Diabetes and vascular diseases of the eye

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Gresham College Dec 2010

Vascular diseases and the eye

Vascular diseases are the #1 killer

Chronic insidious onset

Many patients unaware

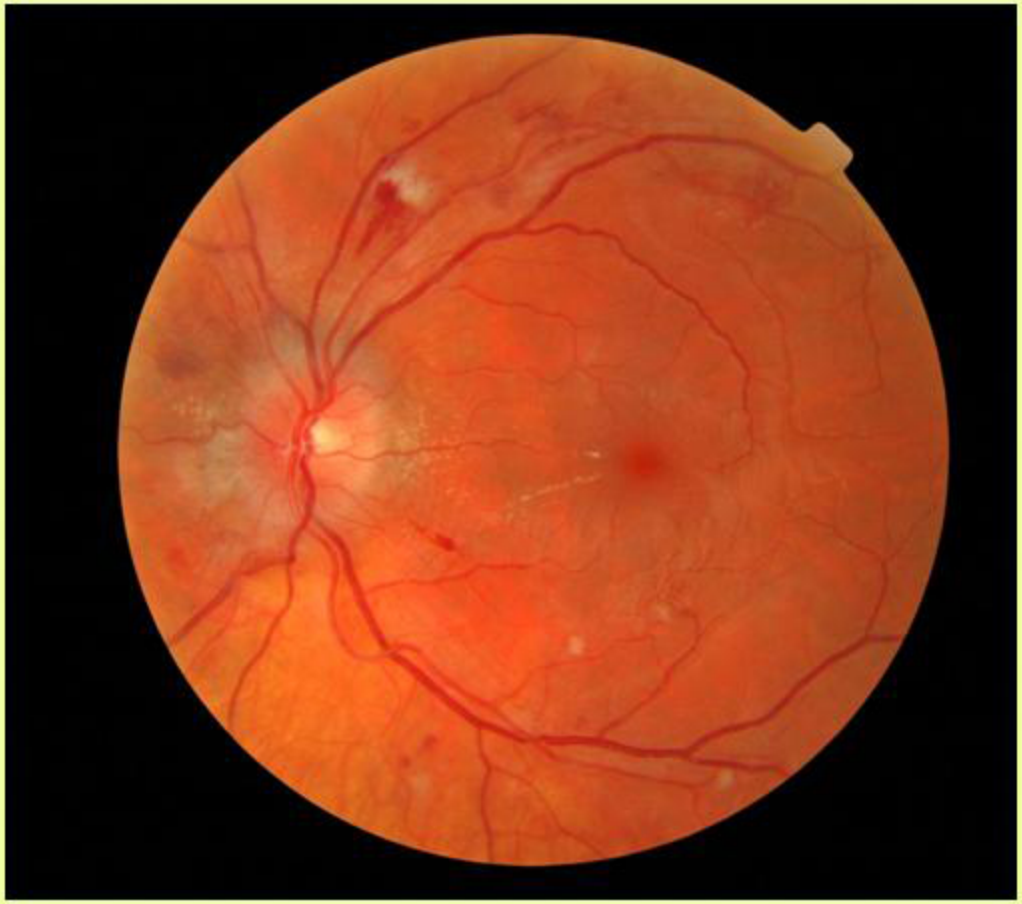
Screening

Eye as a diagnostic tool

Eye as a target organ

Blinding diseases as well as lethal

- **Discovery of the vascular system**
- **circulation of the blood**
- **Diabetes**
- **Hypertension**
- **Imaging the eye**



The Yellow Emperor's Manual of ***Corporeal Medicine.*** two texts each of eighty-one chapters or treatises in a question-and-answer format between the emperor and his ministers.

Huangdi 黃帝 (Yellow Emperor; Xuanyuan Shi 軒轅 the vehicle man), was the chief of the legendary Five Emperors)

System of water courses, streams, huge rivers, man-made canals and irrigation systems, and the ocean. It was envisioned that the body had a similar system of moving, life-giving fluid.

This fluid was the **qi,** and the pathways through which it flowed were the meridians. Not actually blood vessels. A dual circulation theory ***(yin) and ch'i (yang).***

Galenic vascular system

four humors of Hippocratic medicine:
black bile (*melankholia*),
yellow bile *(cholera)*,
phlegm *(phlegma)*,
blood *(sanguis)*.

Wall painting from Casa di Sirico, Pompeii, 1st Century BCE: Aeneas receiving medical attention from Iapyx

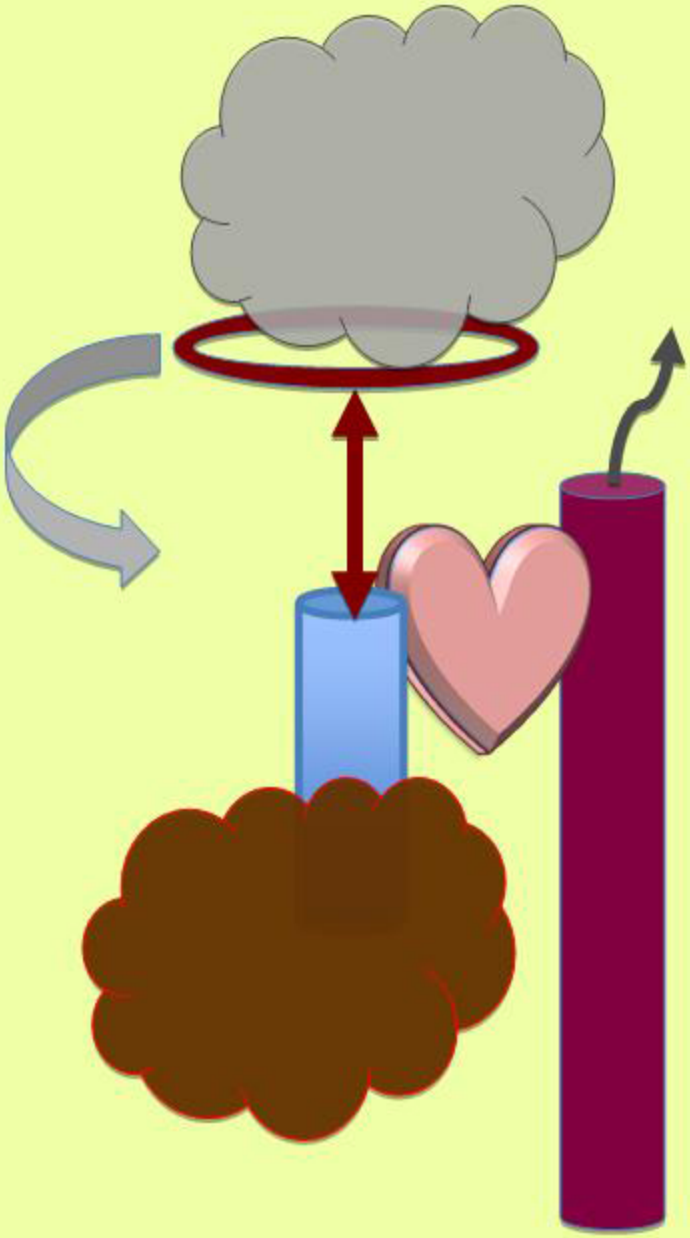
Galen of Pergamon: Gk Asia Minor 129-c200AD ; famous library. physician to the gladiators of the High Priest of Asia. Genius for medical research using barbary ape and ungulates.

'Nutritive blood' made by the liver, carried through veins to the organs, where it was consumed.

'Vital spirit' made by the heart.

Animal spirit made by brain from blood in reticulum

heart sucked blood in from the veins, blood flowed through the septum of the heart from one ventricle to the other through a system of tiny pores. did not discover that the blood left each ventricle through arteries (vivisection vs dissection).



Ibn al-Nafis

b. 1213 Damascus. Medical College Hospital (Bimaristan al-Noori)

Political turmoil, Crusades, Mongols sack of Baghdad in 1258,

1260. Mongols defeated by Mamluks at Ain Jalut

stimulus for writing, encylodaedias to preserve the legacy. ***Comprehensive Book on Medicine***, planned to be 300 volumes reached 80 by his death.

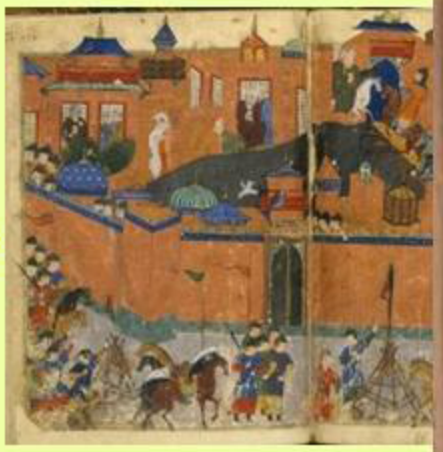
1236, moved to Cairo. Al-Nassri Hospital, and Al-Mansouri Hospital, Chief of Physicians to Sultan Baibars

1242: ***Commentary on Anatomy in Avicenna's Canon***, contained new discoveries, including the pulmonary and coronary circulations.

Commentary on compound drugs, deals with the circulatory system critique of Galen-Avicenna theories on blood vessels. pulmonary transit of the blood initially accepted but by 14thC ignored in the Islamic world

Latin translation Andrea Alpago of Belluno (d. 1520). A printed version, omitted the pulmonary circulation, pub Venice 1547

Predicts capillaries "there must be small communications or pores (***manafidh***) between the pulmonary artery and vein;



opening page of one of Ibn al-Nafis's medical works. C17th India

the blood from the right chamber of the heart must arrive at the left chamber but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible pores as some people thought or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa (pulmonary artery) to the lungs, spread through its substances, be mingled there with air, pass through the arteria venosa (pulmonary vein) to reach the left chamber of the heart and there form the vital spirit..."

William Harvey 1578-1657

16th April 1616 addressed the College of Physicians in Knightdale Street, nr St. Paul's. "I finally saw that blood forced by the action of the left ventricle into the arteries…impelled by the right ventricle into the pulmonary artery.."

Padua MD, Cambridge, London College of Physicians1604.

October 1609, he became the Physician in charge at St. Bartholomew's Hospital, "In God's most holy name; endeavor yourself to do the best of your knowledge in the profession of physic to the poor then present, or any other of the poor at any time of the week which shall be sent home unto you by the Hospitaller... You shall not, for favor, lucre or gain, appoint or write anything for the poor but such good and wholesome things

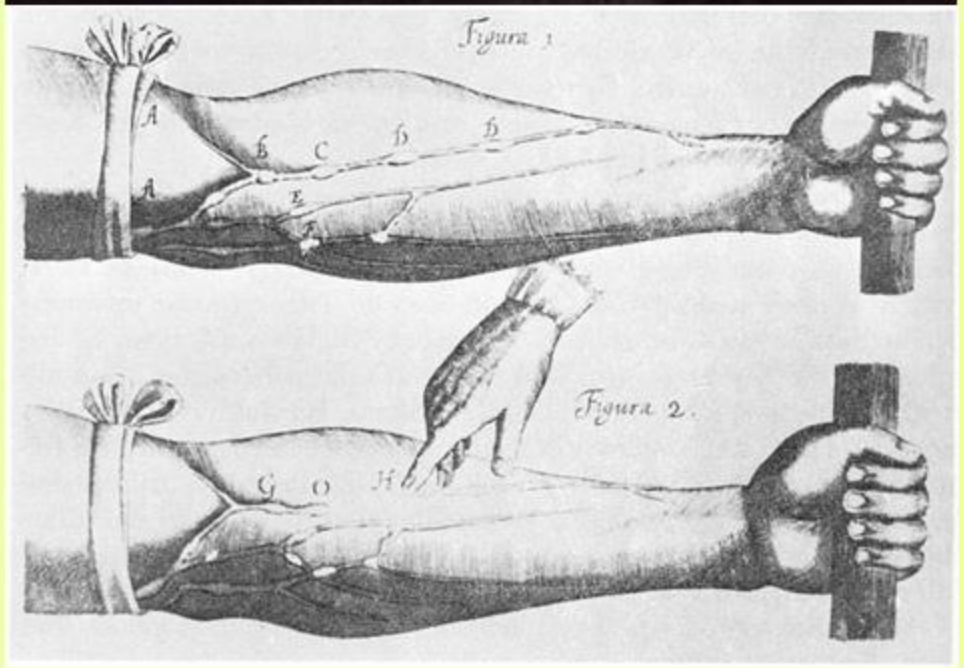
Lumleian Lecturer:

1628: De Motu Cordis

Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus, (An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings

Used ligatures

Blood pumped around the body in a "double circulation", after being returned to the heart, re-circulated in a closed system to the lungs and back to the heart, and on to the systemic circulation.



Early compound microscopes

1595, **Zaccharias Jansseen**

Middleberg: Counterfeiter and murderer of 2 rivals narrowly escapes death penalty. With father, **Han Jansseen,** invents microscope: 2 lenses in a 21/2 ft brass tube enlarges the object, a reverse telescope.

William Boreel, letter to the French king 1650s.

Not widely used for 50yrs;

Henry Power, Yorkshire publishes observations using microscope. Crude woodcuts

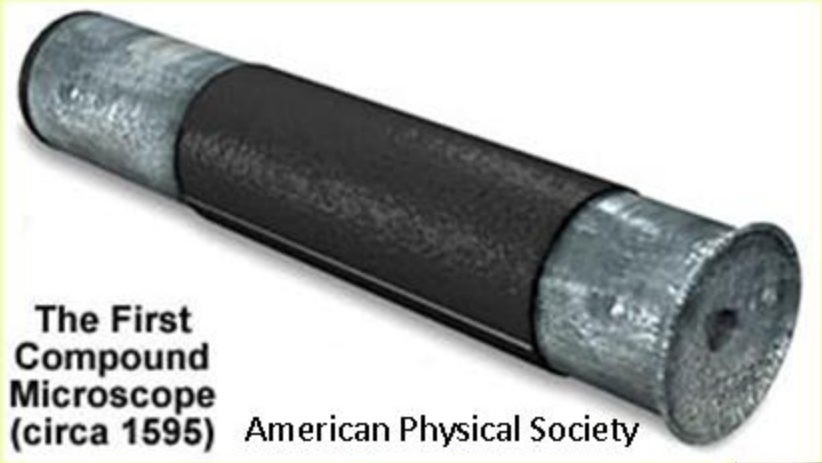
Robert Hooke. 1638–1703)

Fellow of the Royal Society in London, holding the position of Curator of Experiments

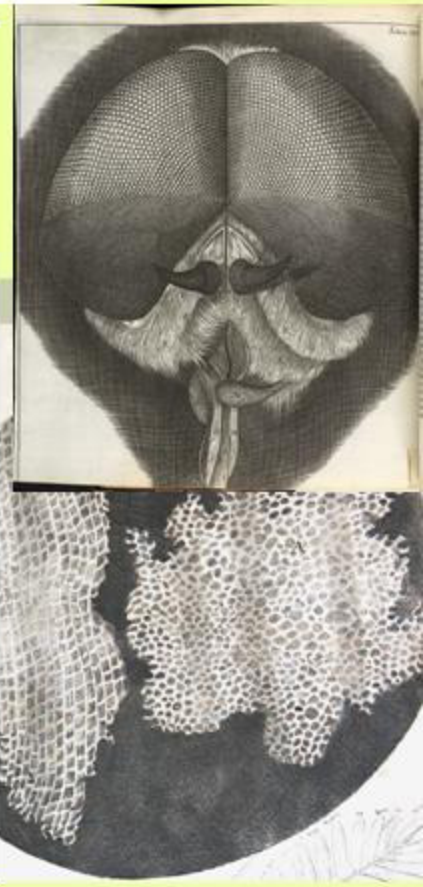
Micrographia 1665

tiny pockets of air named "cells" monastery. the remains of the primary structure of life. modified the Jansseen compound microscope into the modern version built by instrument maker Christopher Cock.

Lenses with very short focal lengths needed for magnification. This meant the use of double convex or spherical lenses, improved the resolution, and magnification.



The First Compound Microscope (circa 1595) American Physical Society



Antonie Van Leeuwenhoek (1632-1723)

b. Delft; Dutch draper with no formal scientific training, used magnifying glasses to count the threads in cloth. Made microscopes; pioneering discoveries; protozoa, red blood cells, capillaries, life cycles of insects. influenced by Hooke's accomplishments;

Also made his own equipment and secret lenses.

1673: sends findings to the Royal Society *Philosophical Transactions,* 1st peer-reviewed scientific journal.

Powerful microscope; images of structures too small for Hooke's equipment to capture. Controversy about single cell organisms, deputation visits him in Delft; fellow of the Royal Society.

Single, tiny, double-convex lenses mounted in a small hole between 3" brass plates and held close to the eye. Glass lens 270X (early compound microscopes of 20-30X). Technique kept a secret; fusing glass wire, not polishing a lens.

Specimen mounted on the sharp point in front of lens, position and focus adjusted by two screws.

1674, he gave the first accurate description of red blood corpuscles

1981 : Brian Ford found original specimens in Royal Society.

University Museum of Utrecht University, aspherical lens 295x.

Folded packets containing sections of cotton seeds, stored in paper envelopes, attached to one of Leeuwenhek's

Marcelo Malpighi 1628-1694

b. Crevalcore, Bologna, the year of Harvey's *De motu cordis,* Studied Aristotelian philosophy at the University of Bologna graduated MD. 1667:

Journal articles to the Royal Society, an unusual practice for the period.

