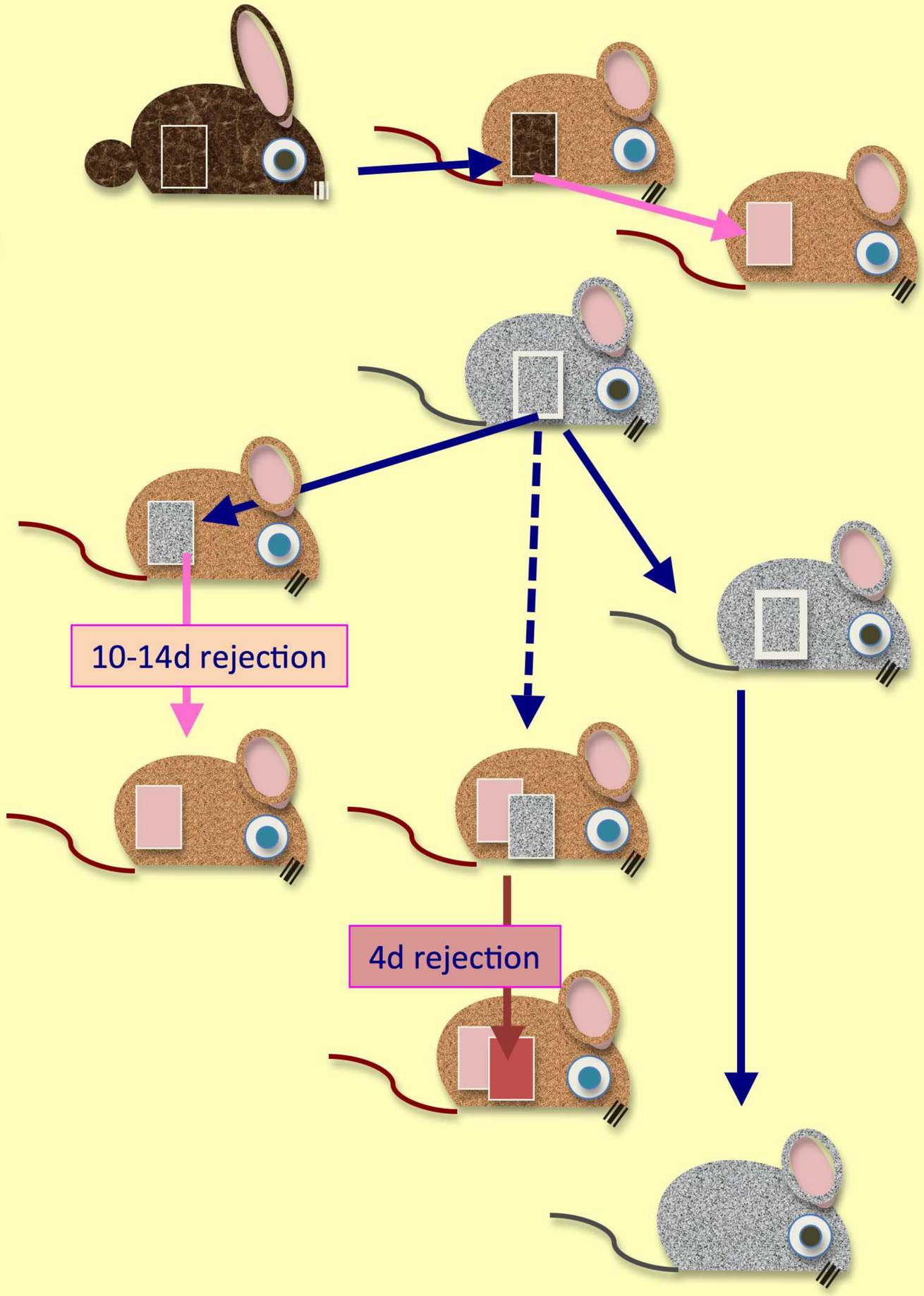


Science of transplantation

1903, **Jensen:** genetic differences control rejection of tumors in albino mice

1912, **Georg Schoüne:** ***"Heteroplastische und Homoplastische Transplantation"*** summarized the experimental work to date; coined the term **"Transplantationsimmunitaüt"**

Clarence Little: observations on transplant rejection codified into " laws of transplant immunology" by **George Snell**



Xenogeneic transplants invariably fail

Allogeneic transplants also fail

There is an initial take of a first allograft which is then followed by rejection

Second grafts undergo accelerated rejection if recipient has previously rejected a graft from the same donor or if recipient has been pre-immunized with material from donor

Graft success is more likely when donor and recipient have a closer "blood relationship"

Autografts are almost always successful

Graft rejection is an immunological process

Sir Peter Medawar 1915-87

hypothesized that the concept of "self" was defined by the immune system during embryogenesis.

Aware of immunity hypotheses of Scho□ne, Holman, etc explain rejection.

Rabbit skin graft model to prove that this was an immunologic phenomenon.

Reports to the War Wounds Committee

Journal of Anatomy 1944 and 1945.

Mechanism by which foreign skin is eliminated is by actively acquired immune reactions.

Animal learned to recognise the donor

Developed memory

Unrelated second donor no accelerated rejection

The process is specific

White cells called lymphocytes responsible for rejection

Rejection mediated by lymphocytes

Injecting lymphocytes from a recipient who had rejected a graft transferred the memory of the donor to a naïve recipient!

Specific Response

Lymphocytes recognised the foreign tissue

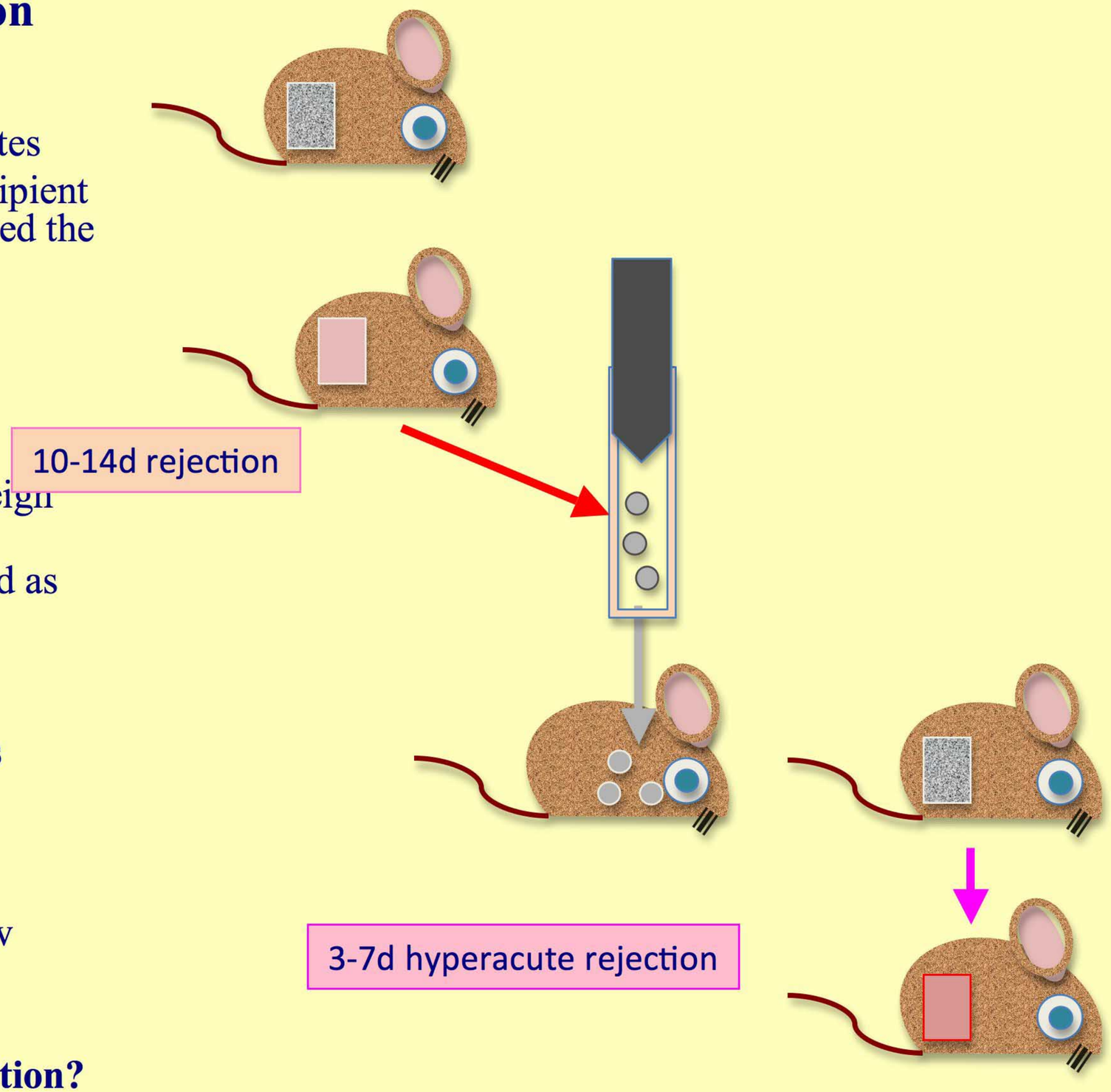
The molecules that are recognized as foreign on allografts are called **alloantigens**

Two sorts of lymphocytes

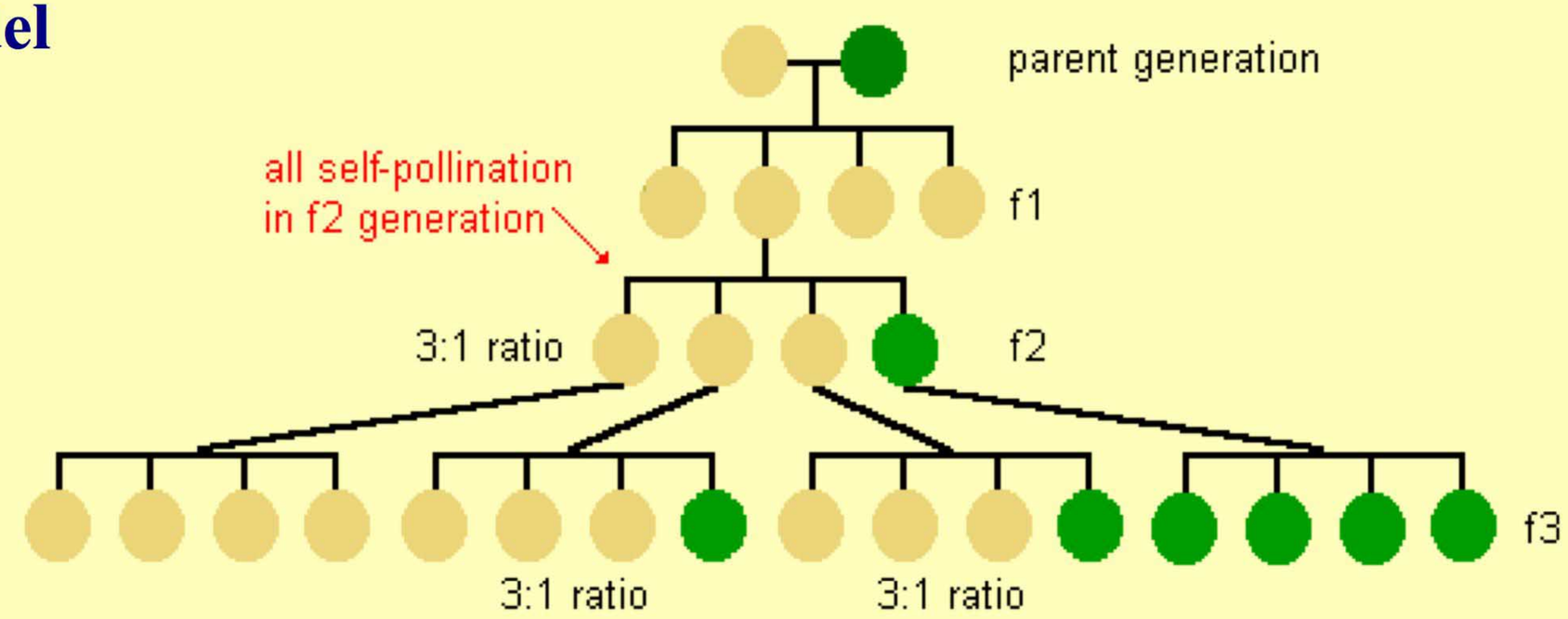
T-cells: Develop in Embryonic Thymus

B-cells: Develop in Bone Marrow (Bursa of Fabricius)

What was genetic basis of rejection?



Jojhann (Gregor) Mendel (1822–1884),



pea seed color.

Three deductions:

1. inheritance of each trait is determined by "units" or "factors" that are passed on to descendents unchanged (genes)

2. individual inherits one unit from each parent for each trait

3. trait may not show up in an individual but can still be passed on to the next generation.

Disproved Lamarck's theory of the inheritance of acquired characteristics

Dominant and recessive

Parent plants homozygous for pea seed color.

Each had two identical forms (or alleles) of the gene for this trait

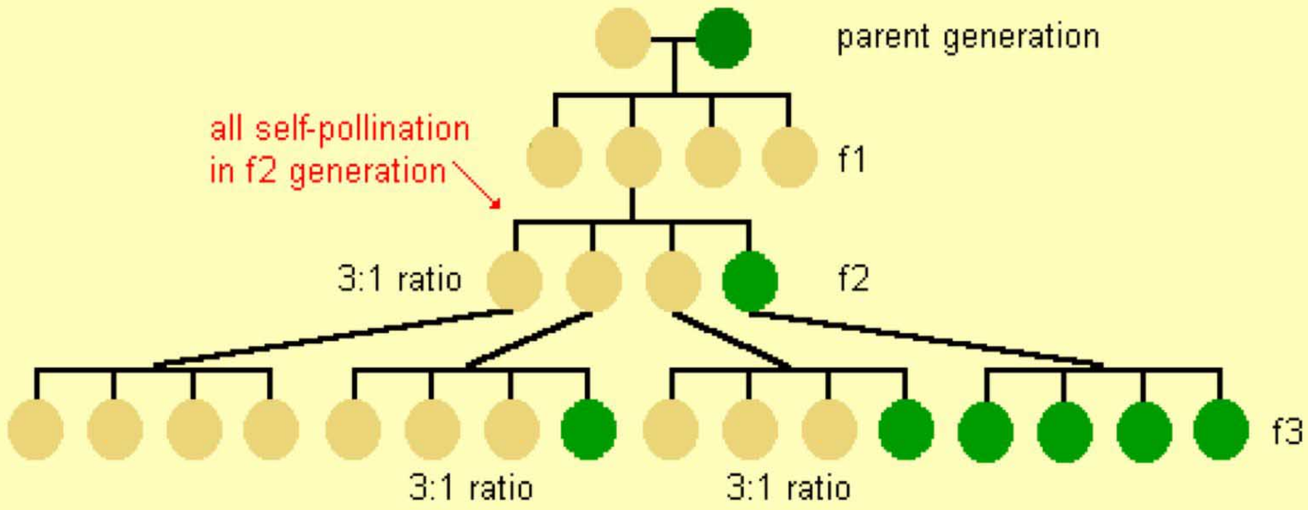
f1 generation were all heterozygous .

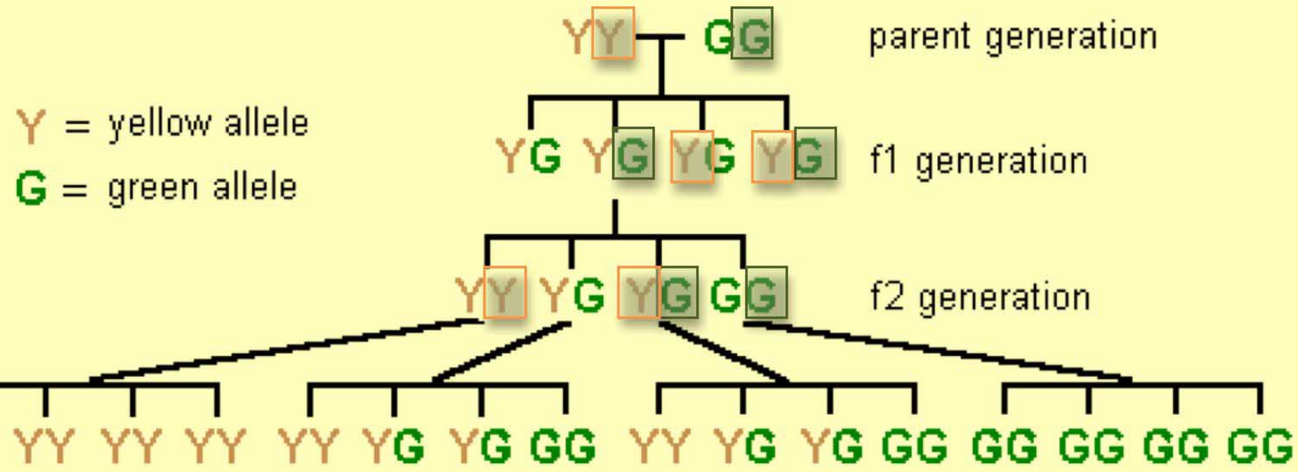
each had inherited two different alleles--one from each parent

1909: Wilhelm Johannsen coined the word "gene" ("gen" in Danish) to describe the fundamental physical and functional units of heredity

Mendel's landmark discovery would have been impossible if he had selected traits that show more complex patterns of inheritance.

Remarkably few traits are simply mendelian.





the genotype for pea seed color is YG (heterozygous)
the phenotype is yellow.
The yellow allele is dominant

Mendelian characteristics

1914: **Clarence. C. Little**: Harvard: Studies inheritance of mouse coat colours under WE Castle.

Develops laboratory mouse strains. **Trying to see if recently rediscovered laws of Mendel also applied to animals.**

Controversial Eugenics, birth control, cancer.

Founds Jackson Laboratory Maine

Miss Lathrop: bred for mouse fanciers (creamy buffs or ruby-eyed yellows)

supplier for several academic laboratories, including that of Little

At her peak she was ordering a ton and a half of oats each month

If coat colour is determined by expression of a dominant allele **A**.

F1 generation would be '**Aa, Aa**.

All F1 mice will be **Grey**

¾ F2 will be **Grey**

Do animals obey the laws of Mendel?

F1 mice express the dominant coat colour

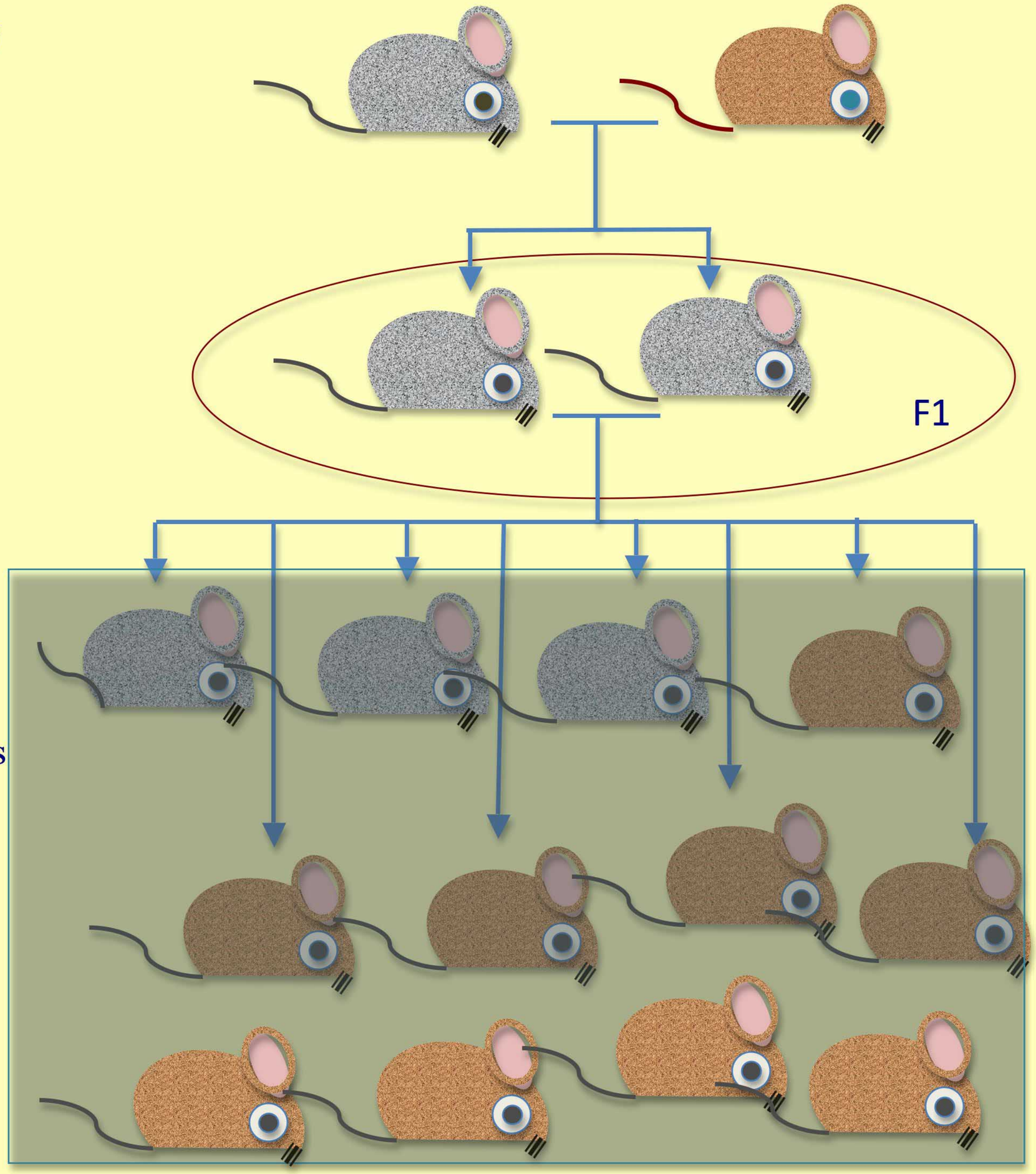
If the trait is dominant.

F1 generation bred together

F2 generation more than expected recessive phenotype

Why?

