Lab Testing in Optometric Practice: The Basics

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Disclosures

Paid consultant for:

Sun Pharmaceuticals: Speaker bureau

Avellino: Advisory Board

Dompe: advisory board

RVL Pharmaceuticals: Advisory board

Agenda

- Review the diagnosis, diagnostic testing and common clinical findings in:
  - Diabetes
  - Thyroid dysfunction
  - Pituitary adenoma
  - Sarcoidosis
  - STI’s (syphilis, chlamydia, gonorrhea)
  - Tuberculosis
  - Blood disorders (anemia, leukemia)
  - Autoimmune diseases (rheumatoid arthritis, lupus, Sjogrens)

Case

- 48 YOF presents with acute loss of vision in her right eye and decreased vision in her left
  - She was scheduled 2 weeks previously for an eye exam on a referral from her PCP but had fallen and was unable to make that appointment
  - She reports that her vision in her right eye seems to be getting worse over the past several weeks.
  - Was diagnosed with diabetes 1.5 years ago
    - BS control has been erratic with range between between 6.7-13.3 (120-240)
    - Last A1C: 9.1

Entrance Skills/Health Assessment

VA: OD: finger count

OS: 6/12 (20/40)

CVF: OD: unable to assess

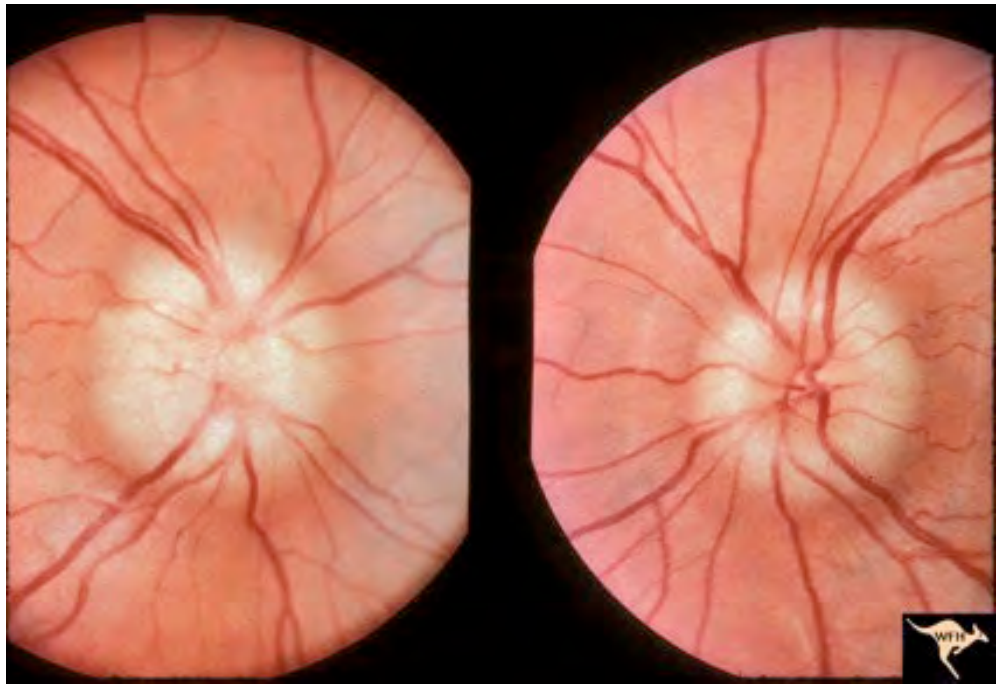
OS: temporal hemianopsia

Pupils: sluggish reactivity with a 2+ RAPD OD

SLE: corneal arcus noted, no other significant findings

IOP: 16, 16 mmHG OD, OS

DFE: see photos



Note: not patient photos
http://content.lib.utah.edu/cdm4/item_viewer.php?CISOROOT=/EHSL-WFH&CISOPTR=159

Physical Presentation

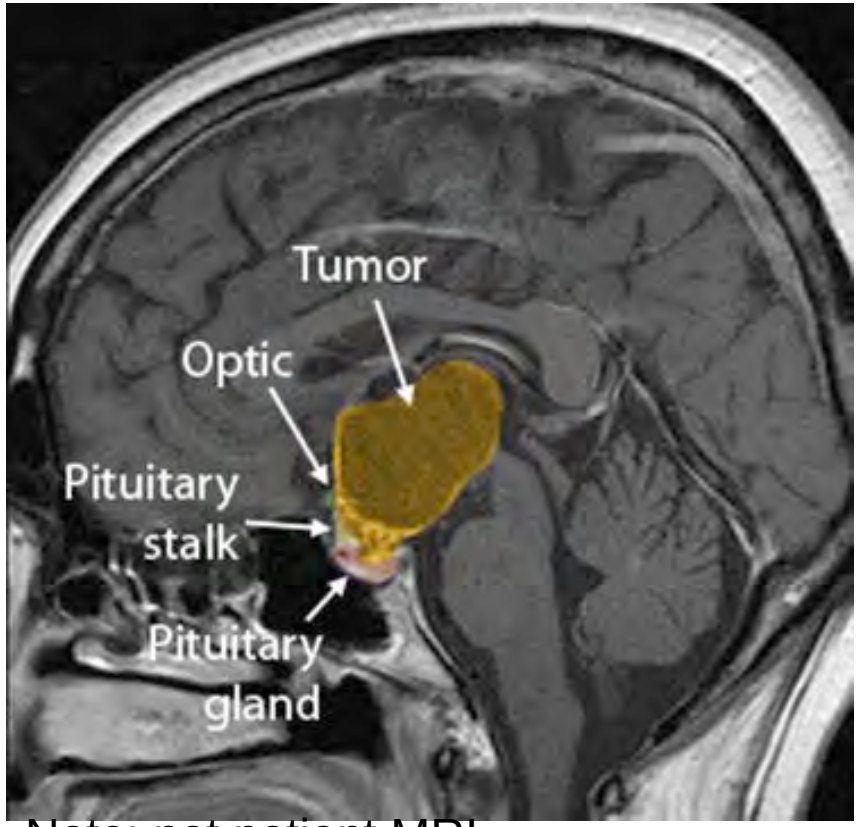
- Upon entering the room I noted that her right hand was twitching
  - I asked her how long that had been going on and she said about 2-3 weeks
  - I asked her if she experienced headaches, to which she said she had bad headaches that even woke her up at night

Referral

- Contacted her PCP who reported that she had examined the patient 3 weeks prior and had not noted any of these findings
- Referred the patient for an immediate MRI
  - wasn't able to be scheduled until the next day

Imaging/Surgery Referral

- MRI revealed large mass in her brain
  - Patient was diagnosed with a **Craniopharyngioma**
- She was referred for immediate surgery
  - Neurosurgeon reported that she removed a tangerine sized Craniopharyngioma
  - was the largest tumor she has ever removed



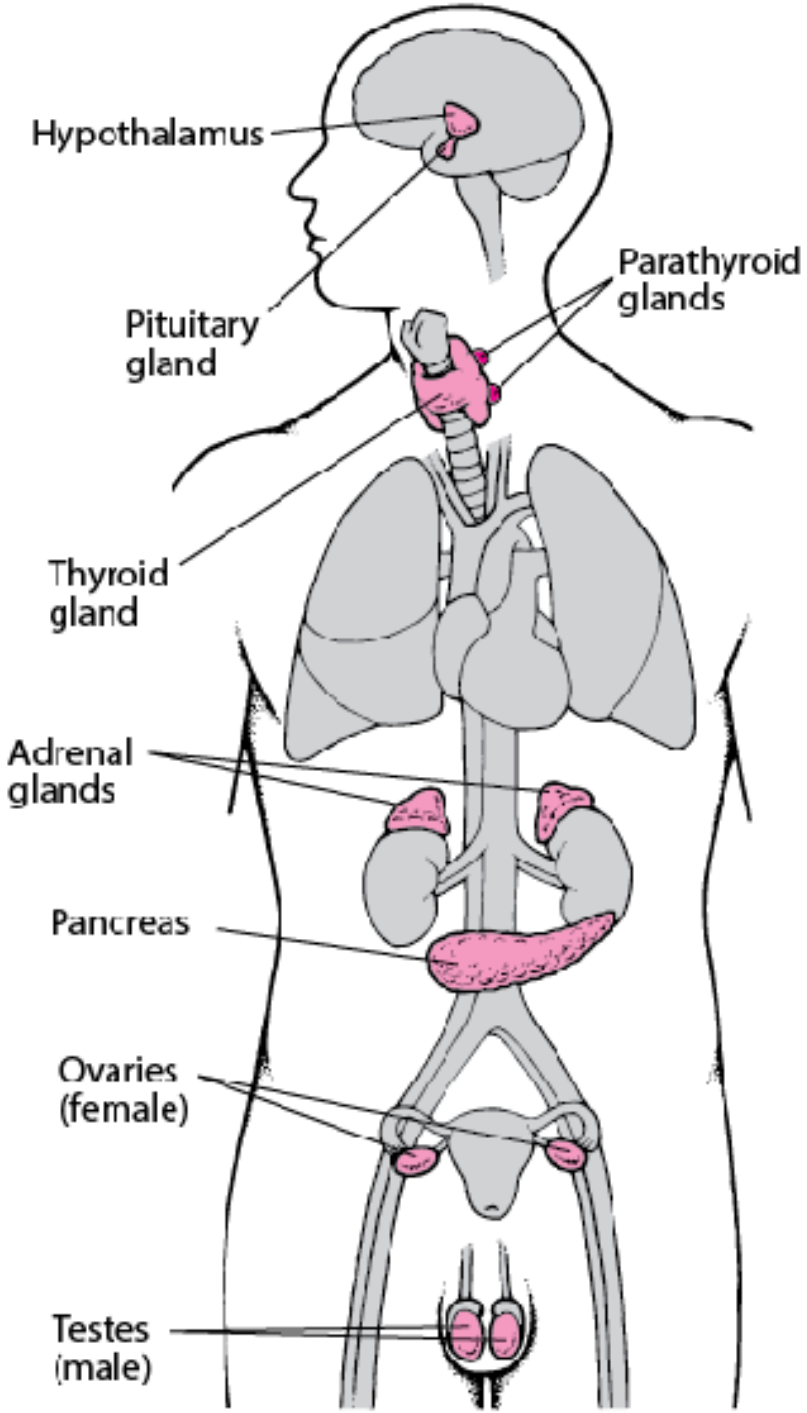
Note: not patient MRI
http://neurosurgery.ucla.edu/images/Pituitary%20Program/Craniopharyngioma/Cranio_Sag_Preop_fullylabeled.jpg

Craniopharyngioma

- Craniopharyngioma:
  - slow-growing,
  - epithelial-squamous origin,
  - calcified cystic tumor
  - arises from remnants of the craniopharyngeal duct
- Craniopharyngiomas have a benign histology but malignant behavior
  - they have a tendency to invade surrounding structures and recur after what was thought to be total resection
- No variance by sex or race is found
- Distribution by age is bimodal
  - peak incidence in children aged 5-14 years and older adults aged 65-74 years

Our Patient

- Patient had a complete resection of the tumor in addition to radiation therapy
- She developed several significant perioperative complications:
  - Leakage of CSF which resulted in her having to have a shunt
    - She subsequently developed an infection post surgically
  - She is NLP in her right eye, but did regain 20/40 vision in her left eye
    - Retains a temporal hemianopsia OS
  - Diabetes control became erratic and was put on several hormone replacement medications



Endocrine Function

The endocrine system coordinates functioning between different organs through hormones, which are chemicals released into the bloodstream from specific types of cells within endocrine (ductless) glands.

The basic function is to maintain homeostasis by secreting hormones that influence the body's functions

Endocrine disorders result from disruptions of the endocrine glands and/or their target tissues.

Endocrine Function

Hormones produce widespread effects in the body which produce signs and symptoms that are often generalized and nonspecific:

- Changes in appetite/thirst
- Changes in body size/shape
- Changes in the skin (dry, greasy, acne)
- Changes in hair (loss or excess)

- Secretion of pituitary hormones is controlled by the hypothalamus.

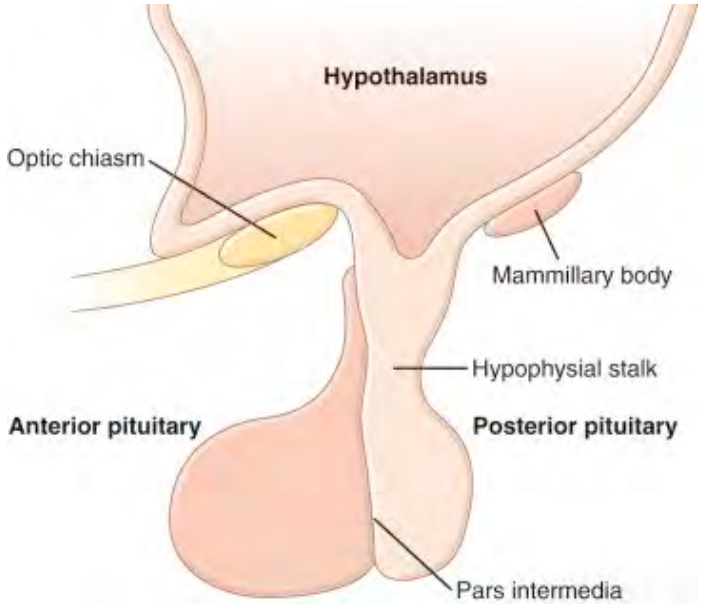
The major glands of the endocrine system, each of which produces one or more specific hormones, are the
Hypothalamus
Pituitary gland
Thyroid gland
Parathyroid glands
Islet cells of the pancreas
Adrenal glands
Testes in men, and the ovaries in women

Hypothalamic-Pituitary Stalk

Almost all secretion by the pituitary is controlled by either hormonal (anterior lobe) or nervous signals (posterior lobe) from the hypothalamus

The pituitary gland sits in sella turcica 2 lobes (anterior is larger approximately 80%) connected to hypothalamus by stalk

Right below the pituitary is the optic chiasm



Pituitary Gland (hypophysis)

- Often referred to as the “Master gland” as it controls the function of many of the other endocrine glands.

- housed within a bony structure (sella turcica) at the base of the brain. The sella turcica protects the pituitary but allows very little room for expansion.

- The hormones produced by the pituitary are not all produced continuously. Most are released in bursts every 1 to 3 hours, with alternating periods of activity and inactivity.