1661 4yrs after Harvey's death; announced his observations on the anatomy of the frog lung; a network of tiny thin-walled tubules, he named capillaries, hypothesized these were connection between arteries and veins that allowed blood to flow back to the heart

1689, in the awesome presence of senior churchmen; formal indictment was pronounced on Malpighi at Rome... condemned Malpighi's rash work and pronounced it all useless. **"It is our firm opinion that the anatomy of the exceedingly small, internal conformation of the viscera, which has been extolled in these very times, is of use to no physician."**


MARCELLI
MALPIGHII
Consultationum Medicinalium
CENTURIA PRIMA,
HIERONYMUS GASPARI,
JO: FRANCISCO
MAUROCENO
DIVI MARCI EQUITI,
D. D. D.
PATAVII,

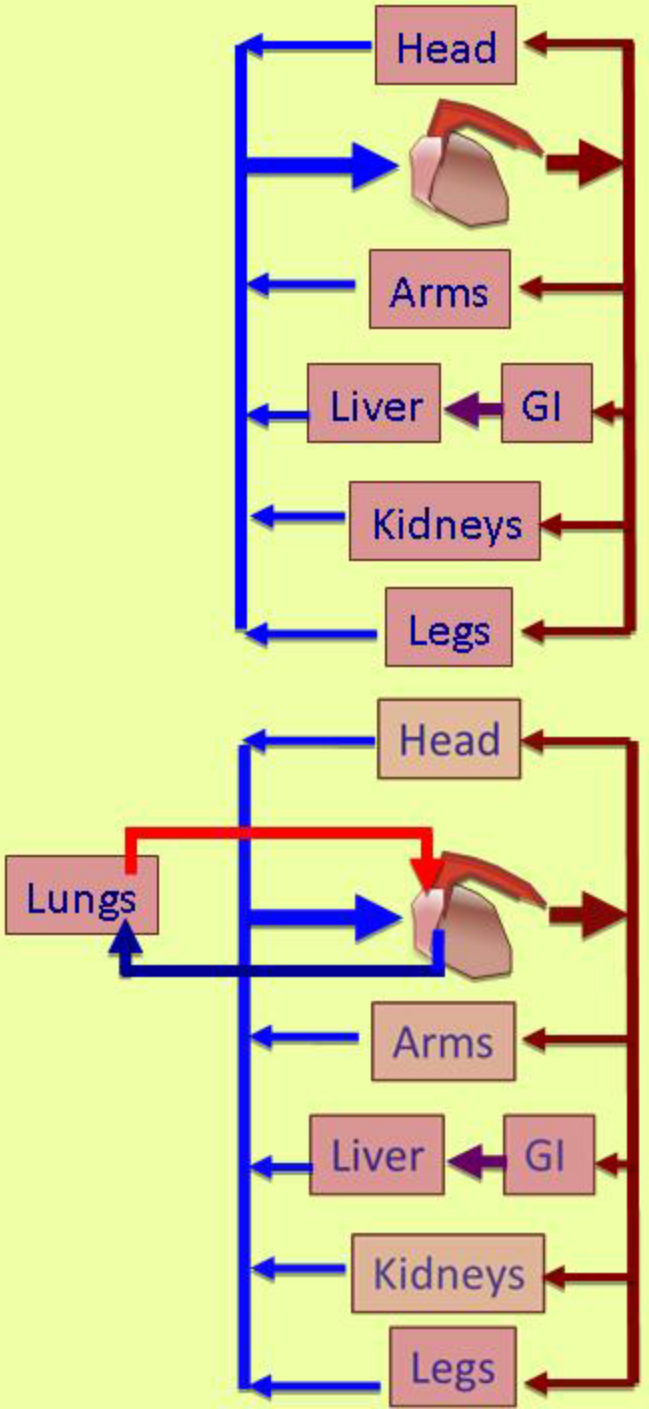
The vascular system

Blood leaves the heart through the aorta distributed to major organs by **large arteries**,

carotid, brachial, superior mesenteric, renal, iliac;
parallel circulations.
gastrointestinal and hepatic circulations; in-series:
venous drainage from the intestines to
portal vein which supplies most of the blood flow to the liver.

Capillaries leaky small channels connect to venous system

venous vasculature, 70-80% of the blood volume



What can go wrong?

Vascular diseases #1 killer

Targets

Heart: Myocardial Infarction

Brain: Stroke

Kidneys: Renal failure

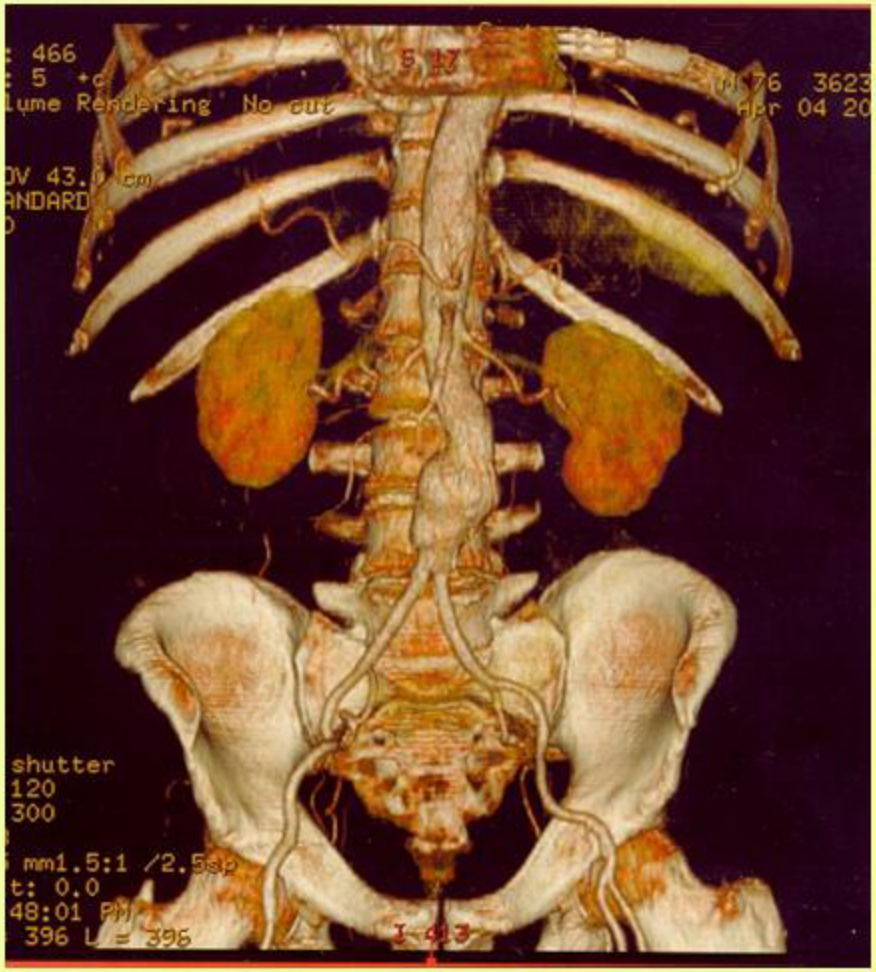
Diabetes and High blood pressure

2 most common pathways to damage the system

Other rarer causes: Inflammatory vasculitis, clotting disorders, infection (syphilis), congenital, hereditary.

Imaging a problem.

Eyes give us a living window



Michel de Villeneuve

Stephen Hales 1677-1761

Palpation of the pulse was ancient technique

However measurement of the pressure in circulation not done despite observation of blood spurting from arteries.

b. Kent, studies Cambridge.1708 Curate Teddington where buried.

Experimenter elected FRS 1718. ventilator for St. Georges Hospital, ships and Newgate prison.

1727: 'Vegetable Staticks; on rising sap of plants

1733: Vol II Statistical essays: Haemostaticks

"force of the blood" in various animals, its rate of flow, and the capacity of the different vessels.

'In December I caused a mare to be tied down alive. Crural artery laid open into which a brass with a glass extension 1/6"diam. The blood rose 8'3" rising and falling 2-4" with each pulse.

1710, first precise definition of the capacity of a heart. He bled a sheep to death and then led a gun-barrel from the neck vessels into the still-beating heart. Through this, he filled the hollow chambers with molten wax and then measured from the resultant cast the volume of the heartbeat and the minute-volume of the heart, which he calculated from the pulse-beat.

1727, to determine arterial blood pressure, when he measured the rise in a column of blood in a glass tube bound into an artery."

Non-invasive measurement

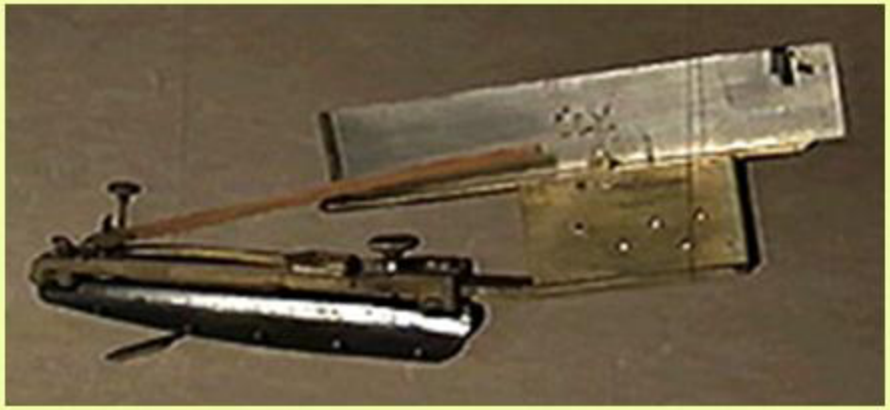
1855: **Karl von-Vierordt**: Tubingen: Measure the pressure needed to close off arterial pulsation.

Samuel Siegfried Karl Ritter von Bach. B Prague 1837 q Vienna 1862. Used inflatable rubber filled with water connected to a mercury manometer.

BMJ opined that sphygmomanometer "pauperise our senses and weaken clinical acuity"

Harvey-Cushing visiting Pavia found the device usefu in saving lives during anaesthesia; spread its popularity in the USA.

1896: **Scipione Riva-Rocci**: q. Turin 1888. Un nuovo sfigmomanometro.



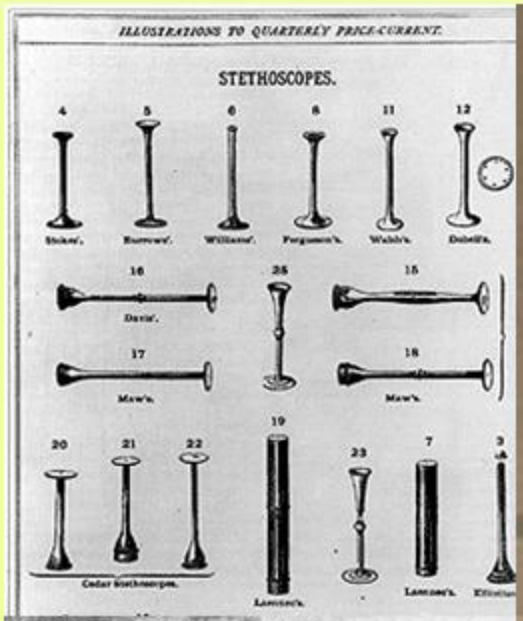
Listening to the heart.

1816: Laennec needed to examine an obese young woman, not keen to put his head to her chest. He rolled up some papers into a cylinder, and placing one end on the chest "was surprised and pleased to hear the beating of the heart much more clearly than if I had applied my ear directly to the chest,"

Lub: the ventricles contract and the blood is pushed against, and bounces back from, the closed valves between the atria and ventricles.

Dup: second part of a heartbeat when the blood exiting the heart via the aorta and the pulmonary artery bounces back from the closed pulmonary and aortic valves.

1905: **NC Korotkoff.** 1874-1920. q Moscow 1898. surgeon Manchurian War 1904 Manchuria. Interest in blood vessels. Auscultatory method: reported using a stethoscope distal to the Riva-Rocci cuff to hear tapping sounds.



Normal Blood pressure

Blood is pumped out of the heart under pressure into the arteries. The mean arterial pressure (MAP) depends on the amount of blood ejected (Cardiac Output) and the resistance of the system (Systemic Vascular Resistance)

MAP = (CO × SVR) + CVP

Because CVP is usually at or near 0 mmHg,

MAP approx = CO × SVR

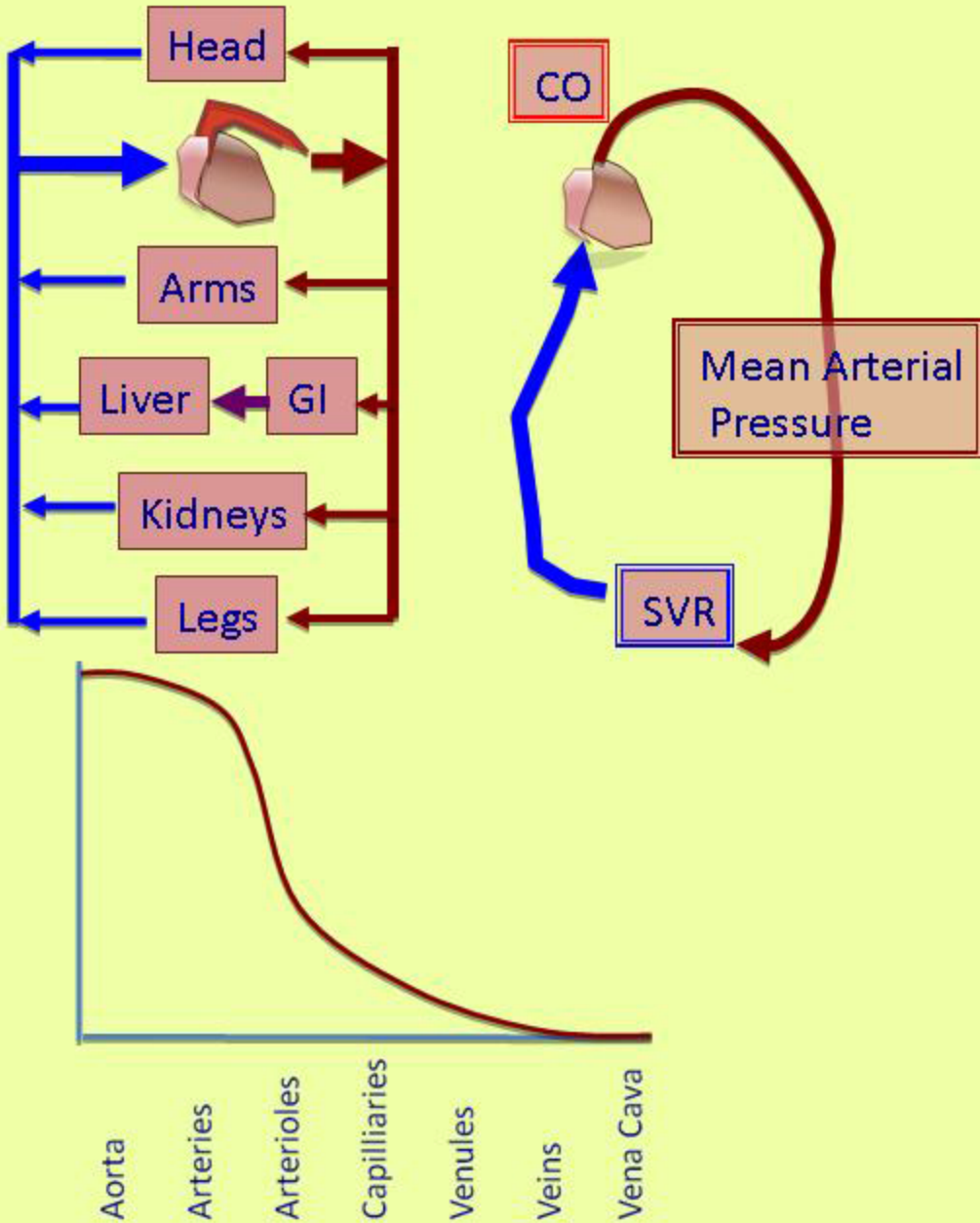
Aorta and arteries have the highest pressure ~95 mmHg. It reduces only slightly as the blood flows down the aorta and through large arteries.

Arterioles: Lots of nerves and hormone receptors that control their diameter, large fall in mean blood pressure as the arterioles are reached.

Capillaries have no muscle in their walls. Mean pressure ~25-30 mmHg.

Veins: The pressure falls further as blood travels into the veins and back to the heart.

Vena cava near the right atrium close to 0, fluctuates with respiration.



Systolic and diastolic

When the left ventricle ejects blood into the aorta, the aortic pressure rises. The maximal aortic pressure following ejection is termed the systolic pressure.

As the left ventricle is relaxes for refilling, the pressure in the aorta falls. The lowest pressure in the aorta, is diastolic pressure.

Normal systolic pressure is under 120 mmHg, diastolic 80 mmHg or less. The mean aortic pressure is the average pressure (geometric mean) during the aortic pulse cycle.

Control of blood pressure depends on

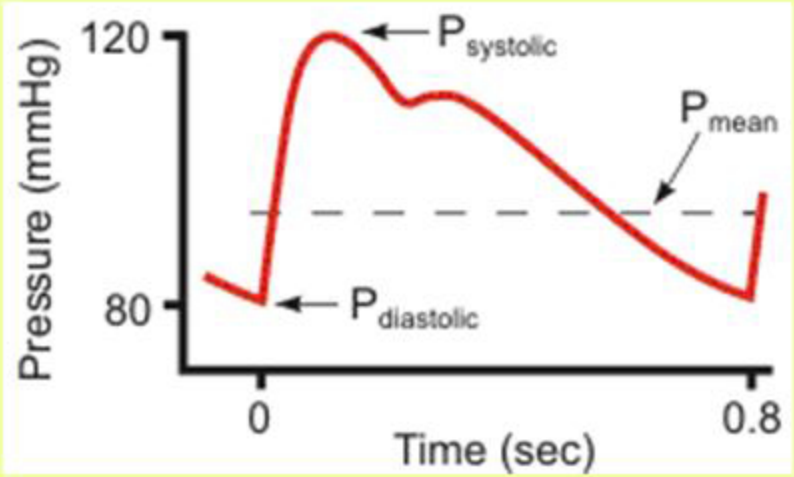
cardiac output (the amount of blood in the system)

The resistance in the tubes (systemic vascular resistance)

Many mechanisms could cause hypertension.

Increased blood volume caused by abnormal Na^{2+} handling by kidney, initiate secondary changes in the vessels increasing resistance to flow compounding problem.

Long term damage causes thickening of their walls.



Hypertension

High blood pressure, "hypertension,"

1 billion people worldwide and is a leading cause of morbidity and mortality.

More than 20% of Americans are hypertensive, and one-third of these don't know.

the "silent killer."

This disease is usually asymptomatic until the damaging effects:

stroke,

myocardial infarction,

renal dysfunction,

visual problems

Mechanism of essential hypertension

Increased vascular tone mediated by enhanced sympathetic activity or by increased circulating levels of angiotensin II.

renin, angiotensin, and aldosterone.

Renin, from kidneys, stimulates production of angiotensin in tissues, which in turn stimulates the release of aldosterone from adrenal cortex.

Angiotensin increases vascular resistance and blood pressure.