Animals not behaving like Mendel's peas



'A Mendelian explanation for the inheritance of a trait that has apparently non-Mendelian characteristics'.

If a given colour is determined by the **coexpression** of **A**, **B**, **C** dominant alleles.

'**ABC**' loci were bred with a **abc** mouse

F1 generation '**Aa**, **Bb**, **Cc**'.

express the colour, the trait is dominant.

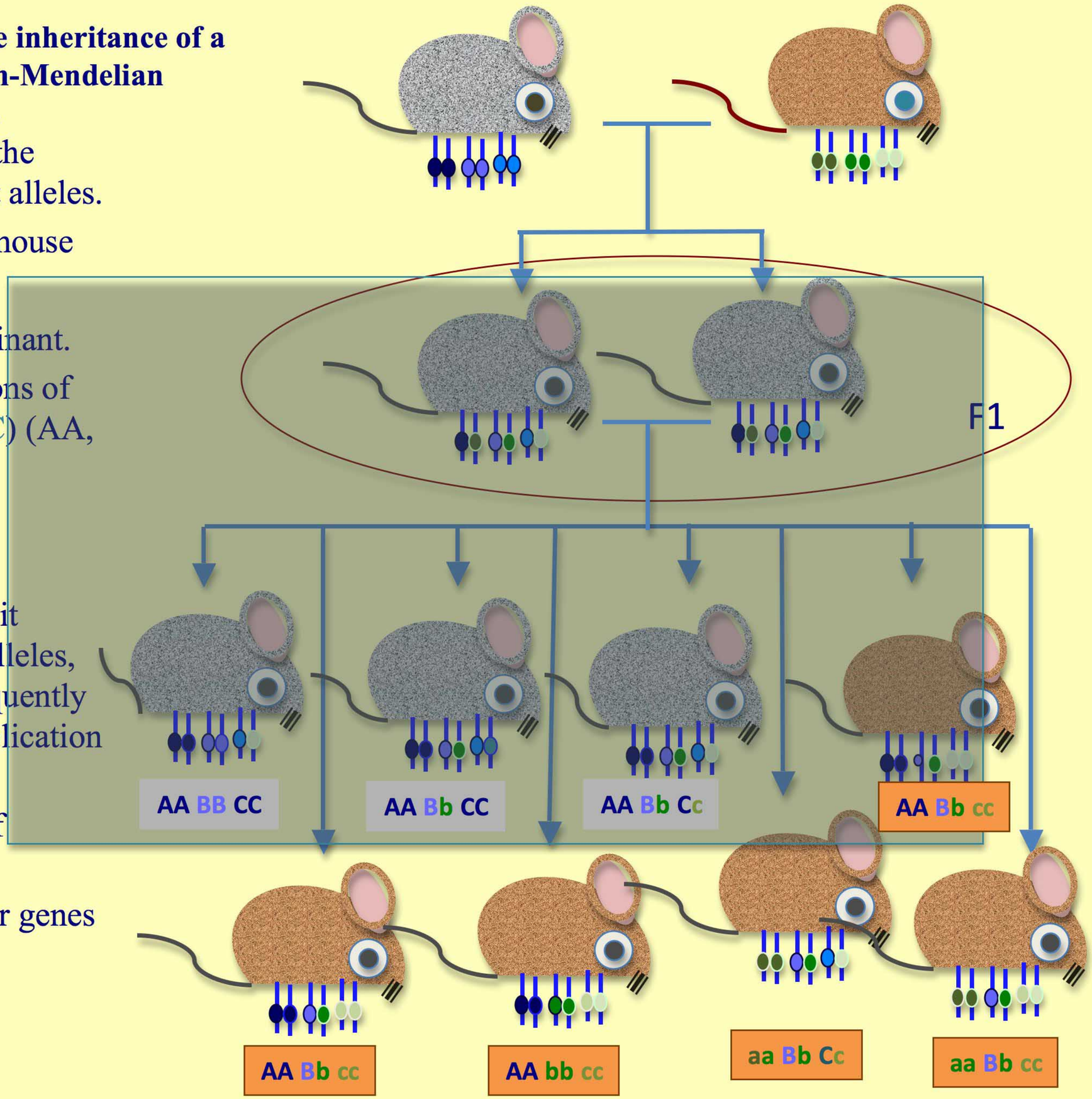
F2 generation, multiple combinations of alleles (AA, **BB**, CC) (AA, **B**b, CC) (AA, **Bb**, C**c**)

(AA, **Bb**, **cc**) (AA, **bb,** CC), etc.

If the inheritance of a particular trait requires co-expression of several alleles, then its inheritance occurs less frequently than would be predicted by the application of simple Mendelian laws

Unaware of the anatomical basis of pigmentation, its biochemistry

DBA mouse: named for coat colour genes dilute, Brown, non-Agouti



Why is inheritance of coat colour apparently non-mendelian?

Mammals make two kinds of pigments

Made in special cells: **MELANOCYTES.**

Pigment granules, synthesized in 2 types of vesicles **PHAEOMELANOSOMES** specialize in making yellow-red phaeomelanins.

EUMELANOSOMES specialize in making brown-black eumelanins.

Both pigments derive from amino acid ***tyrosine***

The yellow (called red) and black pigment are the basis for all mouse colours.

Distribution & intensity of these two pigments; full, diluted or absent

The relative proportions of these pigments are regulated **α-MSH**, binds **melanocortin receptor** on melanocytes and stimulates production of ***tyrosinase***

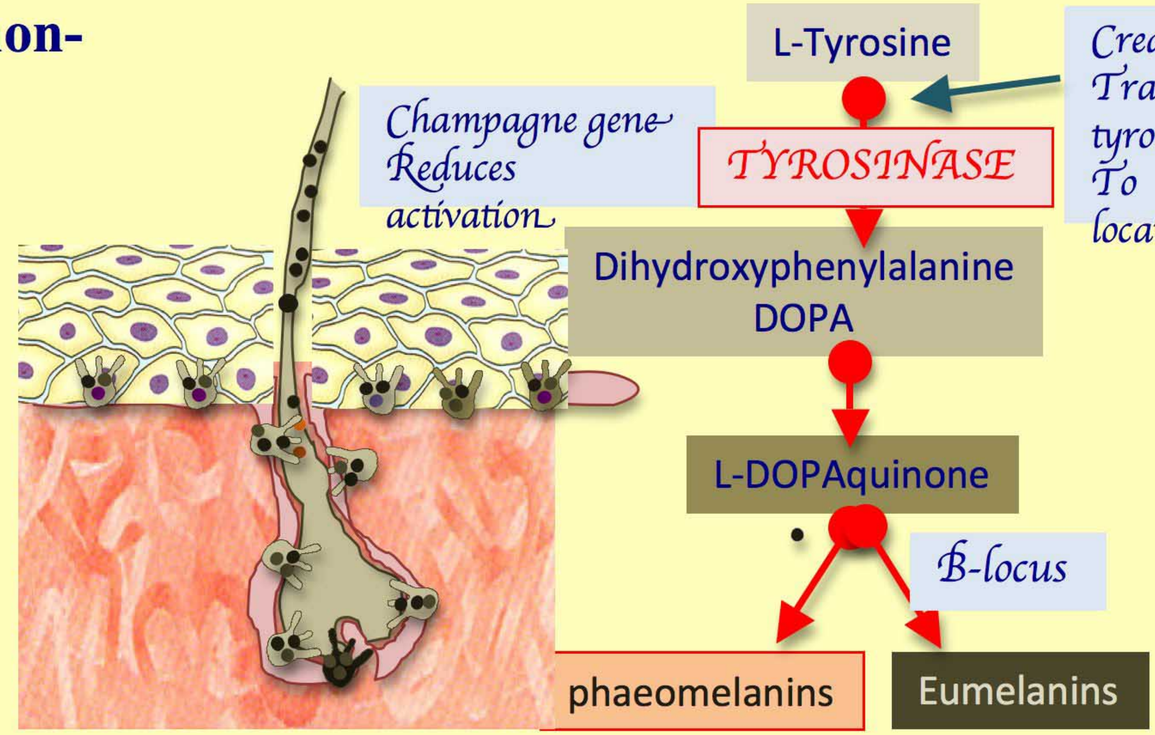
Phenotype results from the cumulative effect of many determinants

Variations (*alleles*) from the "wild type" produced by mutations

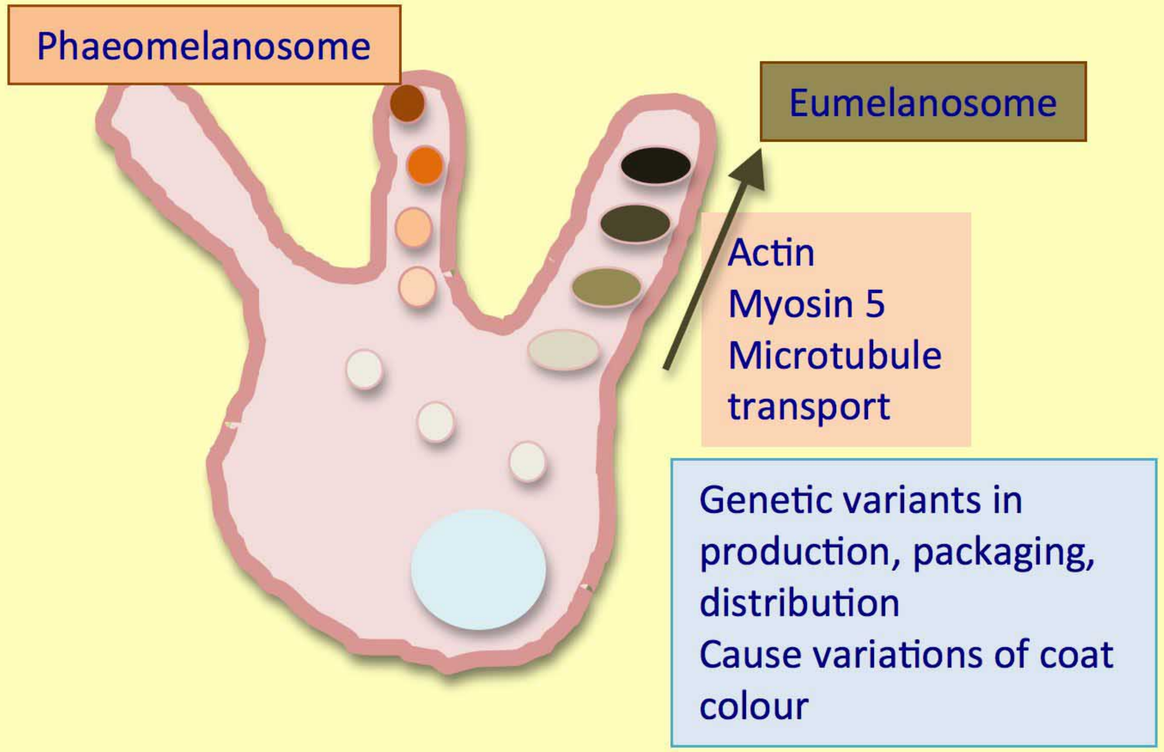
House mouse (*Mus musculus*) more genes have been identified which affect coat color than any other trait.

130 coat-colour determinants in 50 locations (Loci)

Genetic and non-genetic (epigenetic)



Enzyme ***tyrosinase*** (coded *chinchilla gene*) converts colourless tyrosine into dopaquinone: **Phaeomelanins** are made out of these. To make **eumelanin**, dopaquinone is converted into dopachrome. Dopachrome can take two pathways to eumelanin



Eye colour

1907, Charles & Gertrude Davenport:

Brown eye colour dominant

Blue-eyed parents always produce blue-eyed children, never brown eyes.

There is **no blue pigment in human eyes**,

Like skin & hair colour; controlled by the amount and type of melanin.

The overall number of **melanocytes** is roughly equivalent for all people,

Amount of melanin inside each melanosome & number of melanosomes varies.

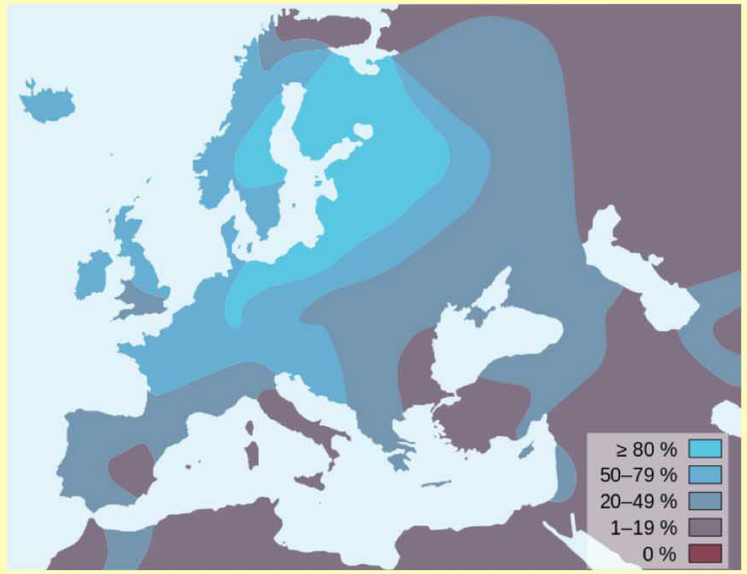
Many genes involved in the production, processing and transport of melanin

Lots of melanin gives brown eyes

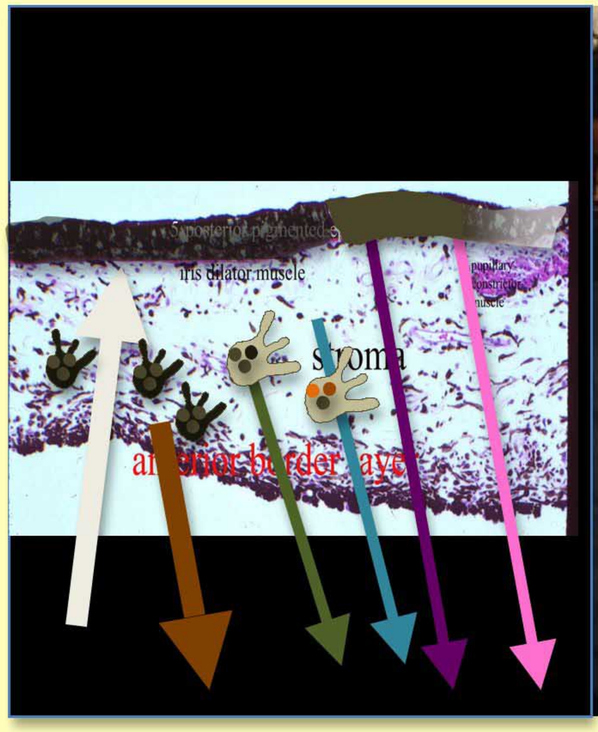
Less melanin in the stroma of the iris gives green.

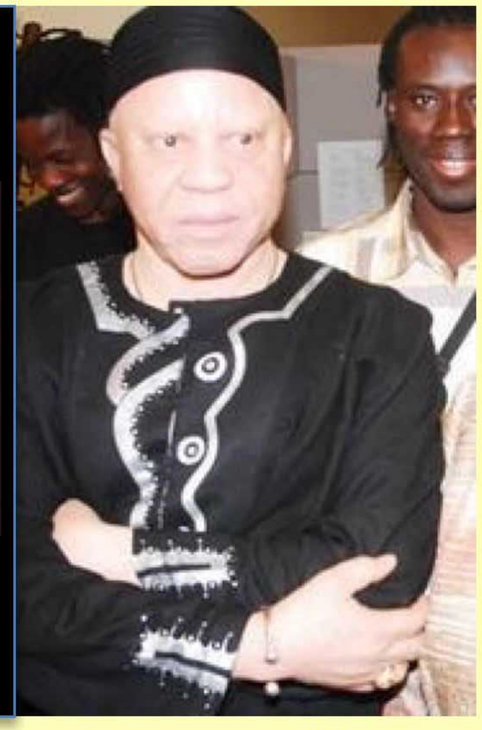
Little or no melanin gives blue eyes.

The allele associated with blue eyes occurred only within the last 6,000 – 10,000 years within the European population.



Melanocytes: Special cells produce melanin, stored in **melanosomes.**





Malian singer Salif Keita

Cornea first successfully transplanted organ

Transplants in myth
The need for transplants
Injury
Burns
Auto transplants
Allotransplants

The mechanism of recognising self
How do we recognise foreign tissue

Mendelian Genetics
Co-dominant genetics
Eye and skin colour

Barriers to transplantation
Genes of immune system

Transplant rejection

Ocular tissue transplants

Thanks to
Prof Vojin Sljivíc
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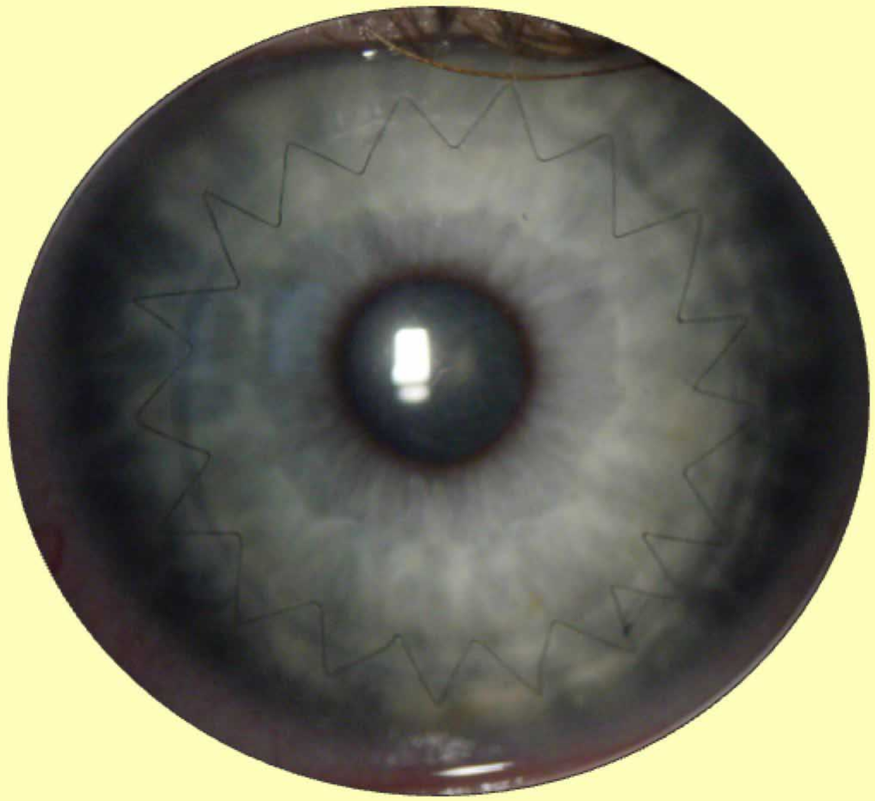


Eye colour is also determined by many genes

Ocular Cutaneous Albinism2: Key brown eye gene.

People with blue eyes have one of at least three different changes in the gene that led to not having brown eyes.

A mutation in **HERC2** gene adjacent to OCA2 on chromosome 15, affects expression of OCA2 in eye

Major role in controlling the brown/blue spectrum.

OCA2: produces **P-protein** involved in the formation and processing of melanin.

The allele increasing **P-protein** is linked to **Brown eyes**.

Another allele, reduces the P-protein. **Blue eyes**

An unidentified gene causes **green eyes gey**.

More colors than just brown, green, and blue

OCA2 and **gey** do not explain these other colours

At least eight genes influence eye colour.

(*TYRP1*, *ASIP* and *ALC42A5*) function in the melanin pathway alter total amount of melanin present in the iris

The combined effects may increase melanin levels to produce hazel or brown eyes, or reduce total melanin resulting in blue eyes.

Iris structure and distribution of freckles and peripupilar pigment distribution.

two separate genes.

1: **OCA2**, comes in two forms, brown (**B**) and blue (**b**).

2: **gey**, comes in two forms, green (**G**) and blue (**g**).

The **B** version of OCA2 tells the eye to make lots of melanin.

The G version of the gey gene tells the eye to make some.

if both are present? Lots of melanin gets brown eyes.

	B/G	B/g	b/G	b/g
B/G	BB/GG	BB/Gg	Bb/GG	Bb/Gg
B/g	BB/Gg	BB/gg	Bb/Gg	Bb/gg
b/G	Bb/GG	Bb/Gg	bb/GG	bb/Gg
b/g	Bb/Gg	Bb/gg	bb/Gg	bb/gg

Mouse coat colour is complicated

Mouse coat: 3 types of overhairs 20%: and underhairs.
Many genes influence the synthesis of melanin

The *agouti* and *extension* series of genes determine the relative amount and distribution of pigment in the hairs of the coat.

Agouti protein: signalling molecule causes hair follicle melanocytes to synthesize the yellow **pheomelanin** instead of the dark **eumelanin**
Inhibits **MSH** from binding to **MCR1**
Agouti also inhibits melanogenesis reduces the synthesis of both pigments.
A = aguoti
a = non-agouti

Mice with agouti protein alternate between brown-black and red-yellow pigment production,
Produce banded hair shafts, the wild-type phenotype
Grayish with brindled, “salt and pepper,” appearance.
Common colour of mammals in nature.

Agouti fur is a **dominant trait**
Solid colour fur, is the **recessive phenotype**

lethal A^Y, is another allele of this gene; it makes the entire shaft yellow called red by fanciers

Agouti fur is a dominant trait resulting in individual hairs having a light band of pigment on anotherwise dark hair shaft.
solid color fur, recessive phenotype (*A* = agouti; *a* = solid colour).

Genetic variants in production, packaging, distribution
Cause variations of coat colour

5 major genes interact to determine the coat colour : *A*, *B*, *C*, *D*, and *S*.

A-gene: ***determines distribution of pigment in hair***

The effect is caused by a band of yellow on the otherwise dark hair shaft.

Non-Agouti phenotype (determined by **allele *a***), yellow band is absent, solid pigment throughout

A^y removes the black pigment, leaving only yellow pigmented hairs (red).

Red is a very old mutation. "yellow mice" in Chinese dating back to 80BC.