Pituitary Gland (hypophysis)

Anterior lobe (adenohypophysis) (produce hormones)

Triggered by the hypothalamus to produce 6 hormones

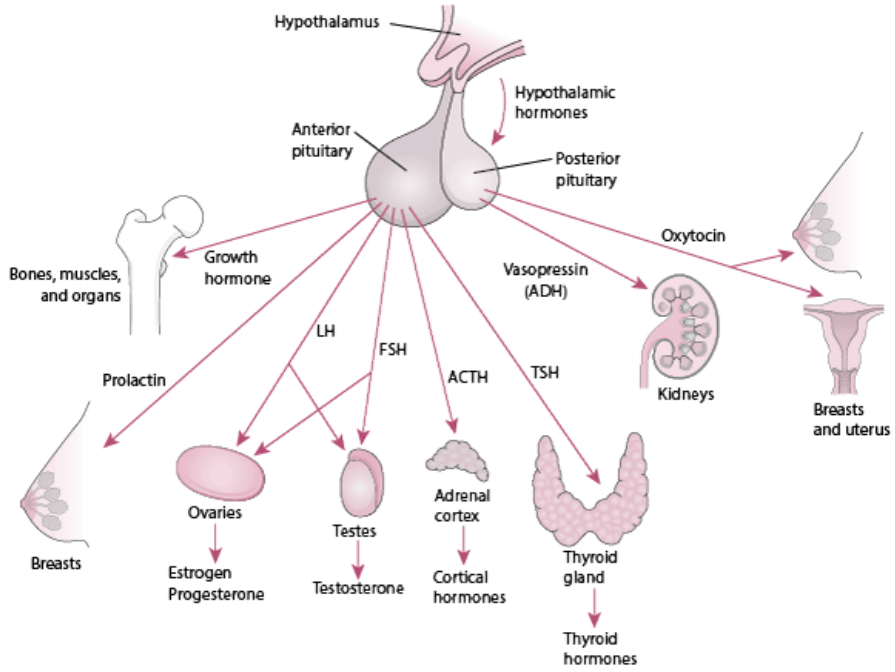
- Growth hormone (GH): stimulates somatic (body cell) growth and regulates metabolism
- Adrenocorticotropic hormone (ACTH): ACTH induces the adrenal cortex to release cortisol and several weak androgens
- Follicle-stimulating hormone (FSH): LH and FSH control the production of the sex hormones
- Luteinizing hormone (LH): LH and FSH control the production of the sex hormones
- Prolactin (PRL): major function is stimulating milk production
- Thyroid stimulating hormone (TSH): regulates the structure and function of the thyroid gland and stimulates synthesis and release of thyroid hormones

Posterior lobe (neurophypophysis) (transmits hormones, no production)

Secretes 2 hormones produced by the hypothalamus

Antidiuretic hormone (ADH): acts primarily to promote water conservation by the kidneys by increasing the permeability of the distal tubular epithelium to water

Oxytocin: uterine contractions during birth



Pituitary Adenoma

Pituitary adenomas arise from the cells of the anterior pituitary gland

Classified by the type of hormone secreted

- Prolactinomas account for 32% to 66% of adenomas and present with amenorrhea, loss of libido, galactorrhea, and infertility in women and loss of libido, erectile dysfunction, and infertility in men;
- No hormone: 30% (inactive)

- Classified by size:
  - Microadenoma <10mm in size
  - Macroadenoma >10mm in size
  - Approximately 50% are microadenomas

Pituitary Adenoma

Epidemiology

- Pituitary adenomas are quite common and are often found incidentally
- Constitute 10-15% of all intracranial neoplasms
- Asymptomatic microadenomas present in 6-24% of autopsies
  - Majority of adenomas are benign, slow-growing tumors

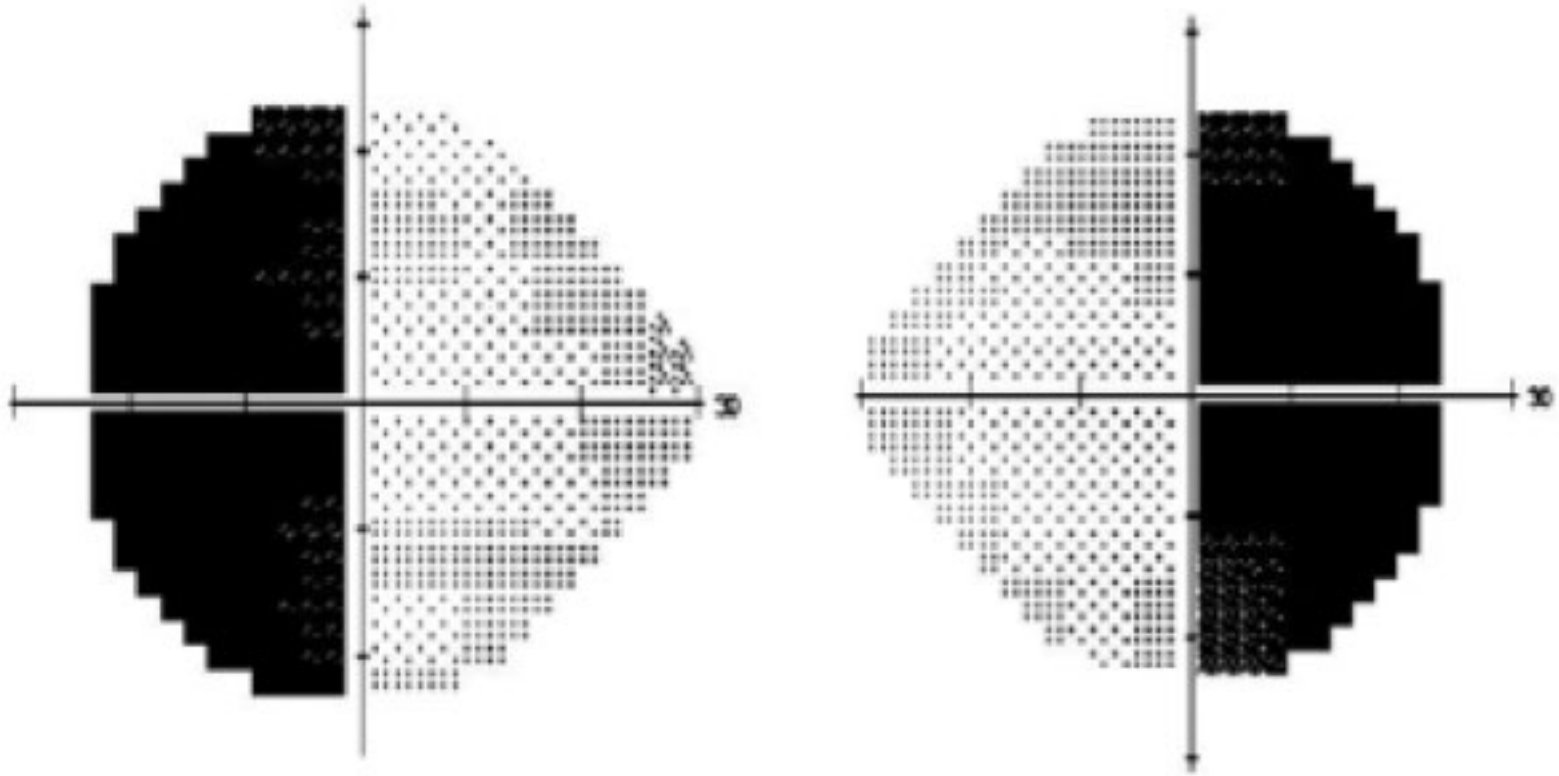
Pituitary Adenoma

Symptoms of pituitary adenoma are primarily from mass effect or from hormone hypersecretion

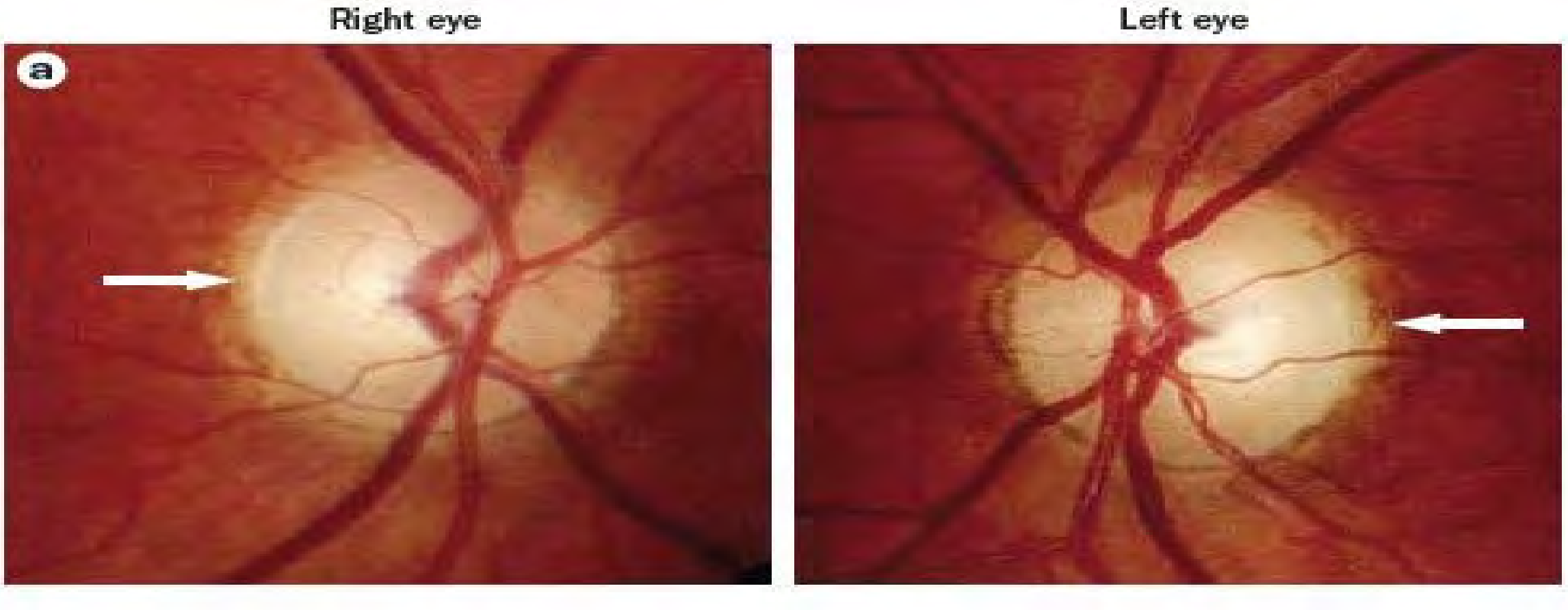
Symptoms

- From mass effect
  - Headache
  - Visual Changes: secondary to pressing on the optic chiasm
    - (+)red cap test
    - Bitemporal hemianopsia
    - Reduced contrast sensitivity
    - Acuity loss
    - Diplopia
  - Hypopituitarism-decreased secretion of hormones from anterior pituitary gland (from compression)

Bitemporal hemianopsia from pituitary adenoma



Bilateral Disc Atrophy from Pituitary Adenoma



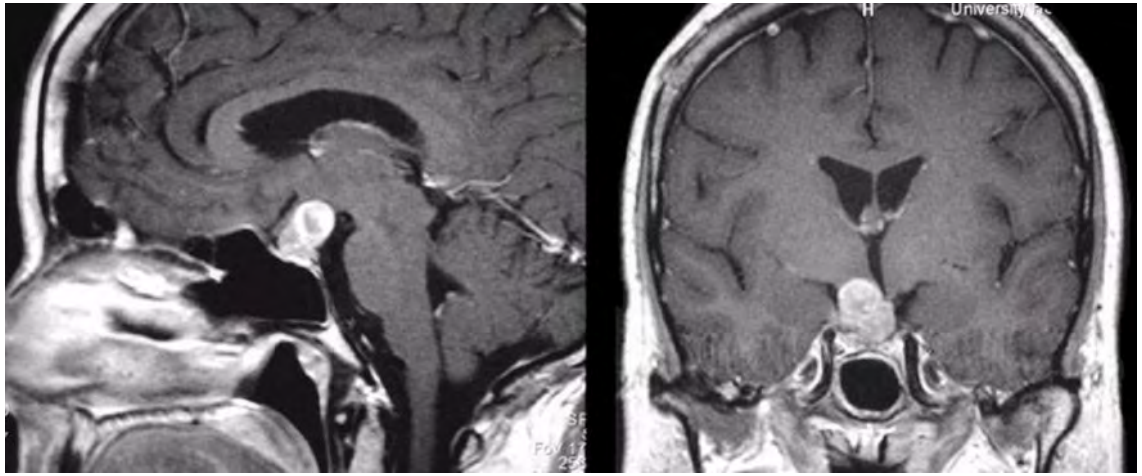
Pituitary adenomas

- are diagnosed through imaging and lab tests

Diagnostic Testing

- Imaging: MRI/CT
- MRI better with soft tissue details, can see if its pressing on a nerve
- CT better with hard tissue details

- Lab tests: primarily looking for elevated hormone levels



Pituitary adenoma. Note the large enhancing mass in the region of the sella that is growing up into and displacing the optic chiasm and hypothalamus. This is an enhanced MRI scan with gadolinium.

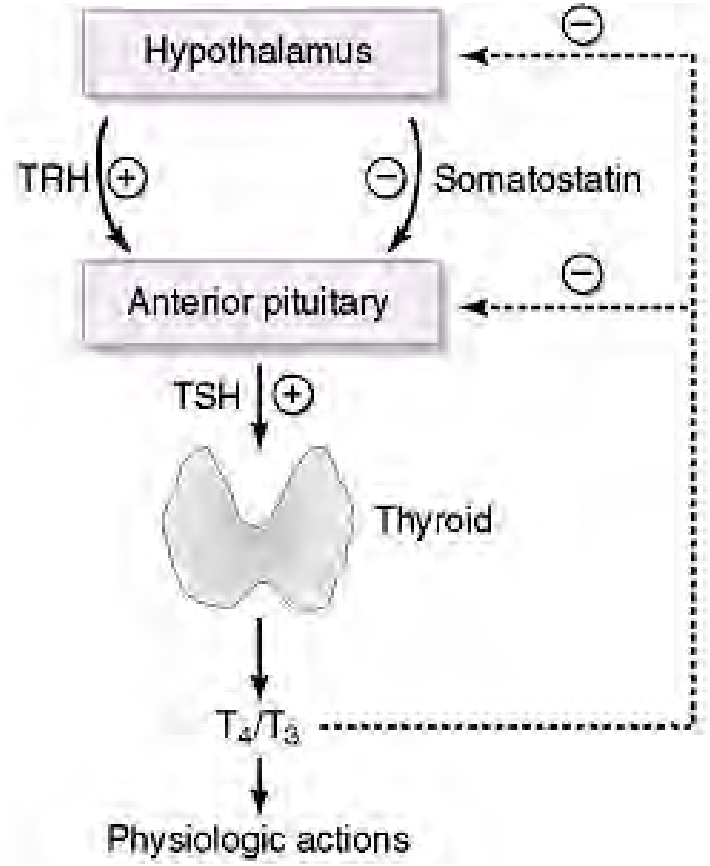
Pituitary Adenoma Management

Management

- Surgery
  - Indicated when there is mass effect on the optic tract or other cranial nerves, cerebral spinal fluid (CSF) leakage, pituitary hemorrhage, no response to medical management
  - Get rid of mass effects and then stabilize the hormones
- Radiation
  - Reserved for patients that do not respond to surgery
- Medical Management
  - Indicated for hormone-secreting adenomas

Thyroid

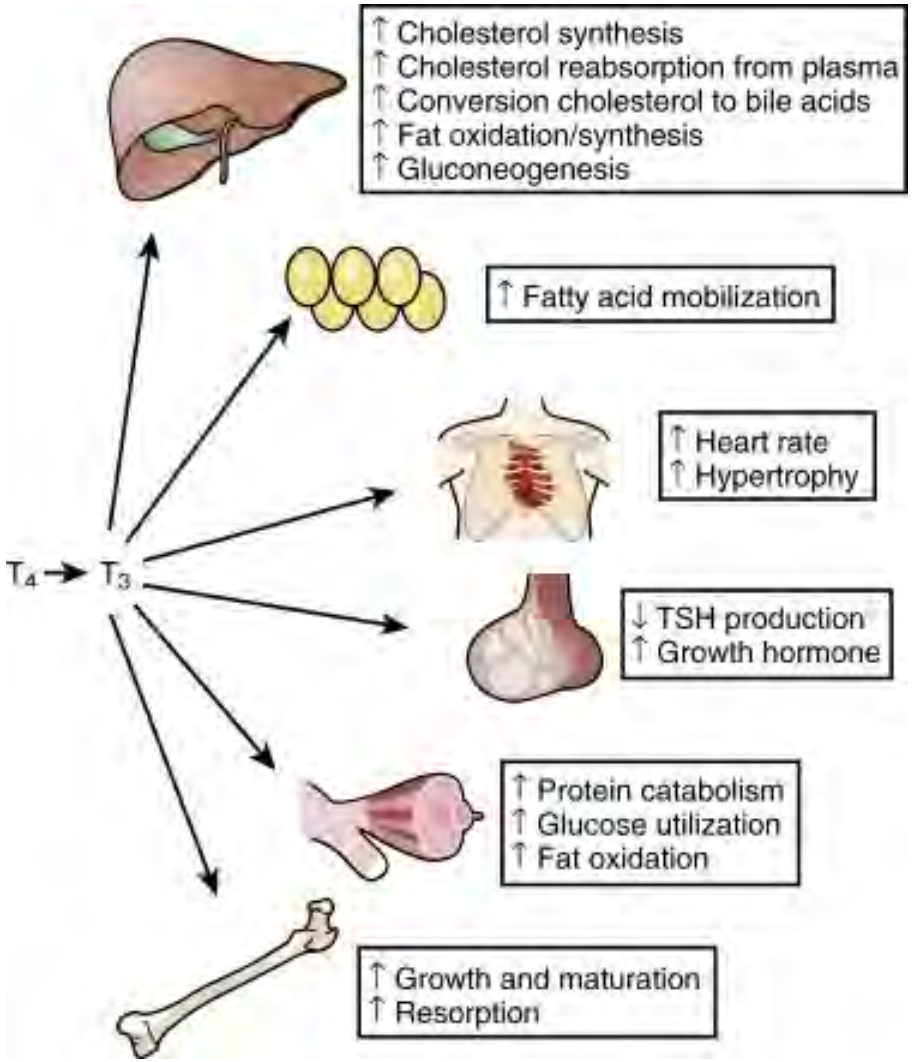
- The growth of thyroid tissue and production of thyroid hormones are controlled by the hypothalamus and pituitary gland
- Thyrotropin-releasing hormone (TRH) is produced by the hypothalamas to stimulate the anterior pituitary produce thyroid stimulating hormone (TSH)
- Thyrocytes produce T_3 and T_4, which exert negative feedback at the level of the hypothalamus and pituitary gland