Aldosterone increases Na^{2+} reabsorption by kidney tubules

Sympathetic nervous system: increase cardiac output, systemic vascular resistance (both arteries and veins), and arterial blood pressure. Sympathetic activity increased during exercise, emotional stress

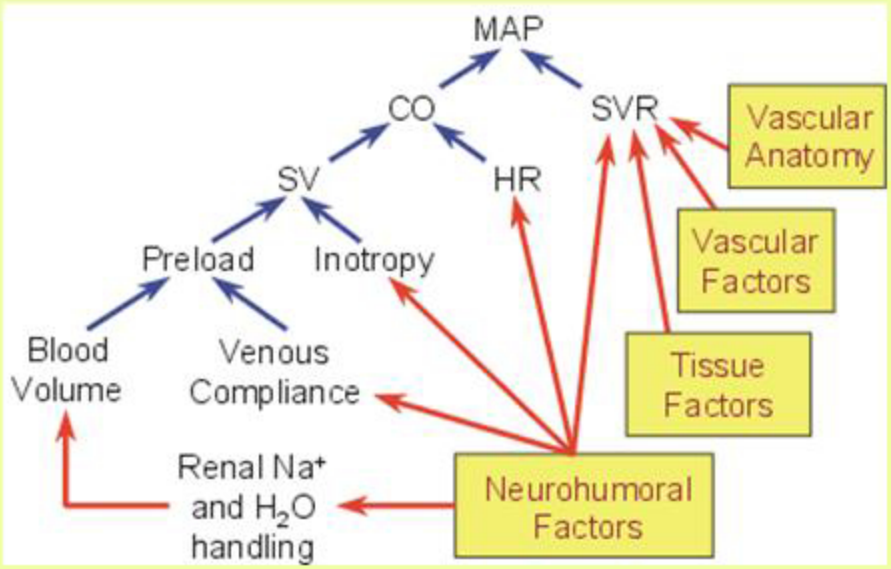
vascular endothelial function:

endothelium in HT makes less NO

vascular smooth muscle is less sensitive to this vasodilator.

endothelin production, enhances vasoconstrictor tone.

hyperglycemia in type 2 diabetes causes endothelial dysfunction by enhanced oxygen free radical mediated damage and decreased nitric oxide bioavailability.



Treating blood pressure

Reduce Cardiac output

Reduce systemic resistance

Treatment pharmacologic intervention to modify factors (e.g., angiotensin II, sympathetic activity, calcium entry into cells) in a way that leads to a reduction in arterial pressure.

treatments do not target the cause(s) of the underlying disease.

The three broad classes of drugs

diuretics (to reduce blood volume, altering how the kidney handles sodium. Thiazide, furosemide, amiloride.

vasodilators (to decrease vascular resistance)

Cardio-inhibitory drugs (to decrease cardiac output).

CCBs relax vascular smooth muscle decrease systemic vascular resistance as well.

alpha-blockers	doxazosin
ACE inhibitors;	**Captopril, Ramipril**
Angiotensin receptor blockers (ARBs)	candesartan
Calcium-channel blockers (CCBs)	amlodipine
Centrally acting sympatholytics	clonidine
Nitrodilators	isosorbide
Potassium-channel openers	minoxidil
Renin inhibitors	Aliskiren

(beta-blockers	Propranolol
Calcium-channel blockers	amlodipine
Centrally acting sympatholytics	clonidine

Diabetes

Hesy-Ra c2625BC. 3rd Dynasty Egyptian physician, time of **Netjerikhet (Djoser)**; tomb at Saqquara contained wooden panels. Described a rare disease that causes the patient to lose weight rapidly and urinate frequently.

Susruta, described the disease around 500 B.C., noting a sweetness in the urine in certain cases.

Aretaeus the Cappodacian (81-138AD). Contemporary of Galen, quotes for literary effect from Hippocrates, Thucycides & Homer. Latin translation by J. P. Crassus, Venet. 1552:

Described a disease of constant thirst (polydipsia), excessive urination (polyuria) and loss of weight.

Diabetes: διαβαίνειν to stand legs apart/siphon/a flowing through.

'the melting down of flesh and limbs into urine.' "...For fluids do not remain in the body, but use the body only as a channel through which they may flow out. Life lasts only for a time, but not very long. For they urinate with pain and painful is the emaciation. For no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine."

Galen (131-201CE) noted the rarity of this condition proposed it was a disorder of the kidneys.

Ibn Sina; Avicenna (980-1037): described complications and natural course.

Thos Willis (1621-75): Added "mellitus" (honey) Willis' disease

384 ARETAEI

Curatio morborum in articulis & coxendice, cap. XII.
Curatio elephantiaseos, cap. XIII.

CVRATIO DIABETIS, siue profluentis vrinæ, cap. II.

Diabetis, id est vrinæ profluuij, morbus hydropis species est, quòd ad eam & habitum attinet: loco vnde humor effluit, solo differt. Nam ascitis peritonæum conceptaculum est, nec defluuiũ habet, sed illic permanens exundat: in diabete verò idem est à patiente lapsus humoris, eadémque colliquatio: in renes autem & vesicam exeundo fertur effusio. aqua intercute laborantes hac via procedant, si à morbo conualescant: ac bonũ est, si causa soluatur, nec ponderis dũtaxat leuatio fiat: his autem maior sitis adest. humidũ enim defluens exiccat. Remedia ad colliquationẽ sedandam eadem quæ ad hydropas valent: ad sitim verò medicina magna est

CVRAT. DIVT. LIB. II. 385

opus. ea enim in omnium dolorum genere maxima est. et si humidum bibat, meiendi prouocatio est: adde quòd & effluens his humor secũ abducit ea quæ de corpore colliquat. Opus est igitur medicamentis sitim depellentibus. sitis enim magna est, ac potus insatiabilis cupiditas. nullus enim potus quantus quantus is fuerit, sitim medeatur. Omnino stomacho, vnde sitis fons scaturit, succurratur necesse est. Igitur vbi iuera purgueris, epithematis vitor, nardo, masticke, palmulis, malis cydoniis crudis. horum quidem succus cum nardo & rosaceo ad humectãdũ optimus, caro verò cũ masticbis & palmulis cataplasma fiat. cum cera verò & nardo vngento horum mixtio bona est, vel succi acacię & hypocystidis, tum ad humectãdũ, tum ad cataplasmatis fouendum. Caterum & aqua quæ potui dabitur, cum pomis decoquatur. Alimenta sint lac, & cũ eo cibaria, amyli, alicæ, forbilla, vinum adstringens, ad stomachum roborandũ: idque moderatius sit præstat, ad euaporãdos & dissipandos alios humores. nam

Getting information about the internal system

Examine skin

Pulse

Eye discolouration

Tongue

Faeces

Urine

Depiction of the Persian physician Al-Razi, in Gerard of Cremona's "Recueil des traités de medecine" 1250–1260.

Uroscopy

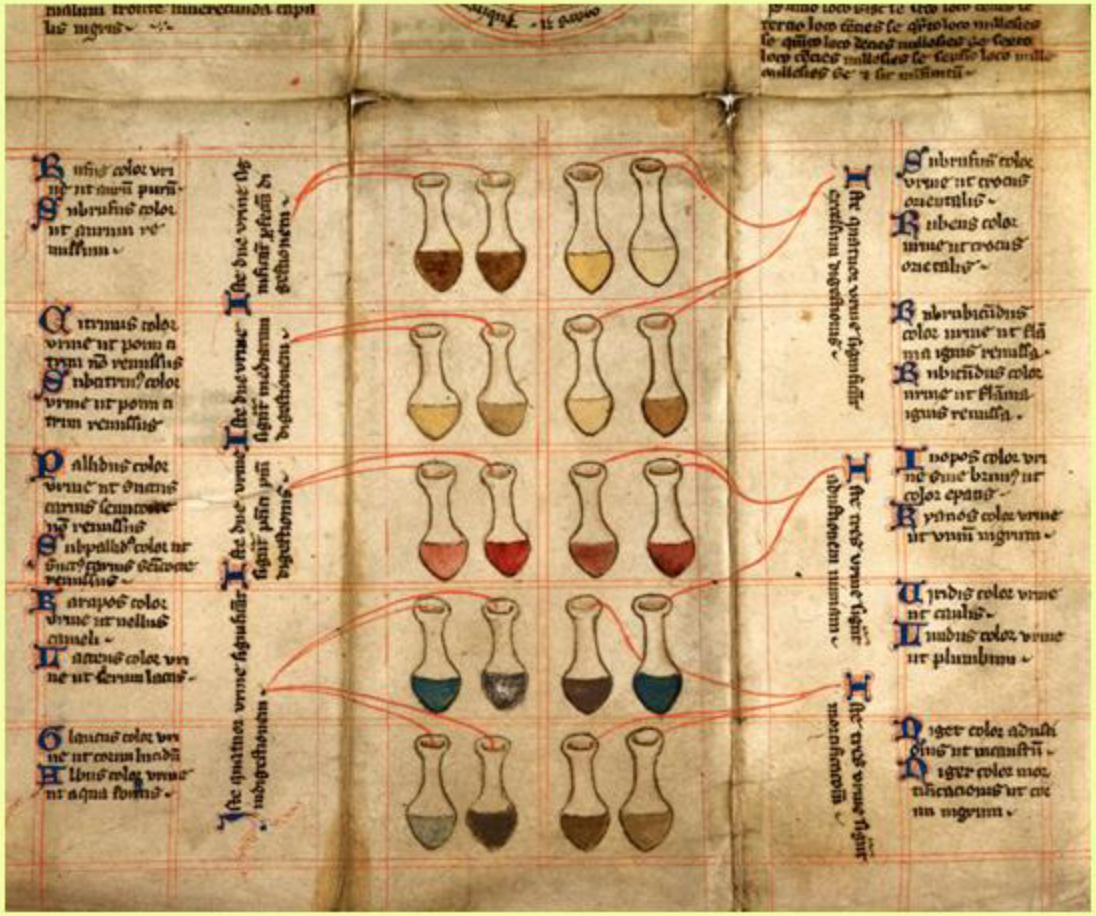
400BC: Sumerian and Babylonian physicians Hippocrates.

Johannes de Ketham: Owner of a bundle of medieval manuscripts Fasciculus medicinae in 1491. First illustrated printed medical book.

17th C, urine and pulse taking were the only diagnostic tools available to physicians to assess the health or disease of their patients.

The urine was examined in a specially designed glass flask **matula**; each region of the flask corresponded to a part of the body. The urine was assessed for its "thickness," contents (sediment and foam), and colour.

Numerous medieval manuscripts contain elaborate uroscopy charts, indicating about 20 gradations of colour, and other features of the urine and explanations of their significance.



John Somer, Robert Grosseteste
Folding Physicians almanac 1406:
BL Harley 5311

Yellow Sanguine personality.

Bilirubin and urobilinogen give yellow colur to urine. Darker if more concentrated. carotenaemia, diabetes, ,anorexia nervosa Serratia marcescens infection

White (colourless) Mortal in acute fevers

Orange: Death, hectic fever in dropsy

High levels of bilirubin/urobilinogen. Beetroot, Porphyria, some medications.

Pink-red: Choleric personality fever from excess blood needing bloodletting.

Haematuria: Bladder infections, cancer, extreme exertion, trauma, dyes, porphyria.

Blue: Melancholic personality

Indoles in Urine

Black: Mortification due to extinguished natural heat.

Alkaptonuria, medicines, cascara tree bark

Brown: A multitude of corrupted humours

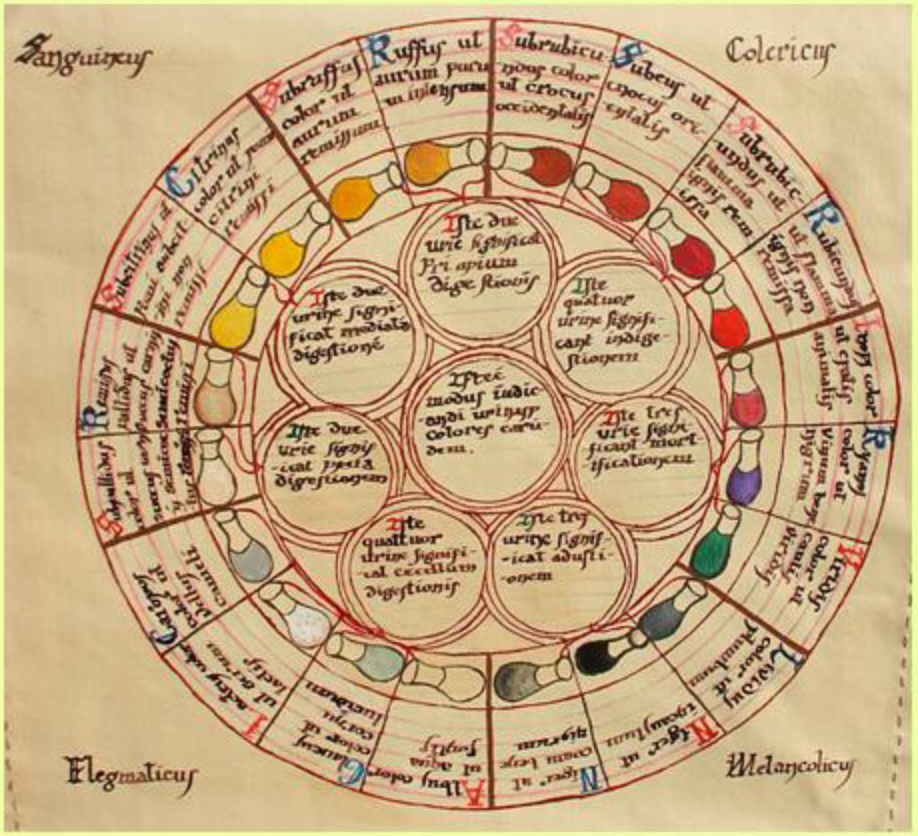
Drugs, porphyria

Green: Phlegmatic personality

Biliverdin, pseudomonas, drugs.

Milk-like: dropsy

Proteinuria.



Charles Diskin Nephrologist, Auburn Ala

Dou, Geritt The Dropsical Woman Louvre

1663 Gerrit Dou, pupil of Rembrandt,

medical practice in 17th century Europe--the careful visual inspection of urine as a diagnos tool

doctor, robe and hat physician, examining a specimen of urine.

Hooke's microscope 200yrs, Blood pressure 300yrs, Laennec's stethoscope 400 yrs in the future.

Unethical physicians and charlatans, who claimed to predict a patient's prognosis based the contents in the flask, abused the practice o uroscopy.

condemned by many physicians,

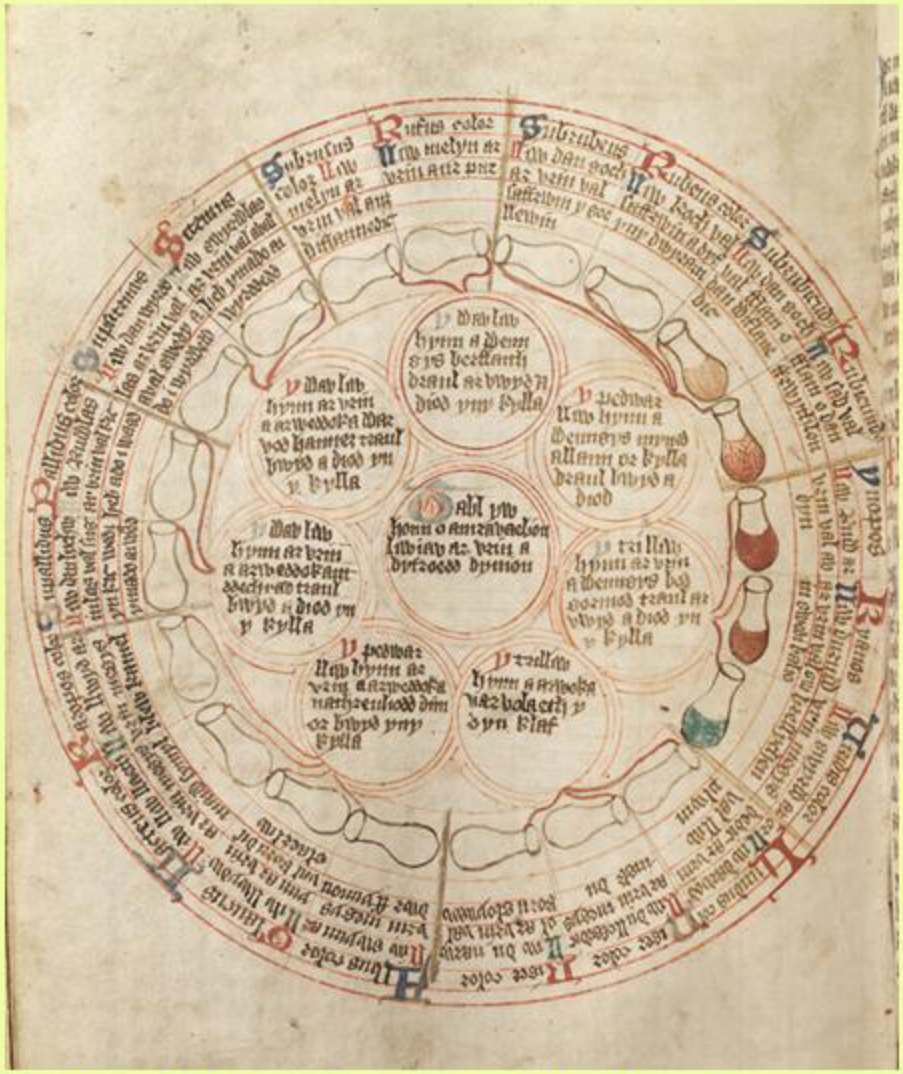
Thomas Brian, 1637 pamphlet, The Pisse-Prophet or Certain Pisse-Pot Lectures.

Thomas Brian The pisse-prophet

Certain pisse-pot lectures. Wherein are newly discovered the old fallacies, deceit, and jugling of the piss-pot science, used by all those (whether quacks, and empiricks, or other methodical physicians) who pretend knowledge of diseases, by the urine, in giving judgement of the same.

By Tho. Brian, M.P. lately in the City of London, and now in Colchester, in Essex.

Never heretofore published by any man in the English tongue. printed by S. and B. Griffin and are to be sold by Ben. Thrale at the sign of the Bible at the lower end of Cheapside London 1679



Gutun Owain. Noble born; Oswestry Gruffudd ap Huw ab Owain. student of Dafydd ab Edmwnd (fl. 1450-97) both were present at the Carmarthen Eisteddfod of 1450.