One of the original 1895 varieties of the **National Mouse Club**

B gene: ***determines the colour of pigment.***

2 alleles: ***B*** coding for **black pigment** and ***b*** for **brown (chestnut in horses)**.

AA:BB normal agouti colour, ***a*/*a***. **solid black A/A; *b*/*b* agouti brown cinnamon *a*/*a*; *b*/*b* solid brown (chocolate)**

C GENE: ***permits colour expression***

allele c prevents colour expression. *c*/*c* animals, lack coat pigment, albinos

D gene: controls the intensity of pigment specified by the other genes

genotypes ***D*/*D*** and ***D*/*d*** permit full expression of colour in mice

d*/*d "dilutes" the colour, making it look "milky."

dilute cinnamon

due to an uneven distribution of pigment in the hair shaft.

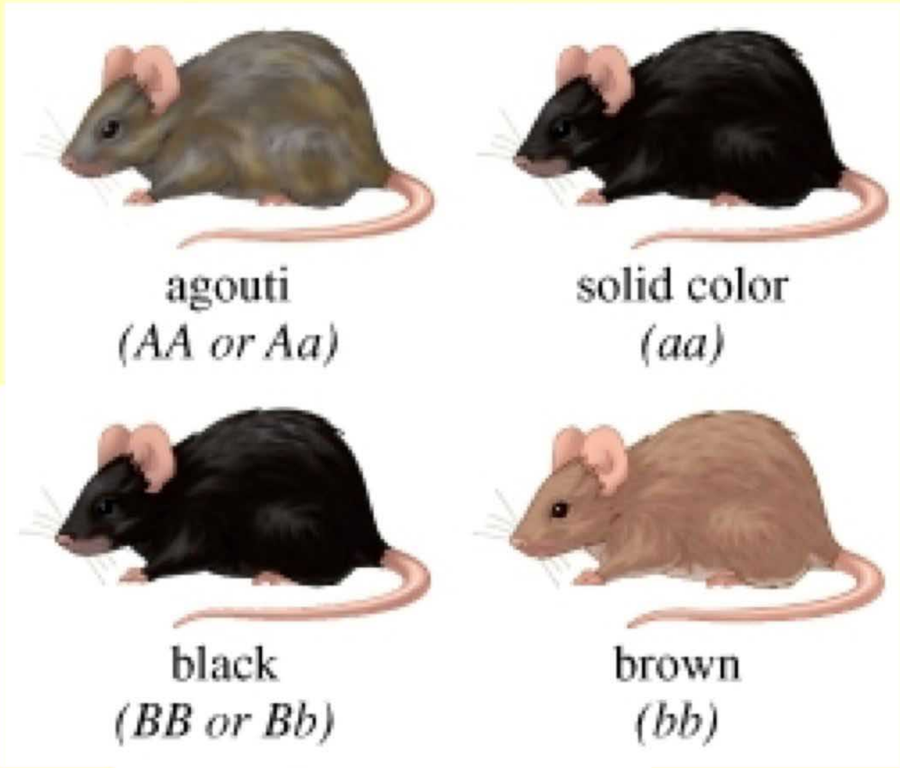
Example of a modifier gene.

S gene: ***controls the distribution of coat pigment throughout the body***

Determines the presence or absence of **spots**.

The genotype ***S*/–** results in no spots

s*/*s produces a spotting pattern called **piebald** in both mice and horses



Lethal yellow (A^y) top dominant of the agouti series: does not matter with which of the series it is heterozygous, the phenotype is rich yellow. An old mutant Cúenot (1905) lethal when homozygous. **Agouti allele (A)** is dominant over non-agouti (a). **Black allele (B**) is dominant to the brown allele (b). **Full colour allele (C)** dominant over the albino allele The agouti gene also controls appetite.

Epigenetics

Genome contains all the information to make us,

Details determined by gene regulation

Chemicals attached to DNA change the way genes are read

Exposure of parents (even grandparents!) can change the way their children's genes are expressed.

Dutch Hunger affected grandchildren of those pregnant 1944

Agouti protein binds to **melanocortin receptor** blocks skin making black pigment. Gene turned "on" in mutant mice, receptor is always blocked, and the animals are yellow.

Agouti genes kept in "off" position by **epigenome**, **methyl groups** attached to regions of DNA silence genes.

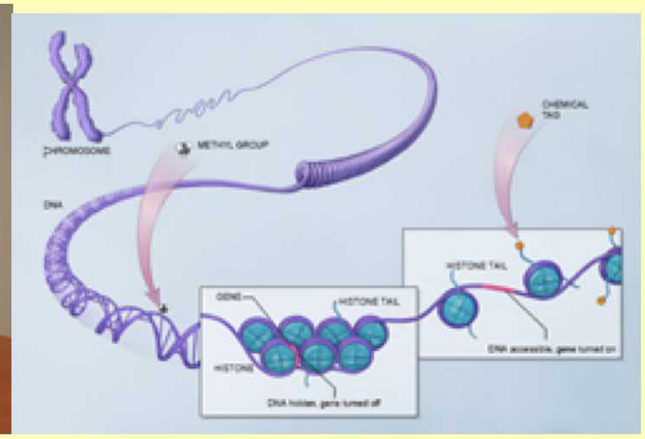
Chemical found in plastics, including baby bottles: **Bisphenol A.**

Jirtle exposed pregnant mice to **BPA**: more pups yellow, obese mice than expected: **BPA** removed methyl groups from DNA.

Melanocortin receptors in appetite centre of brain.

Agouti protein causes differences in genetically identical mouse twins: coat color and body weight.

The genome of each of these mice is the same, but the gene expression differs



Adding chemical tags changes how DNA gets read.
BPA turns **agouti gene** on. Pregnant yellow mice exposed to BPA, more yellow, obese pups.
If BPA-exposed pregnant mice eat more methyl-rich foods, the effects on the pups were reversed, there were more brown pups than yellow.

rise of obesity coinciding with the widespread use of bisphenol A in everything is a causal connection? DEBATED

INTERNATIONAL FOOD INFORMATION COUNCIL FOUNDATION

"Well he would say that, wouldn't he?"
Mandy Rice Davies

Mother supplemented
DNA Methylated

Tumour allografts Non-Mendelian characteristics'.

Ernest Tyzzer: Harvard: studies on the genetic basis of cancer susceptibility

C Little: used his inbred mice.

Malignant cells injected into same strain, grow vigorously and cause death.

Injected into other strains, tumors would usually fade away, allowing survival.

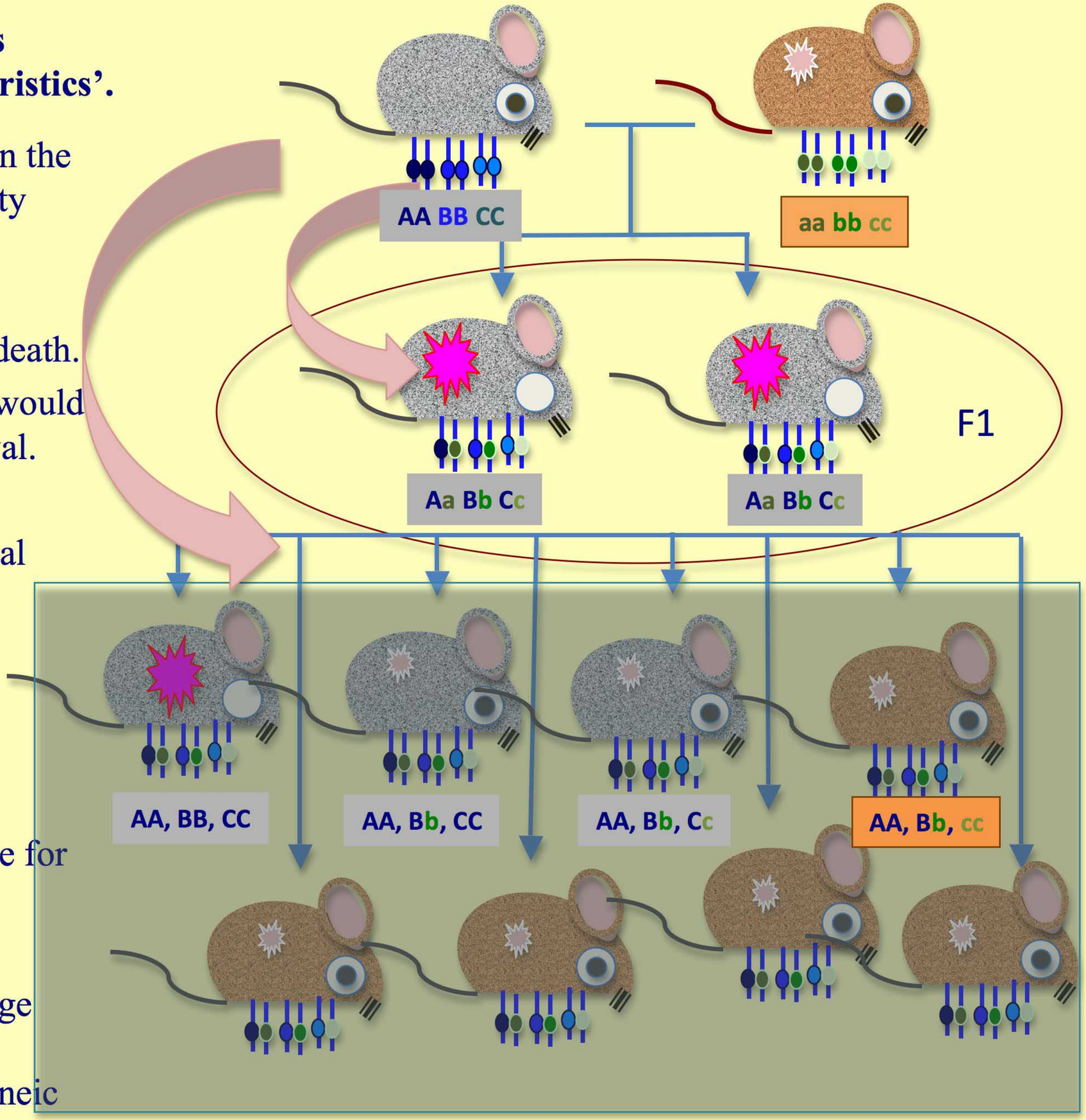
Rate of acceptance 100% in parental strain,

100% in the F1 generation,

1.6% in the F2 generation.

1916 calculated that there were approximately 12 genes responsible for cancer resistance

He accidentally discovered that large number of histocompatibility loci determine the acceptance of allogeneic tissues (tumours)



Laws of Transplantation

1930s decline of transplantation research.

except for corneal grafting, all attempts at skin and organ transplants will fail due to rejection

George Snell: Jackson Lab: inspired by Little "The Genetics of Tumor Transplantation"

Discovered the genetic factors that determine the possibilities of transplanting tissue from one individual to another.

Introduced the concept of H antigens (histocompatibility) locus that controls (tumour) graft rejection.

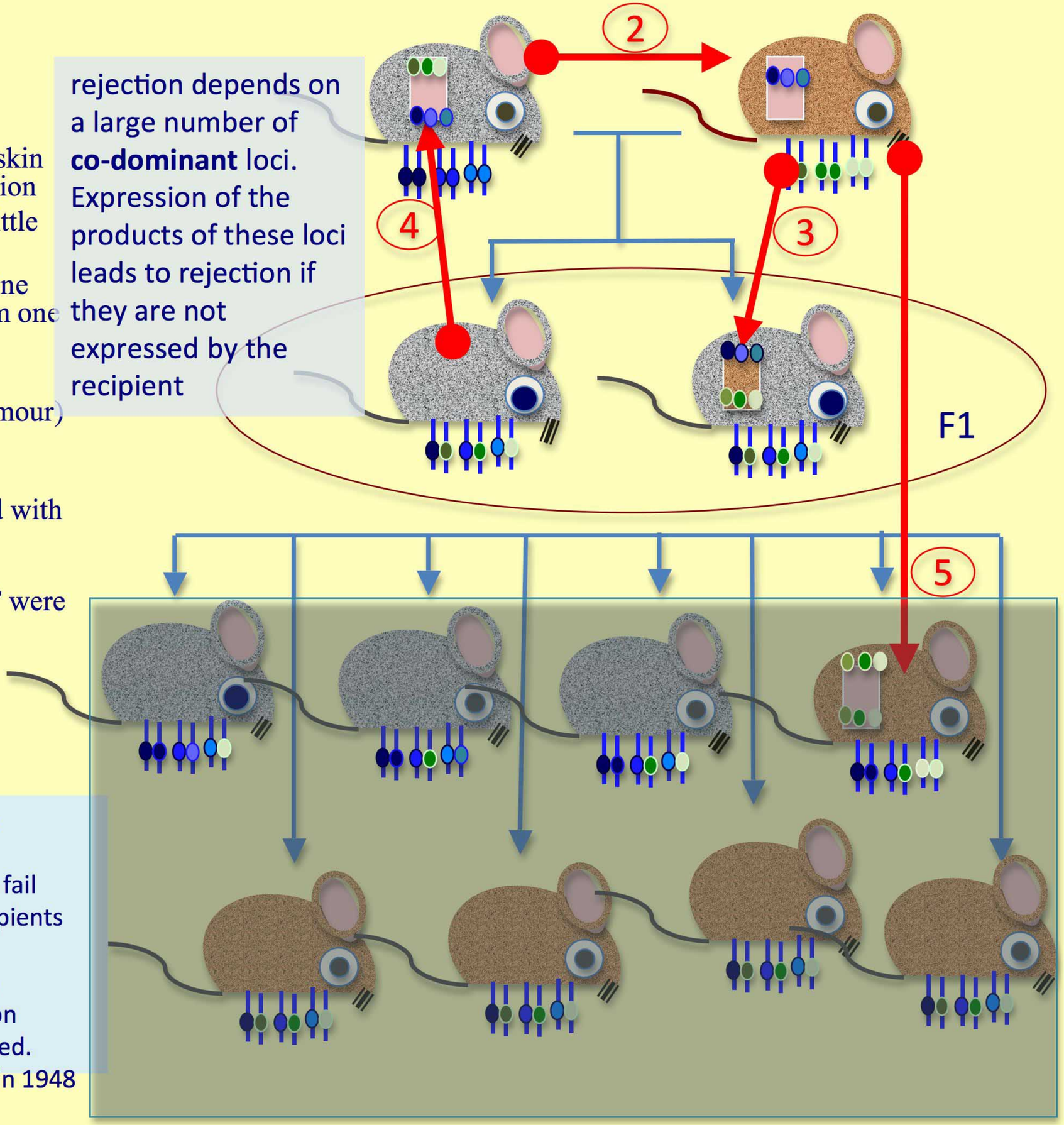
Peter Gorer: sera from rabbits immunized with mouse red blood cells, which led to the discovery of antigen II

1946: Gorer visited Snell and "H" and "II" were combined as "H-2,"

"A **Major Histocompatibility Gene,"**

nine alleles were identified.

rejection depends on a large number of **co-dominant** loci. Expression of the products of these loci leads to rejection if they are not expressed by the recipient



(1) Strain A transplants to Strain A recipients succeed
(2) Strain A transplants to Strain B recipients fail
(3) Strain A (or B) transplants to (AxB)F1 recipients succeed;
(4) (AxB)F1 transplants to Strain A (or B) fail;
(5) Strain A (or B) transplants to F2 generation almost always fail, but occasionally succeed.

These 'laws' were formulated by George Snell in 1948

Tolerance

Why don't we reject our own tissues Developing Autoimmunity?

1956: Billingham, Brent & Medawar

Autoimmunity exception not rule

Developing tissues are shown to immune system in Thymus.

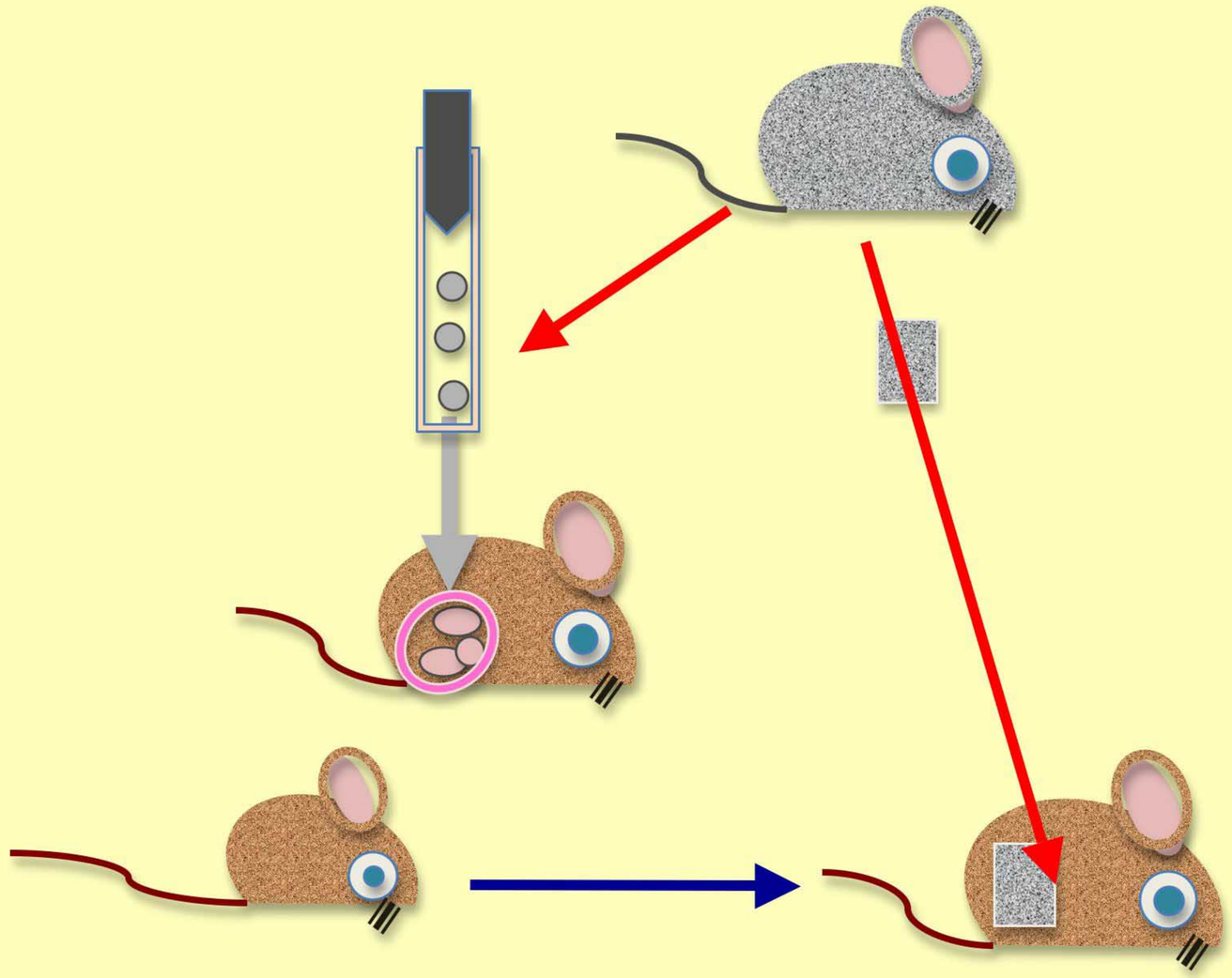
Those T-cells that react are eliminated

Clonal deletion

Only those cells that do not recognise self remain to form clones in the adult.

Other mechanisms also involved to maintain tolerance

Eye, brain, testes.



Autoimmunity

Some tissues are sequestered and are not presented

Breakdown of tolerance

Later damage or infection can lead to autoimmunity

Sequestered Antigens

Never seen by immune system before and therefore reactive cells not deleted in the thymus

Antigens are released after tissue damage.

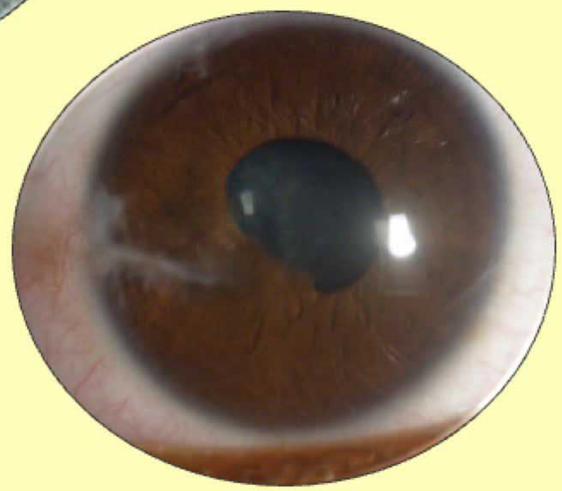
The corresponding T-cells react against the tissue

Horror autoxicus

Autoimmunity

Mumps orchitis

Sympathetic Ophthalmia



Markers of self

The **major histocompatibility complex** (**MHC**) is a set of cell surface molecules encoded by a large gene family in all vertebrates.

Three subgroups: class I, class II and class III.

Choice of a gene variant (allele) at each locus

Very variable

MHC genes are inherited together (linkage) as a group (**haplotype**)

one from each parent.

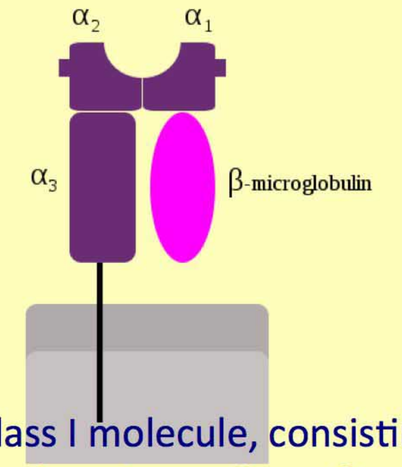
Each **haplotype** containing 3 class-I (B, C and A) and 3 class II (DP, DQ and DR) loci.

Haplotypes, normally, are inherited intact: proteins encoded by different loci are inherited together (e.g., A2; B27; Cw2; DPw6; DQw9; DRw2

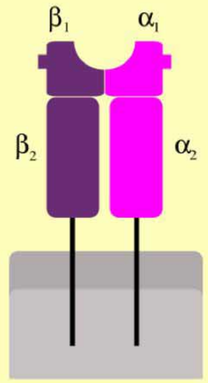
Expressed on the cell surface in a **co-dominant** manner: products of both parental genes are found on the same cells

Expression of class II antigens is restricted.