Actions of Thyroid Hormone

Thyroid hormones exert an effect on almost all tissues

- Increase metabolism
- Decrease serum cholesterol levels
- Increase in lipolytic events
- Increase cardiac contractions and heart rate
- Negative feedback on TSH and TRH production. Increase GH.
- Increase skeletal muscle expenditure and muscle catabolism
- Required for normal bone growth brain development, and normal skin function



Hyperthyroidism

Epidemiology

- More common in women than in men (about 8:1)
- Onset usually between ages 20-40
- Patients with hyperthyroidism secondary to Graves have an increased risk of other systemic autoimmune disorders including:
  - Sjogrens
  - Celiac disease
  - Pernicious anemia
  - Myasthenia gravis
  - Systemic lupus
  - Type I diabetes
  - Alopecia
  - Cardiomyopathy

Hyperthyroidism

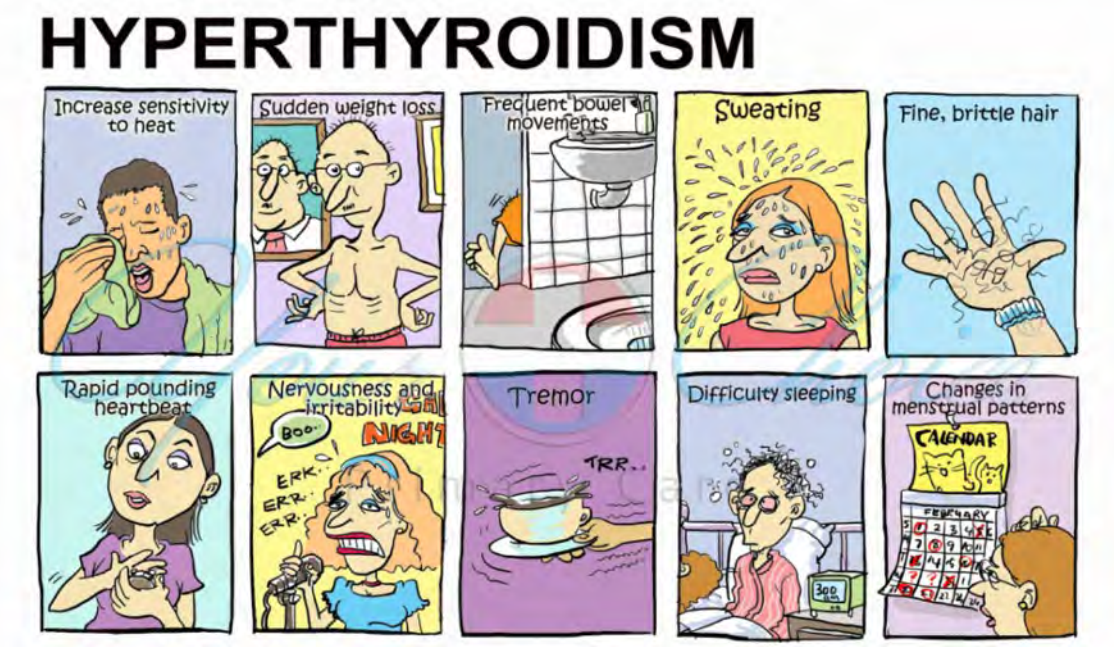
Causes

- Graves disease (most common cause): autoimmune disorder affecting the thyroid gland which increases synthesis and release of thyroid hormones
- Toxic multinodular goiter: more prevalent among older adults and in iodine deficient regions
- Medications: Amiodarone- amiodarone is 37% iodine by weight and half life is approximately 100 days which can increase TSH levels
- Pituitary adenoma (rare)

Hyperthyroidism

Signs/Symptoms

- Increased metabolism, elevating basal body temperature
- Tachycardia and cardiac hypertrophy
- Fatigue, dyspnea
- Upper and lower lid retraction
- Warm, moist skin
- Thin hair
- Physical development is normal but fertility is reduced
- Plummer's nails (onycholysis)
- Tremor and insomnia



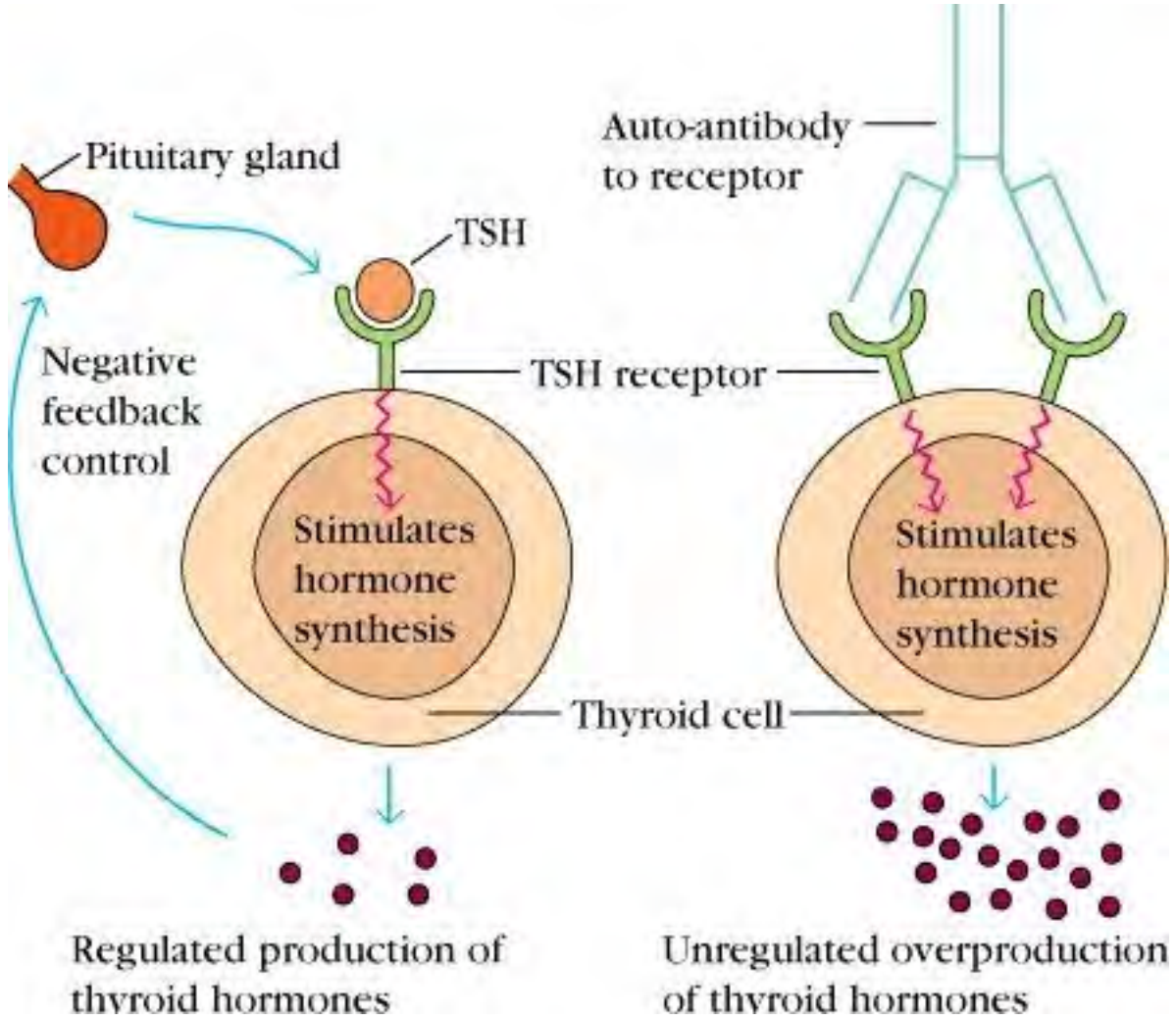
Graves' Disease

Graves' Disease is an autoimmune disorder

Thyroid stimulating hormone receptor autoantibodies (TRAbs) stimulate the thyroid to secrete T_4 and T_3

- normal TSH activated thyroid production would be regulated by production of thyroid hormones with a negative feedback loop to the pituitary.

- Classic presentation: hyperthyroidism, diffuse goiter, exophthalmos

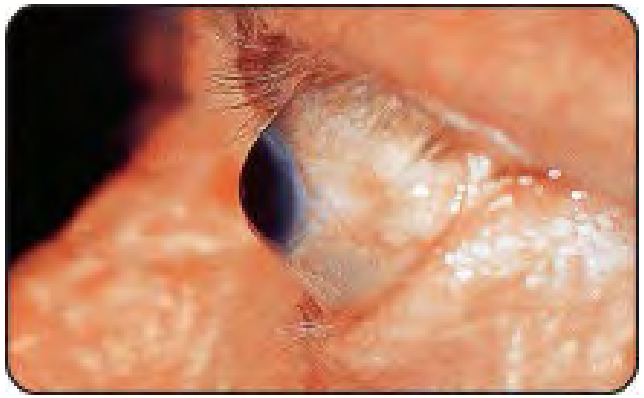


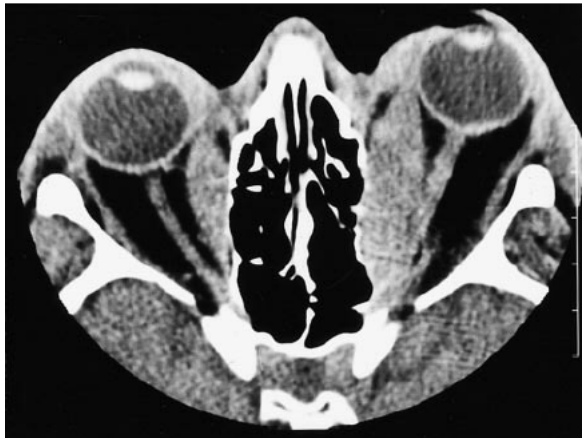
Thyroid Eye Disease (TED)

a.k.a. Graves' Ophthalmopathy, graves' orbitopathy

Clinical signs or symptoms of ophthalmopathy are present in ~50% of patient's with TED with a wide variability of disease severity

- Although a systemic disease, ocular involvement can be asymmetric
- Smoking increases risk of developing ophthalmopathy by 7-8 times
- Proptosis secondary to increase in volume of extra-ocular muscles (EOMs), adipose tissue, and connective tissue in the orbit
- Measure with an exophthalmometer (measured in mm) difference of more than 2mm is significant





Thyroid Eye Disease (TED)

- Diplopia:
  - from restricted EOMs
  - Most often in lateral and up gaze
  - Inferior rectus and medial rectus most often damaged
- Increased IOP
  - Increased IOP because of mass in the orbit
- Optic nerve compression by surrounding structures
  - Optic edema and subsequent atrophy
- Decrease visual acuity
  - Optic atrophy, dry eyes

superior limbic keratoconjunctivitis(SLK) and Grave's Disease

33% of patients with SLK have Graves

Onset: 4^{th}-5^{th} decade

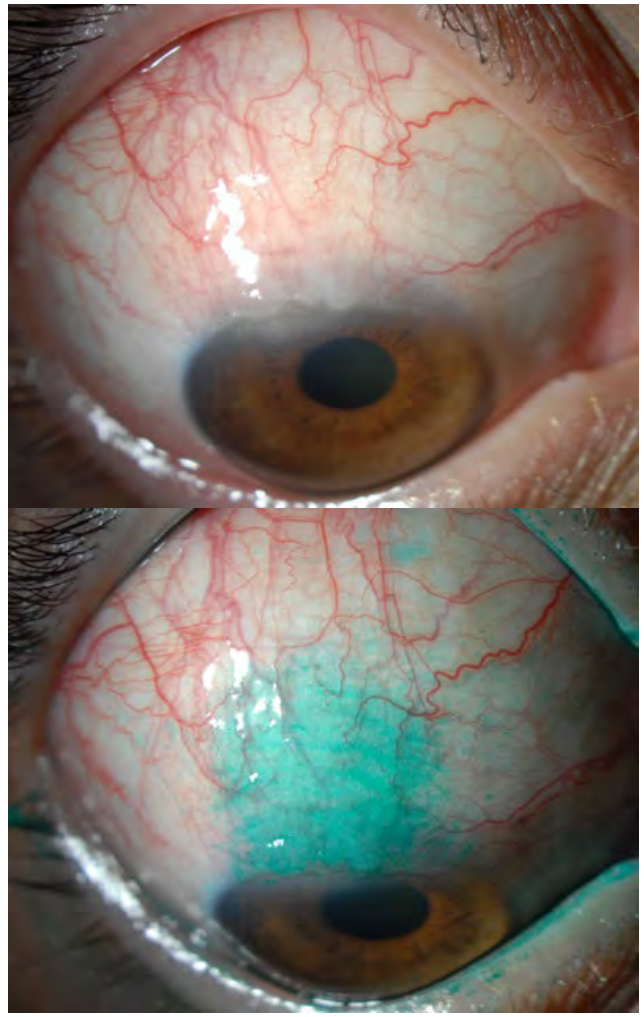
Etiology:

- Mechanical trauma? Proptosis results in pressure on cornea from the upper lid
- Chronic inflammation?

Symptoms:

- Foreign body sensation
- Irritation
- Burning

Treatment: aggressive lubrication, cyclosporine A, surgery



a) Significant superior limbic keratoconjunctivitis causing thickened bulbar conjunctiva, superior corneal pannus and neovascularization. **b**) Note the localized lissamine green dye staining of the superior bulbar conjunctiva.