Modern Uroscopy

Odour: Fresh no smell. Standing ammonia. Fishy smell in infection. Ketoacidosis and anorexia cause a chemical pear-drop smell.

Colour: Straw coloured and clear. Cloudiness and debris indicate disease

Protein

Blood

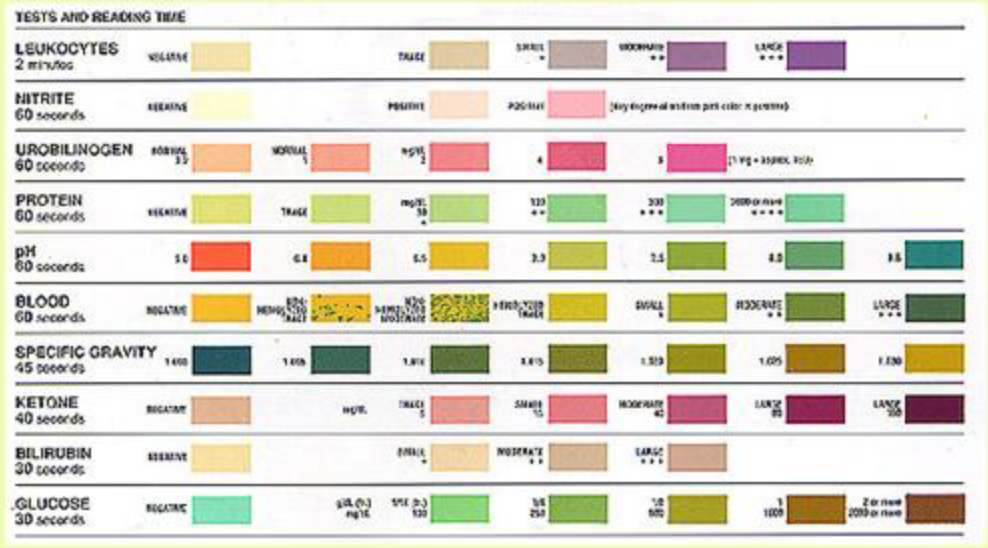
Ketones

Nitrite

Glucose

Urobilinogen

Bilirubin



The finding of sugar in the urine

1674: **Thomas Willis** Pharmaceutice rationalis, some forms of the *"pissing evil", the urine of patients was "wonderfully sweet"*.

William Cullen (1710-90) Edinburgh distinguished 2 types of poluria:

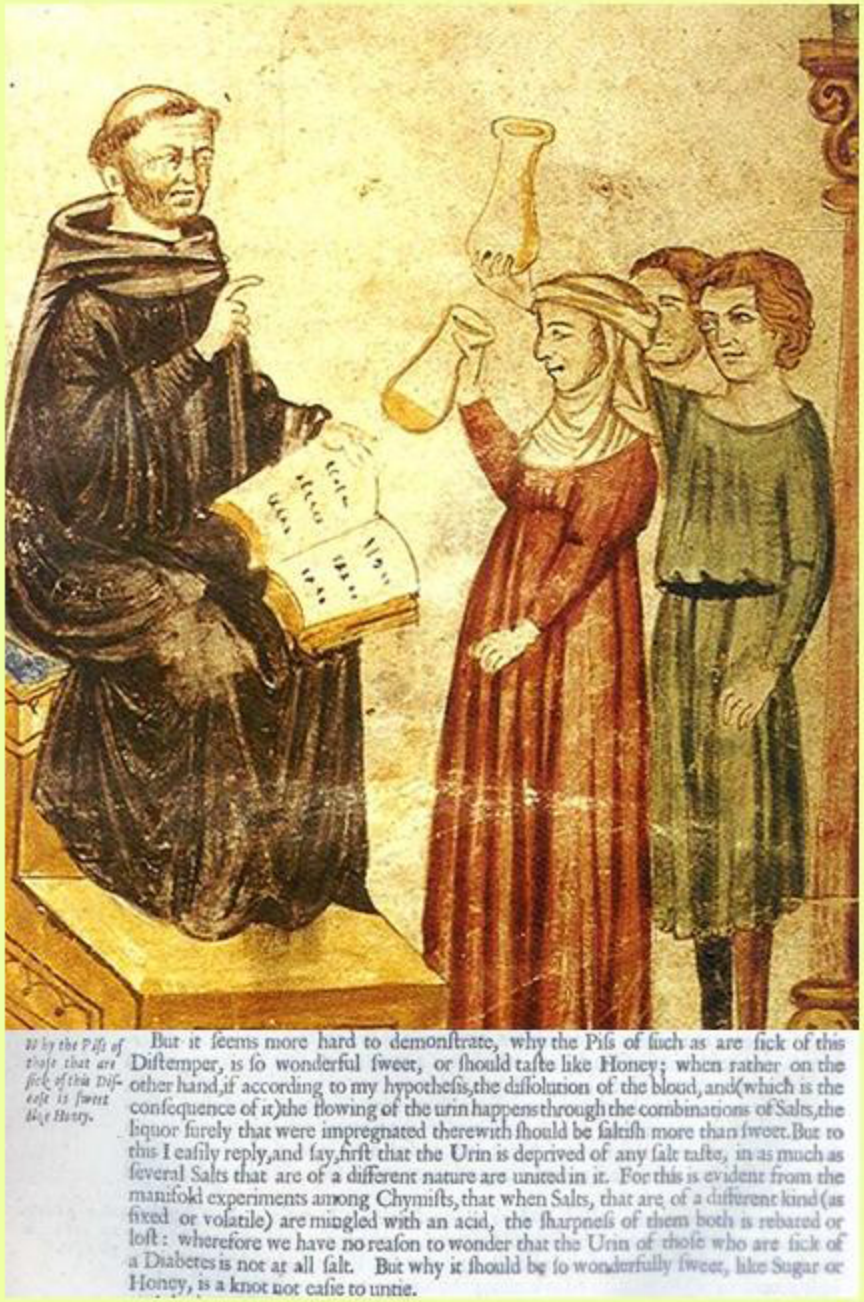
Urine sweet Diabetes mellitus

Urine tasteless diabetes insipidus

Francis Home (1719-1813) mixed half a pint of yeast with 24 pints of a diabetic's urine. It fermented for 3 days when it lost all sweetness and tasted like a tolerable small beer.

1776: **Matthew Dobson**, (1731-1784) Liverpool evaporates two quarts of urine from a patient with diabetes. The residue is granulated and smells and tastes like sugar, conclusively establishing the presence of 'saccharine materials' as a diagnosis of diabetes.

1797: **John Rollo** Scot, Surgeon General to Royal Artillery: creates the first medical therapy to treat diabetes. He prescribes an 'animal diet' for his patients of 'plain blood puddings' and 'fat and rancid meat' so to manage the disease with foods their bodies could assimilate.



Why the Piſs of thoſe that are ſick of this Diſeaſe is ſweet like Honey.

But it ſeems more hard to demonſtrate, why the Piſs of ſuch as are ſick of this Diſtemper, is ſo wonderful ſweet, or ſhould taſte like Honey; when rather on the other hand, if according to my hypotheſis, the diſſolution of the blood, and (which is the conſequence of it) the flowing of the urin happens through the combinations of Salts, the liquor ſurely that were impregnated therewith ſhould be ſaltiſh more than ſweet. But to this I eaſily reply, and ſay, firſt that the Urin is deprived of any ſalt taſte, in as much as ſeveral Salts that are of a different nature are united in it. For this is evident from the manifold experiments among Chymiſts, that when Salts, that are of a different kind (as fixed or volatile) are mingled with an acid, the ſharpneſs of them both is rebated or loſt: wherefore we have no reaſon to wonder that the Urin of thoſe who are ſick of a Diabetes is not at all ſalt. But why it ſhould be ſo wonderfully ſweet, like Sugar or Honey, is a knot not eaſie to untie.

Relationship of sugar to diabetes

19thC, chemical tests to detect sugar in urine.

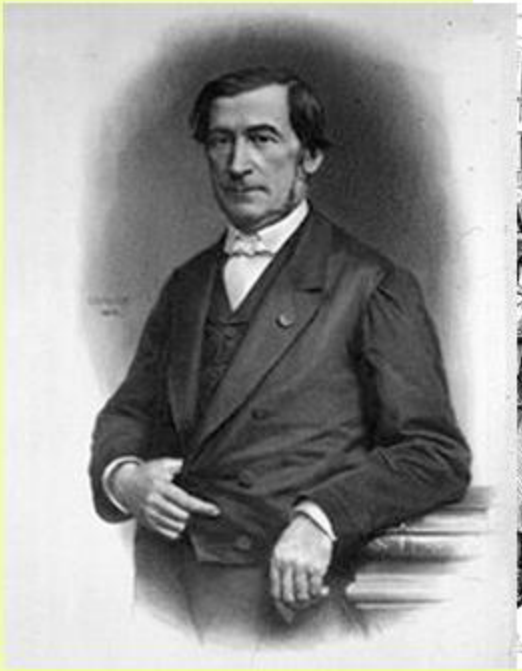
Apollinaire Bouchardat (1809-1866) glycosuria resolved in his diabetes pts food rationing in Paris while under siege by Germany during the Franco-Prussian War noticed that restricted diets helped his patients, *Bouchardat's treatment.*

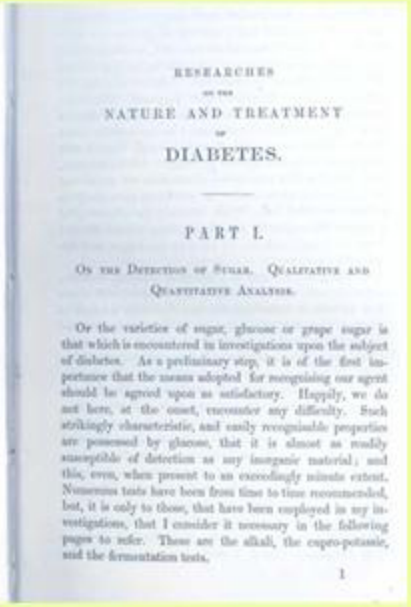
Gen. Leonhard Graf von Blumenthal, Crown Prince and Moltke, opposed bombardment. All of them had married English wives and as a result they were accused of coming under English liberal influence

Frederick Pavy (1829-1911) ***Researches on the nature and treatment of diabetes***
London, 1862: had the largest number of diabetic patients in London. concluded that there was a quantitative relationship between the degree of hyperglycaemia and glycosuria.

Queen Victoria's physician, Sir William Gull:

"What sin has Pavy committed, or his fathers before him, that he should be condemned to spend his life seeking a cure for an incurable disease?"





RESEARCHES
ON THE
NATURE AND TREATMENT
OF
DIABETES.

PART I.

ON THE DETECTION OF SUGAR. QUALITATIVE AND QUANTITATIVE ANALYSIS.

Of the varieties of sugar, glucose or grape sugar is that which is encountered in investigations upon the subject of diabetes. As a preliminary step, it is of the first importance that the means adopted for recognising our agent should be agreed upon as satisfactory. Happily, we do not here, at the onset, encounter any difficulty. Such strikingly characteristic, and easily recognisable properties are possessed by glucose, that it is almost as readily susceptible of detection as any inorganic material; and this, even, when present to an exceedingly minute extent. Numerous tests have been from time to time recommended, but, it is only to those, that have been employed in my investigations, that I consider it necessary in the following pages to refer. These are the alkali, the cupro-potassic, and the fermentation tests.

1

Discovery of Pancreas

1869: **Paul Langerhans** German medical student, announces in a dissertation that the pancreas contains contains two systems of cells. One set secretes the normal pancreatic juice, the function of the other was unknown.

Later called the 'islets of Langerhans.'

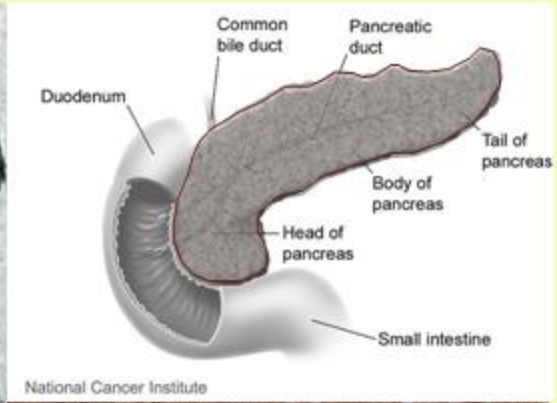
Develops Tuberculosis and 1875 moves to Madeira. Studies Marine worms. Marries a widow happily for 3 years dying aged 40.

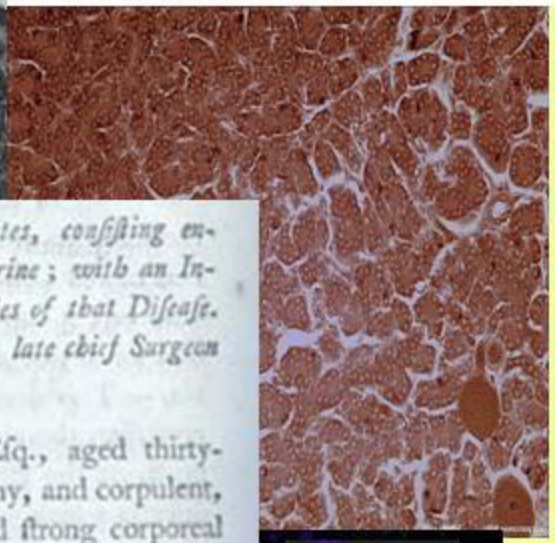
1893: Oskar Minkowski and Joseph von Mering University of Strasbourg, removing dog's pancreas produces diabetes. Noted swarms of flies on the urine. Pancreas related to diabetes.

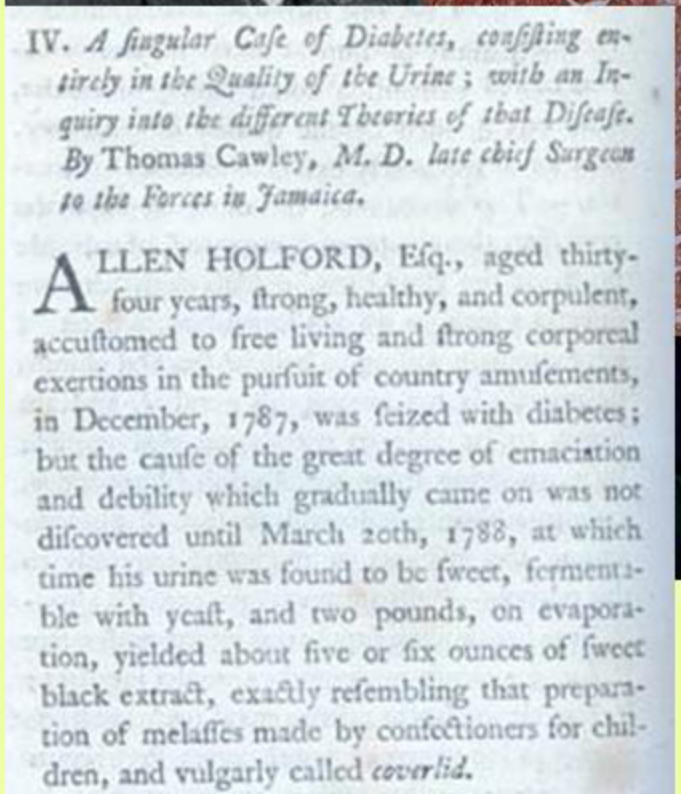
1704: **Johan Brunner** Leiden; noted that removal of the pancreas made dogs very thirsty and produce copious urine).

Moses Barron: autopsy on pt c stones in the pancreas and diabetes; described the microscopic changes in the islets of Langerhans. linked the Langerhans cells with the basis of diabetes mellitus.

Thomas Cawley: Surgeon to Forces in Jamaica had already described a similar case of a pt who died of diabetes and had stones in his pancreas. ***A singular case of diabetes (London Medical Journal) London, 1788***

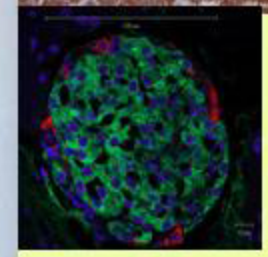






IV. *A ſingular Caſe of Diabetes, conſiſting entirely in the Quality of the Urine; with an Inquiry into the different Theories of that Diſeaſe. By* Thomas Cawley, *M. D. late chief Surgeon to the Forces in Jamaica.*

ALLEN HOLFORD, Eſq., aged thirty-four years, ſtrong, healthy, and corpulent, accuſtomed to free living and ſtrong corporeal exertions in the purſuit of country amuſements, in December, 1787, was ſeized with diabetes; but the cauſe of the great degree of emaciation and debility which gradually came on was not diſcovered until March 20th, 1788, at which time his urine was found to be ſweet, fermentable with yeaſt, and two pounds, on evaporation, yielded about five or ſix ounces of ſweet black extract, exactly reſembling that preparation of melaſſes made by confectioners for children, and vulgarly called *coverlid*.



Discovery of Insulin

J. J. R. Macleod, 4th Ed textbook that "the pancreas might be the seat of a hormone to control diabetes, but that it was more likely a detoxifying centre

Sir Edward Sharpey-Schafer (1850-1935) ***The endocrine organs: London, 1916*** Prof Physiology Edinburgh 1899-1933. Theorised islets of Langerhans secrete a substance which governed carbohydrate metabolism. Suggested the name insuline.

Sir Frederick Banting 1921: WW1 military surgeon from Ontario. October, 1920, late at night, preparing some lecture notes on the physiology of the pancreas, read article by Moses Barron; dreamed if the protein dissolving secretion of the pancreas eliminated, mysterious substance "X" could be identified, to cure diabetes.