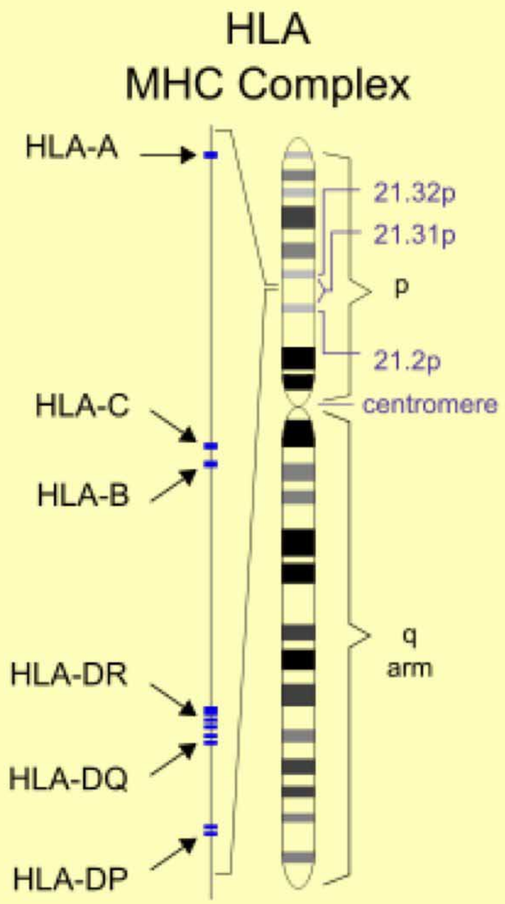
B lymphocytes, some macrophages and monocytes, skin associated (Langerhans) cells, dendritic cells and occasionally on other cells.

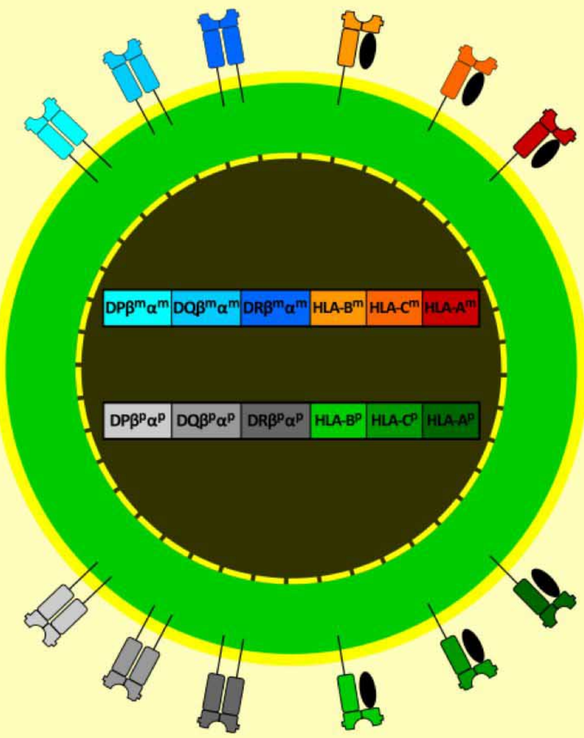


MHC class I molecule, consisting of three α-domains and one β_2-microglobulin



MHC class II molecule, consisting of two α-domains and two β-domains

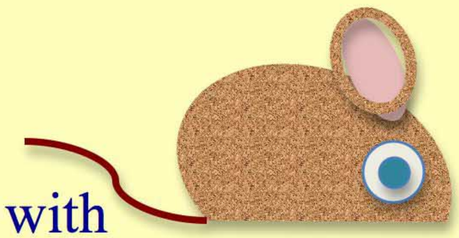




HLA A 1,884
HLA B 2,490
HLA C 1,384

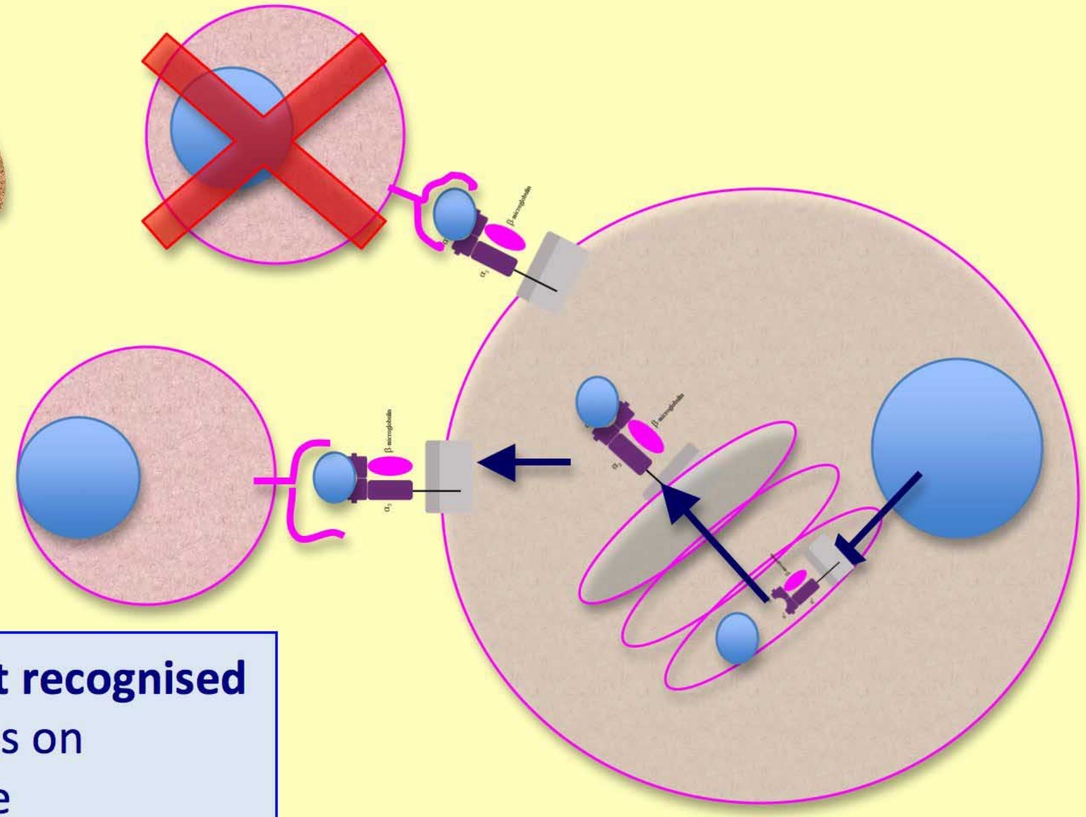
Markers of non-self

Every cell in your body is covered with **MHC** self-marker proteins



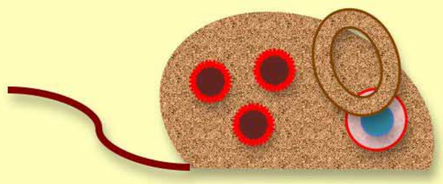
Individuals carry different sets.

An **MHC** protein is scaffold that presents pieces of **self-protein (peptides)** to immune cells.

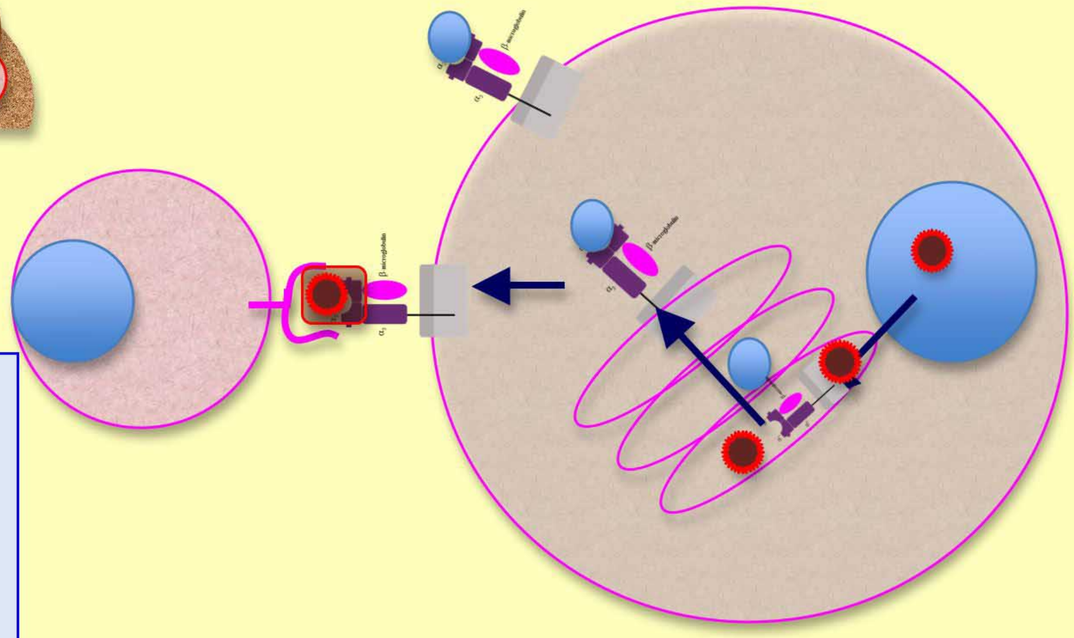


Peptide not recognised
T-cell moves on
Surveillance

Lymphocytes that can react to these are inactivated during development **(tolerance)**



Immune cells distinguish between **MHC-self peptides** and **MHC-bound peptides** from foreign source (**antigens**) e.g. viral infection.



Recognition
3 fates
Activation
Death
Anergy

Transplants in legend

Xenotransplants

Concept of prolonging life by transplantation is 5,000 yrs old

Hindu txts: After beheading him for humiliating his wife, Lord Shiva transplanted a goat's head to Daksha.

Another time elephant's to Ganesha

Giovanni Lanfranco (1582–1647)
St Peter Healing St Agatha circa 1614

Allograft.

Jacobus de Varagine: 1230-98: Archbishop of Genoa; compiler of hagiographies, golden legend **Legenda Aurea**.

Saints Cosmos and Damian replaced the gangrenous leg of the Roman deacon Justinian with a leg from a recently buried Ethiopian Moor. cadaveric allograft

Autotransplants.

Saint Peter re-implanted the breasts of Saint Agatha pulled off during torture

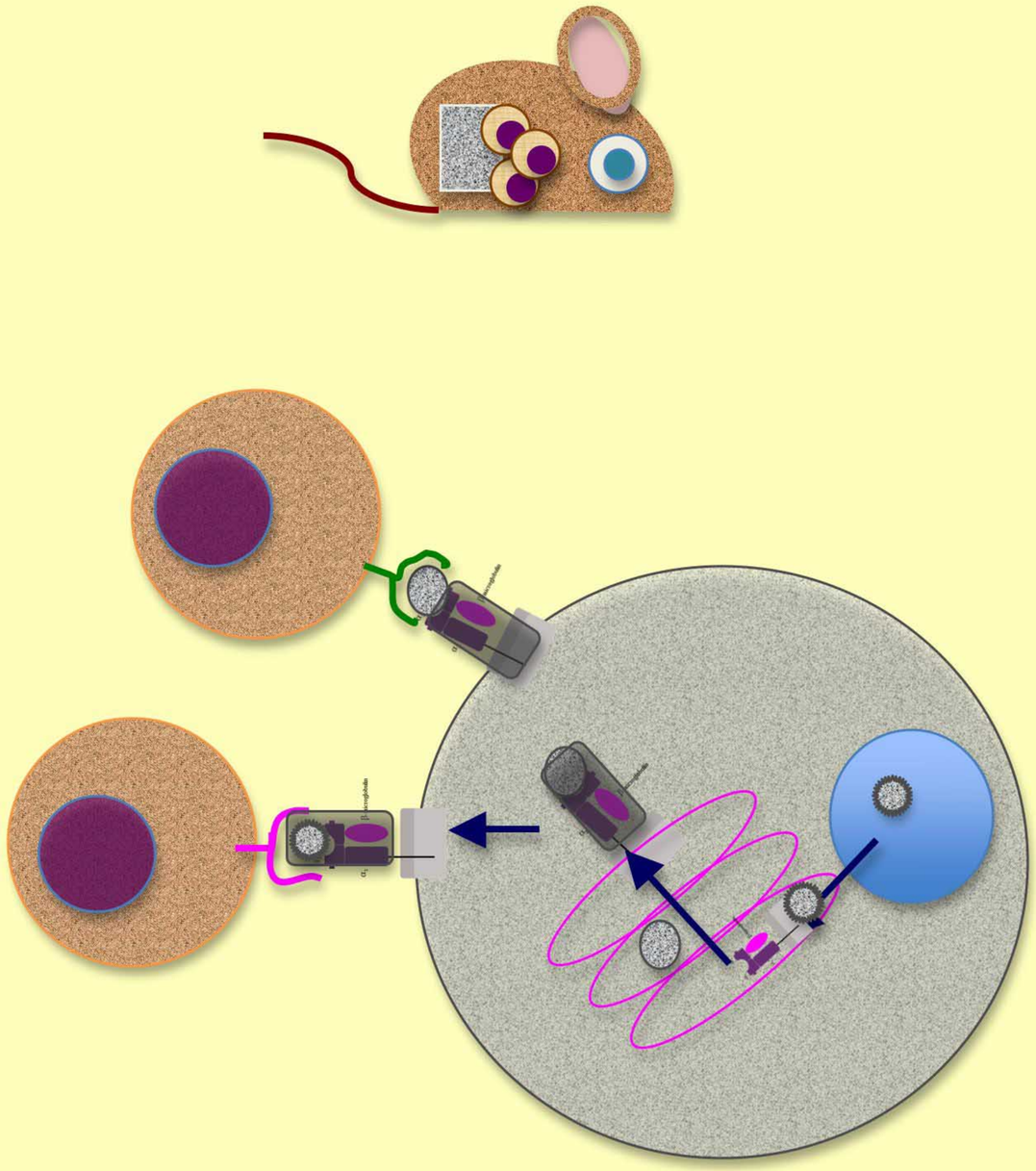
Fra Angelico (1395–1455)
The Healing of Justinian by Saint Cosmas and Saint Damian
1438-1440 tempera on panel. Museo di San Marco, Florence

Κοσμάς και Δαμιανός: twin brothers, physicians, and early Diocletian martyrs, born in Cilicia, Turkey

Transplanted tissue carries the **donor MHC** "tissue type"

Recipient not tolerised to these

Recognised as foreign and immune cells attack.



Allorecognition

Processing and presentation of graft antigen (**alloantigen**)

T cells (produced in the **t**hymus) circulate throughout the body until they recognise foreign peptides (antigens) loaded on **MHC molecules** on the surface of **antigen presenting cells**

Direct allorecognition, Dendritic cells migrating from the graft
T cells recognise allogeneic MHC plus associated peptides directly.

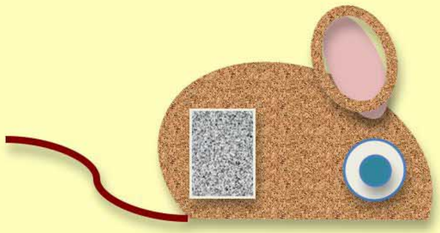
Indirect allorecognition, recipient APCs pick up fragments of donor MHC and present allogeneic peptides to recipient T cells in association with self-HLA

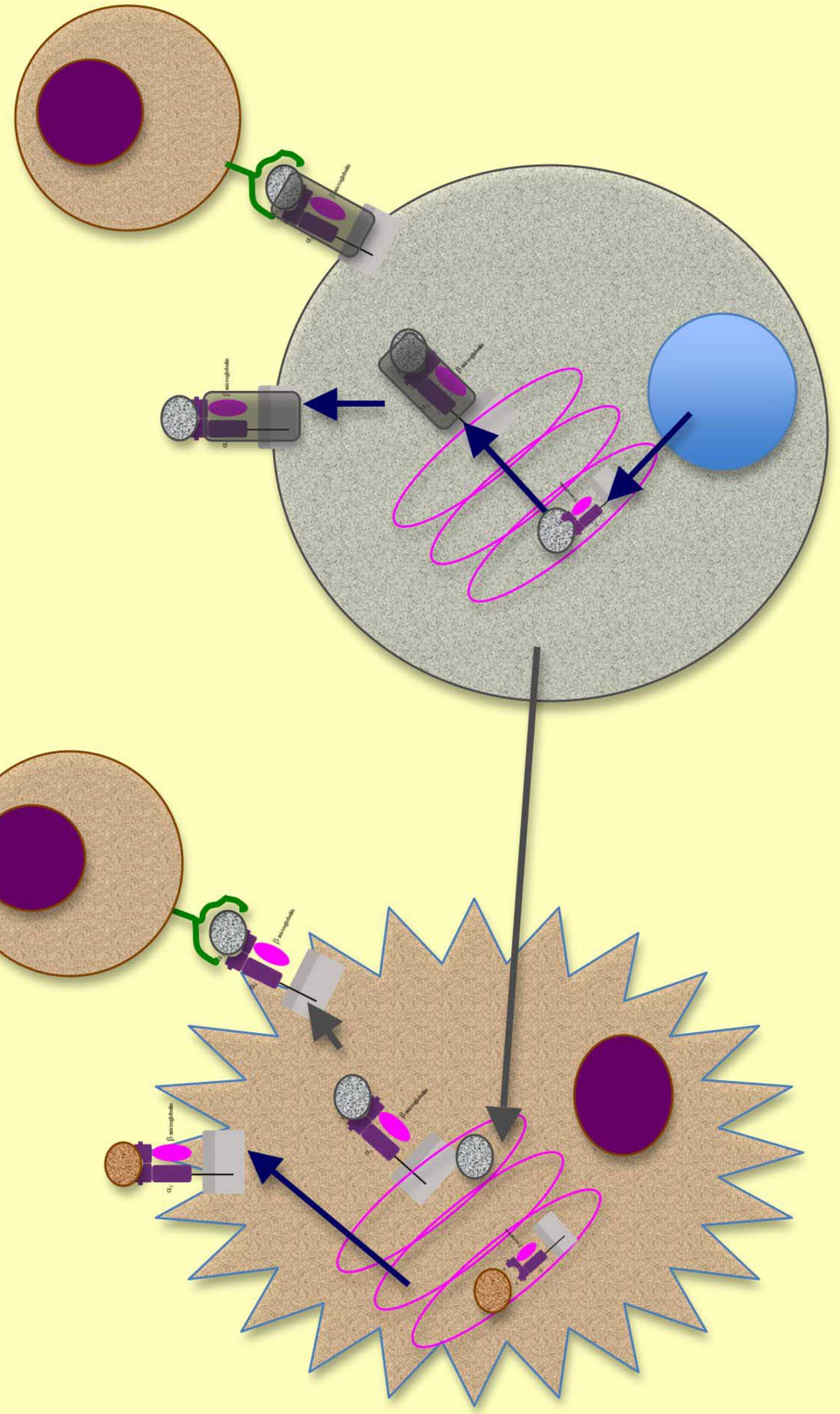
Specific

T-cell won't recognise other peptides

Recognition
3 fates

Activation
Death
Anergy





Co-stimulation determines fate of cell after antigen recognition

T cell receptor binding to antigen-loaded MHC:

Need secondary signals to become activated

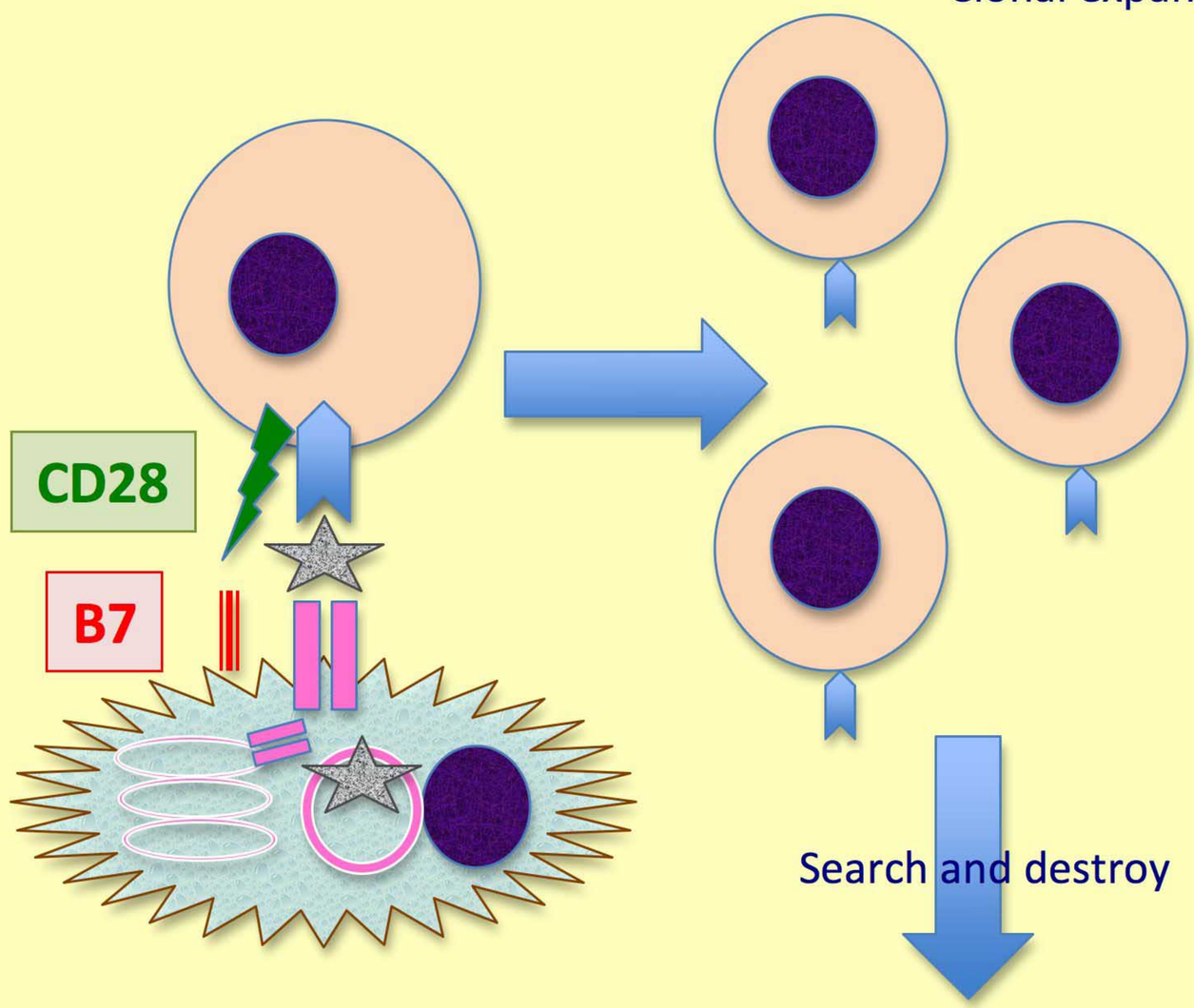
Th cells: **CD28** on the T cell binds to molecules on the **APC** – **B7**

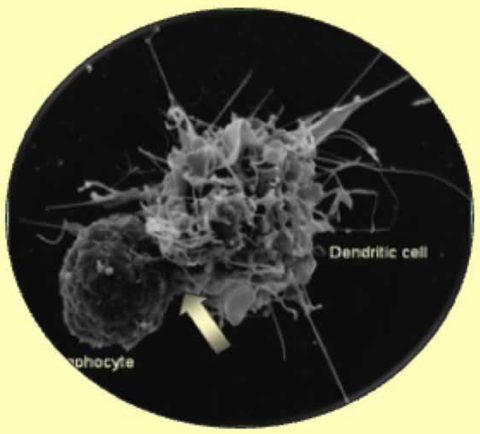
Production of many millions of T cells that recognise that antigen.