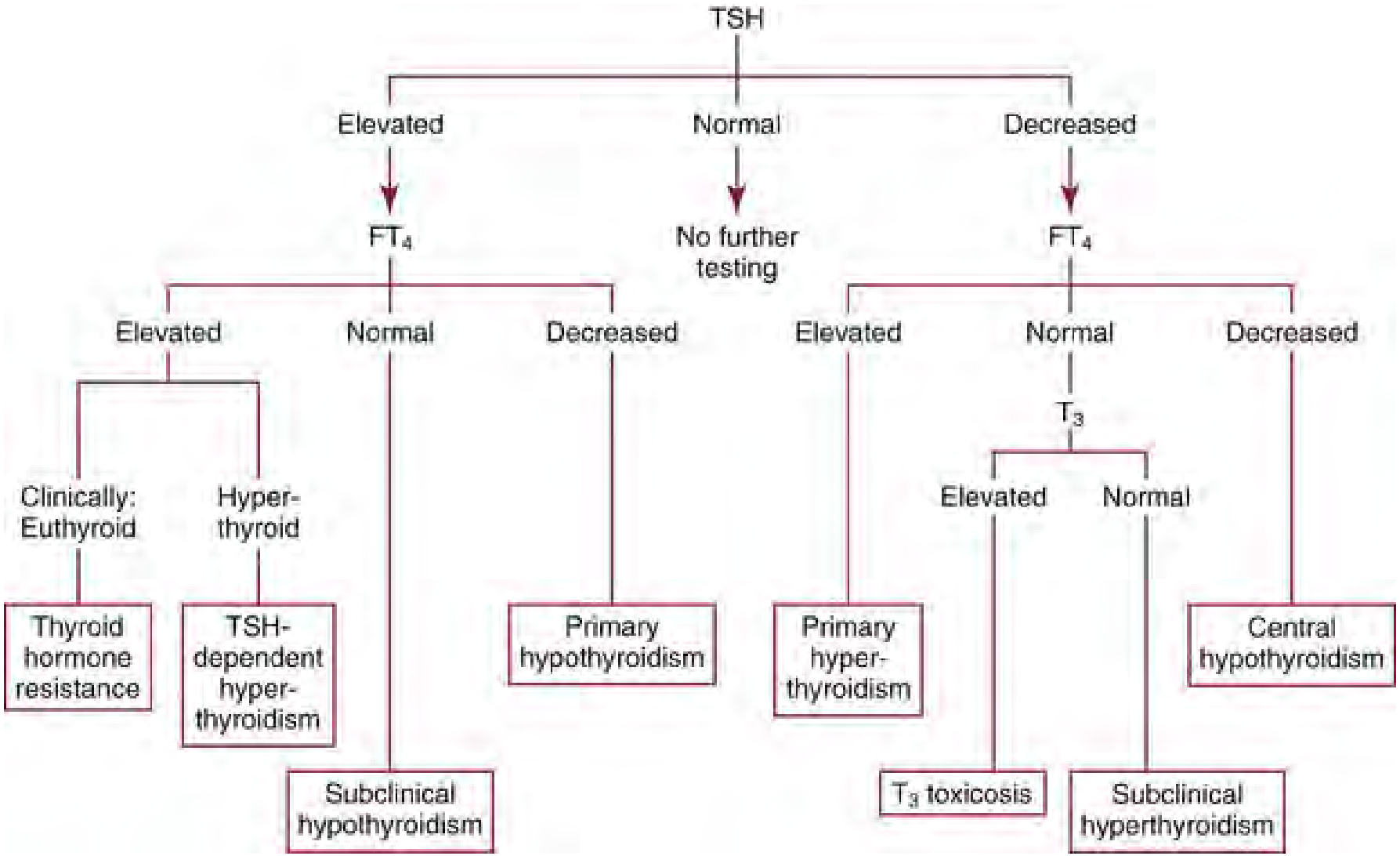
Diagnosis of hyperthyroidism

- Patient history and signs/symptoms (e.g. heat sensitivity, tachycardia, increased sweating, muscle weakness)
- Thyroid examination usually reveals a diffusely enlarged thyroid, often asymmetric

Lab tests:

- TSH (abnormal then test t4/t3)
- T_4 & T_3
- TRAb assay (receptors)-test TSH receptor antibodies
- Radioactive iodine uptake (RAIU) with thyroid imaging

Thyroid Testing Algorithm



Key points about Grave's disease:

- Most common cause of eyelid retraction
- Most common cause of bilateral or unilateral proptosis.
- More common in women
- Associated with hyperthyroidism in 90% of patients; 6% are euthyroid
- Smoking is associated with increased risk and severity of ophthalmopathy.
- The course of ophthalmopathy does not necessarily parallel the activity of the thyroid gland or the treatment of thyroid abnormalities.

Hyperthyroid Management

Proper management of hyperthyroidism requires co-management with other specialties

Team approach: endocrinology, radiology, radiotherapy, otolaryngology, neurosurgery, ophthalmology/optometry

- Methimazole (antithyroid drug):
  - Antithyroid drug-no compression lesions yet, but are likely. This slows symptoms
- Oral/IV steroids
- Radioactive Iodine:
  - Excellent way to destroy overactive thyroid tissue without significant chance of developing thyroid cancer, leukemia or other malignancies.
- Surgical therapy
  - Orbital decompression
    - Need more space in the orbit so decompress by controlled “blowout”
  - Cosmetic management
    - Can improve proptosis by up to 12 mm

TEPEZZA™ (teprotumumab-trbw)

- Horizon Therapeutics Ireland DAC.
- IV treatment (8 doses, 1 treatment every 3 weeks) each dose cost 15k!
- Tepezza was approved based on the results of two studies (Study 1 and 2) consisting of a total of 170 patients with active thyroid eye disease who were randomized to either receive Tepezza or a placebo.
- Of the patients who were administered Tepezza, 71% in Study 1 and 83% in Study 2 demonstrated a greater than 2 millimeter reduction in proptosis (eye protrusion) as compared to 20% and 10% of subjects who received placebo, respectively.

TEPEZZA™ (teprotumumab-trbw)

- 70% saw improvement of their diplopia (50% had complete resolution)
- The most common adverse reactions observed in patients treated with Tepezza are muscle spasm, nausea, alopecia (hair loss), diarrhea, fatigue, hyperglycemia (high blood sugar), hearing loss, dry skin, dysgeusia (altered sense of taste) and headache.

Hypothyroidism treatment

Hypothyroidism treatment goal is to restore the balance of thyroid hormone

Treatment:

Thyroid hormone replacement therapy with levothyroxine

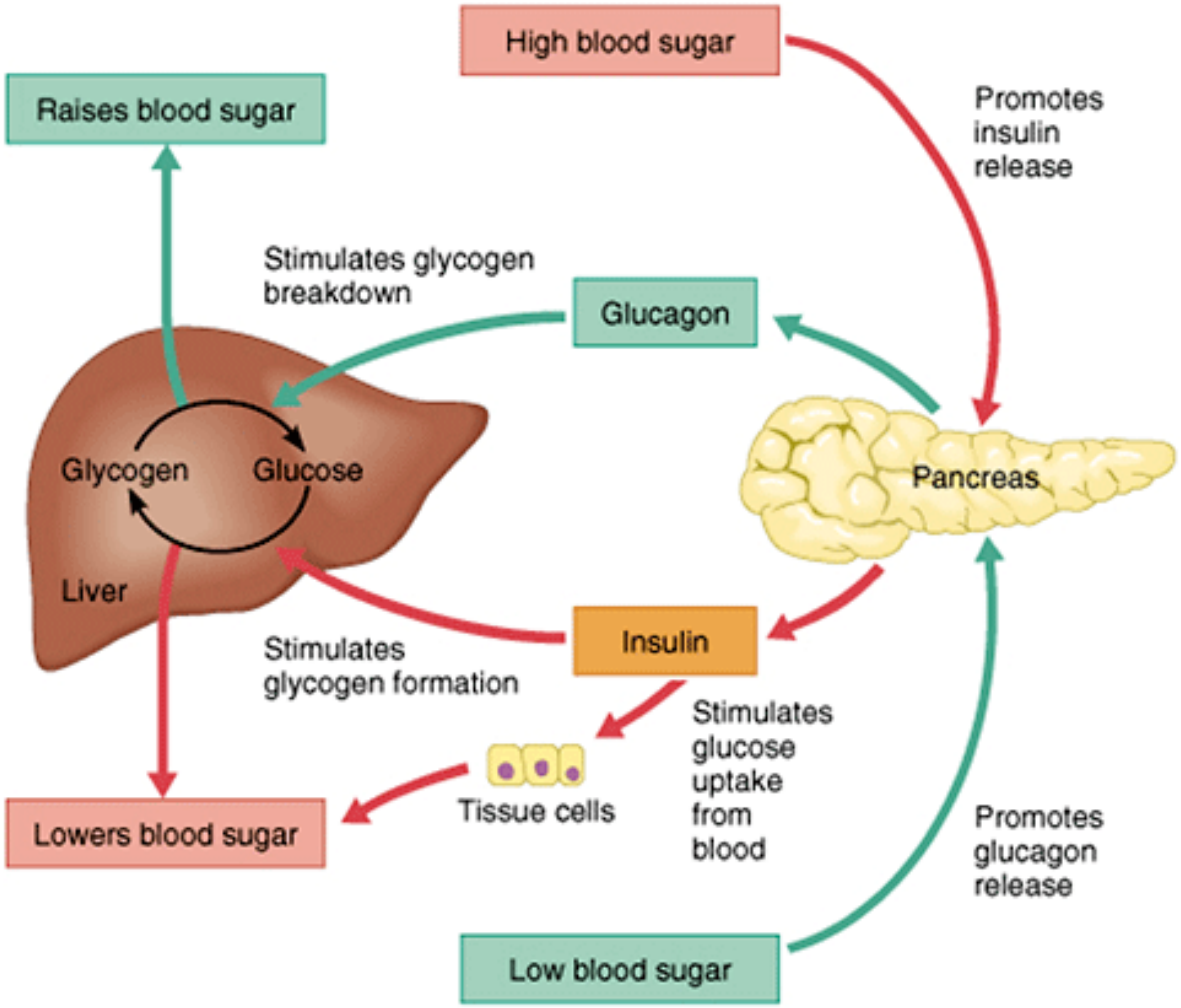
- synthetic levothyroxine is the preferred preparation

Chronic periodic monitoring of TSH levels

Pancreas Endocrine Function

- The endocrine portion is arranged as discrete islets of Langerhans, which are composed of five different endocrine cell types (alpha, beta, delta, epsilon, and upsilon) secreting at least five hormones including glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide, respectively.
- Glucagon: works to raise the concentration of glucose and fatty acids in the bloodstream
  - released when the concentration of insulin (and indirectly glucose) in the bloodstream falls too low
  - causes the liver to convert stored glycogen into glucose, which is released into the bloodstream.
- Insulin:
  - regulates the metabolism of carbohydrates, fats and protein by promoting the absorption of carbohydrates, especially glucose from the blood into liver, fat and skeletal muscle cells.

Glucagon/Insulin Control of Blood Sugar



Blood glucose levels

In a normal person, the blood glucose concentration is narrowly controlled

Fasting levels: 4.44-5.0 mmol/L

After meal: 6.67-7.78 mmol/L

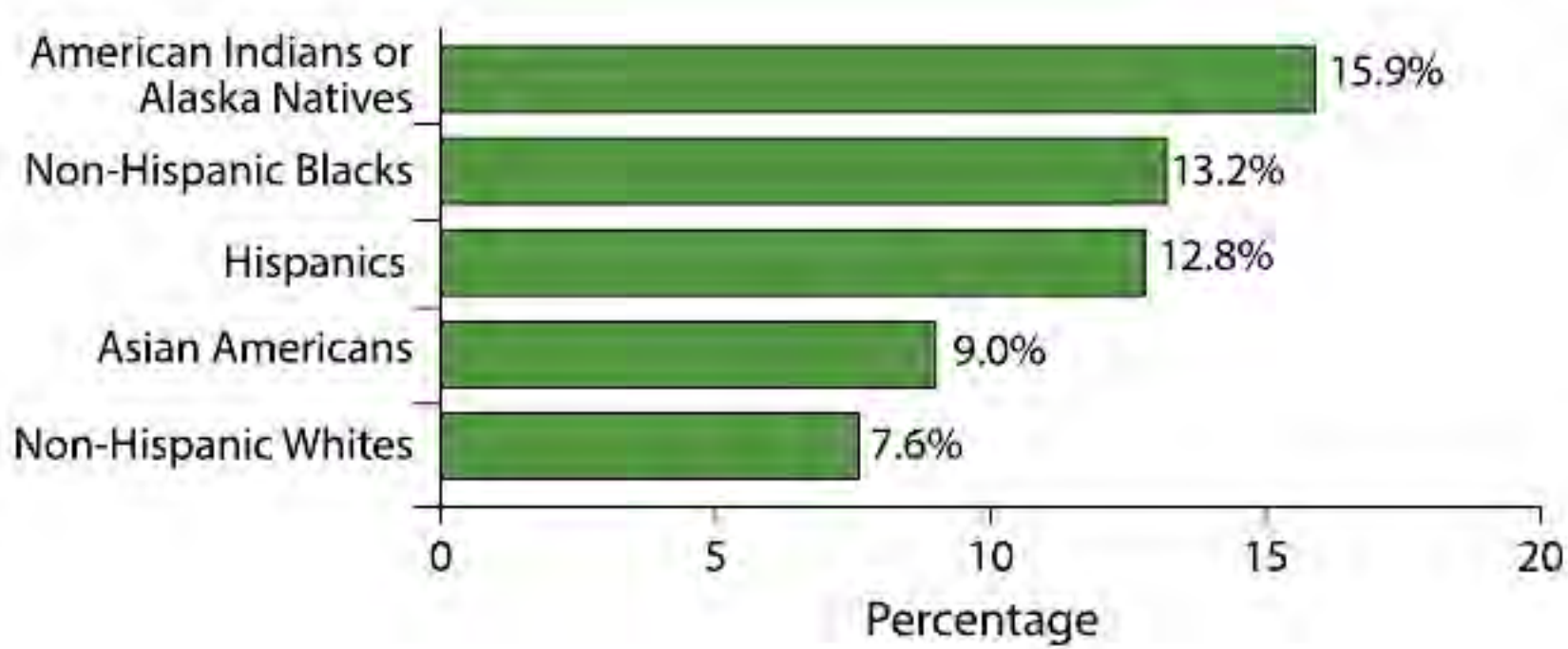
Feedback systems for blood glucose rapidly return the blood glucose back to control levels within 2 hours

Important mechanisms for tight control:

- Liver function
- Glucagon & Insulin

Type 2 diabetes prevalence among Canadian adults - dietary habits and sociodemographic risk factors (2019)

- Among Canadians 20-79 years of age, 12.4% had prediabetes, and 7.5% had diabetes.
- Among all diabetes cases, 37.3% were undiagnosed.
- All 3 diabetic categories were more prevalent among older age groups (60-79 years) compared with younger age (20-39 years) groups.
- Diagnosed diabetes and prediabetes were more prevalent among less educated individuals compared with the higher educated ones.
- Diagnosed diabetes was more common among individuals with lower-middle income level compared with the highest income level.


American Indians or Alaska Natives
15.9%
Non-Hispanic Blacks
13.2%
Hispanics
12.8%
Asian Americans
9.0%
Non-Hispanic Whites
7.6%
0
5
10
15
20
Percentage

Diabetes Mellitis

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism

There are two main types of diabetes:

- Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM)
  - occurs when the pancreas is unable to produce insulin.

- Type 2 diabetes, or non–insulin-dependent diabetes mellitus (NIDDM)
  - occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that is produced.

However there are other conditions that can result in altered blood sugar:

- Prediabetes refers to blood glucose levels that are higher than normal, but not yet high enough to be diagnosed as type 2 diabetes. Although not everyone with prediabetes will develop type 2 diabetes, many people will.