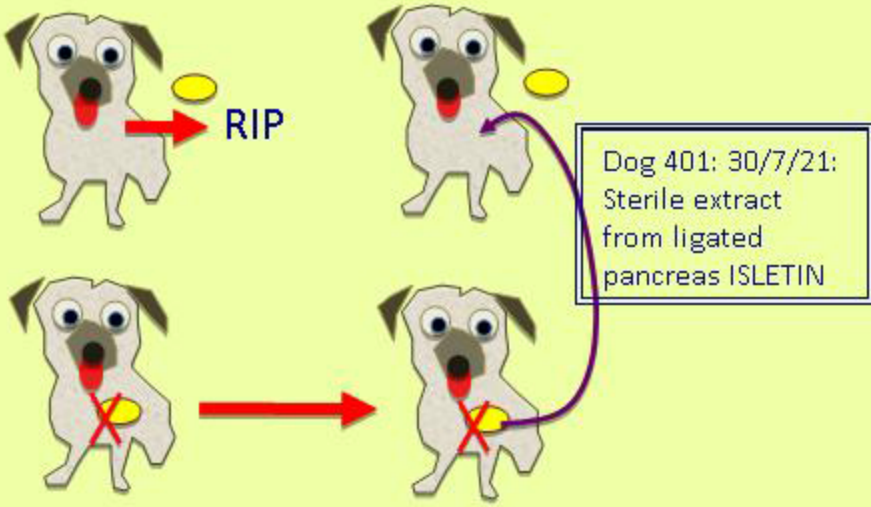
Borrowed Toronto Lab of Prof. Macleod whilst he was in Scotland for the summer.

Of 2 students a flip of the coin led to **Charles Best,** a brilliant mature medical student, WW1 officer, becoming assistant.

1921: discovered insulin, named after the 'islands' of cells described by Langerhans. Nobel Prize, controversially omitted Best but included the sceptic Macleod.

Bovine foetal pancreas extract lowers blood sugar levels of depancreatized dogs, plentiful, cheap source for insulin

Eli Lilly started large-scale production of the extract.1923, producing enough to supply the entire North America.



January 1922 in Toronto General Hospital, Charity Pt: 14yrs, Leonard Thompson near death, first person with diabetes to receive insulin, rapidly regained strength and appetite. Died age 27 Pneumonia.

Purifying Insulin

MacLeod freed Collip from his other research to enable him to join the research team. Collip's task was to prepare insulin in a more pure, usable form than Banting and Best had been able to achieve to date.

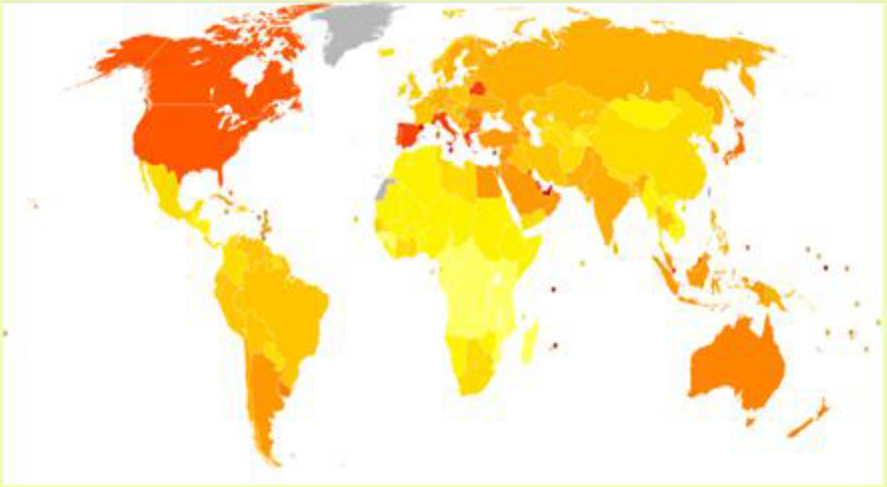
Within a month, Collip achieved the goal of preparing a pancreatic extract pure enough to use in clinical trials.

Children with diabetic keto-acidosis were nursed in huge wards, 50 or more patients mostly comatose. Grieving family members were often in attendance, awaiting their child's inevitable death.

Banting, Best, and Collip went from bed to bed, injecting an entire ward with the new purified extract. Before they had reached the last dying child, the first few were awakening from their coma, to the joyous exclamations of their families

Worldwide diabetes epidemic

A state of absolute or relative insulin deficiency characterised by hyperglycaemia and the risk of microvascular and macrovascular complications WHO 1999



The World Health Organization estimate that over 200 million people worldwide including 2.6 million people in the UK have diabetes

Prevalence of diabetes in England increased from 3.3% in 2004–05 to 4.1% in 2009–10

Most have type 2. "**Diabesity**"

Wt gain of 11-15Llb increases risk of diabetes by 50%.

Obesity and insulin resistance

Diabetes chronically damages the tissues

Atherosclerosis accelerates, strokes MI and peripheral vascular disease.

Microvascular complications: In US

diabetic retinopathy is leading cause of blindness in adults 20-74yrs.

Diabetes is expensive
Poorly managed is even more expensive
Human cost

Health care expense:

24m; 7.8% of Americans (20% of retired age)

NIH estimate cost to USA $132b per year!

UK: 4m people by 2025

10% NHS budget ~£9b

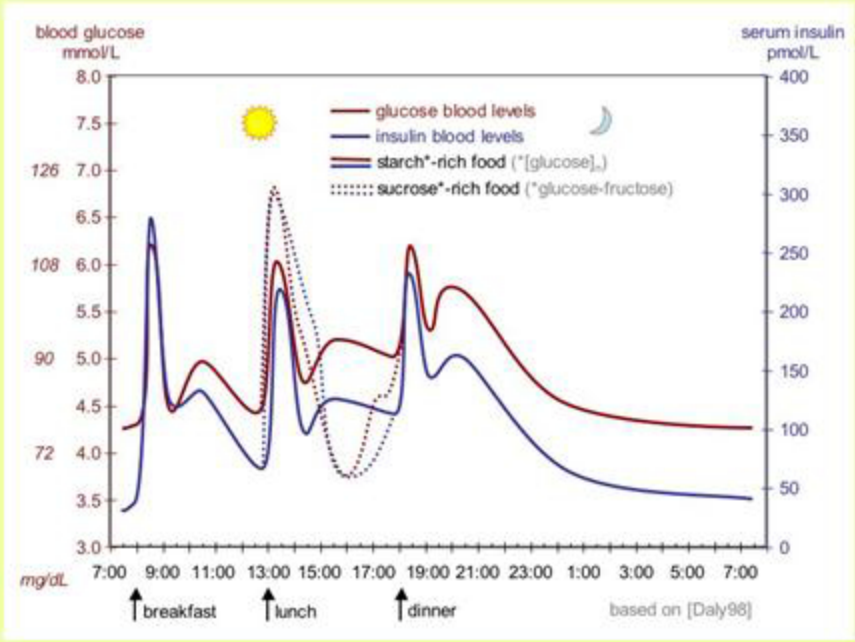
2009–10: primary care England dispensed more than 35.5 million different items by prescription for diabetes, cost £650 million.

2004–05, 24.8 million items were dispensed, cost £458.6 million.

NHS Information Centre

Prescribing for Diabetes in England: 2004/5 to 2009/10,

£1m per hour



Prevention of complications

Almost 1 in 3 people with type 2 diabetes develops overt kidney disease

Within 20 years of diagnosis of type 2 diabetes, 60% of people diagnosed have some degree of retinopathy

1998: The United Kingdom Prospective Diabetes Study (UKPDS) importance of good glucose control and good blood pressure control in the delay and/or prevention of complications in type 2 diabetes.

Glucose control, weight loss and exercise reduce complications.

William Banting (1797-1878) Obese Kensington Undertaker. weight loss diet based on limiting intake of refined and easily-digestible carbohydrates: 1863, Banting wrote a booklet called *Letter on Corpulence, Addressed to the Public*

"do you bant?" referred to his low carbohydrate method, and eventually to dieting in general.

Related to discoverer of Insulin

Dr. William Harvey, who in turn had learnt of this type of diet, but in the context of diabetes management, from attending lectures in Paris by a Mons. Bernard.

Imaging the retina

Why is the pupil is black?

Ancient explanations: the moisture in the eye was black.

However Pliny observed that the eyes of nocturnal animals, shone in the dark. Why?

Before ophthalmoscope speculation as to what was behind the black hole. theories about why the eye became luminous under certain conditions.

- phosphorescence;
- light absorbed during the day gave off light at night
- electricity emitted by the retina, similar to a firefly.

Edmé Mariotte; The dog's eye is luminous because its "choroid" is white, hence the image of a light is painted on it clearly, whereas in man and in animals with black "choroid" no such clear image could be formed.

Gruithuisen later correctly described the reflective layer the tapetum lucidum

Imaging the retina

3 problems to be solved:

- The retina of the patient must be adequately illuminated
- The observers pupil and the light source must aligned.
- The observer and patient have to made emmetropic so that parallel rays emitted are focused by the observer.

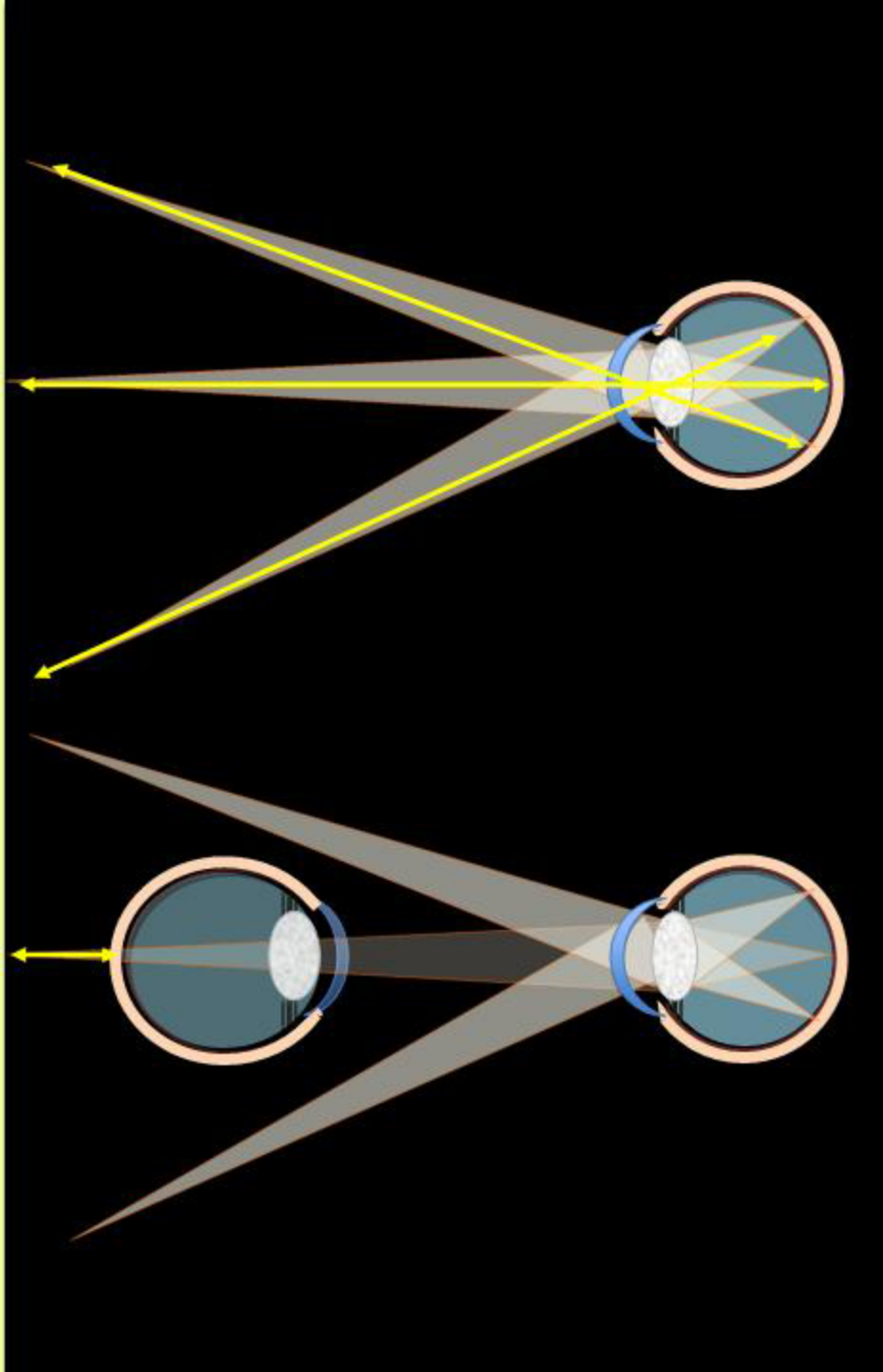
1810 **Bénédict Prevost** (1755-1819): Prof of Philosophy Montaubon, animal luminosity disappears in complete darkness 'It is not the light which proceeds from the eye to an object that enables the eye to perceive that object, but the light which arrives in the eye from it.'

luminosity could only be observed when light entered the eye from without.

1821 Karl Asmund Rudolphi. the luminosity of an animal eye depends on the direction of the ingoing rays. Same effect in eye of a decapitated cat.

1735: **Duddell:** human albino,

Fermin had noted luminosity of the eye of an Ethiopian albino (and concluded that this patient could thus see at night, because his eyes were like those of night animals)



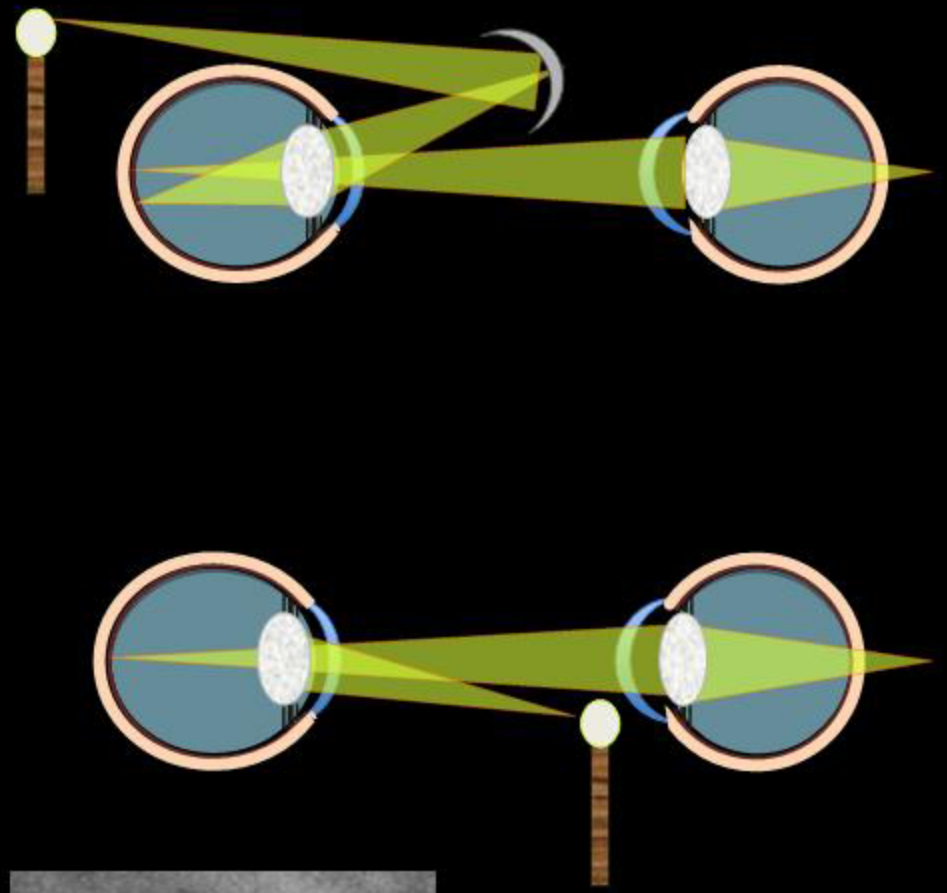
The problem of illumination

The **HUMAN** retina is *not very reflective. Only about 1/10,000 - 1/100,000 of light entering the eye is reflected back out*

1823 **Jan Evangelista Purkinje** (1787–1869) that under certain conditions of illumination dog & human eyes could be made luminous by using his myopic spectacles as a concave mirror to reflect light from a candle placed behind the pt.

'I examined the eye of a dog by using the spectacle lens of a myope and placing a candle behind the dog's back ... I found the light as the source, which is reflected from the concavity of the spectacle lens into the interior of the eye. From there it is again reflected. I immediately repeated the experiment on a human eye and found the same phenomenon'

published in Latin ignored.



The problem of imaging

1703, **Jean Méry** (1645-1722) luminosity of the cat's eye also seen when the animal was held under water; i.e an optical phenonemon. Observed the retinal vessels. Thought that water filled in unevenness of the cornea.