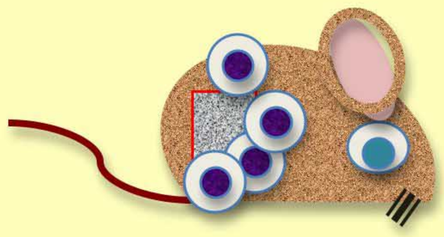
If the T cell does not receive a signal through **CD28** it

- dies,
- becomes unresponsive (anergic)
- develops into a regulatory inhibitory cell.

Tc cells require signals from other co-stimulatory molecules such as **CD70** and 4-1BB (**CD137**)







Controlling the response

CD28:B7 causes production of **CTLA-4 which** blocks CD28 for B7

winds down the immune response.

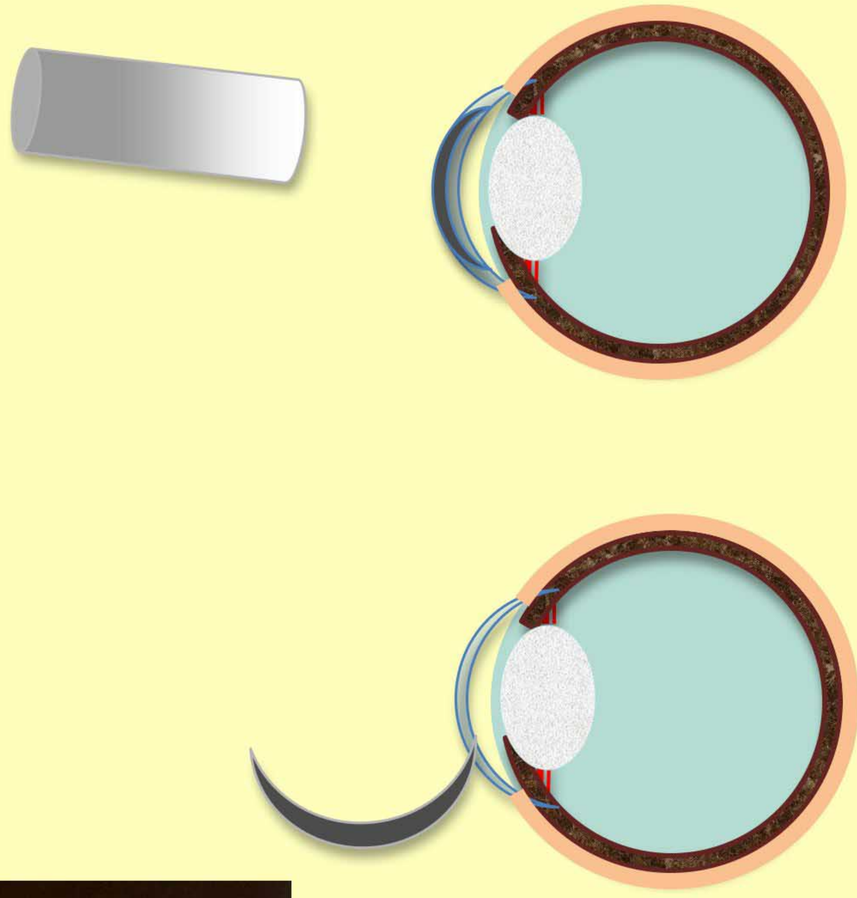
Early treatment of corneal opacity

1796: Erasmus Darwin: After ulcers of the cornea which have been large, the inequalities and opacity of the cicatrix obscures the sight in this case could not a small piece of the cornea be cut out by a kind of trephine about the size of a thick bristle, or a small crow-quil and would it not heal with a transparent scar

Zoonomia,.

Chevalier Taylor advised to 'pare off the excressence' or to rub it hard with a brush of barley awns.

1789: Pellier de Quengsy sugested the insertion of a crystal into the opacity of a corneal scar



Erasmus Darwin
Joseph Wright (c.1792–3),
Derby Art Gallery

Early attempts at corneal transplantation

1818, Franz Reisinger: suggested living cornea for transplantation: ‘I was struck with the idea of simulating the clear human cornea by replacing the opaque cornea with a like tissue – the clear cornea of a living animal – with which the eye could unite organically.’

Transplantations in rabbits and chickens unable to achieve clear grafts.

1837 S Bigger: Claims that the first successful cornea transplant

Captive of Bedouin restores sight of a pet gazelle with graft from another animal. Dublin J Med Sci 1837.

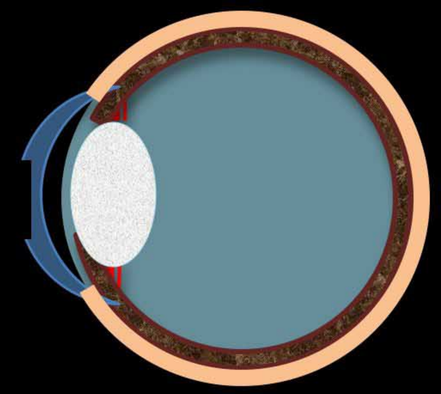
1838: Richard Kissam U.S. Only 2 sutures used, porcine corneal xenograft was rejected.

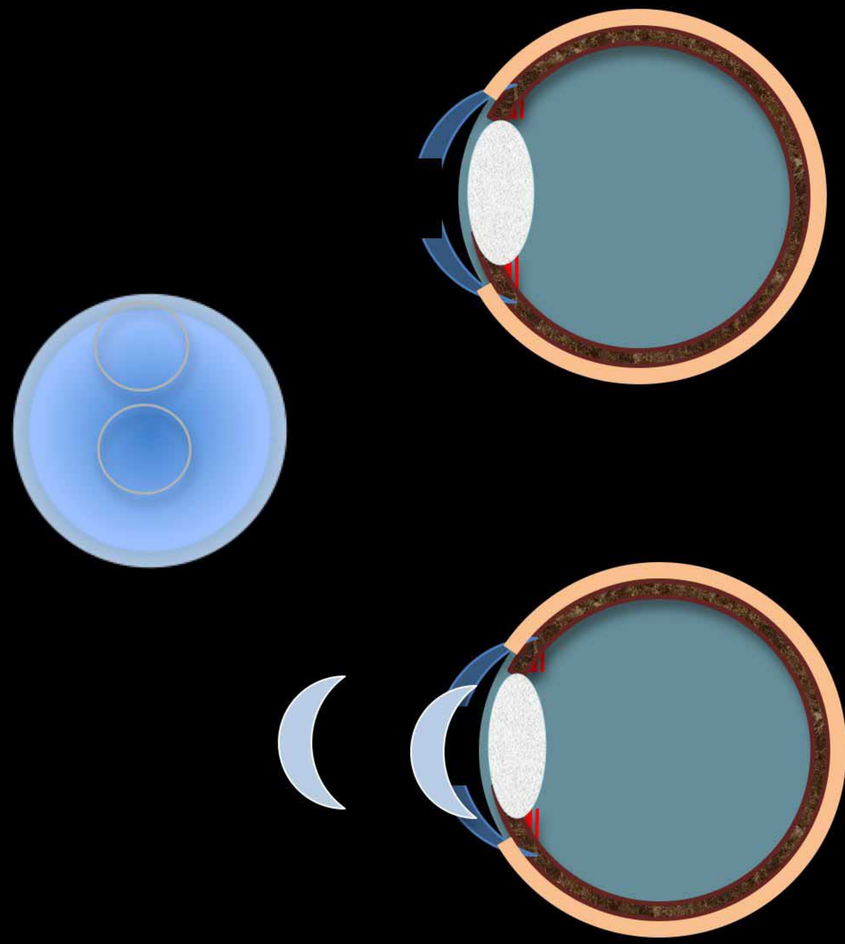
1868: May rabbit corneal grafts to humans, but concluded that the failures in the first 24 attempts were the result of "imperfect technique and the inability to keep the eyes properly bandaged.”

1886: von Hippel: lamellar xenograft full thickness rabbit cornea into a lamellar bed.

clockwork trephine with which to cut both donor and recipient

1884: Karl Koller Vienna: cocaine anaesthesia suggested by Sigmund Freud





1914, Anton Elschnig, Austria, second successful corneal transplant

1920s Vladimir Filatov lamellar keratoplasty

1930: used a donor cornea from a cadaver for a penetrating keratoplasty

Ramon Castroviejo, research fellowship at the Mayo Clinic, developed a double-bladed knife for square grafts

Paufique: Lamellar transplants

Dermot Pierce: Croydon

1930s success rates of 20-40% despite the lack of any form of immunosuppressive treatment

Skin transplants 0% survival

D. RAMÓN CASTROVIEJO
Doctor en Medicina - Año 1928

Columbia Medical Center's Dr. Ramon Castroviejo has successfully grafted the cornea of a stillborn infant upon the opaque eye of a grown man (TIME, April 15, 1935).

Indications for corneal transplantation

Corneal transplant is one of the most common transplant procedures.

approximately 100,000 procedures are performed worldwide each year

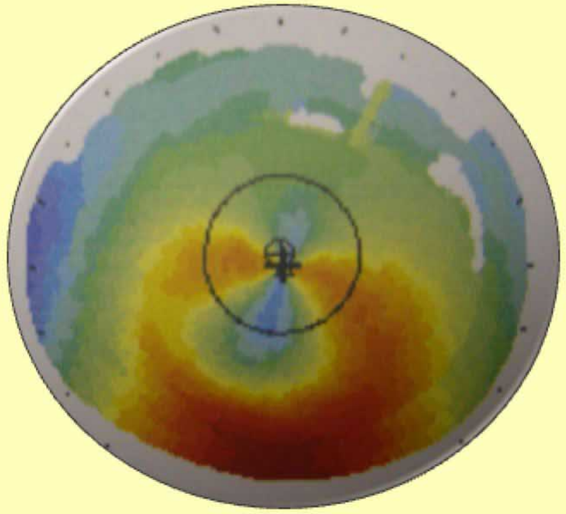
2,300 corneal transplant procedures are performed each year in the United Kingdom

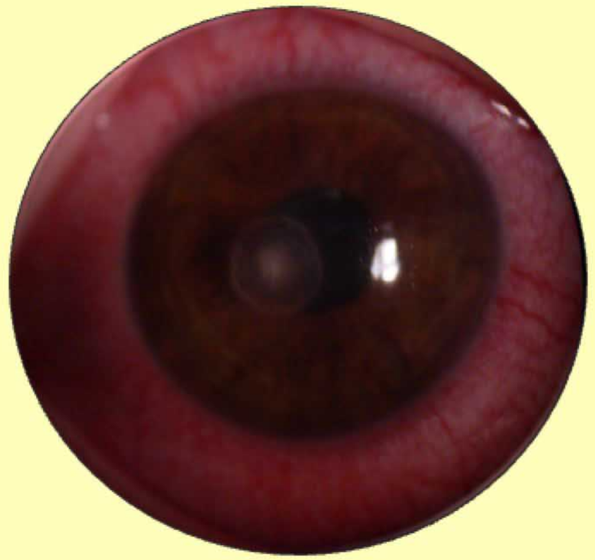
Cornea shape (keratoconus)