- Gestational Diabetes- type of diabetes that is first recognized or begins during pregnancy

Other causes: medication, neonatal diabetes, chemical-induced diabetes

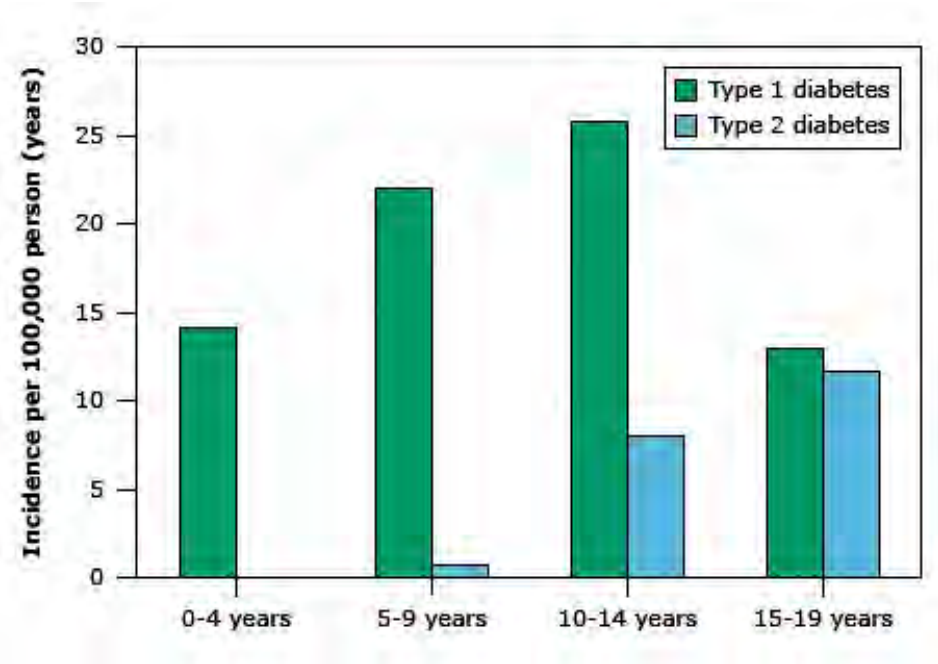
Type I Diabetes

- DM Type I is caused by autoimmune destruction of β cells in the pancreatic islets (95% of Type 1 sometimes referred to as Type 1 A)
  - Autoimmune targeting beta cells, the rest are not affected

- 3–5% of total cases of diabetes mellitus and usually presents in children

- Autoantibodies detected in 85-90% of DM Type 1
  - 30% risk if 1 type of autoantibody in blood
  - 70% 2 types
  - 90% 3 types of autoantibodies in blood

- The incidence of DM I peaks at ages 4-6 and again in early puberty



Type 1 DM

The risk factors for the development of DM I are environmental and genetic

- Genetic risk (approximately 1/3rd of the disease susceptibility is due to genes)

Environmental factors: (2/3rd of the risk of development)

- Demonstrated in an increase in the incidence of DM Type I in multiple populations
- Diabetes more common in Scandanavian countries and becomes progressively less frequent in countries nearer the equator
- Breastfeeding in the first 6 months of life is thought to be protective

Presenting Symptoms of DM I

Clinical manifestations of DM I appear after gradual loss of β cells
- Diabetes won't develop clinically until 80% loss in the beta cells

- Polyuria: kidneys typically reabsorb the sugar in the blood but in DM can't keep up with the sugar in the blood so sugar is excreted in urine and this draws more water into urine
- Polydipsia: increased fluid movement via urination increases thirst
- Polyphagia: burn a lot of calories so they will eat a lot
- Weight loss: excessive burning of calories and excretion of sugar in urine
- Fatigue

Diabetic ketoacidosis (start metabolizing fat), in 20-40% of children when they initially manifest with DM I

Diagnostic tests for DM: A1C

- A1c- how much sugar is bound to hemoglobin in RBCs
- A1C shows the average level of blood glucose over the previous 3 months
- Other names: HbA1C, Glycated hemoglobin, glycosylated hemoglobin, glycohemoglobin
- New RBC starts with no glucose but it easily binds it. The more sugar in blood the more then binding and the higher A1c
- Normal: Less than 6.0%
- Pre-diabetes: 6.0-6.4%
- Diabetes: 6.5% or higher

- Goal is individualized, but commonly <7%

	mg/dl*	mmol/l†
A1C (%)		
5	97 (76–120)	5.4 (4.2–6.7)
6	126 (100–152)	7.0 (5.5–8.5)
7	154 (123–185)	8.6 (6.8–10.3)
8	183 (147–217)	10.2 (8.1–12.1)
9	212 (170–249)	11.8 (9.4–13.9)
10	240 (193–282)	13.4 (10.7–15.7)
11	269 (217–314)	14.9 (12.0–17.5)
12	298 (240–347)	16.5 (13.3–19.3)

Data in parentheses are 95% CIs. *Linear regression eAG (mg/dl) = 28.7 × A1C − 46.7. †Linear regression eAG (mmol/l) = 1.5944 × A1C − 2.5944.

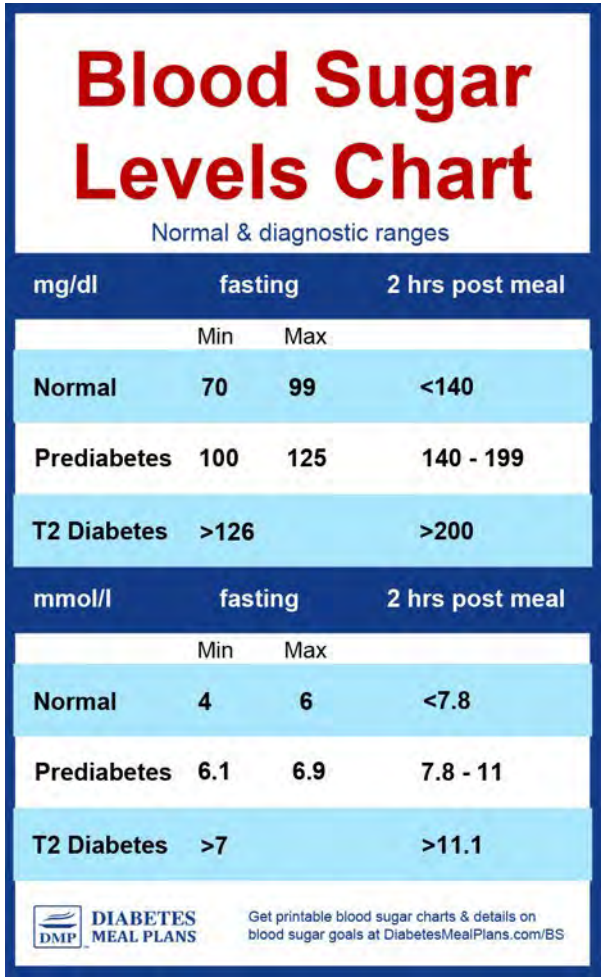
Diagnostic test for DM: Fasting Blood Sugar

- Fasting blood sugar can be assessed after 8 hours of fasting
- Less sensitive but quicker and easier

- Normal: 3.9-7.8 mmol/L (70-140 mg/dl)

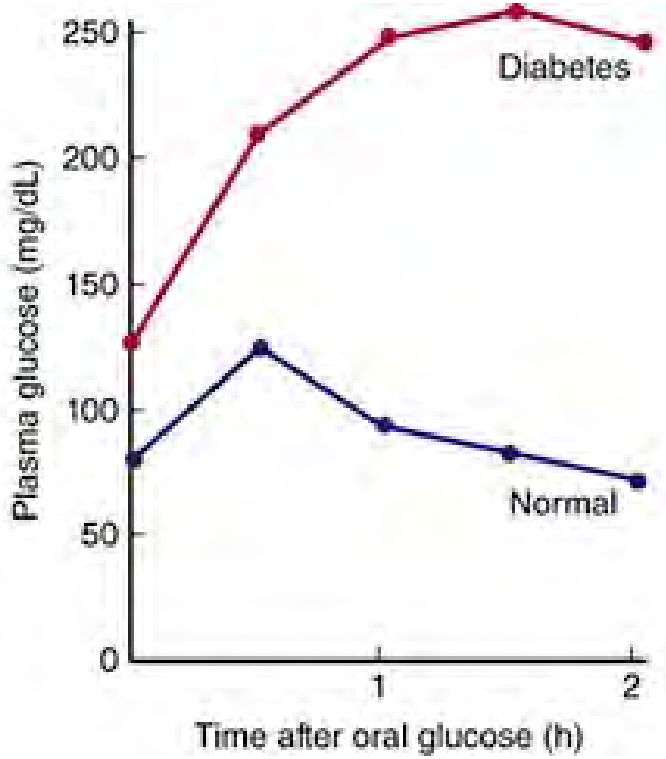
- Impaired fasting glucose (IFG): ≥5.56 to 6.94 mmol/L (100-125 mg/dl)

- Diabetes: ≥7 mmol/L (126 mg/dl)
  If confirmed by another test on a different day unless classic symptoms of DM are present



Diagnostic tests for DM: Oral Glucose Tolerance Test (OGTT)

- Oral glucose tolerance test (OGTT) is commonly done to check for gestational diabetes
- Take fasting blood glucose and then drink syrupy drink and see how it changes the blood glucose levels for next 3 hours Hour two is the determining factor



- Adults are given 75 g of glucose in 300 mL of water

- After 2 hours, the plasma glucose is measured:
- Normal after OGTT: <7.8 mmol/L (<140 mg/dl)
- Impaired glucose tolerance: 7.8-11.1 mmol/L (140-200 mg/dl)
- Diabetes after OGTT: > 11.1 mmol/L (>200 mg/dl)

Diagnostic test for DM: Random Plasma Glucose

This test is typically done to confirm diabetes with severe diabetes symptoms

Random plasma glucose is done at a time to get a "snapshot" of the glucose concentration in the bloodstream

- it is often done in optometric offices if diabetes patients do not know what their blood sugar value or you have a suspicion a patient may have diabetes.

Normal: 3.89-6.1 mmol/L (70-110 mg/dl)

Diabetes: >11.1 mmol/L and classic symptoms of diabetes

Diagnosis of Diabetes

- **FPG ≥7.0 mmol/L**
  - Fasting = no caloric intake for at least 8 hours
- or
- **A1C ≥6.5%** (in adults)
  - Using a standardized, validated assay in the absence of factors that affect the accuracy of the A1C and not for suspected type 1 diabetes
- or
- **2hPG in a 75 g OGTT ≥11.1 mmol/L**
- or
- **Random PG ≥11.1 mmol/L**
  - Random = any time of the day, without regard to the interval since the last meal
  -

Blood Sugar

DIAGNOSIS OF PREDIABETES & DIABETES

Test	Result	Dysglycemia category
FPG (mmol/L) No caloric intake for at least 8 hours	6.1 – 6.9	IFG
	≥7.0	Diabetes
2hPG in a 75 g OGTT (mmol/L)	7.8 – 11.0	IGT
	≥11.1	Diabetes
A1C (%) Standardized, validated assay, in the absence of factors that affect the accuracy of A1C and not for suspected type 1 diabetes	6.0 – 6.4	Prediabetes
	≥6.5	Diabetes
Random PG (mmol/L)	≥11.1	Diabetes

Pros and Cons of Diagnostic Tests

Test	Advantages	Disadvantages
FPG	Established standard Fast and easy Single Sample	Sample not stable Day-to-day variability Inconvenient to fast Glucose homeostasis in single time point
2hPG in 75 g OGTT	Established standard	Sample not stable Day-to-day variability Inconvenient, Unpalatable Cost
A1C	Convenient Single sample Low day-to-day variability Reflects long term glucose	$$$ Affected by medical conditions, aging, ethnicity Standardized, validated assay required Not applicable to every patient type

A1C Level and Future Risk of Diabetes

A1C Category (%)	5-year incidence of diabetes
5.0-5.5	<5 to 9%
5.5-6.0	9 to 25%
6.0-6.5	25 to 50%

Diabetes Lab Testing

- A comprehensive metabolic panel is a blood test that measures sugar (glucose) level, electrolyte and fluid balance, kidney function, and liver function.
- The following lab tests are included in a comprehensive metabolic panel:
  - Albumin
  - Blood Urea Nitrogen (BUN)
  - Glomelular filtration rate (GFR)
  - Calcium
  - Carbon Dioxide (Bicarbonate)
  - Chloride
  - Creatinine
  - Glucose
  - Potassium
  - Sodium
  - Alkaline Phosphatase (ALP)
  - Total Bilirubin
  - Total Protein
  - Alanine Aminotransferase (ALT)
  - Aspartate Aminotransferase (AST)

Kidney function

- Urinalysis can be used in conjunction with blood testing to help confirm systemic etiology of conditions
  - **Urine Glucose**
    - Any glucose in the urine is abnormal
  - **Urine Protein**
    - Proteinuria is an important indicator of renal disease
  - **Urine Ketones**
    - Ketones are byproducts of body fat metabolism formed in the liver
    - Ketonuria occurs in patients with diabetes

Kidney Function Tests:

Serum Creatinine:

- waste product that comes from the normal wear and tear on muscles of the body.
- Kidney impairment results in rise of creatinine level in the blood

BUN (blood urea nitrogen):

- If kidneys cannot filter wastes out of the blood due to disease or damage, then the level of urea in the blood will rise

Glomelular filtration rate

- rate of fluid filtered through the kidney
- Reduced in chronic kidney disease/renal failure

Liver Tests

- Liver tests (LTs) are blood tests used to reflect the presence of damage or inflammation.
- **alanine aminotransferase (ALT)** and aspartate **aminotransferase (AST)** are the most commonly used tests
- These enzymes normally found in the blood when liver cells are injured.

Liver Tests

- The ALT is felt to be a more specific indicator of liver inflammation as AST is also found in other organs such as the heart and skeletal muscle.
- In acute injury to the liver, as in viral hepatitis, the level of the ALT and AST may be used as a general measure of the degree of liver inflammation or damage.

Cholesterol

Cholesterol is an essential component of cell membranes

- VLDL: Very low density lipoproteins
  - VLDL particles mainly carry triglycerides to your tissues.
- LDL: Low density lipoproteins
  - Moves cholesterol from the liver to the body
  - High levels increase the risk of atherosclerosis
- HDL: High density lipoproteins
  - Moves cholesterol from the body to the liver
  - High levels thought to reduce the risk of atherosclerosis
  - **Known to have anti-thrombus and antioxidant properties**

Current Recommended Lipid Levels

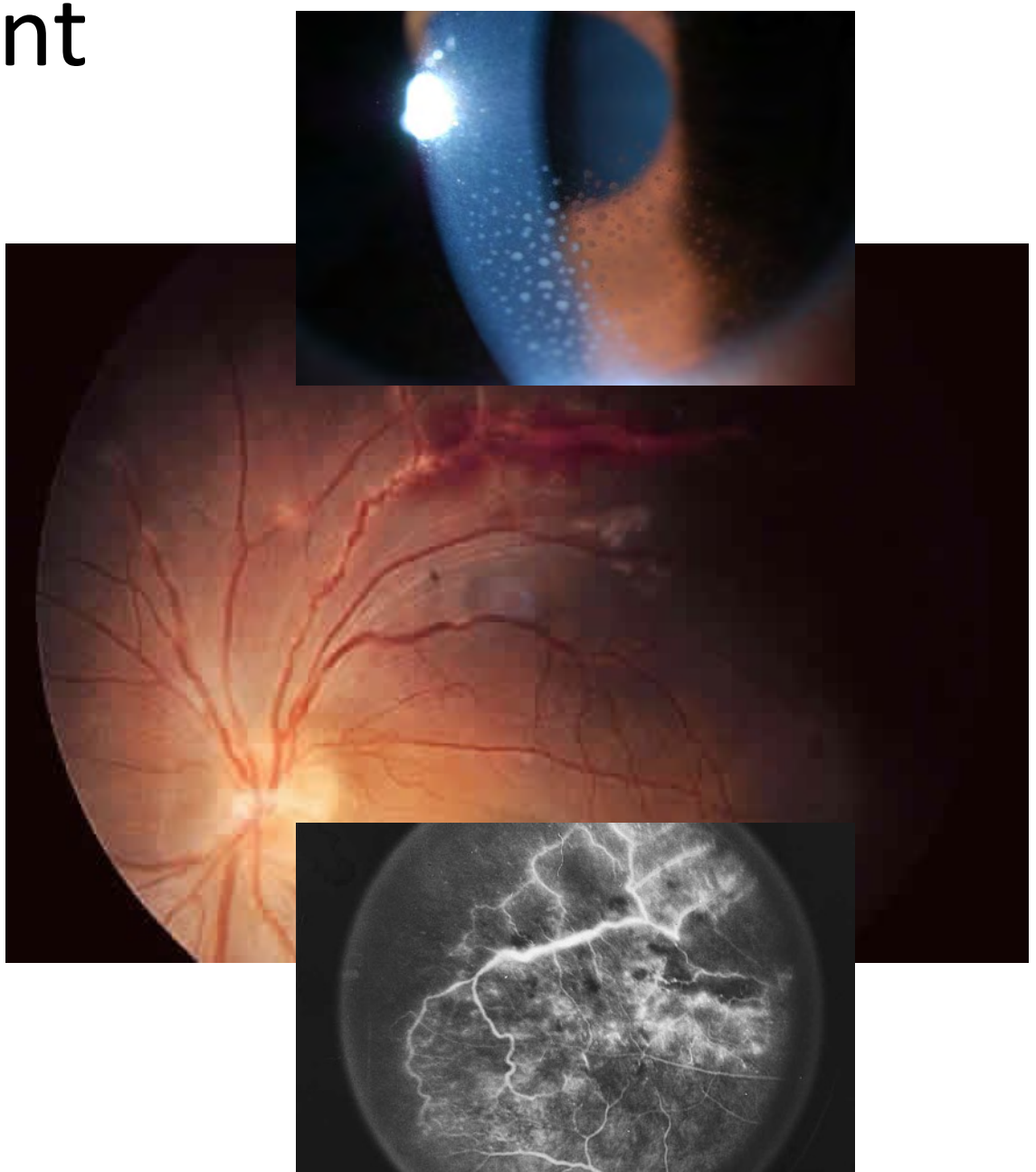
Healthy Cholesterol Range				
	Unit	Optimal	Intermediate	High
Total Cholesterol	mg/dL	<200	200 - 239	>239
	mmol/L	<5.2	5.3 - 6.2	>6.2
LDL Cholesterol (calculated)	mg/dL	<130	130 - 159	>159
	mmol/L	<3.36	3.36 - 4.11	>4.11
HDL Cholesterol	mg/dL	>60	40 - 60	<40
	mmol/L	>1.55	1.03 – 1.55	<1.03
Triglycerides	mg/dL	<150	150 - 199	>199
	mmol/L	<1.69	1.69 - 2.25	>2.25
Non-HDL-C (calculated)	mg/dL	<130	130 - 159	>159
	mmol/L	<3.3	3.4 - 4.1	>4.1
TG to HDL ratio (calculated)	mg/dL	<3	3.1 – 3.8	>3.8
	mmol/L	<1.33	1.34 – 1.68	>1.68

Case

- 30 BF presents with eye pain in both eyes for the past several days
  - Severe pain (8/10)
  - Never had eye exam before
- PMHx:
  - Has chronic bronchitis
  - Rash on legs
  - Has recently lost weight and has a fever
  - Taking acetaminophen for pain

Ocular Health Assessment

- VA: 6/9 (20/30) OD, OS
- PERRL
- FTFC
- EOM”s: FROM with eye pain in all quadrants
- SLE:
  - 3+ injection,
  - 3+ cells and trace flare,
  - deposits on endo (see photo)
- IOP: 18, 18 mmHg
- DFE:
  - see attached fundus image and fluorescein angiography.