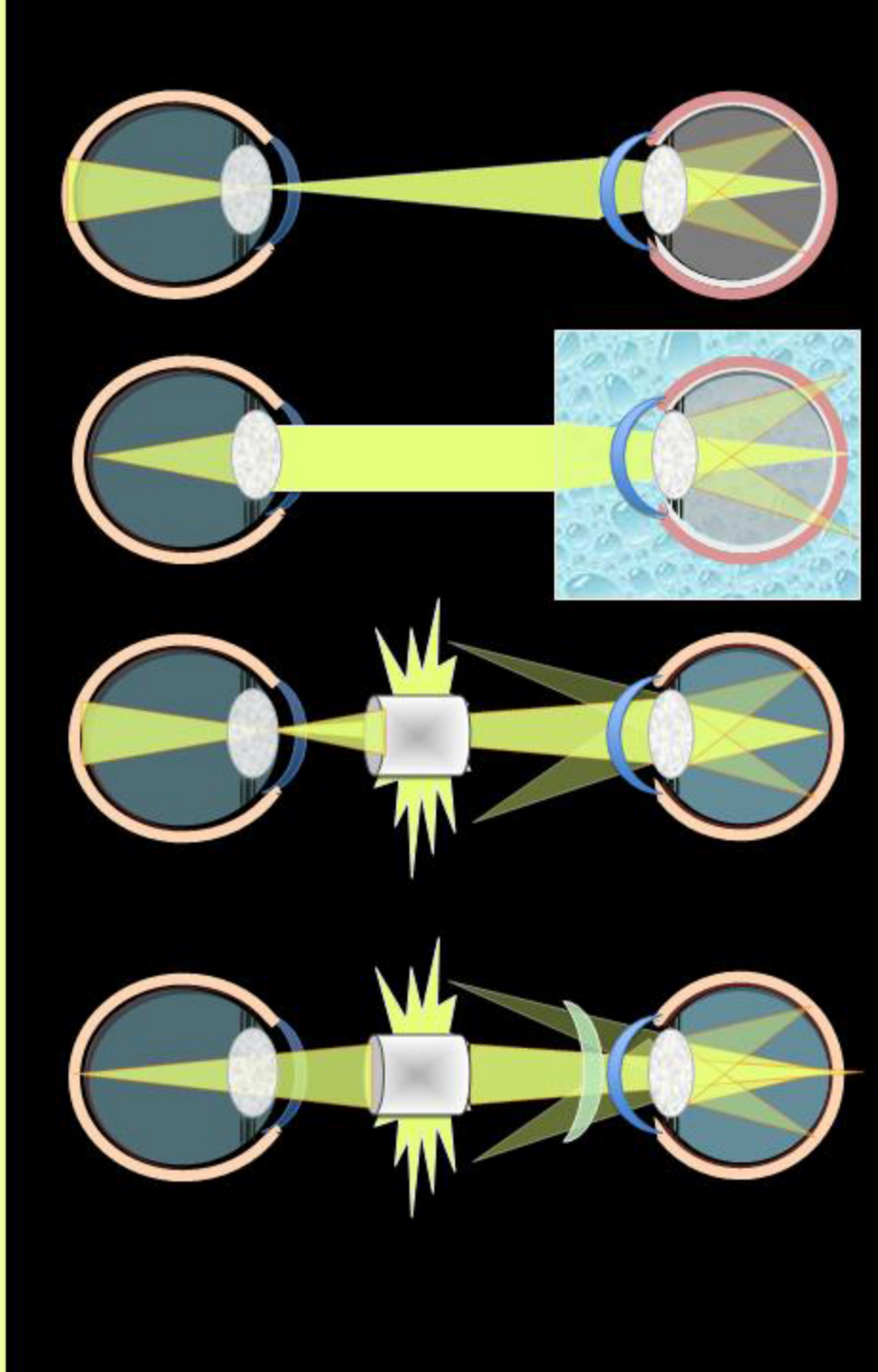
1709: **de la Hire** correct explanation, the cat's fundus was seen by neutralisation of corneal refraction under water; the rays emerged divergent, and some of them focused by the observer's eye.

1845: **Kussmaul:** solved the problem of imaging but not illumination. Concave lens of the same power placed on cornea to neutralise its power; "should be of great value in the diagnosis of certain eye diseases". failed, didn't understand need for illuminating the eye.

1846: **William Cumming**: Royal London Ophthalmic Hospital (later Moorfields Eye Hospital) Solved the problem of illumination but not imaging; "On a luminous appearance of the human eye and its application to the detection of disease of the retina and posterior part of the eye.'

realized that the axis of illumination and observation had to be co-incident one had to stand in the path of the emerging rays.

1847: **Ernst Brücke** Berlin physiologist nearly invented the ophthalmoscope looked through a tube in the flame of a candle illuminating the eye, and thus caught some of the emergent rays



Invention of Ophthalmoscope

1847 **Charles Babbage** (1792-1871), gave a device to ophthalmologist Thomas Wharton Jones,

Mr. Babbage showed me the model of an instrument which he had contrived for the purpose of looking into the interior of the eye. It consisted of a bit of plain mirror, with the silvering scraped off at two or three small spots in the middle, fixed within a tube at such an angle that the rays of light falling on it through an opening in the side of the tube, were reflected into the eye to be observed, .

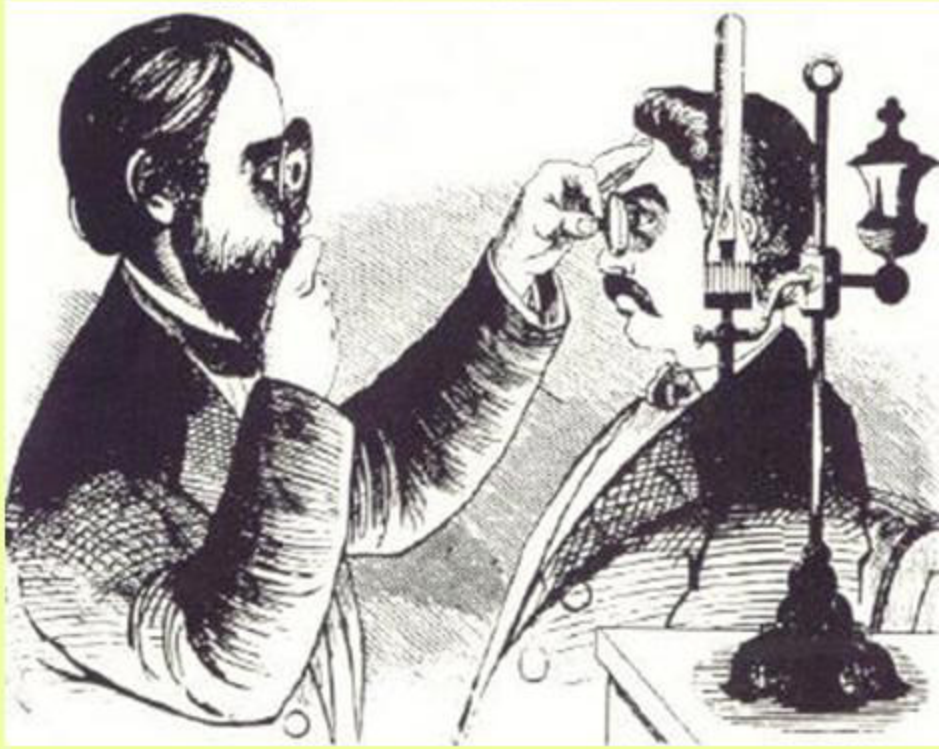
1850: **Hermann von Helmholtz** (1821-1894)

Augenspiegel' "eye-mirror" looking through the lens into the back of the eye only produced a red reflection. With a condenser lens a clearer inverted image, then magnified X5.

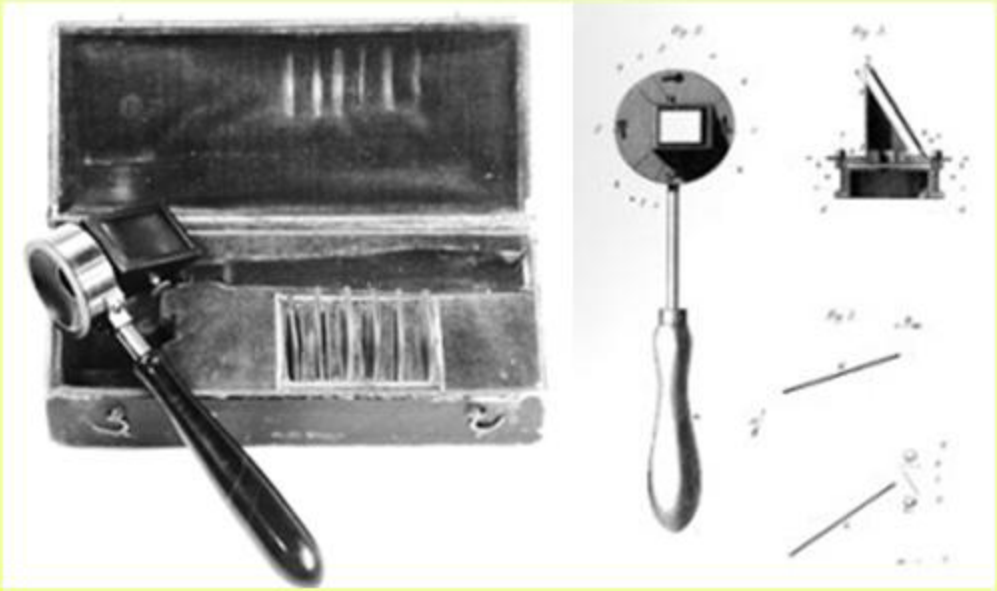
combination of a mirror and condenser lens an indirect ophthalmoscope. In use until 1920.

3 components:

A light source;
mirror to direct light toward the eye
device to focus the image on the retina.



Actually not a mirror but four plates of glass to increase the number of rays reflected into the eye. The illumination was poor.



England ‘eye speculum’

1852: **Maressal de Marsilly** Calais
‘ophthalmoscope’ eye-observer
Modifications followed quickly, the silvered mirror with a central hole

Original no lenses for correcting errors of refraction in the patient and/or the observer.
Egbert Rekoss, Helmholtz's machinist at the university, added two rotatable discs, each containing lenses.

Search for the ideal source of illumination led to attempts with oil, petrol, gas, daylight and almost every conceivable monochromatic flame.

Mystery of Amaurosis solved

Blindness in a normal looking eye was called Amaurosis

Neither the pt nor the ophthalmologist saw anything!

The cause of this condition was a mystery until the back of the eye visualised.

Multiple causes of this previously enigmatic condition were rapidly discovered

It was thought that glaucoma was a disease with a normal appearance of the back of the eye.

later it was thought that the optic disc was swollen.

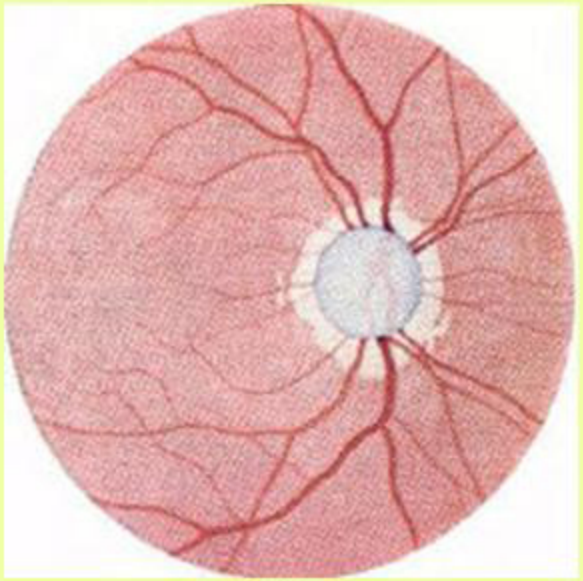
1855 von Graefe, who initially believed the nerve was swolen, demonstrated cupping.

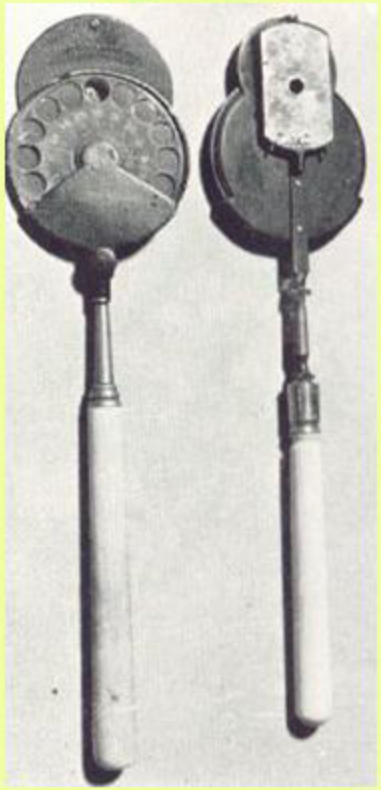
Iridectomy treatment of the previously mysterious and untreatable disease.

von Graefe in 1855 and Heymann in 1856 described renal retinitis,

Coccius in 1853 described detachment of the retina and retinitis pigmentosa.

1855: von Jager describes diabetic retinopathy. Controversial as believed this was due to hypertension, or inflammatory due to elevated albumin “diabetic retinitis”





The retinal vasculature

Arterioles muscular wall

capillaries no muscular wall, leaky

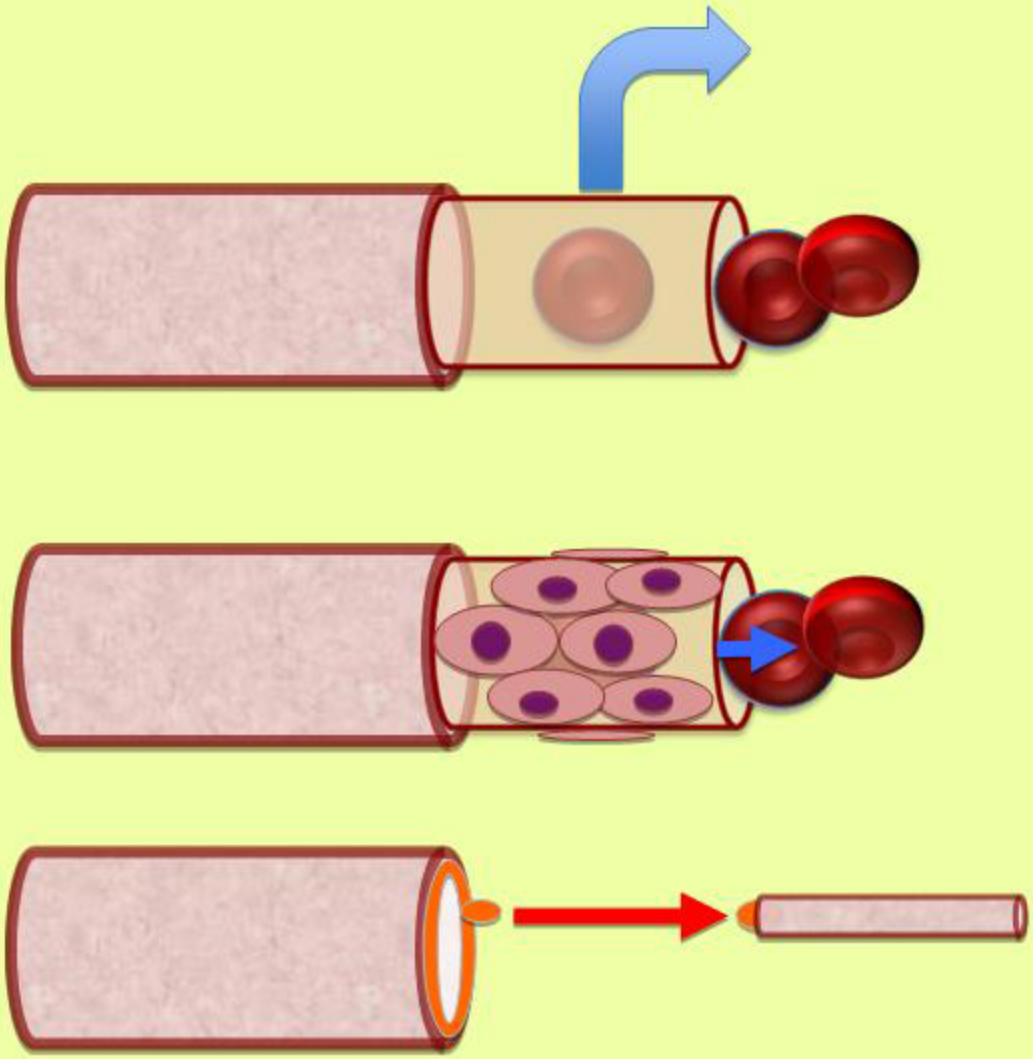
In retina tight junctions cells prevent leaking

Damaged by disease such as diabetes

Vessels become leaky and the retina gets boggy (oedema)

Hardening of large arteries with fatty atheroma plaques:

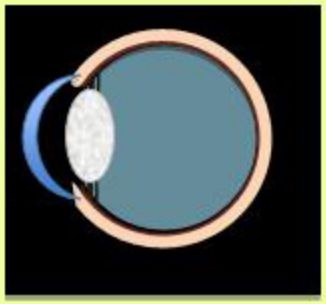
break off and block smaller calibre vessels upstream

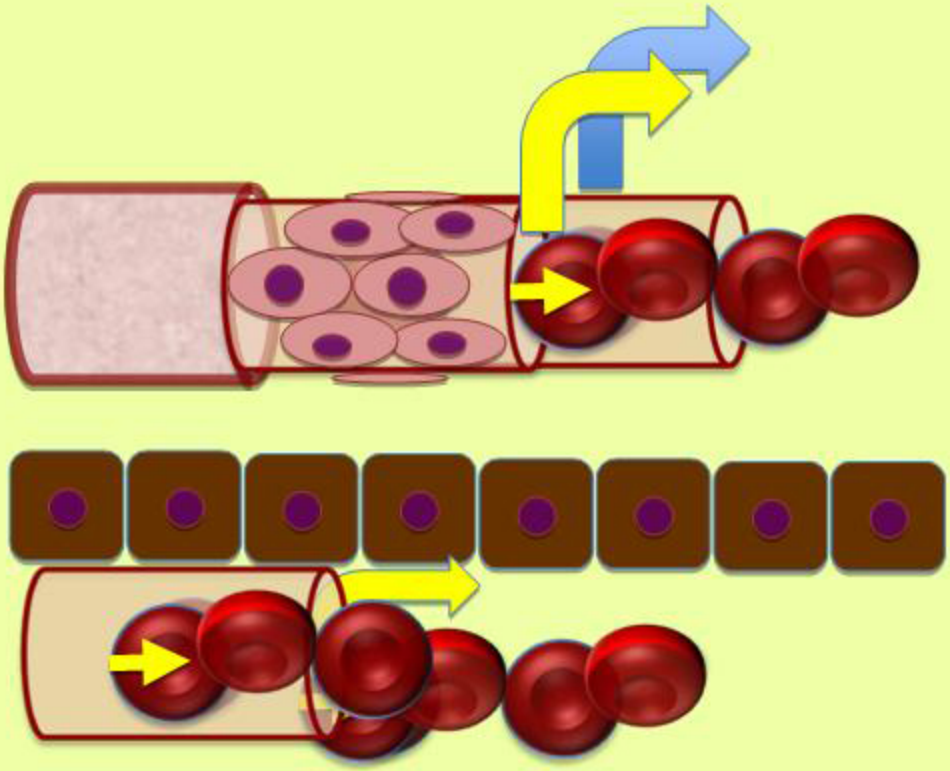


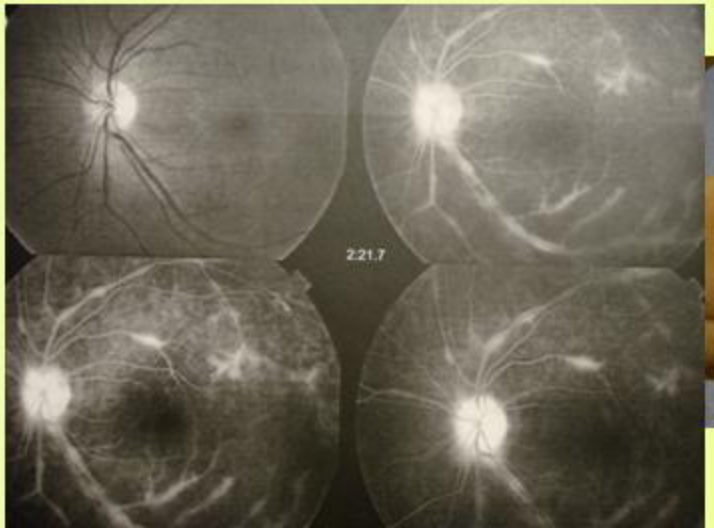
The retinal vasculature

Damage to tight junctions cells allows leaking

Fluorescein dye escapes.