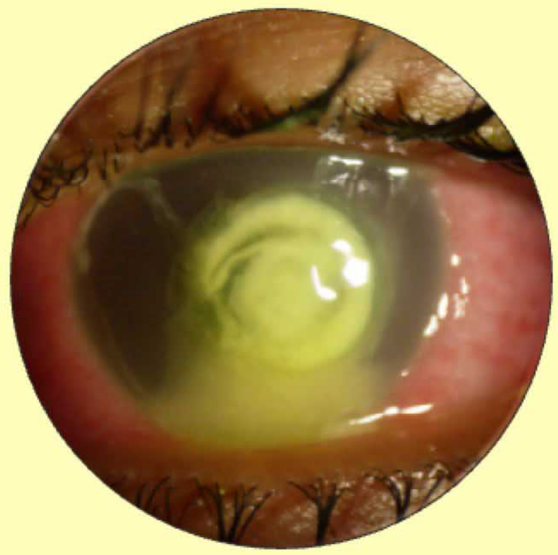
Opacity: Fuch's dystrophy

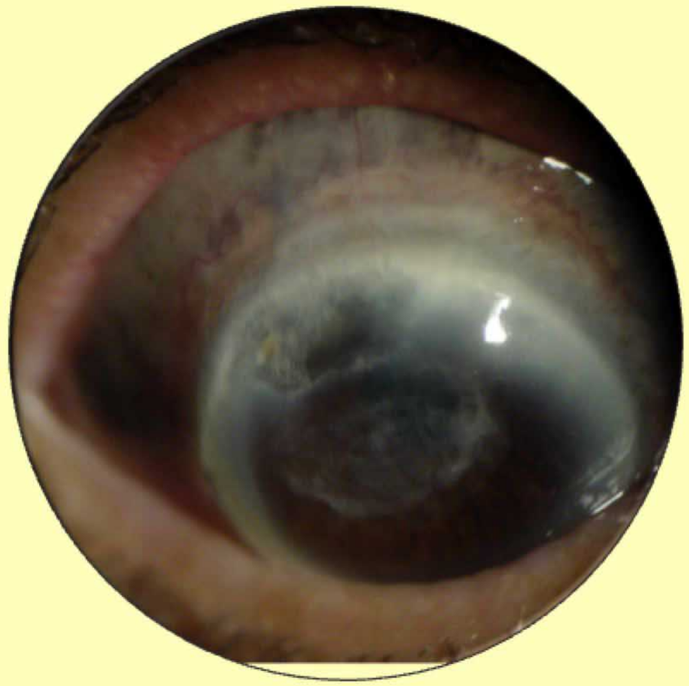
Infections

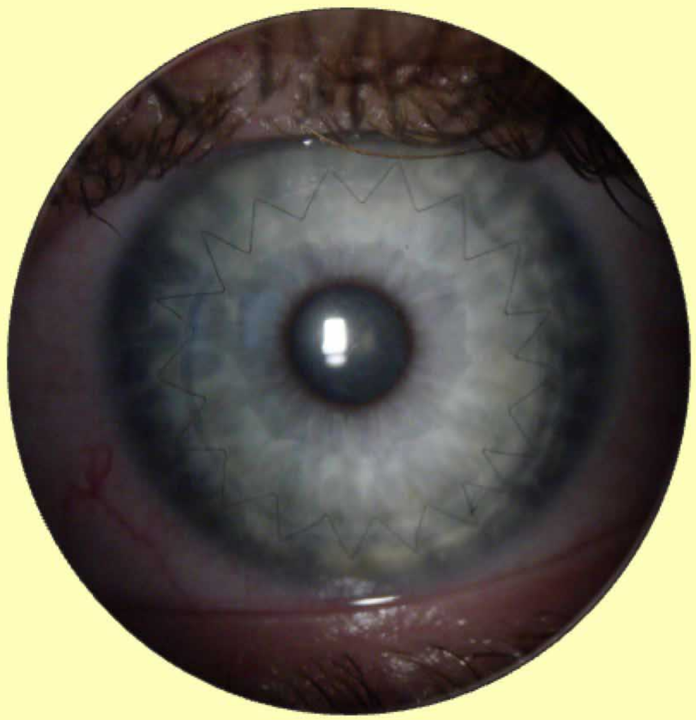
Injuries

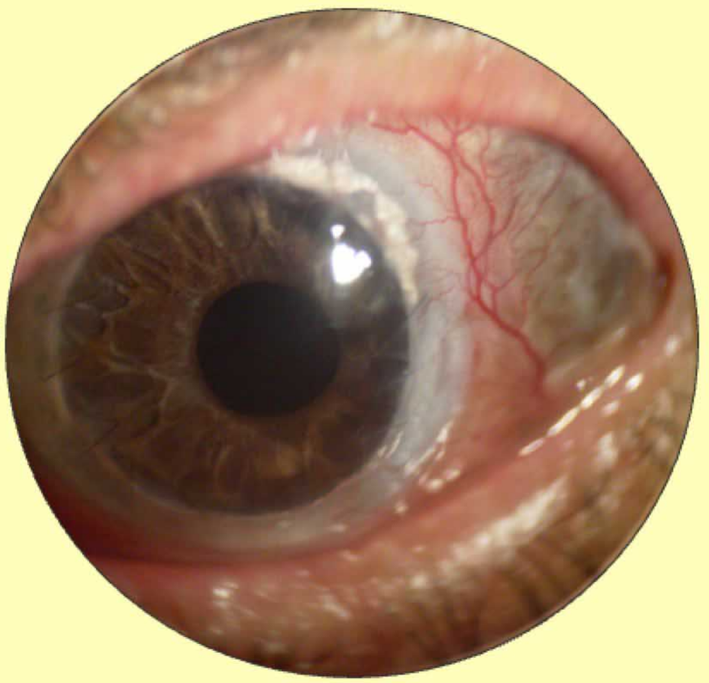




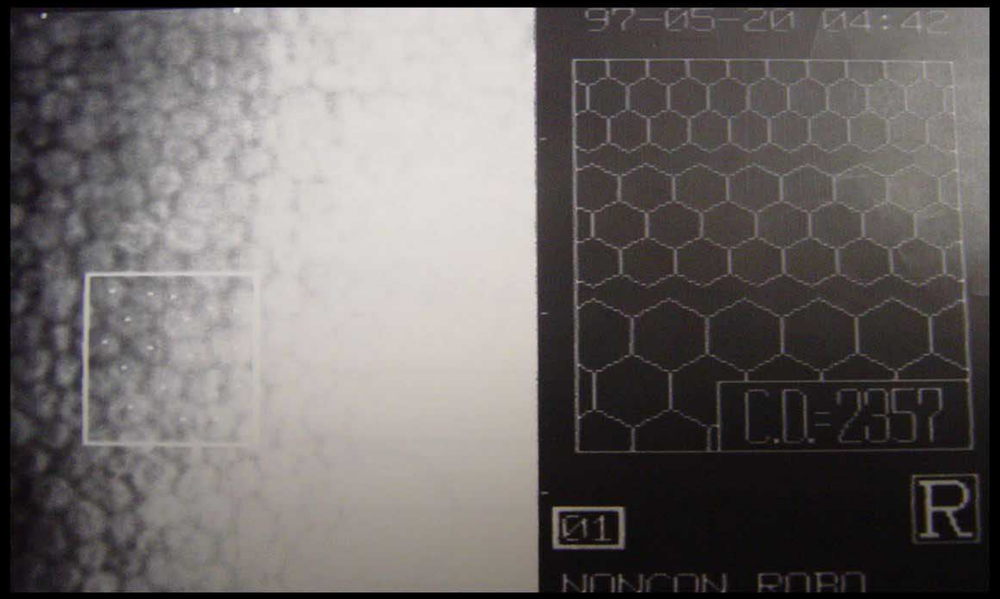


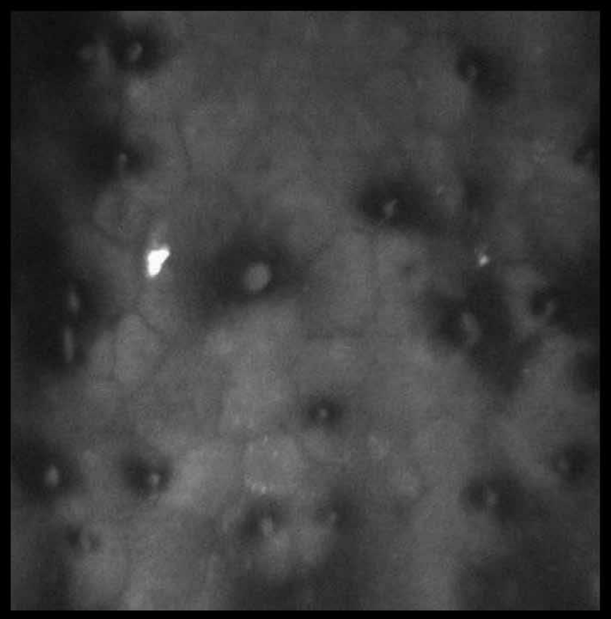


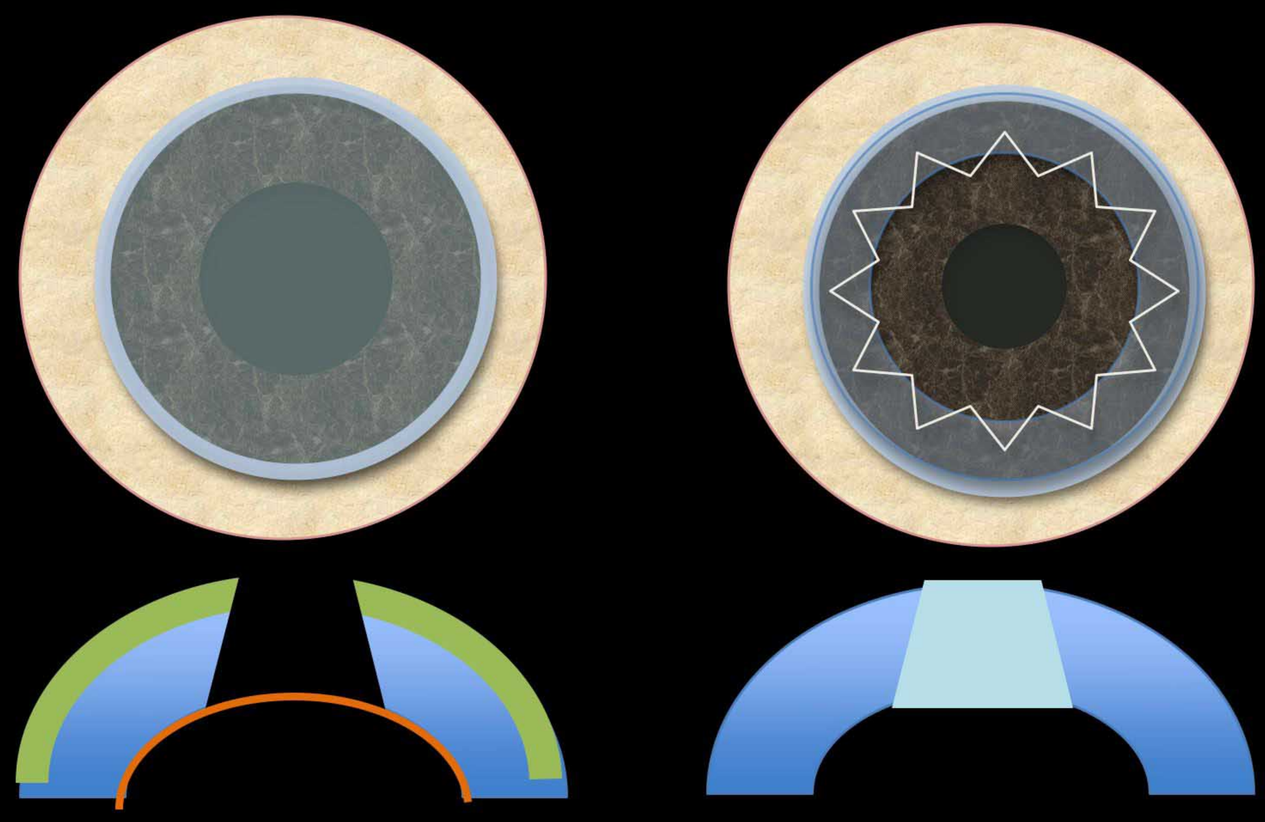


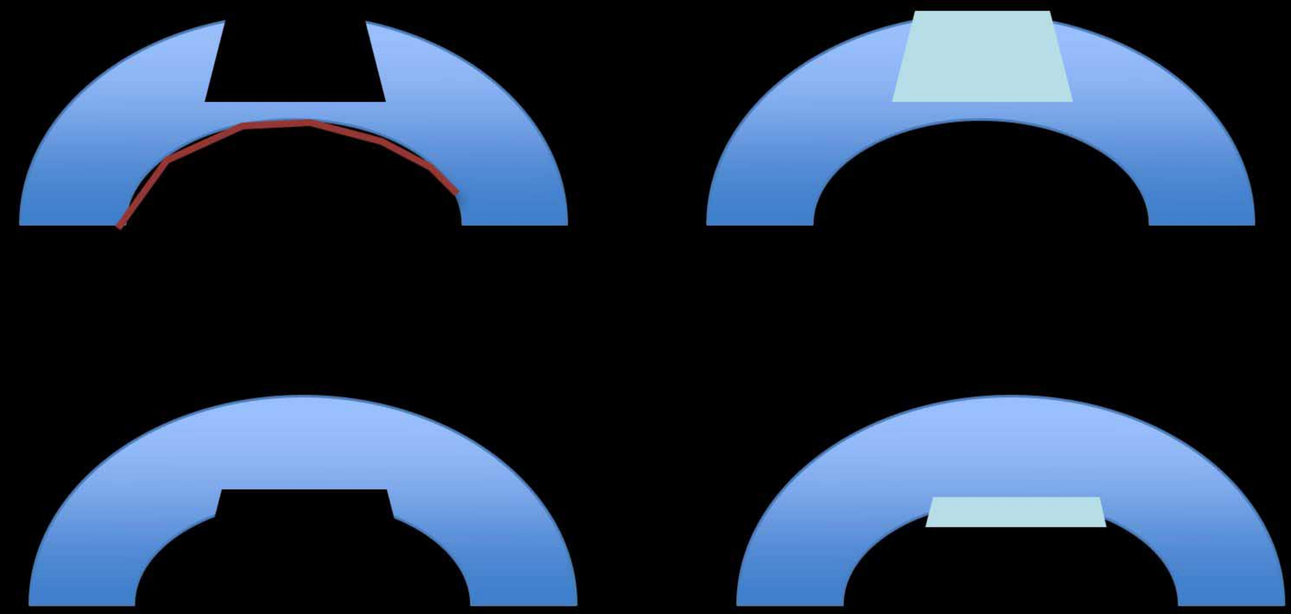


Transplanting the cornea layer by layer

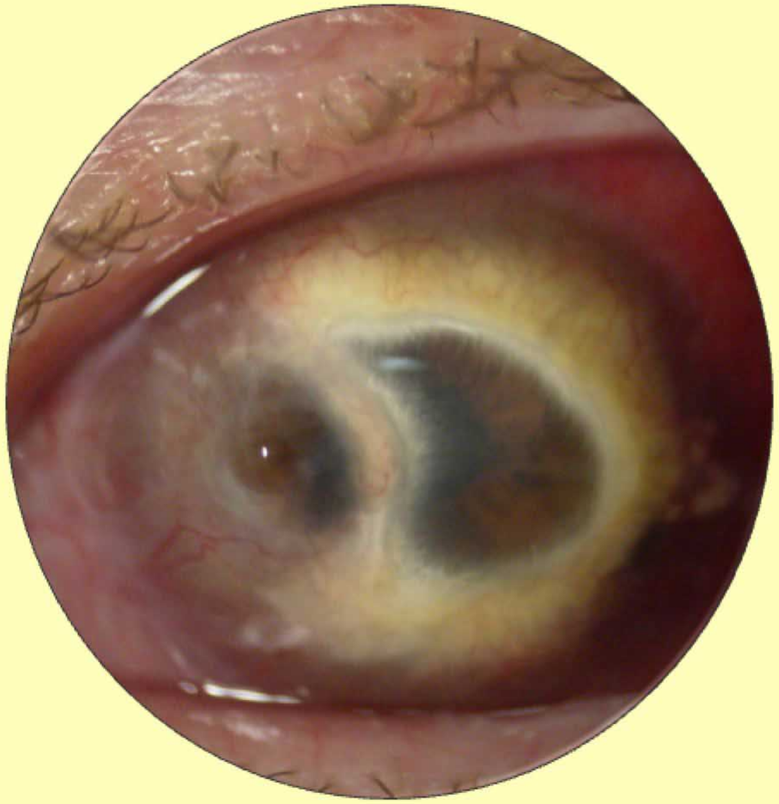


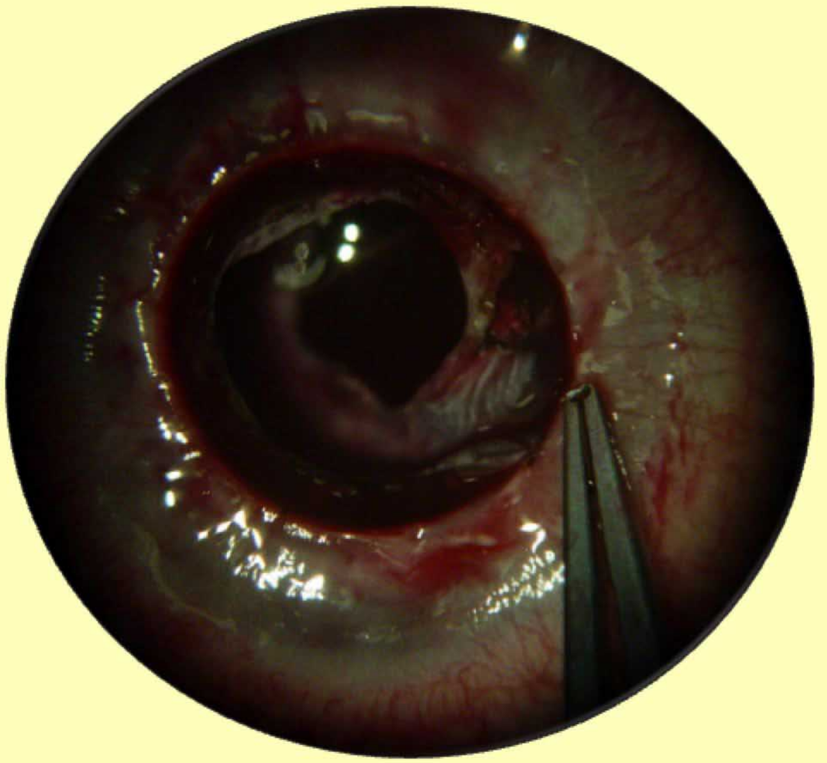


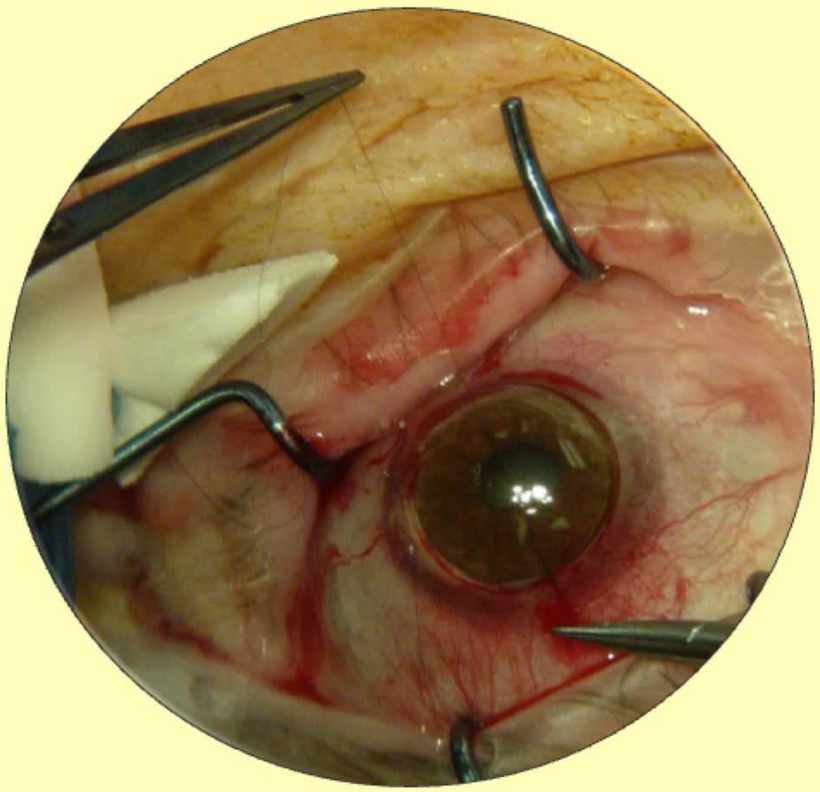


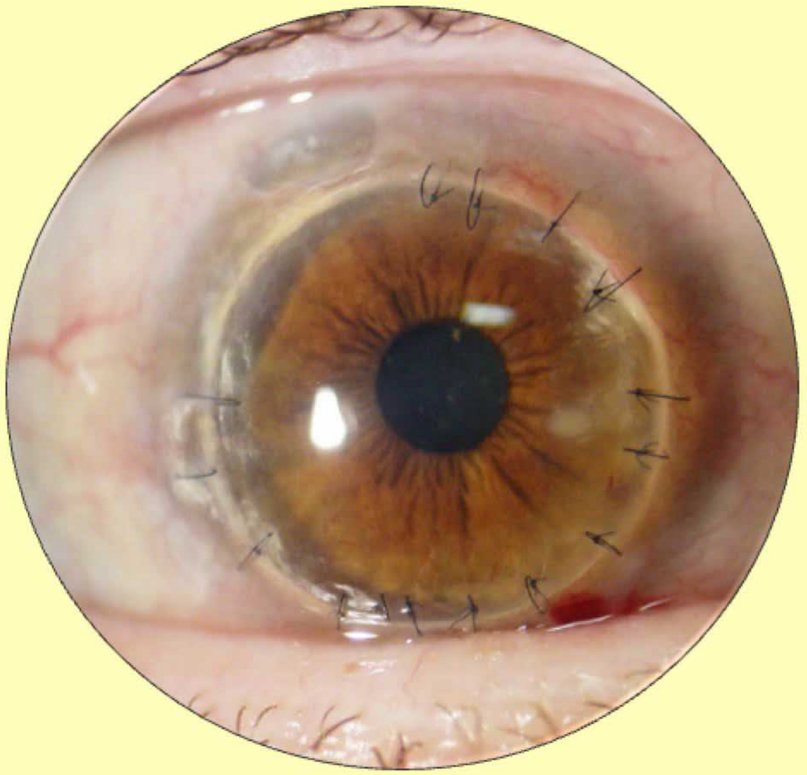


Penetrating
Full thickness









Origins of transplantation

The 16th century was a particularly bad time for noses.

1566: **Tycho Brahe**, 20 yr old and cousin, Danish nobleman Manderup Parsbjerg, guests at party by Prof. Bachmeister in Rostock.

Dec 29, duel. started at 7 p.m. in total darkness, a large portion of his nose sliced off.

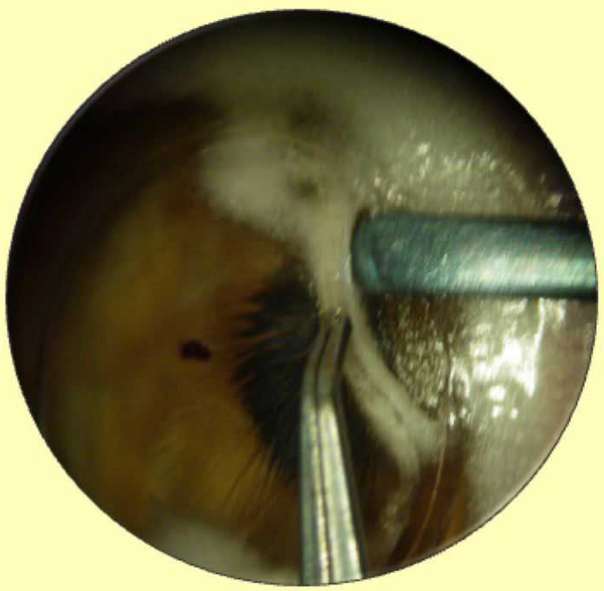
His 3rd cousin killed an opponent in 1568, in 1581Tyco's Uncle killed a second cousin. In 1584 another cousin died in a duel and an uncle in 1592.

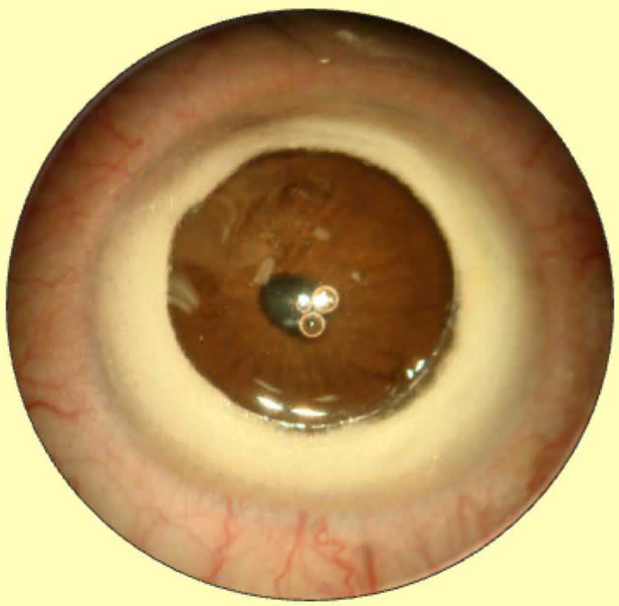
Artificial nose made, **not from wax, but from an alloy of gold and silver** and put it on so skillfully, with glue that it looked like a real nose.

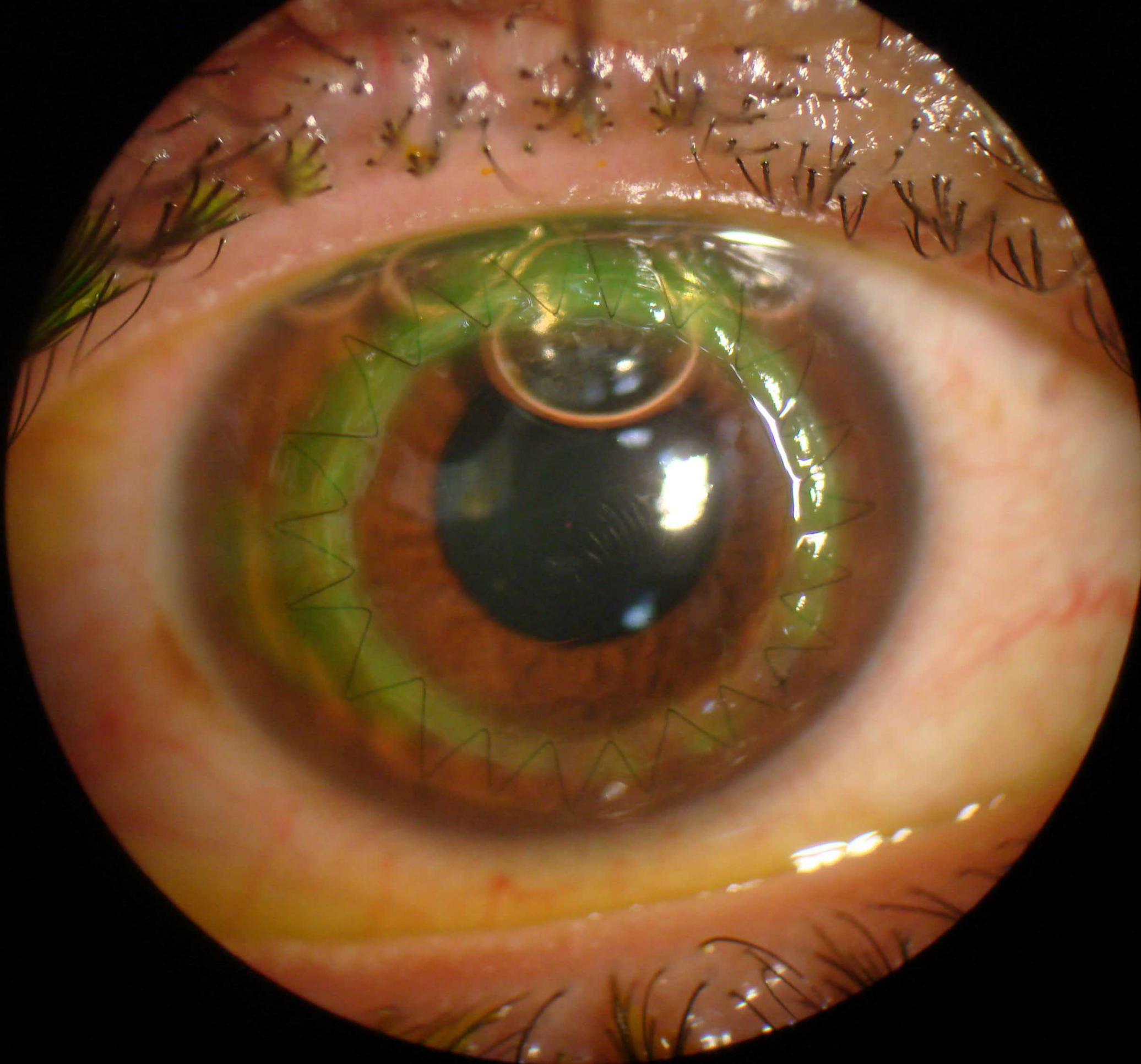
Catalogued stars with naked eye in his observatory, his pet elk broke a leg when drunk, employed a psychic dwarf, Jeppe, under the dinner table, never married the commoner mother of his 8 children, after the death by alcohol of his Royal Patron argued with the relatives and forced to leave Denmark arrives in Prague. Assistant Kepler.

Dies 2 yrs later after a heavy drinking session.