Sarcoid Diagnosis

Lab Test	Findings
CBC with differential	Anemia/thrombocytopenia/leukopenia
Serum calcium/24 hour calcium	Hypercalcemia
Liver/Kidney function tests	AST/ALT/BUN/Creatinine elevated in hepatic disease
ACE (angiotensin converting enzyme)	Elevated in 60% of patients
Pulmonary x-rays	Hilar adenopathy

Blood Chemistry

- Angiotensin-Converting Enzyme (ACE)
  - Found mainly in lung and liver
  - Serum elevations are found in patients with sarcoidosis, and significant levels are achieved in pulmonary sarcoid
  - Cirrhosis of the liver may produce elevated ACE levels
  - Active tuberculosis infection of the lung does NOT produce elevated ACE levels

Diagnosis: Radiographic

- Radiographic involvement is seen in almost 90% of patients.
- Chest radiography is used in staging the disease:
  - Stage I disease shows bilateral hilar lymphadenopathy (BHL).
  - Stage II disease shows BHL plus pulmonary infiltrates.
  - Stage III disease shows pulmonary infiltrates without BHL
  - Stage IV disease shows pulmonary fibrosis.

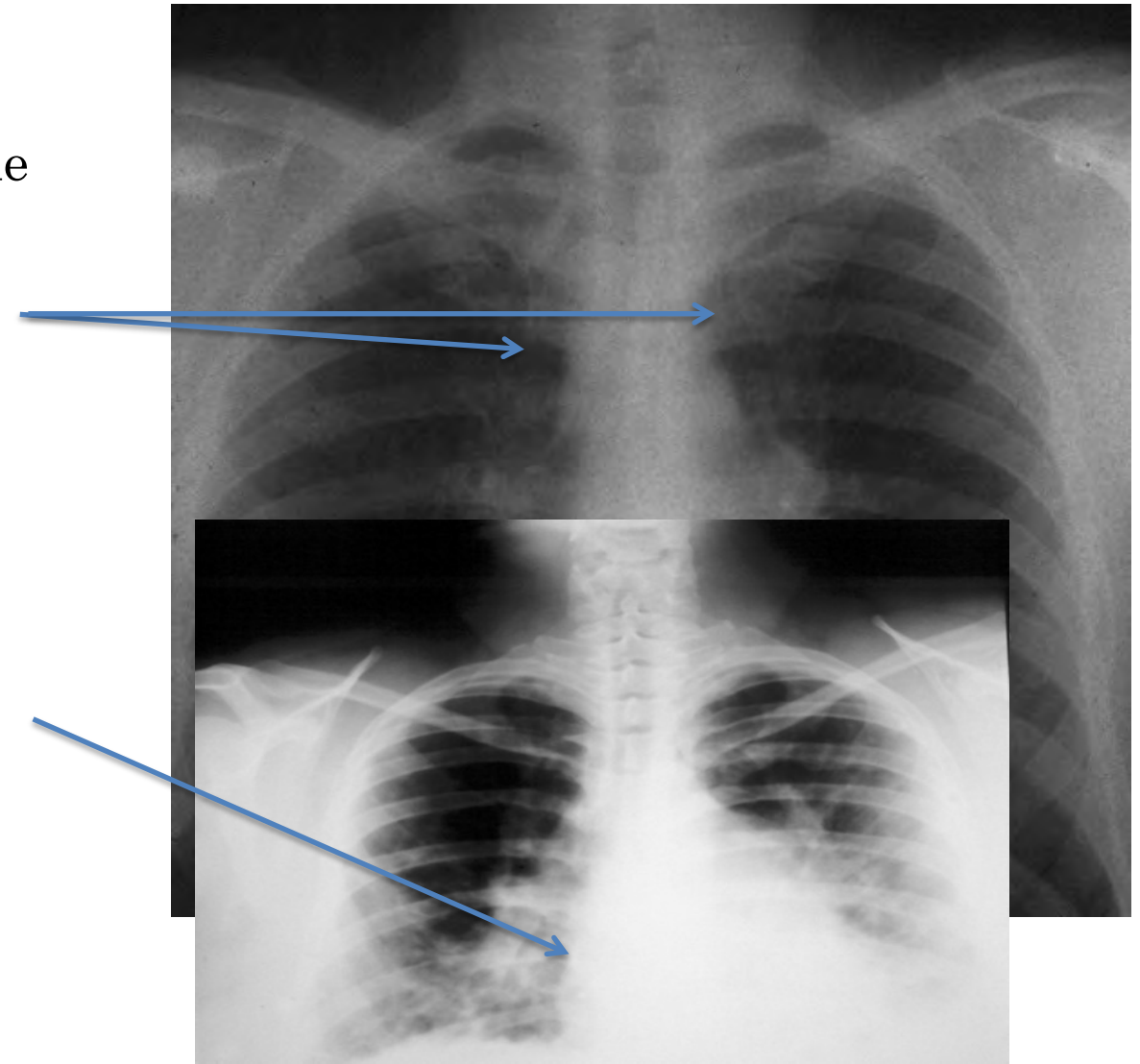


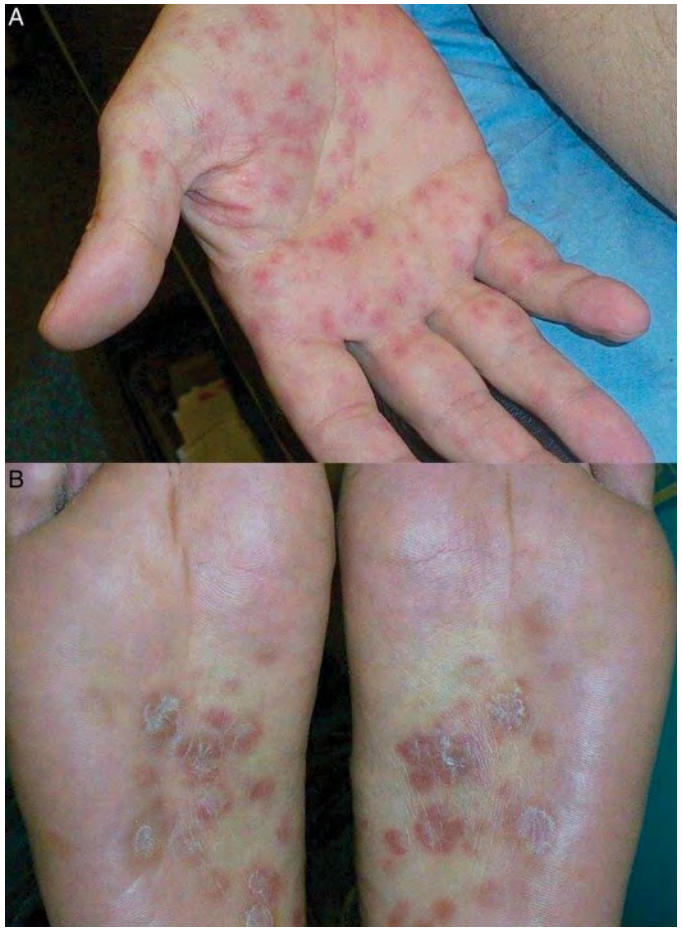
Table 1

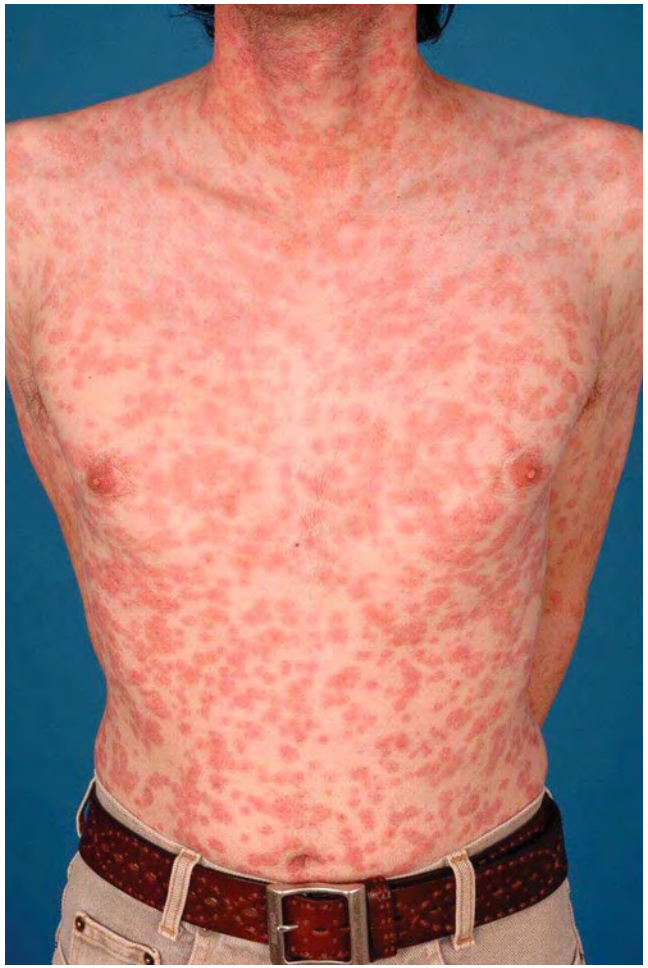
5 Stages of syphilis

Stage	Symptoms
Primary syphilis	Chancre in genitalia (often unnoticed)
Secondary syphilis	Maculopapular, non-tender rash; fever; lymphadenopathy; condyloma latum (genital)
Latent syphilis	Asymptomatic; serum nontreponemal and treponemal antibody tests are positive
Tertiary syphilis	Multiple organ-system involvement: Nerve involvement (deafness), aortic root dilation, aortitis, gummas (liver, bone, skin, spleen)
Neurosyphilis	Any stage can progress to neurologic involvement. Most common presentation is asymptomatic pupillary afferent defect (Argyll Robertson pupil). Focal symptoms include aphasia, paresis, blurry vision, hearing loss, seizures, ataxia, bowel or bladder incontinence, tabes dorsalis, loss of position and vibration senses, progressive ataxia, and sudden and severe pain, loss of balance, delirium, hydrocephalus, transverse myelitis, and stroke-like small vessel changes

https://www.mdedge.com/psychiatry/article/110901/somatic-disorders/psychosis-treated-neurosyphilis-now-time-stop-his/page/0/1?sso=true

Secondary Syphilis Skin Rash





Serological testing: Non-treponemal

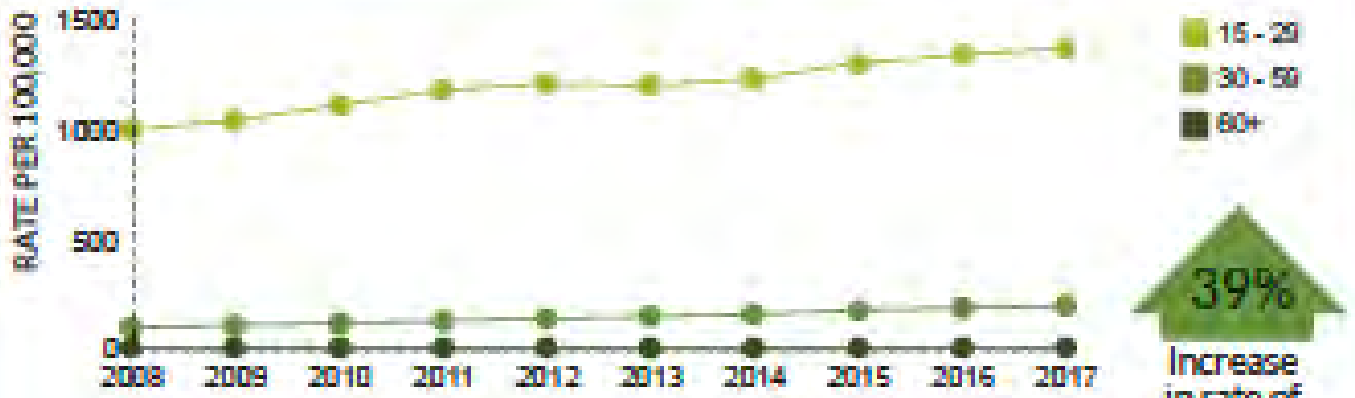
- **Nontreponemal tests** — Nontreponemal tests (also known as tests for reagin antibodies) are based upon the reactivity of serum from infected patients to a cardiolipin-cholesterol-lecithin antigen.
- Although these screening tests are nonspecific, and therefore not definitive, they have traditionally been used for initial syphilis screening due to their relatively low cost, ease of performance, and ability to be quantified for the purpose of following response to therapy.
- Nontreponemal tests include:
  - Rapid plasma reagin (RPR)
  - Venereal Disease Research Laboratory (VDRL)
  - Toluidine Red Unheated Serum Test (TRUST)
- Positive nontreponemal tests are reported as a titer of antibody (eg, 1:32, which represents the detection of antibody in serum diluted 32-fold).
- Titers tend to wane over time even without treatment, but successful therapy accelerates the pace of antibody decline.
- Changes in titer are followed after treatment to detect a therapeutic response.

Serological testing - Treponemal

- **Treponemal tests** — Treponemal tests have historically been more complex and expensive to perform than nontreponemal tests. Thus, they have traditionally been used as confirmatory tests for syphilis when the nontreponemal tests are reactive. However, newer versions of these tests have been automated, enhancing simplicity and facilitating ease of use. As a result, these tests are increasingly used as an initial screening test for syphilis rather than as confirmatory tests (reverse screening).
- Specific treponemal tests include:
  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - Microhemagglutination test for antibodies to *T. pallidum* (MHA-TP)
  - *T. pallidum* particle agglutination assay (TPPA)
  - *T. pallidum* enzyme immunoassay (TP-EIA)
  - Chemiluminescence immunoassay (CIA)
- As a group, these tests are based upon the detection of antibodies directed against specific treponemal antigens and thus tend to be more specific than nontreponemal tests. Treponemal tests are qualitative only and are reported as "reactive" or "nonreactive" .
- Once a patient has a positive treponemal test, this test usually remains positive for life. Thus, these tests are generally not useful for confirming a diagnosis of syphilis in a patient with prior treated disease. However, combinations of treponemal tests directed at different antigens can be used to diagnose late latent syphilis in some patients with discordant treponemal and nontreponemal serologies.