Diabetes and the eye

Eduard Jaeger in 1856. Diabetic macula: yellowish spots observed for the first time

Albrecht von Graefe: no proof of a causal relationship between diabetes and retinal complications

1872 Edward Nettleship

"On oedema or cystic disease of the retina" first histopathological proof of "cystoid degeneration of the macula" in diabetes

Arthur James Ballantyne
Glasgow diabetic retinopathy a unique vasculopathy. (ie not hypertension or atherosclerosis)

Background retinopathy

Diabetic retinopathy is the Leading cause of Blindness

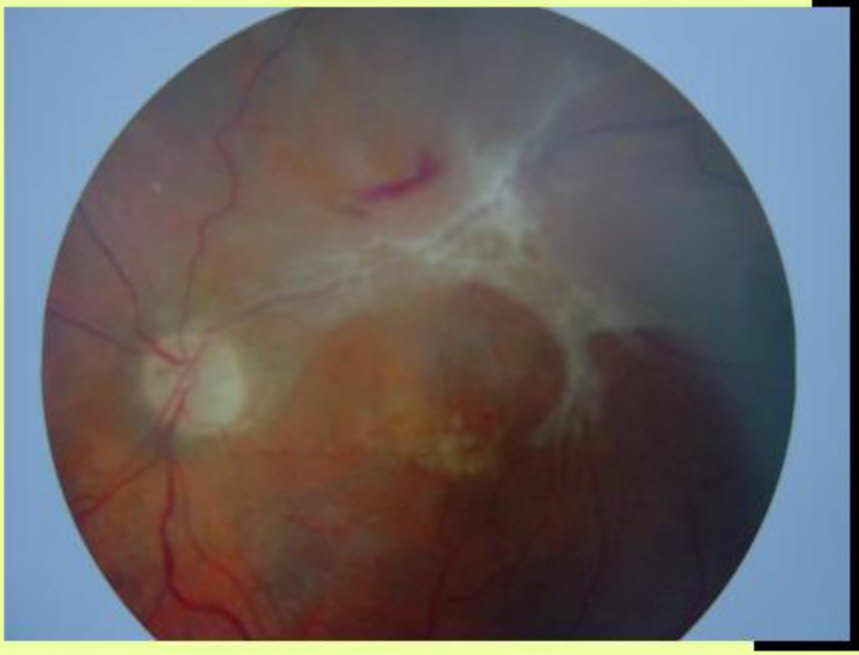
Properly treated the risk of macular oedema is reduced by 50% and blindness from proliferative disease by 90%

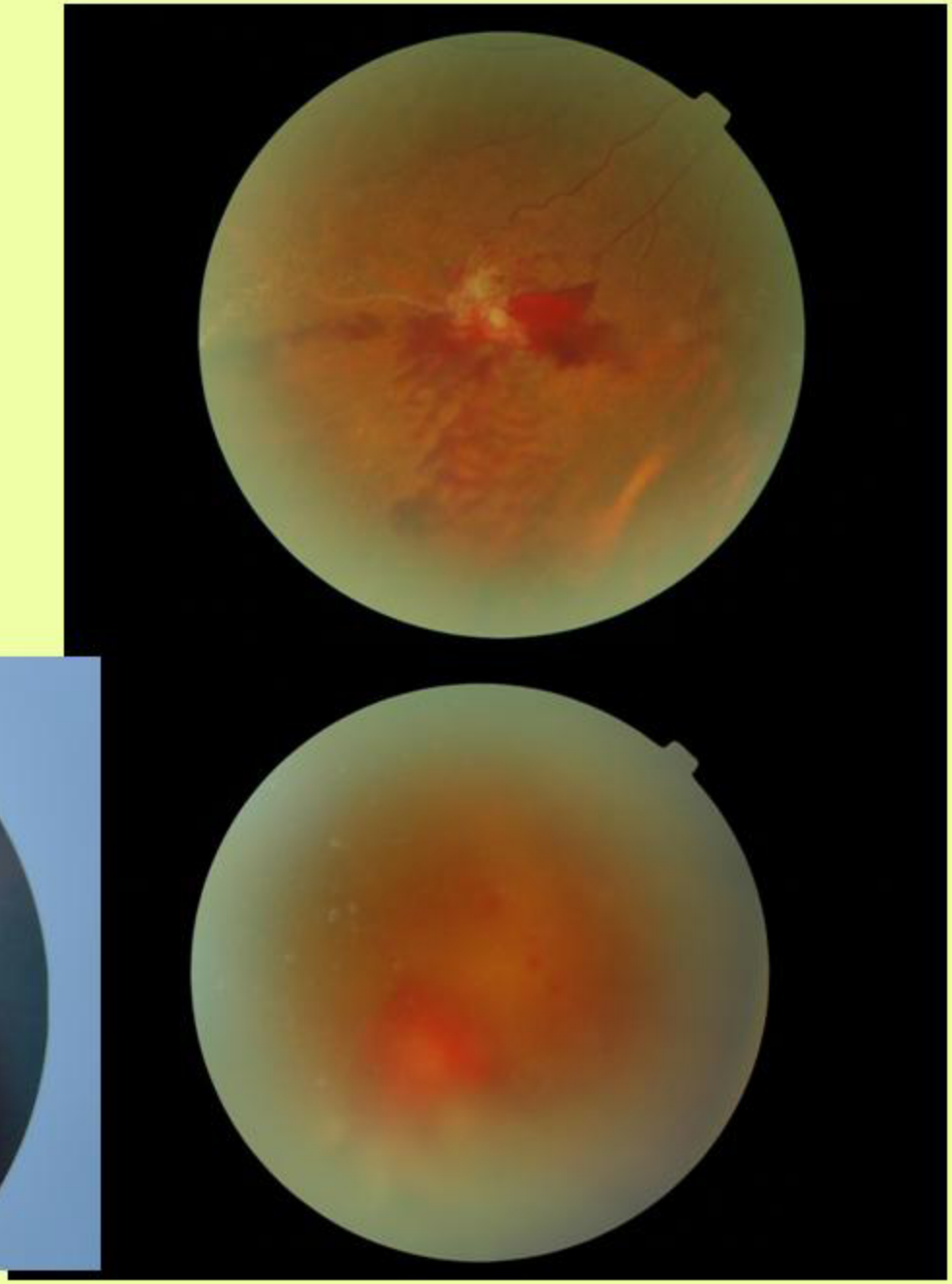
However until recently eye screening was sporadic.

Diabetic maculopathy

Proliferative retinopathy

1876, Wilhelm Manz described the proliferative changes occurring in diabetic retinopathy and the importance of tractional retinal detachments and vitreous haemorrhage.





NVD

Gerd Meyer-Schwickerath, (1920-1992)

University Eye Clinic in Essen in 1959

Retinal scars caused by sunlight exposure during eclipse of July 10, 1945 "resembled the sort of scar resulting from surface diathermy,"

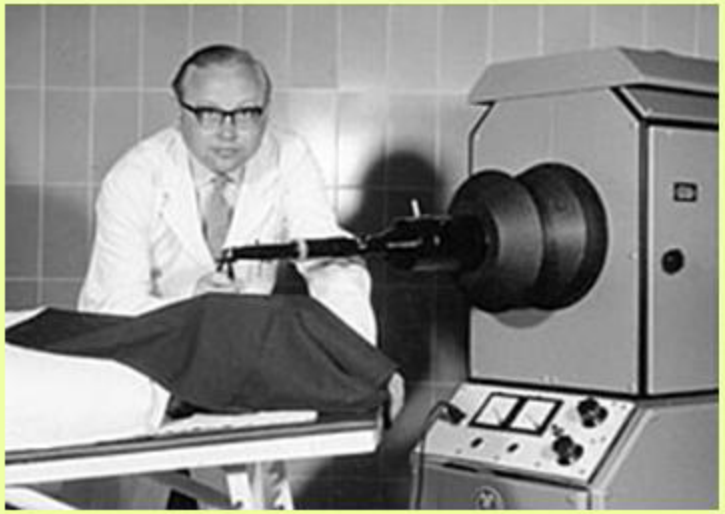
Ophthalmologists applied heat to the eye to seal retinal holes or treat diabetic retinopathy

1950s the American Optical Corporation developed high-pressure xenon arc lamps for a movie producer. These gas lamps produced light so bright that people who looked at it directly ran the danger of unintentionally coagulating their retinas.

Zeiss Laboratories in Oberlochen, Germany, incorporated the xenon lamp into a photo-coagulator.

emitted light at 400 to 1,600 nanometers; danger to the eye with a wide beam 500 to 1,000 μm burns.

painful when iris contracted during the 250 to 1,000 milliseconds required to produce the necessary burn



Laser

controlled multicentre trials (Diabetic Retinopathy Study Research Group 1976;

After 2 yrs severe visual loss 26% control 11% treated with argon or xenon.

More side effects in Xenon group (25% severe loss visual field, 55 in argon group.)

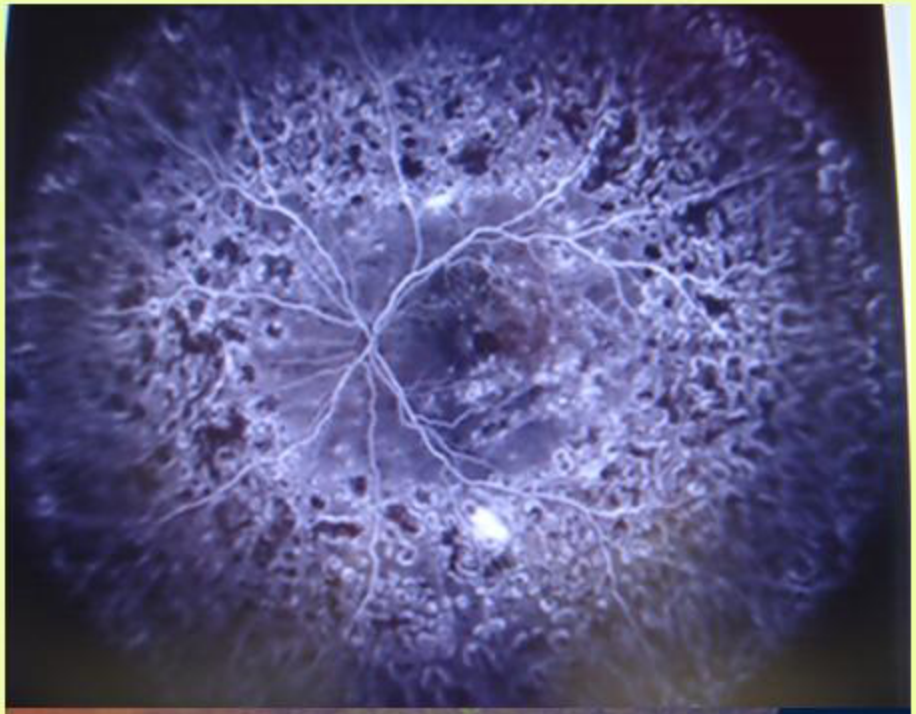
British Multicentre Photocoagulation Trial 1977; Hercules et al. 1977)

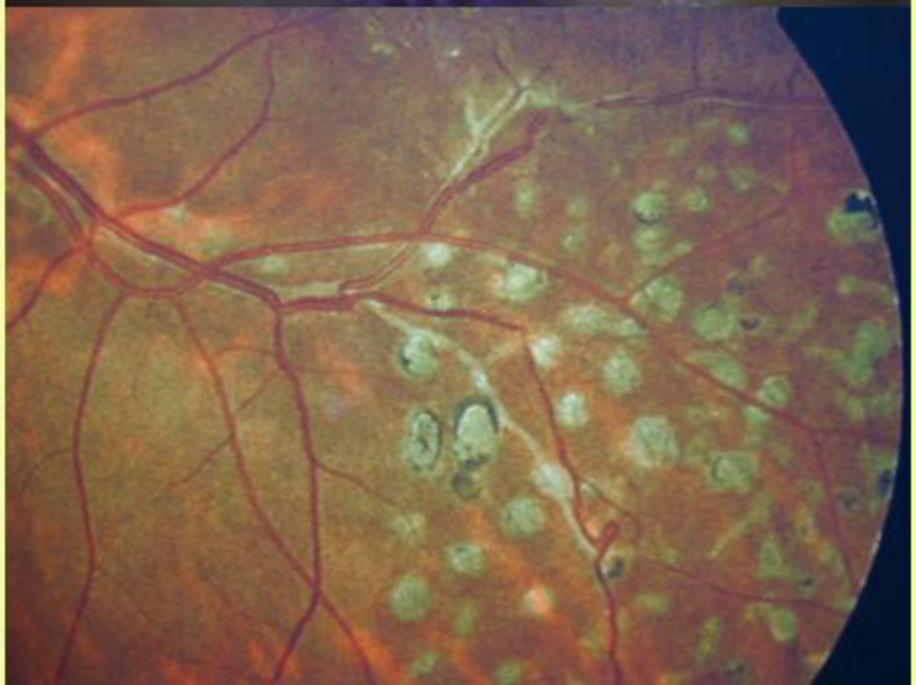
ETDRS: 3,711 pts

Is photocoagulation effective for diabetic maculopathy

Increased gain of vision

Reduced rate of loss of vision by 50%





Medical control

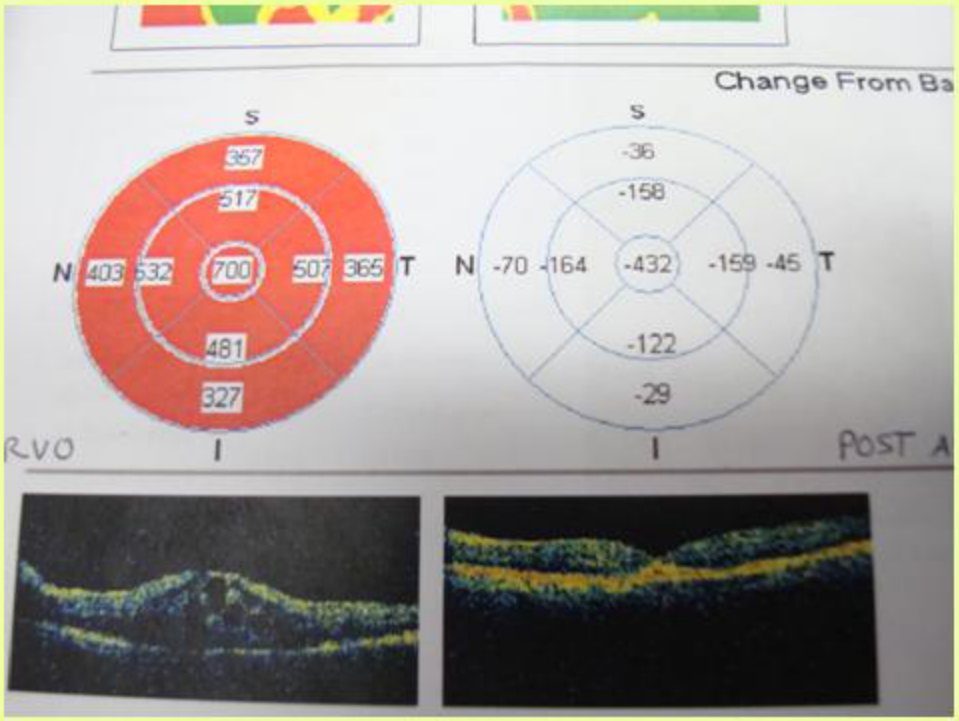
Diabetic Control and Complications trial 1983-1989: 1441 pts, half with half without retinopathy.

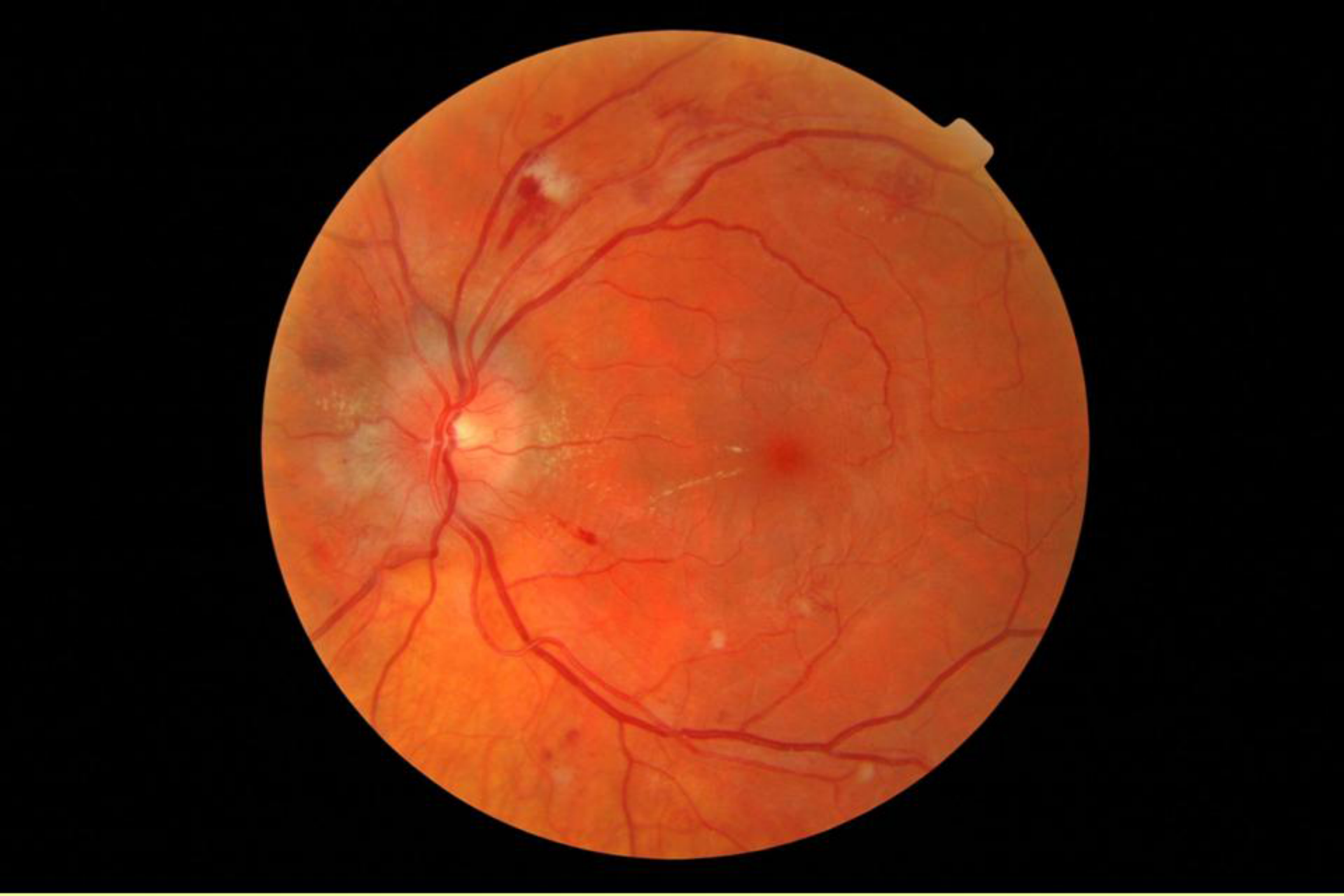
Those assigned to intensive control had less development or less progression of retinopathy. Also good for kidneys and nerves.