Lamellar Transplants





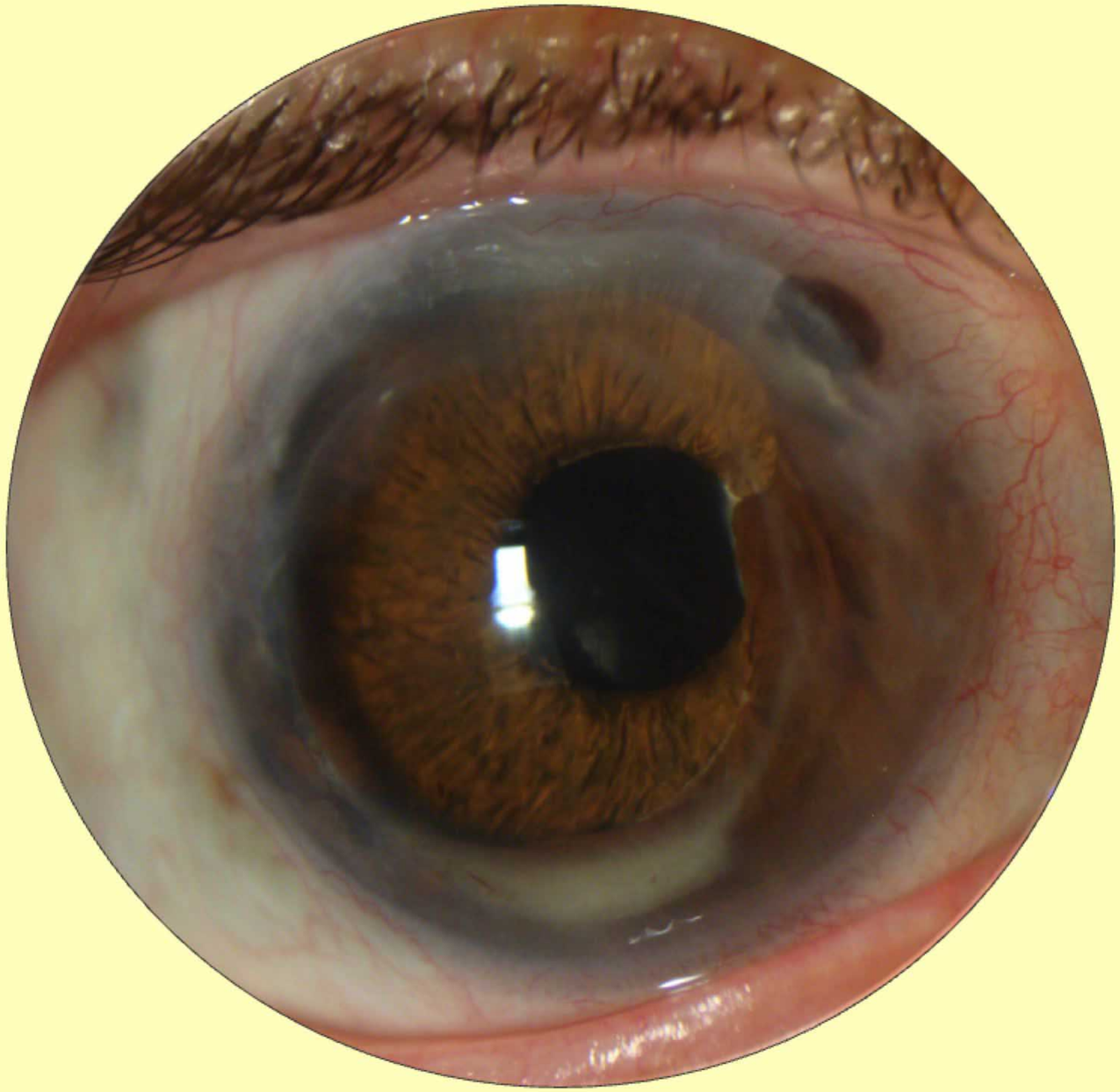


Endothelial Transplants

Gareint Melles: Holland

Price: USA

Donald Tan Singapore



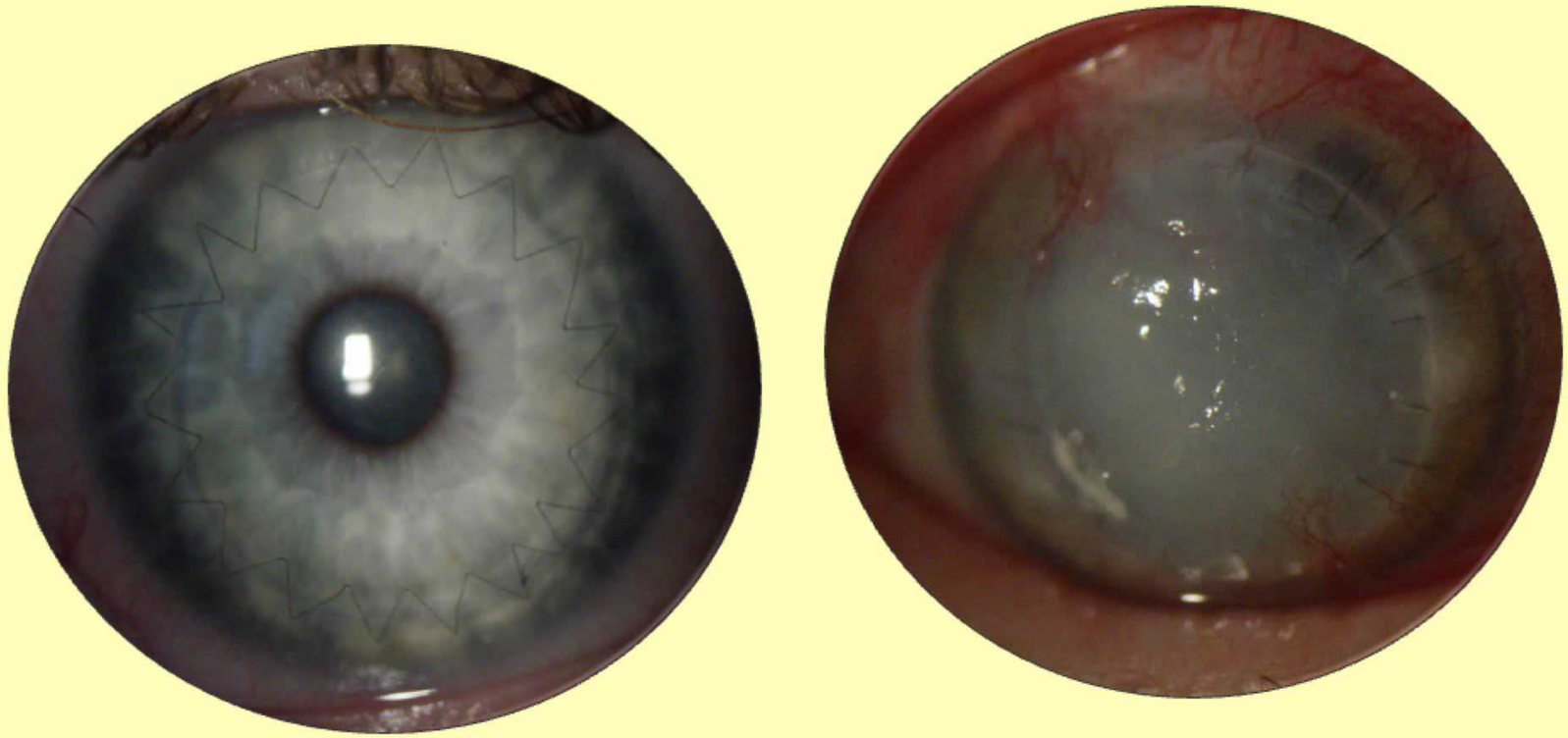
Corneal Transplant failure

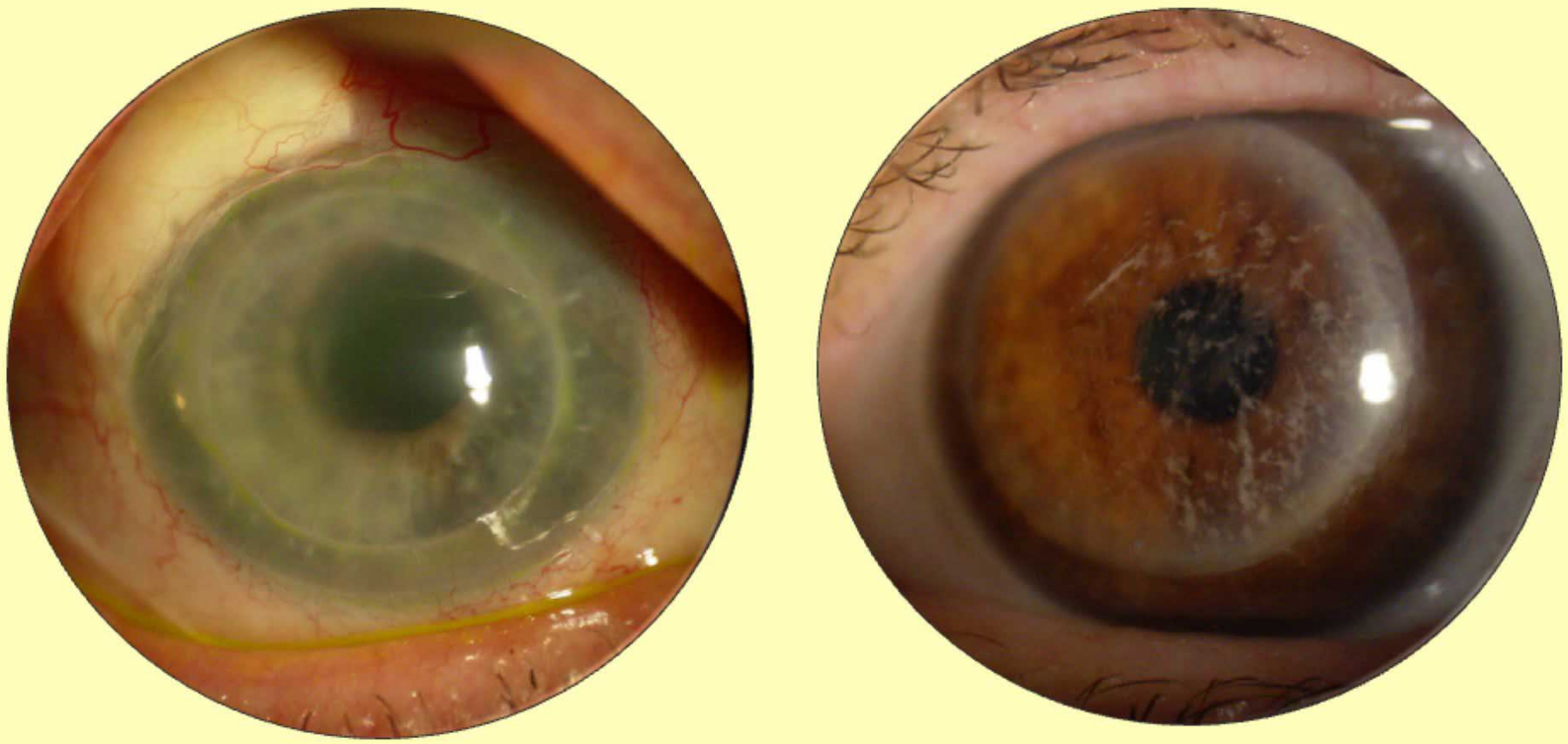
Transplant rejection

Recurrent disease

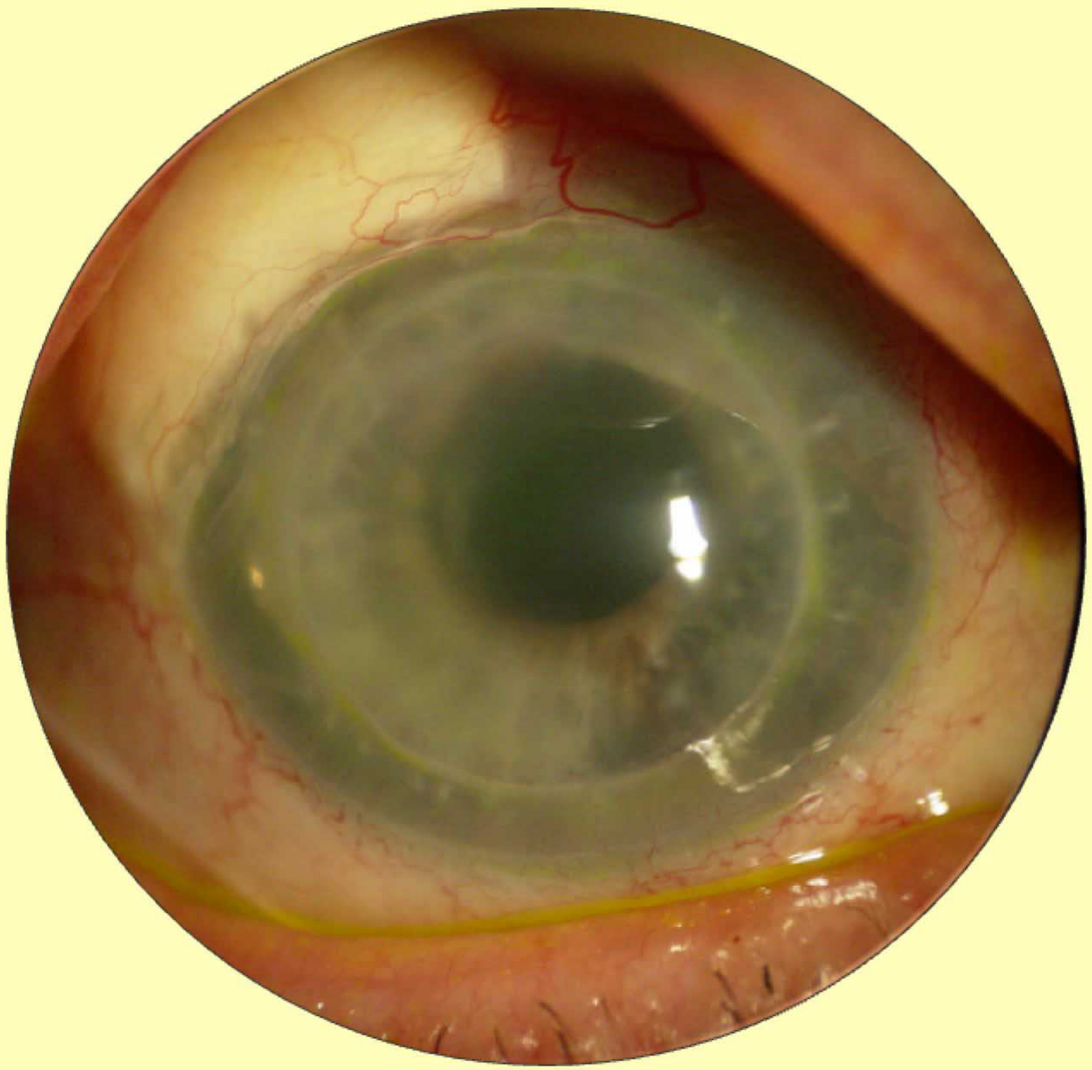
Infection

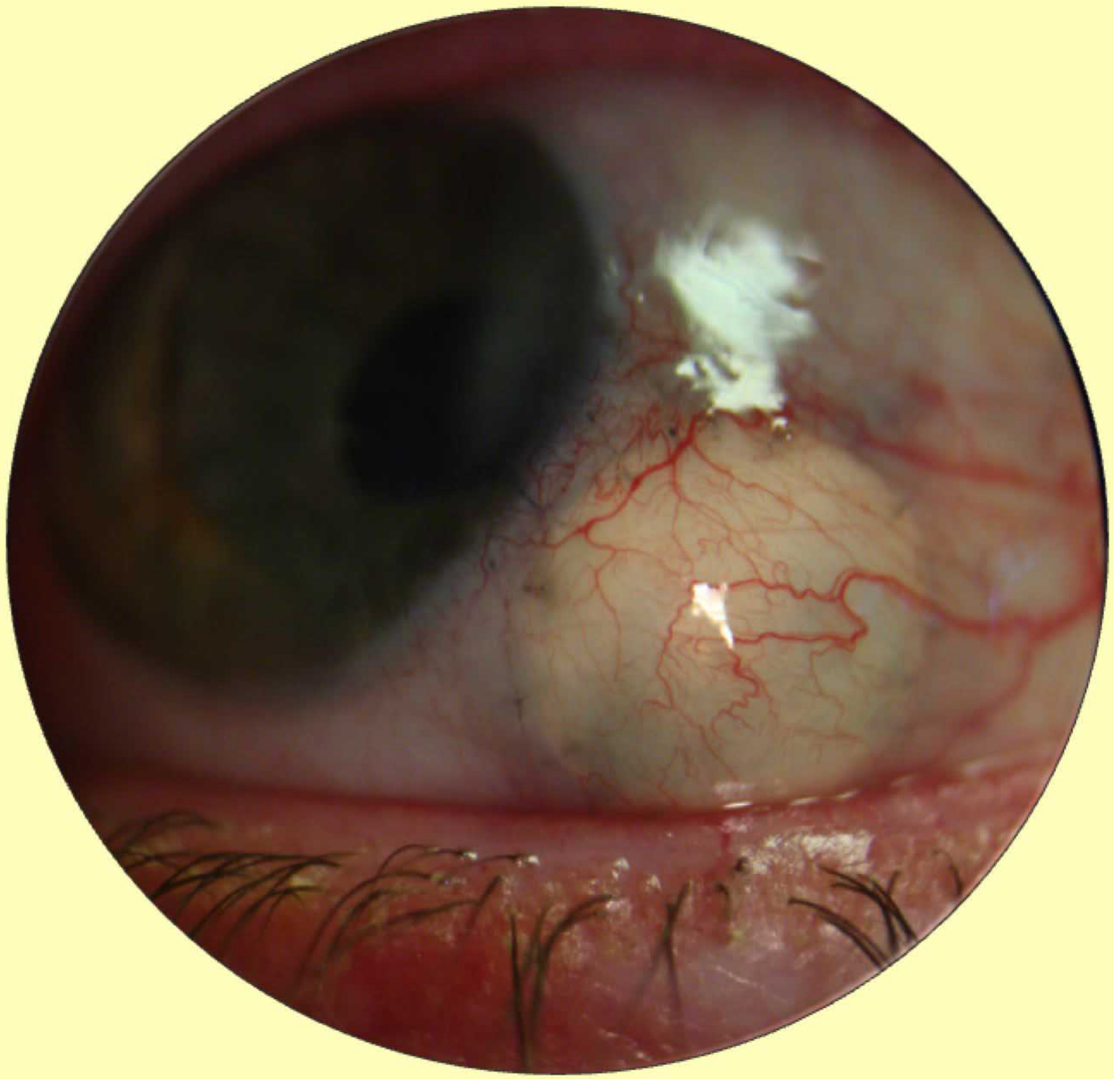
Surgical failure





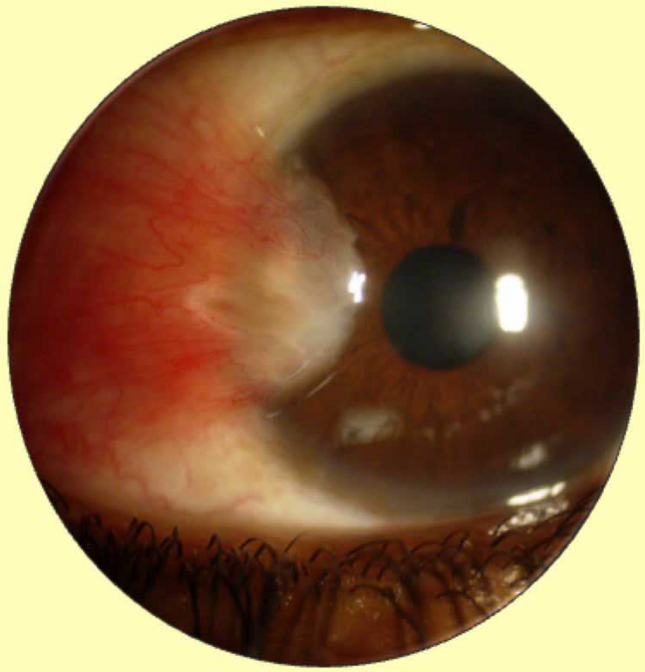
Scleral Transplants

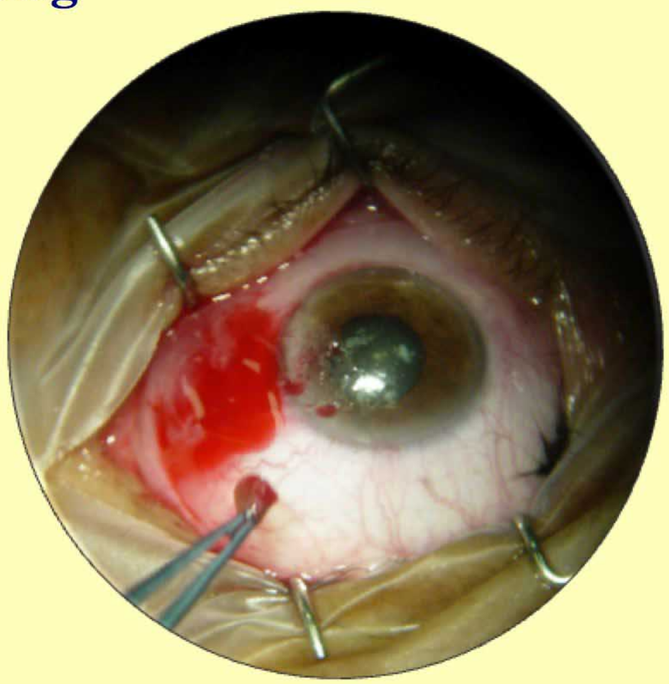


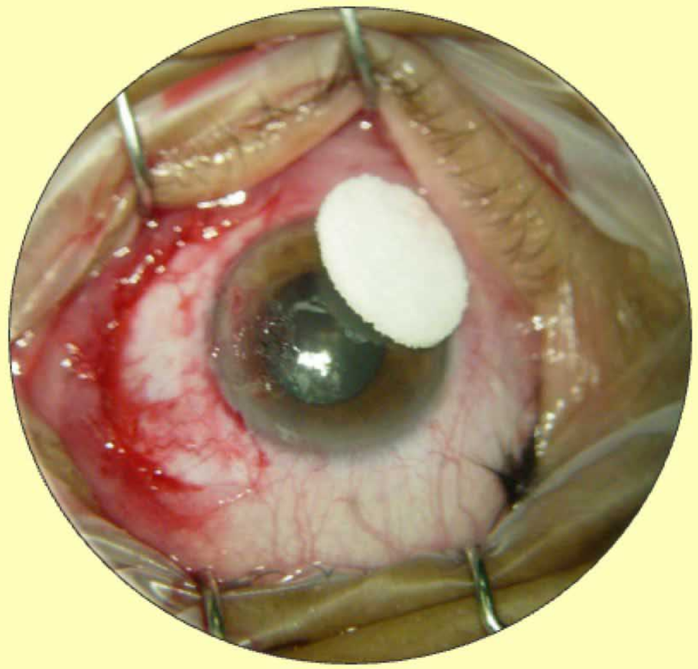


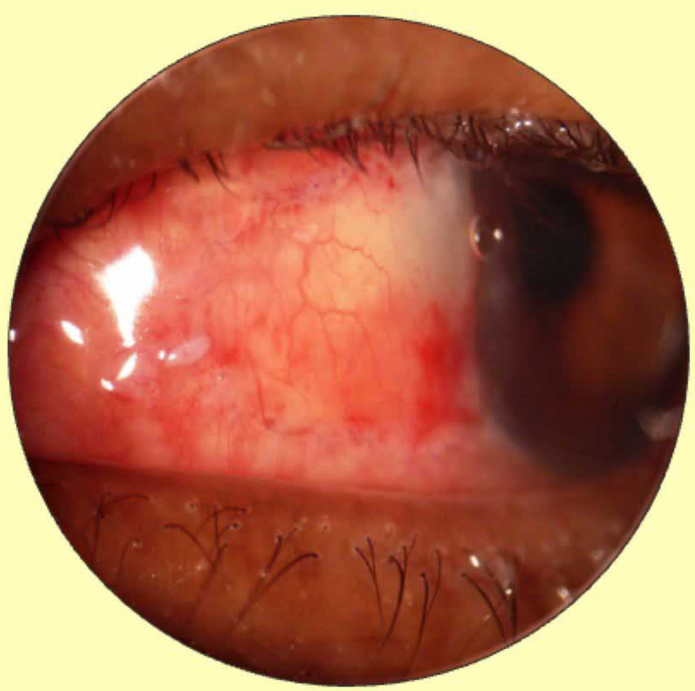
Conjunctiva

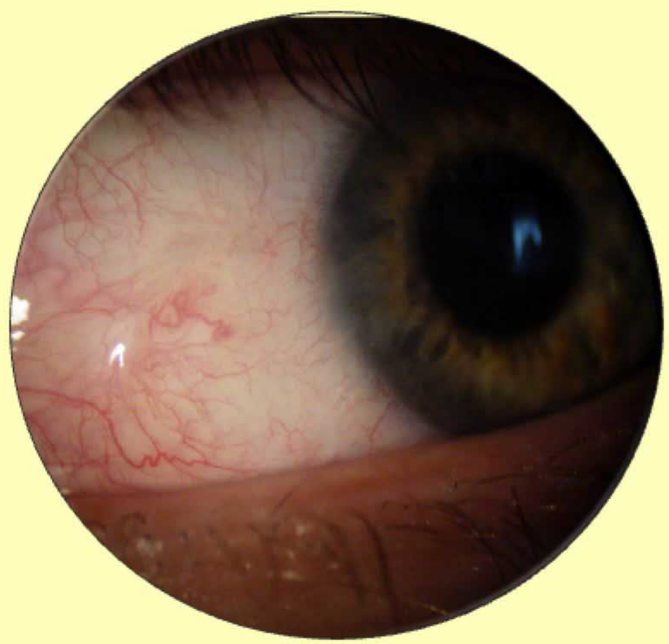
Pterygium excision and autografting











Amniotic Membrane

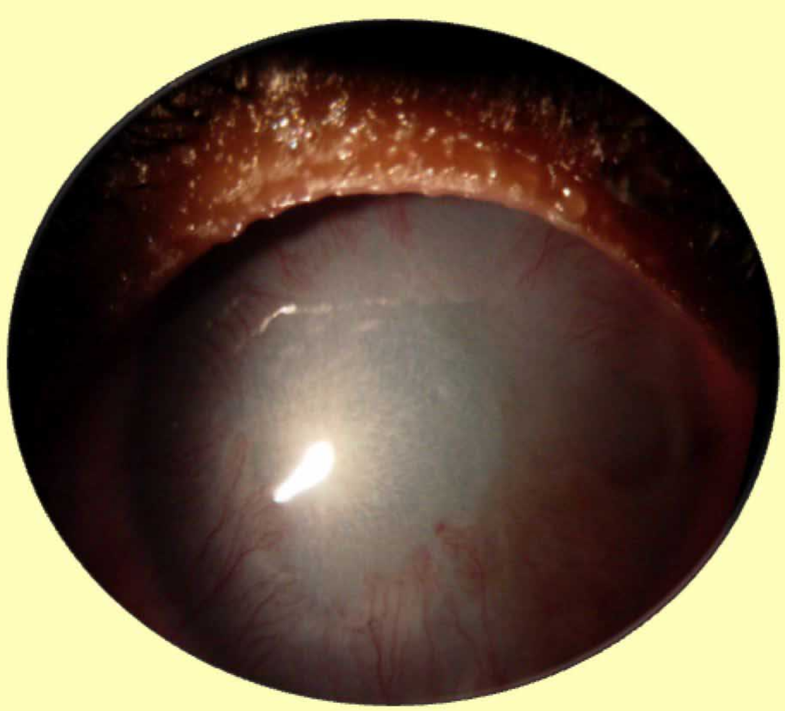
Lime burns

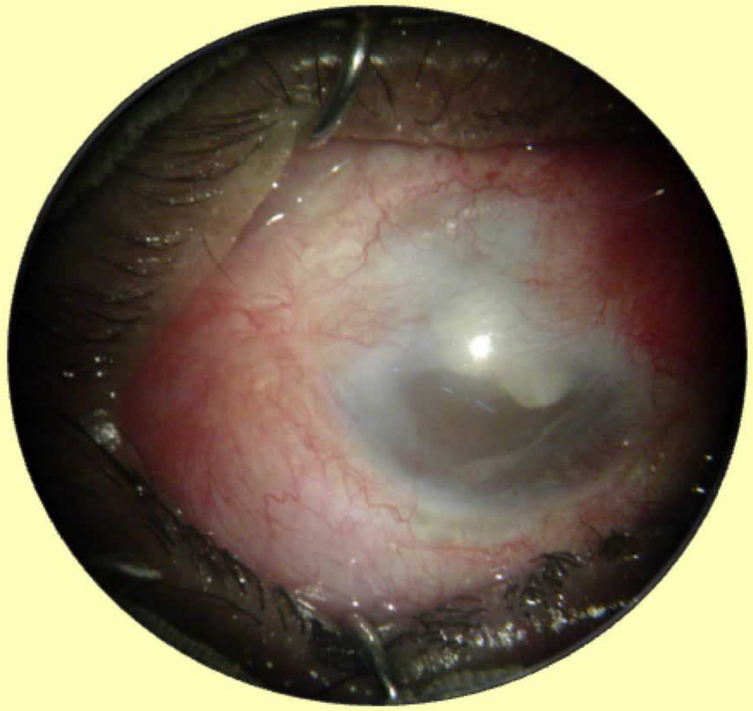
Chemical Industry

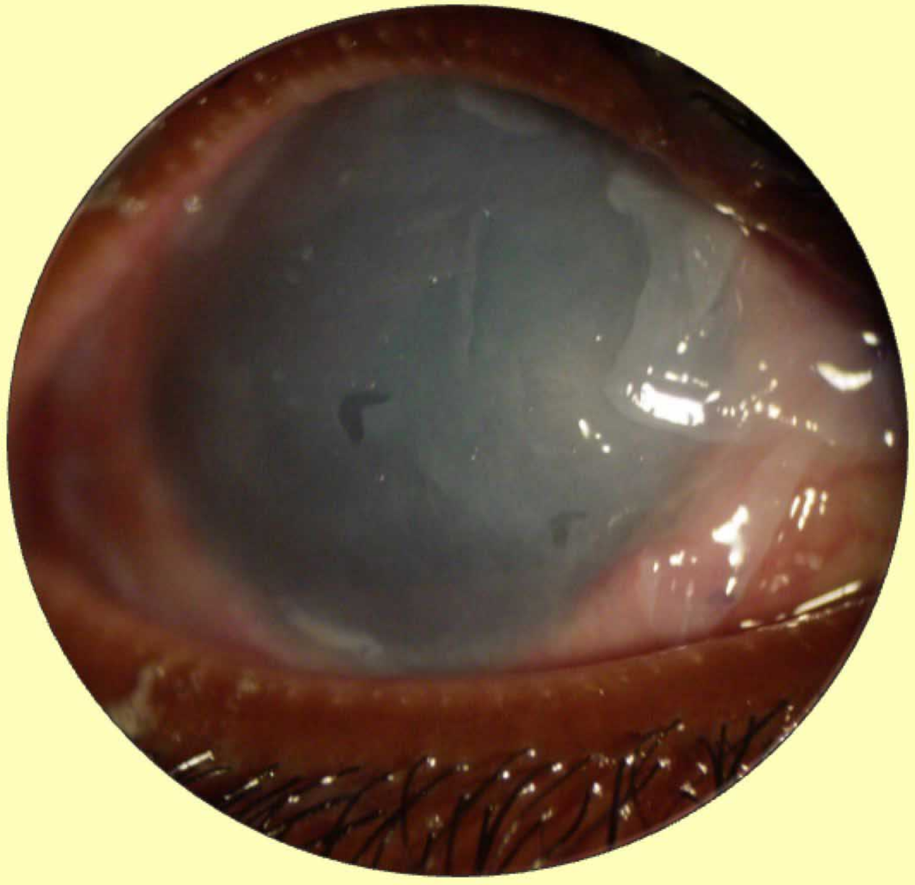
Domestic

Assault

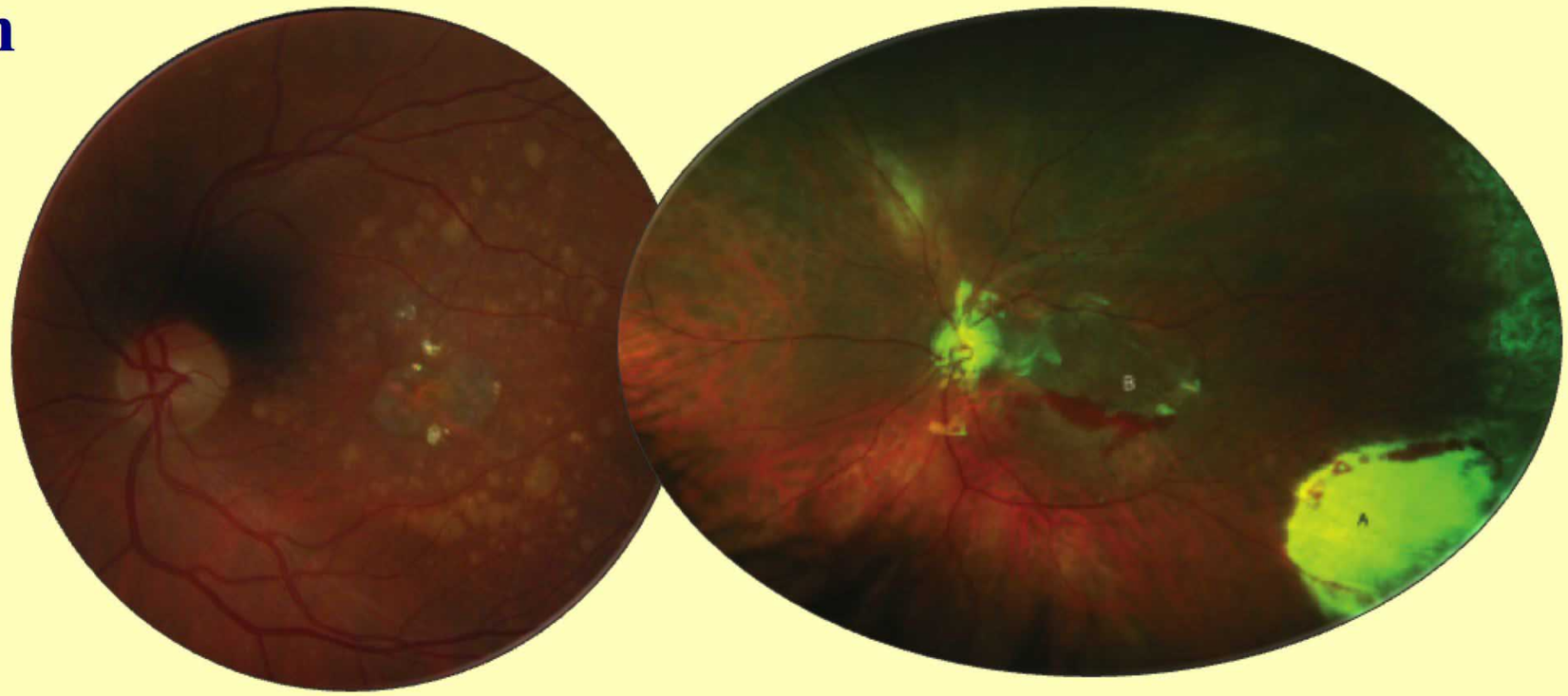
Children in India







Retinal Transplantation



Retinal pigment epithelium

Macular degeneration causes vision loss and scarring of the macula. This damage is eventually permanent, but only affects one central area of the retina.

Macular translocation surgery moves the macula away from the abnormal blood vessels onto a new location of healthier tissue. This procedure may maintain or recover central reading vision.

Neuroretina

Can we generate neural cells from Bone Marrow or do we need neural stem cells

Dr. Szurman full macular translocation

August 2013: Binbin, was drugged kidnapped while playing outside his home.

3 hours later family found him covered in blood and crying.

His eyes were found nearby corneas missing

Organ trafficker behind the attack.

‘We didn’t notice his eyes were gone when we discovered him – he had blood all over his face. We thought he had fallen down and smashed his face.’

Illegal organ harvesting is booming in China, shortage of donors.

multi-million-pound transplant industry

Police seeking a woman suspect

£10,500 for information leading to an arrest.

Corneal Transplant Service

1983: CTS was launched to give equal access to corneas throughout the UK.

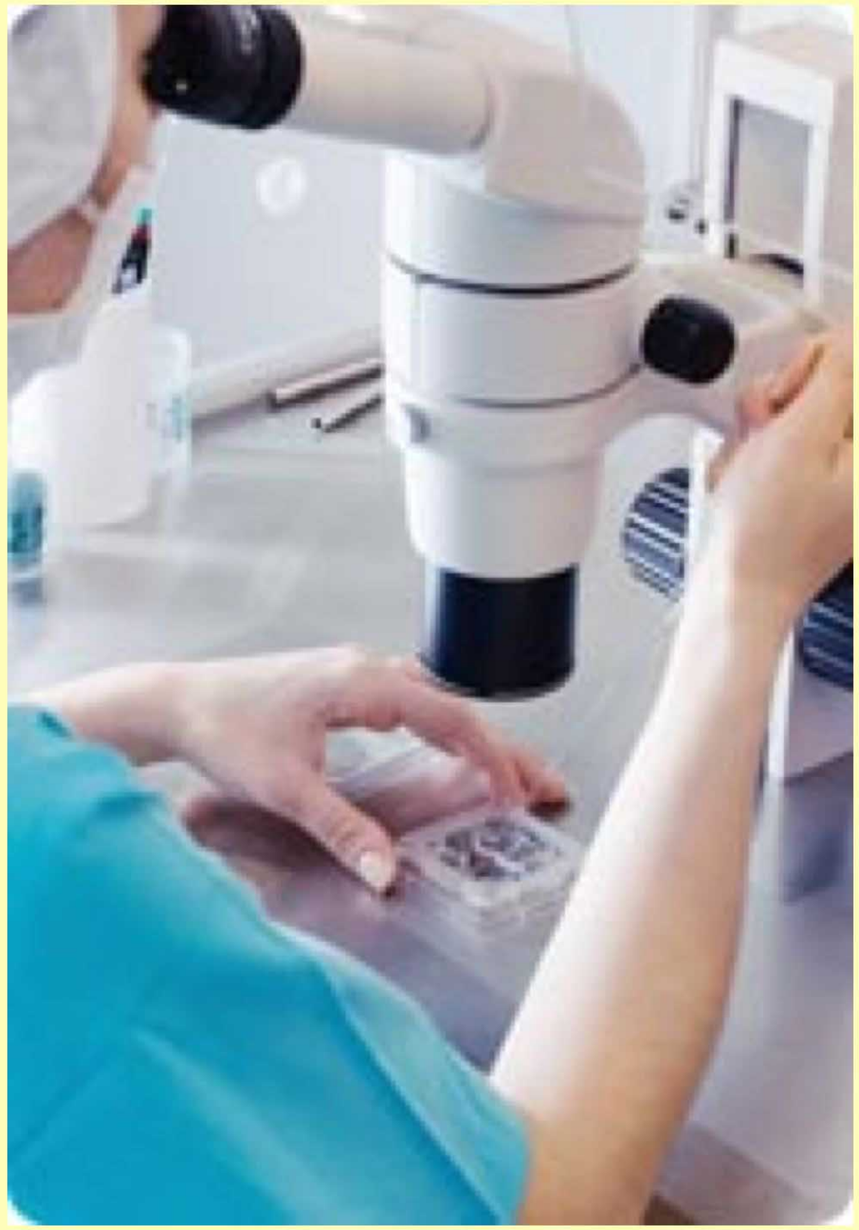
More than 52,000 cornea transplants have been recorded on the UK Transplant Registry since

Corneas sent to Eye Banks for storage and subsequent distribution to more than 200 cornea transplant units.

90% of transplants use corneas stored in the CTS Eye Banks in Bristol and Manchester, store the corneas for up to four weeks.

People of all ages can donate corneas and about 65% of cornea-only donors are over 60 years old

join the NHS Organ Donor Register by calling 0300 123 23 23 or visiting the NHSBT website www.organdonation.nhs.uk



Facial disfigurement

Tthe biggest threat to noses during Renaissance was the new disease sweeping through Europe

1495: syphilis first appeared in Europe

Acute and extremely unpleasant disease.

Ulrich von Hutten (1519), himself a sufferer.

...truly when it first began, it was so horrible to behold”

soft tissue being eaten away to the bone, and the rapid onset of the ‘gummy’ tumours

Changes 50 yrs into a milder, chronic disease

Girolamo Frascatoro: Physician; b. Verona 1478.