CHLAMYDIA

Trends in chlamydia by age and sex, 2008 - 2017



39%

Increase in rate of reported cases

of chlamydia cases are among women

Rates are increasing faster among men

GONORRHEA

Trends in gonorrhea by age and sex, 2008 - 2017

109%

Increase in rate of reported cases

Emerging Threat

63% of gonorrhea isolates are resistant to at least one antibiotic

13% resistant to at least one first line agent[3]

of gonorrhea cases are among men

Laboratory diagnosis

- Nucleic acid amplification tests (NAATs) – preferred test
  - consists of amplifying *C. trachomatis* DNA or RNA sequences using polymerase chain reaction (PCR), transcription-mediated amplification (TMA), or strand displacement amplification (SDA).
  - These sensitive, specific tests have become the "gold standard" and are the preferred diagnostic method, if available
  - Can be used with many different specimens
    - Vaginal swabs preferred for women and first catch-urine preferred for men
    - For conjunctivitis swabs can be used
  - Most sensitive test (80 – 90%)
  - Typically test for gonorrhea infection with same test

Chlamydia/Gonorrhea Management

- Anogenital and conjunctival chlamydia
- Previously a single gram dose of azithromycin was considered standard of care however doxycycline is now the new recommended standard:
  - Non-pregnant and non-lactating adults
    - Doxycycline 100 mg PO bid X 7 days
  - Alternative treatment:
    - **Azithromycin** 1 g orally in a single dose
      OR
      Levofloxacin 500 mg orally once daily for 7 days
  - Sexual partners must be tested and treated
  - Report to state or local health department

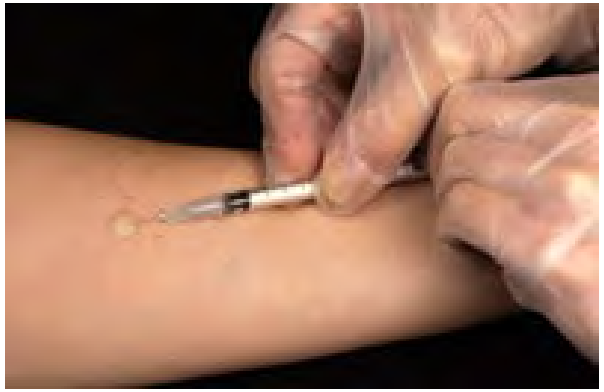
- For uncomplicated gonococcal infections of the cervix, urethra, and rectum
  - **Ceftriaxone** 500 mg* IM in a single dose for persons weighing <150 kg
    - If chlamydial infection has not been excluded, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.
      - * For persons weighing ≥150 kg, 1 g ceftriaxone should be administered.
- For cases with ocular involvement:
  - Adult and children ≥ 45 kg: Ceftriaxone 1 g IM in 1dose
- Should be tested for other STIs
- Sexual partners must be tested and treated
- Report to state or local health department

Tuberculosis (TB)

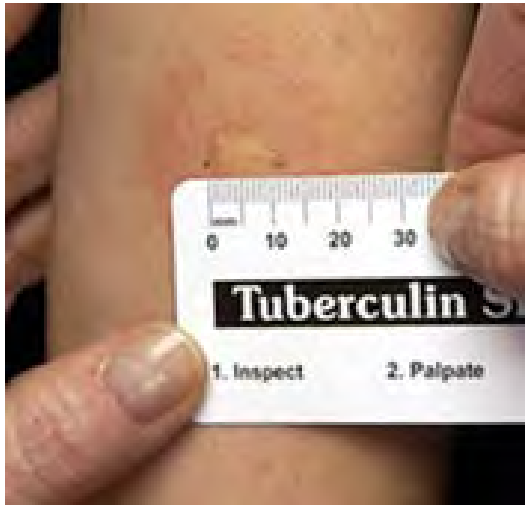
- Tuberculosis (TB) is caused by a bacterium called *Mycobacterium tuberculosis*.
- The bacteria usually attack the lungs, but TB bacteria can attack any part of the body such as the kidney, spine, and brain.
- Tuberculosis is classified as one of the granulomatous inflammatory conditions
- Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of its victims.
  - Majority of TB in Canada is in foreign born immigrants or Indigenous Peoples
  - Canada has one of the lowest rates of TB in the world
- Individuals with latent infection are not infectious

Diagnosis

- Screening:
  - A tuberculin skin test (TST) or interferon-gamma release assay (IGRA) should be performed. These are tools designed for diagnosis of TB infection; a positive result supports (but cannot be used to establish) a diagnosis of active TB disease, and a negative result does not rule out active TB disease
  - Mantoux test/TST/PPD
    - Intracutaneous tuberculin test
    - Purified protein derivative (PPD)
      - tuberculin placed intracutaneously
  - Read 48 - 72 hours later
  - Evaluate for induration (hardness) not redness
  - Test result interpretation depends on risk factors and general health of patient



The TB skin test is performed by injecting a small amount of fluid (called tuberculin) into the skin on the lower part of the arm.



Patient returns 48-72 hours later to have the skin test read. A positive test will be indicated by a raised area of skin in the area of the injection.

- Interferon-Gamma Release Assays (IGRA):
  - IGRAs measure a person's immune reactivity to *M. tuberculosis*.
  - White blood cells from most persons that have been infected with *M. tuberculosis* will release interferon-gamma (IFN-g) when mixed with antigens (substances that can produce an immune response) derived from *M. tuberculosis*.
  - They do not help differentiate latent tuberculosis infection (LTBI) from tuberculosis disease.
  - They are used to screen patient who have come from countries where TB immunization is common
    - Tuberculin skin test will be positive in a patient who has been immunized for TB so have to do IGRA on these patients to distinguish between being immunized versus having been exposed to TB

Ocular Signs of TB

- 1- 2 % of Non-HIV + patients with TB have ocular sign
- ≈ 18% if HIV + patients with TB have ocular signs
- Suggested that patients with TB have ocular exam
- Ocular signs can also be first indication of TB
  - Ocular TB can involve any part of the eye and can occur with or without evidence of pulmonary or extrapulmonary TB disease.

Ocular Signs of TB

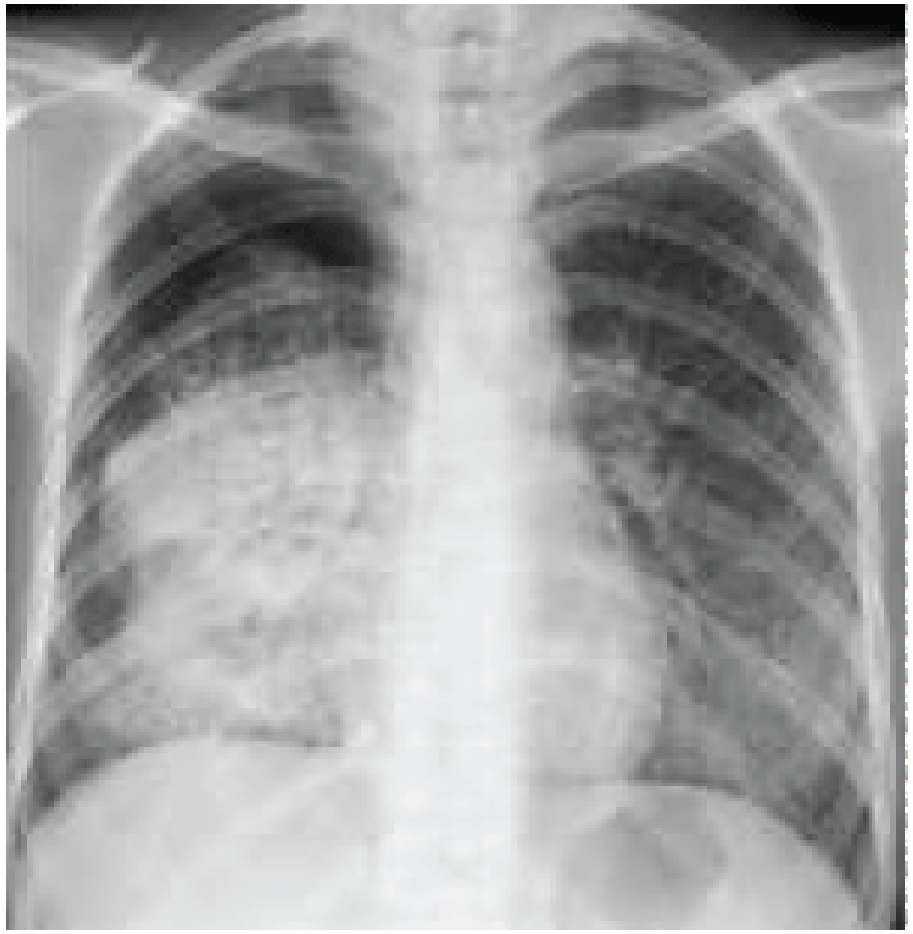
- Ulceration of lids with scarring and ectropion
- Cellulitis
- Dacryoadenitis (gland)
- Phlyctenulosis
- Keratoconjunctivitis
- Interstitial keratitis
- Episcleritis and Scleritis

- Uveitis (granulomatous, often bilateral)
- Choroiditis
- Retinal periphlebitis
- Optic neuritis
- Cranial neuropathy

- The most common ocular TB manifestation is granulomatous uveitis.
  - The most common presentation is posterior uveitis.

Diagnosis

- Chest radiographs
  - Many different appearances
  - Remember the lungs are supposed to be black, the lungs in this picture are not black



TB Management

- The three preferred regimens, chosen for effectiveness, safety and high treatment completion rates, are rifamycin-based. They are
  - three months of once-weekly isoniazid plus rifapentine for adults and children older than age 2, regardless of HIV status;
  - four months of daily rifampin; or
  - three months of daily isoniazid plus rifampin
- The alternative recommended regimens are six or nine months of daily isoniazid, with six months being preferred for HIV-negative adults and children. These regimens also are recommended for individuals who are unable to take a rifamycin-based regimen due to drug intolerability or drug-drug interactions.

Hemogram

- Eight components of the Hemogram (Complete Blood Count):
  - Hematocrit
  - Hemoglobin (Hb)
  - Mean Corpuscular Volume (MCV)
  - Mean Corpuscular Hemoglobin (MCH)
  - Platelet Count
  - Mean Platelet Volume
  - Red Blood Cell Count (RBC)
  - White Blood Cell Count

Giant Cell Arteritis

- vessels most often involved are the arteries over the temples,
  - GCA = "temporal arteritis."
- symptoms, such as fatigue, loss of appetite, weight loss or a flu-like feeling
  - pain in the jaw with chewing (jaw claudication).
  - Sometimes the only sign of GCA is unexplained fever.
  - Less common symptoms include pains in the face, tongue or throat.

Giant Cell Arteritis

- GCA is a clinical diagnosis!
- If patient meets criteria of clinical symptoms then treatment will be started regardless of whether lab test or biopsy are positive
- Treatment should be started before lab results are back.

Erythrocyte Sedimentation Rate

This measures the height of RBC's settling out of plasma per hour

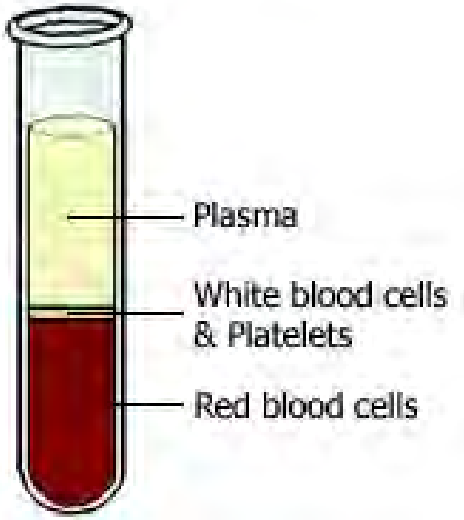
ESR	Males: Age/2	Good sensitivity but poor specificity. Takes time for the levels to become detectable
	Females: (Age + 10)/2	High: Indicative of giant cell arteritis but normal levels do not exclude GCA as a diagnosis

C-Reactive Protein (CRP)

- C-Reactive Protein
  - Normal = no CRP
  - Abnormal serum glycoprotein produced by liver during acute inflammation
  - Disappears rapidly once inflammation subsides
  - 4 hour fast from food/fluids
  - Alternative to ESR
  - More informative
    - ESR high in most elderly
- Elevated in conditions such as: temporal arteritis, preseptal cellulitis, endophthalmitis, HLA-B27 related iritis conditions.

CBC with Differential

- ***Red blood cell indices.*** Helpful in classifying anemias, these indices provide information such as RBC size, weight and hemoglobin concentration.
- ***White blood cell count (WBC) and differential.*** A WBC count reflects the number of WBCs per µL. The differential provides detailed information about the types of WBCs present, along with percentages. This information is useful in the differential diagnosis of certain disease states.
- ***Platelet count.*** This represents the number of platelets per µL and is useful in the diagnosis and management of blood clotting disorders and other diseases.



Why Order a CBC Diff

- helpful for patients with persistent infections, recurrent inflammation, or in those who exhibit signs of anemia or leukemia
- part of a battery of tests performed prior to surgery
- monitor patients for negative side effects associated with certain medications
  - E.g. acetazolamide (Diamox) can result in sodium and potassium depletion

Why Order a CBC Diff

- cases of recurrent or bilateral uveitis, may be useful in identifying a possible non-specific systemic etiology
  - an elevated WBC count (leukocytosis) may be present with underlying bacterial infections
  - elevated lymphocyte count (lymphocytosis) may be present with viral infections
  - Parasitic causes of uveitis may reveal elevated eosinophils (eosinophilia)

Why Order a CBC Diff

- presence of cotton-wool spots and/or retinal hemorrhages of unknown etiology in a patient without a documented history of diabetes mellitus or hypertension should prompt eye care providers to order a CBC to rule out anemia
- CBC could detect polycythemia (elevated RBC count), which is present in serious diseases such as leukemia

Red Blood Cells

- **Survive 120 days***
- 10^{10} RBCs produced per hour
- Erythropoietin (EPO) growth factor increases production
  - Produced in the kidneys (90%) and liver (10%)
- The maturation of red cells in the bone marrow requires several factors; most notably iron, for the synthesis of the O2-carrying pigment hemoglobin, and the essential nutrients folic acid and vitamin B12.
  - Deficiencies in these may cause anemia
- Biconcave discoid shape
- **Acellular**
- Hemoglobin
  - Carries oxygen to the tissue; returns carbon dioxide to the lungs
  - Hemoglobin synthesis occurs in the mitochondria of developing RBC

Red Blood Cell Catabolism

- RBC broken down in the **spleen**
  - Hemoglobin breaks down into heme + globin and iron
- Heme breakdown product becomes bilirubin made in the spleen and sent to the liver to make bile
  - Helps us to absorb what we are eating and fat reabsorption
  - If too little heme then fat in stool
  - Bile: yellow color of bruises, urine, jaundice
- Globin is recycled and reused
- Iron is recycled or stored