This benefit persisted for 7 years after the trial when less intensive control was achieved.

Microvascular complications are due to toxicity of high glucose in the blood. They take years to develop and short-term trials of 2yrs or less will not detect any benefits of control.

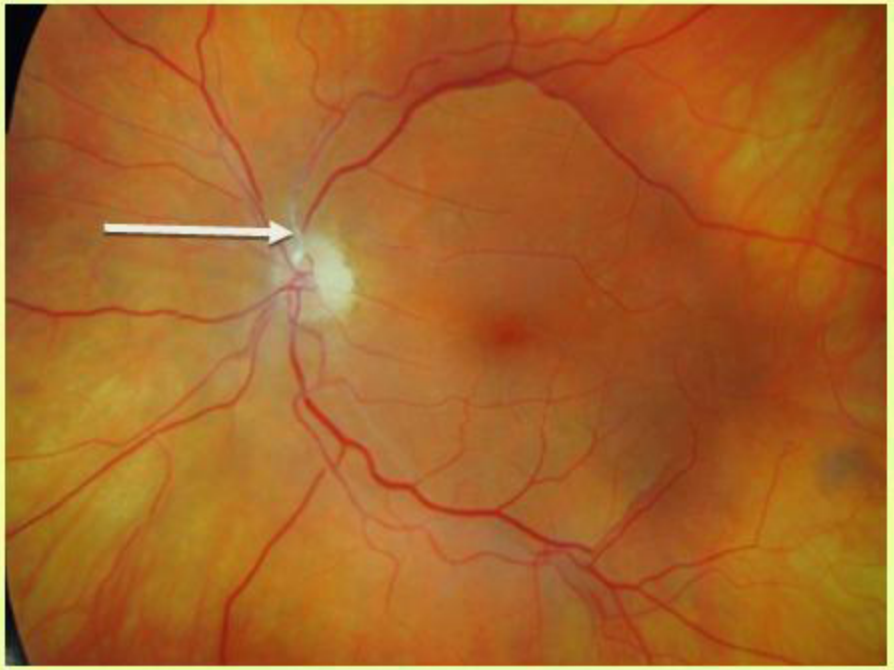
UK prospective diabetic study: whether with ACE inhibitor or beta-blocker were less likely to have progression of retinopathy or develop macula oedema.

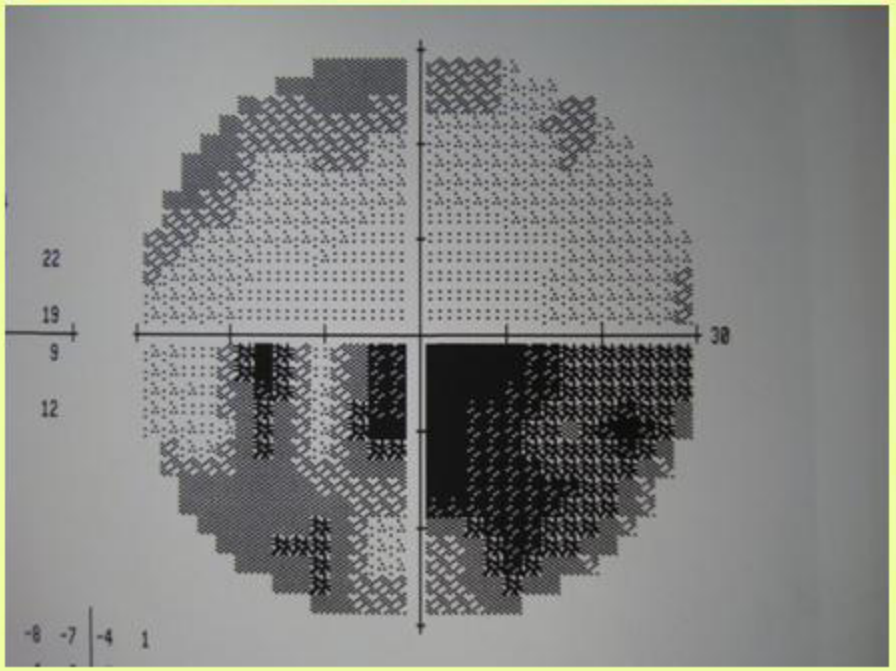




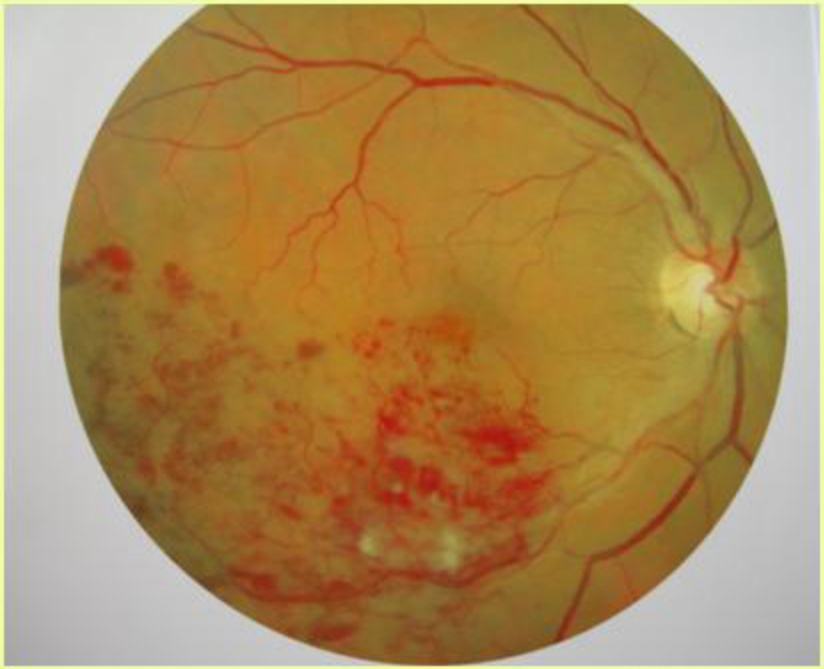
Systemic hypertension

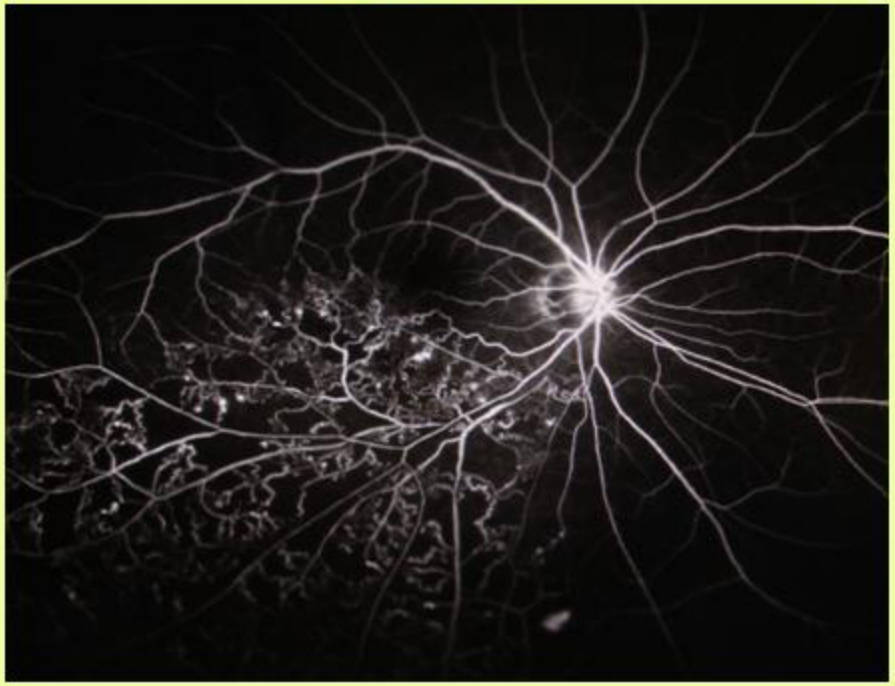
Retinal arteriolar occlusions





BVO

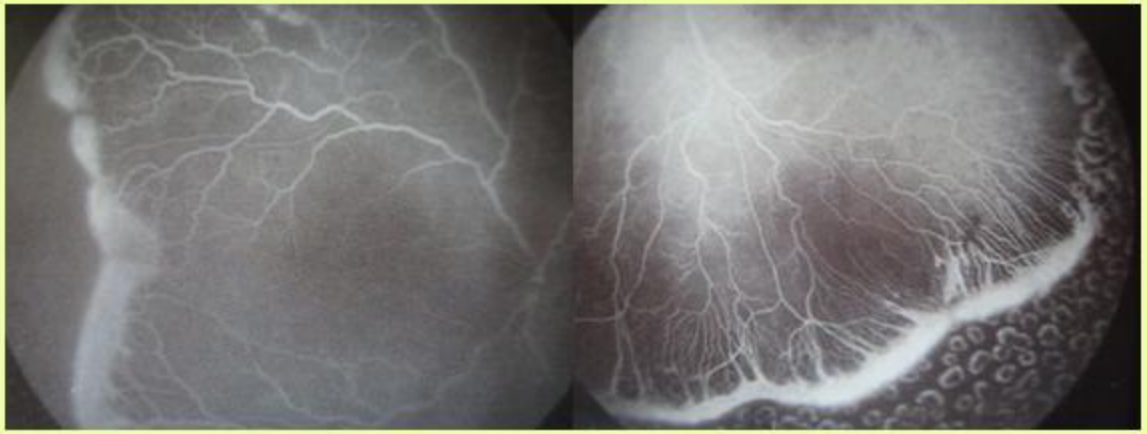




CRVO

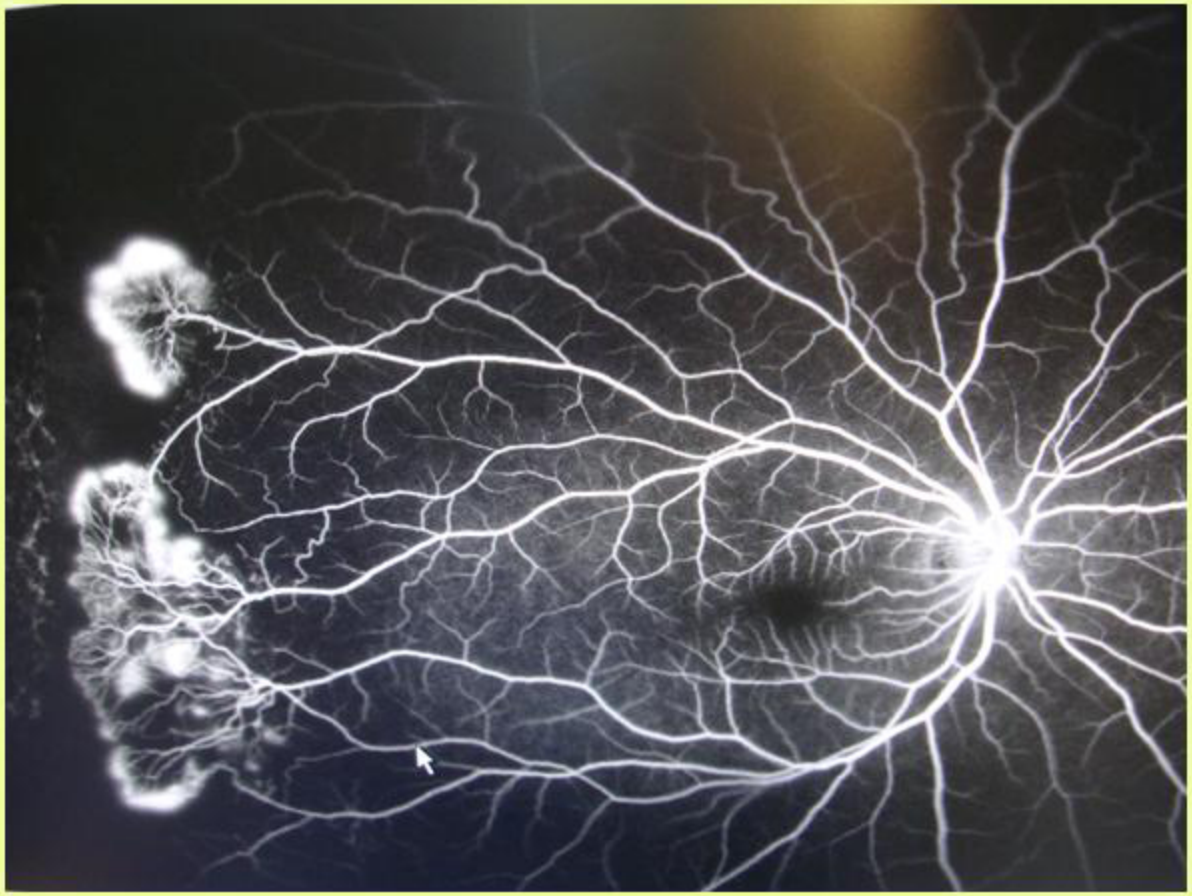
Other vascular diseases of the retina

ROP

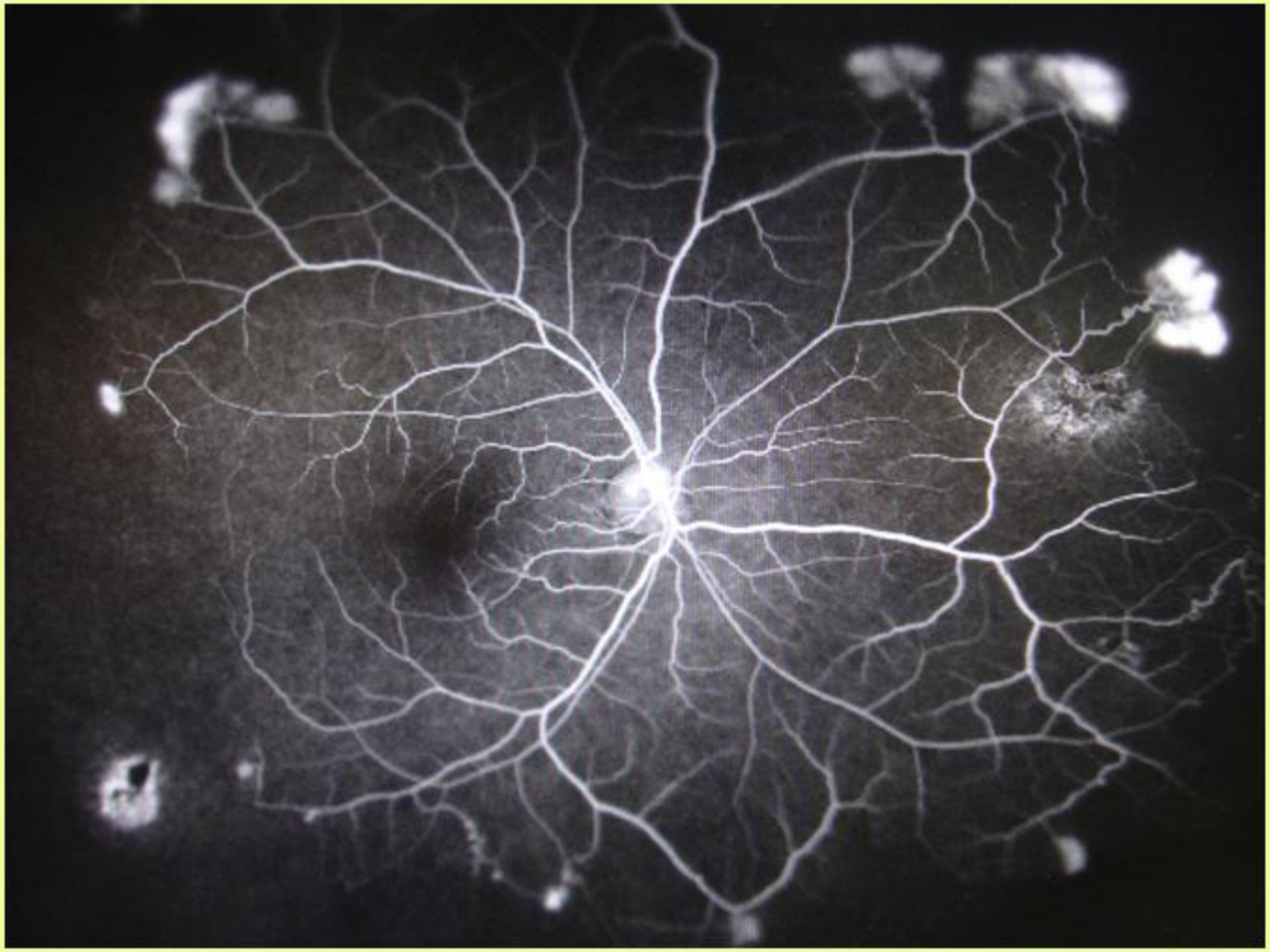


NVE

Sickle



Retinal vasculitis



Thank you