1525: poem ***Syphilis sive morbus gallicus****:* shepherd Syphilis, afflicted with pustular and ulcerative disease as a punishment for blasphemy.

1546: major treatise on contagion.

‘the sickness is in decline, and very soon it will no longer be transmissible even by contagion, for it is getting weaker day by day’

caused by infection with seminaria (seeds)

saddle nose’—bridge of the nose caves into the face and the flesh rots away

’ became a mark of shame, symbolizing the victim’s moral and bodily corruption.

Prosthetics disguise deformities.

Theodericus Ulsenius, Dirk van Ulsen, c. 1460-1508: Nürnberg city physician in: *Vaticinium in epidemicam scabiem*.
Morbus Gallicus: Albrecht Dürer (1496). Earliest depiction of the disease: Wears clothes of *Landsknechten*
Nov 1484 Saturn and Jupiter met in Scorpio: disease caused by unfavourable planetary alignment

Thanks to patients and colleagues for referrals
Goodbye Croydon Eye Unit
Dermot Pierce vs wisdom of managers
THANK YOU

‘no nose clubs’

deformity common

beddingham nose, Tudor; c1500 - 1700, found November 2009 Beddingham, East Sussex

18 February 1874, the *Star*:

Miss Sanborn tells us that an eccentric gentleman, having taken a fancy to see a large party of noseless persons, invited every one thus afflicted, whom he met in the streets, to dine on a certain day at a tavern, where he formed them into a brotherhood

Husband died; found another suitor despite her deformities.

After wedding sold the prosthesis to physician, James Merryweather for £3.

Her new husband liked her noseless look

just the way she was.

(Lindsey Fitzharris; RCS)

Francis Derwent Wood’s Tin noses shop in Wandsworth

Early success with autografts

Sushruta: C2nd BCE, patient's own skin is used to reconstruct nose. Classical cheek flap rhinoplasty later modified to rotation flap from adjacent forehead

"Cowasjee, a Mahratta bullock driver with the English Army in the war of 1792, captured by Tipu Sultan, nose cut off
Allegedly Mr. James Findlay and Mr. Thomas Crusoe surgeons at British Residency in Poona in 1793 witnessed the operation on "Cowasjee" by illiterate man belonging to 'brick-maker' caste
'BL' Letter Gentleman's Magazine" Oct 1794

Nicolò Manuzzi 1638-1717

Venetian adventurer

Henry Bard, Viscount Bellomont, war hero. Accompanies him to Persia on unsuccessful mission for Charles II

They travel on to Surat to petition Shah Jehan.

Stays in India for rest of life.

Wrote manuscript on the Moghul Empire late C17th. Description of Indian Rhinoplasty. Unpublished till 1907

Portrait de Niccolo Manucci herborisant,
BnF, Paris. Cabinet des Estampes, Réserve, codex Od 45

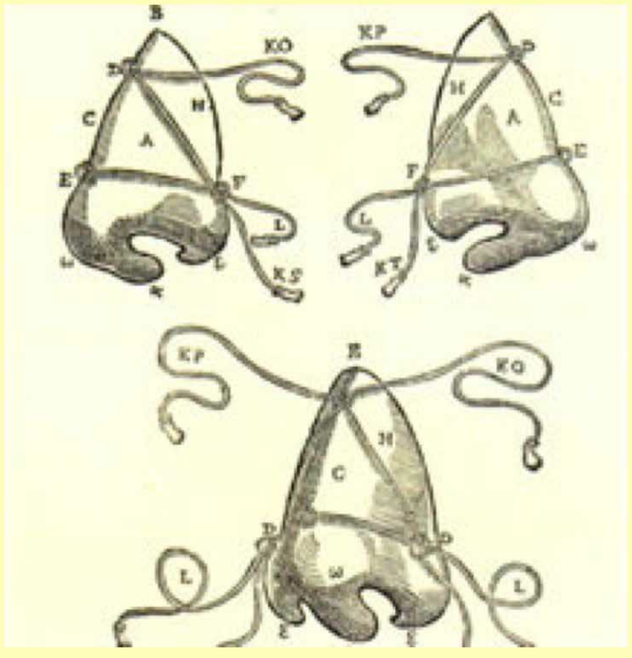
Self tissue transplants

Gaspare Tagliacozzi 1545-99: Bologna,

Flap from the upper arm to reconstruct nose.

Flap cut and skin stretched over a mould

De Curtorum Chirurgia per Insitionem (1597) ("On the Surgery of Mutilation by Grafting"). Described procedures carried out by Branca and Vianeo families of Sicily since the C15th



Gaspare Tagliacozzi (1546-99)
Lodovico Carracci
We restore, rebuild, and make whole those parts which nature hath given, but which fortune has taken away. Not so much that it may delight the eye, but that it might buoy up the spirit, and help the mind of the afflicted