Red Blood Cell Indices

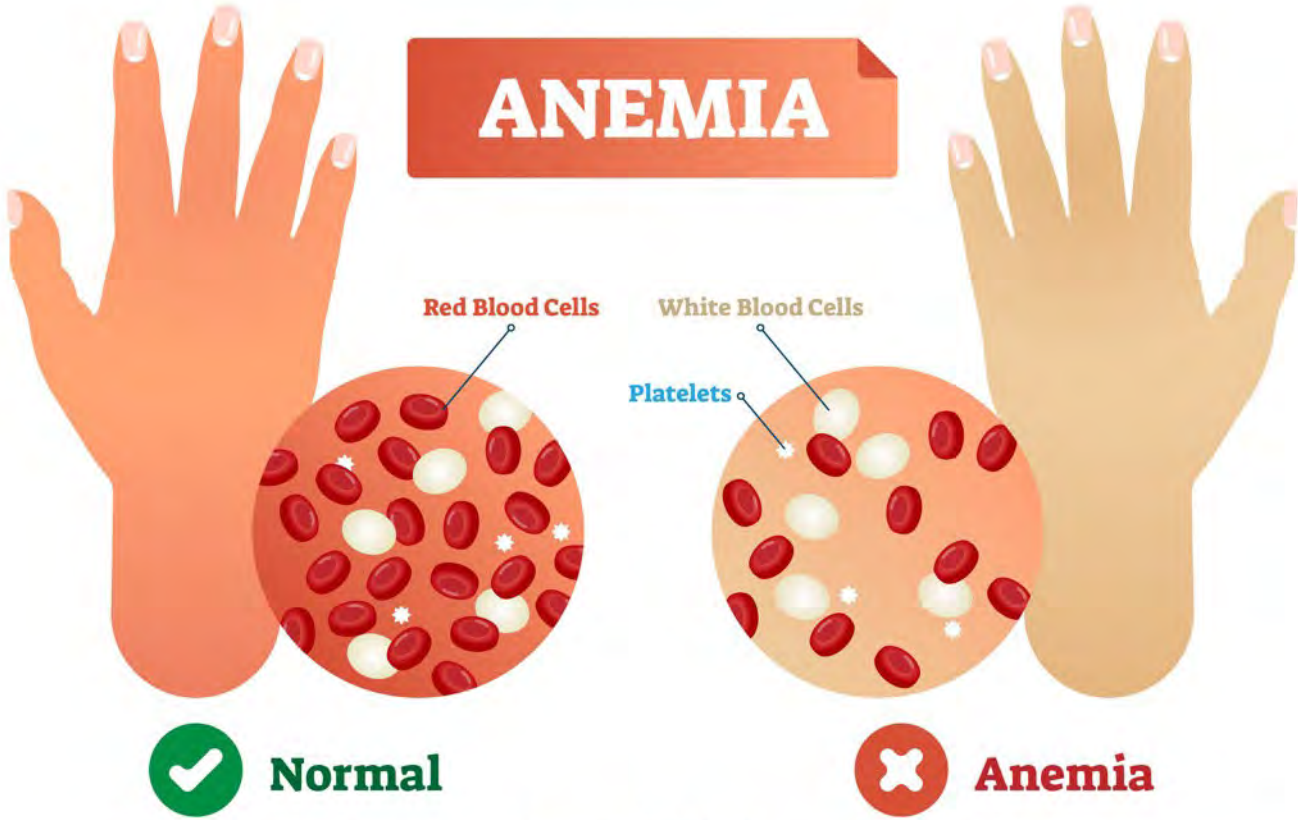
Index	Units/Calculation	Normal Range
Hemoglobin concentration (Hb)	g/dL	• Adult man, 14–18 g/dL • Adult woman, 11–15 g/dL
Hematocrit (Hct)	%	• Adult man, 40–54% • Adult woman, 34–46%
Red blood cell count (RBC)	10^{12}/L	• Adult man, 4.5–6.5 • Adult woman, 3.9–5.6
Mean cell volume (MCV)	(% Hct ÷ 100)/RBC (fL)	82–98 fL
Mean cell hemoglobin (MCH)	(Hb × 10)/RBC (pg)	27–33 pg
Mean cell hemoglobin concentration (MCHC)	(100 X MCH)/MCV (g/dL)	30–35 g/dL (g %)

Anemia

- Anemia is defined as a reduced red cell mass and is most often recognized when laboratory test results are abnormal.
- Anemia is more easily diagnosed if historic data for a patient are available because there is considerable physiologic variation in the hematocrit (Hct)
- The symptoms of advanced anemia include fatigue, dizziness, and shortness of breath.
- A physical examination may indicate signs of compensatory increases in cardiac output, such as strong peripheral pulses and tachycardia.
  - Upon auscultation, flow murmurs may be heard over the branch points of large arteries due to the low viscosity of the blood
- Female* > males (menstrual cycle and pregnancy)

- Signs
  - Pallor-decreased color
  - Cardiac failure
  - Brittle or spoon shaped nails-iron deficiency
  - **Pica-** eating dirt/ice and things that arent edible (body needs more iron)

ANEMIA



SYMPTOMS

- Fatigue
- Weakness
- Pale or Yellowish Skin
- Irregular Heartbeats
- Shortness of Breath
- Dizziness or Lightheadedness
- Chest Pain
- Cold Hands and Feet
- Headache

Sickle Cell

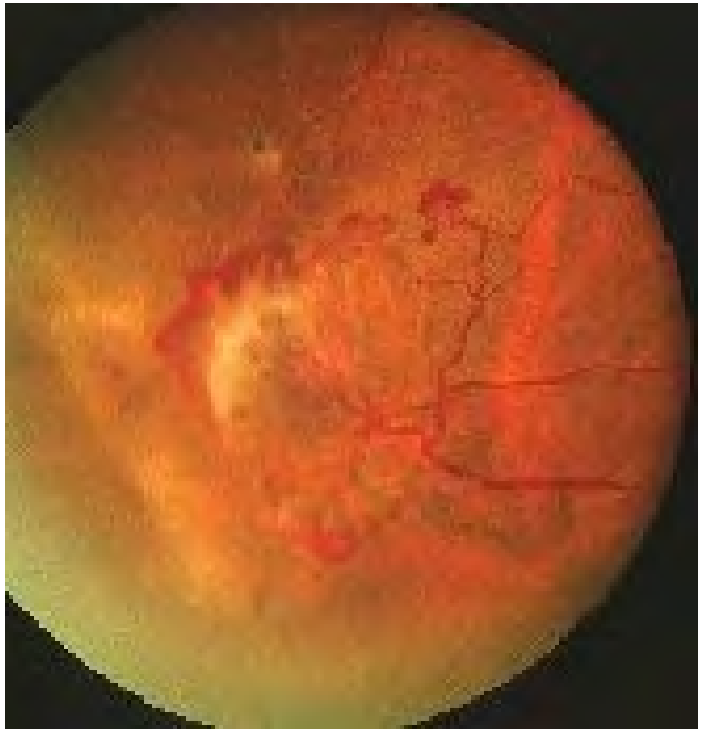
- **Sickle cell trait:**
  - A condition in which a child inherits the sickle cell gene mutation from one parent (one **sickle** gene and one normal hemoglobin gene).
  - the child doesn't get the disease, but can pass the defective gene on to future generations.
  - In most cases, there are no symptoms
  - protective advantage against **malaria**
    - As a result, the frequencies of **sickle cell** carriers are high in **malaria**-endemic areas.
- **Sickle Cell anemia**
  - one of the most common inherited diseases worldwide, is now understood to be a disorder of global importance and economic as well as clinical significance
  - Those affected by the disease live in areas of sub-Saharan Africa, the Middle East, India, the Caribbean, South and Central America
    - Blood testing can confirm the presence of hemoglobin S which is present in sickle cell
    - Genetic testing can confirm the sickle cell disease or trait

Sickle Cell Anemia

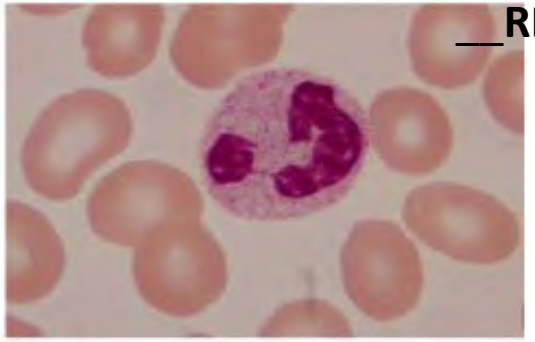
- Sickling cells leads to:
  - sickle cell disease as a condition is not only characterized by vasoocclusion, anemia, and hemolysis but also one with heightened inflammation, hypercoagulability, increased oxidative stress, and defective arginine metabolism.
  - Sickle cell disease is a vasculopathy and also features the presence of multiple nutritional and micronutrient deficiencies that adversely affect the patient.
  - Reduced RBC life
  - Impaired passage through circulation
  - Infections
  - Vaso-occlusive crisis
    - Pain in the hands, feet, **bones** (most common)
    - Pulmonary hypertension (30-40%)
    - Acute chest pain (30%)
    - Neurologic /stroke (25%)
    - Kidney damage (18%)

Sickle Cell Anemia

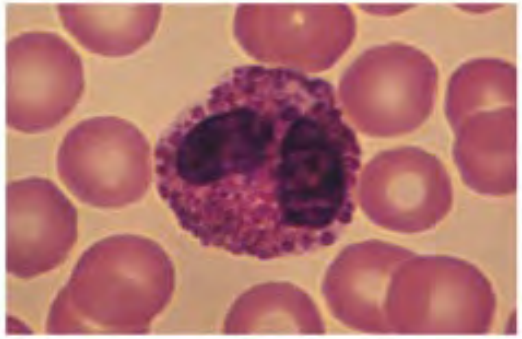
- Ocular manifestations
  - New blood vessel growth (neovascularization) of the iris
  - Snake-like shaped blood vessels
  - Retinal hemorrhage
  - Pigmentations in the retinal periphery
  - Glistening deposits in the retina
  - Salmon patch (orange-pink colored patches) in the retina
  - Angioid streaks
  - Retinal blood vessel occlusion
  - Retinal neovascularization (“sea-fan retinopathy”)
  - Retinal detachment



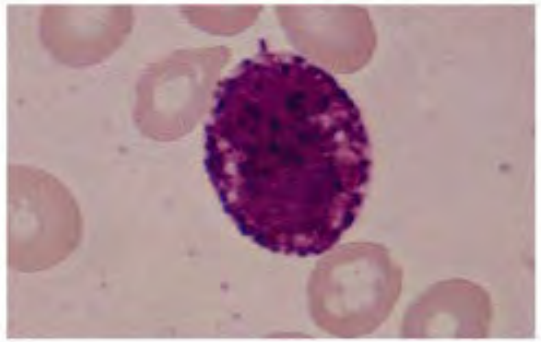
sea fan retinopathy in a patient with sickle cell disease



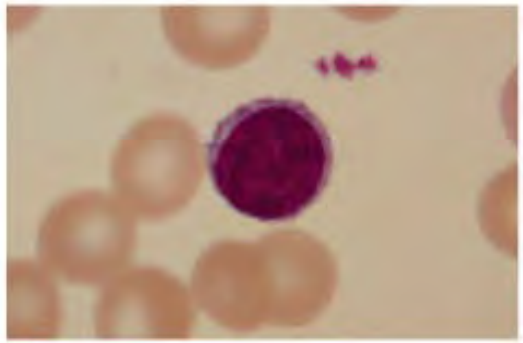
(a) neutrophil



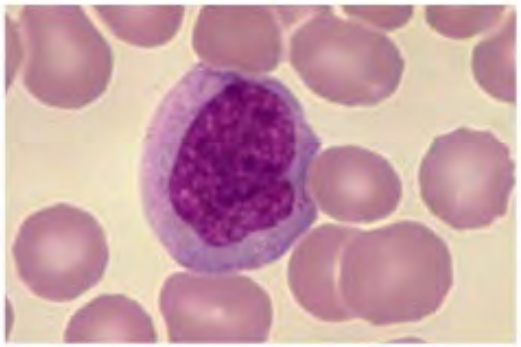
(b) eosinophil



(c) basophil



(d) small lymphocyte



(e) monocyte

Leukocytes

- AKA WBCs: white blood cells
- Are complete cells
- Function outside the blood

Note the size difference compared to erythrocytes

White blood cells/leukocytes

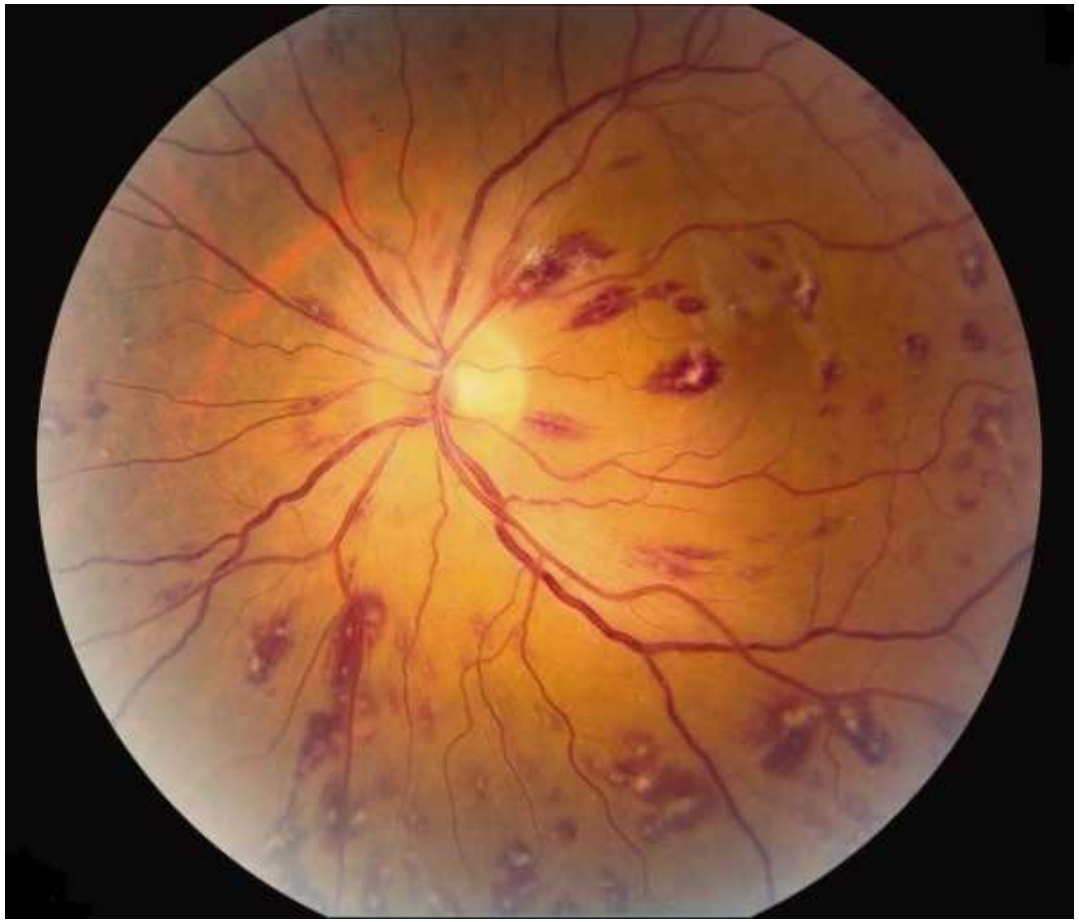
- **White blood cells** (**WBCs**), also called **leukocytes**, are the **cells** of the immune system that are involved in protecting the body against both infectious disease and foreign invaders.
- Five types of leukocytes/ WBC
  - Neutrophils (60-70%): Acute response to ingest and kill bacteria and damaged cells
  - Lymphocytes (~30%): Respond to viral and bacterial infections, create **antibodies**
  - Monocytes (5%): Engulf and kill bacteria, pro-inflammatory response to fight infection, clear cellular debris
  - Eosinophils and Basophils (2-4%): responds to allergic reactions and infections
- **Live for a few days**
- **WBCs are nucleated**

Leukemias

- - Leukemia is a common malignancy in children and adults that occurs when alterations in normal cell regulatory processes cause uncontrolled proliferation of hematopoietic stem cells in the bone marrow.
- Overproduction of white blood cells in the **bone marrow**
- WBC proliferation can suppress other cell formation
- - The prevalence of leukemia is generally higher in whites and in males, and increases with age.
- **Acute leukemias**: Sudden onset, involves immature/blast cells, more aggressive, more common in children
- **Chronic leukemias:** Slow onset, involves mature cells, harder to cure, more common in adults

Leukemia

- Signs and symptoms:
  - **Fatigue***
  - Anemia, thrombocytopenia
  - Abdominal discomfort (splenomegaly)
  - Weight loss, **fever***, night sweats
  - Headaches
  - Recurrent **infections***
  - Lymphadenopathy
  - Bone pain
  - **Retinopathy, Roth spots, proptosis**

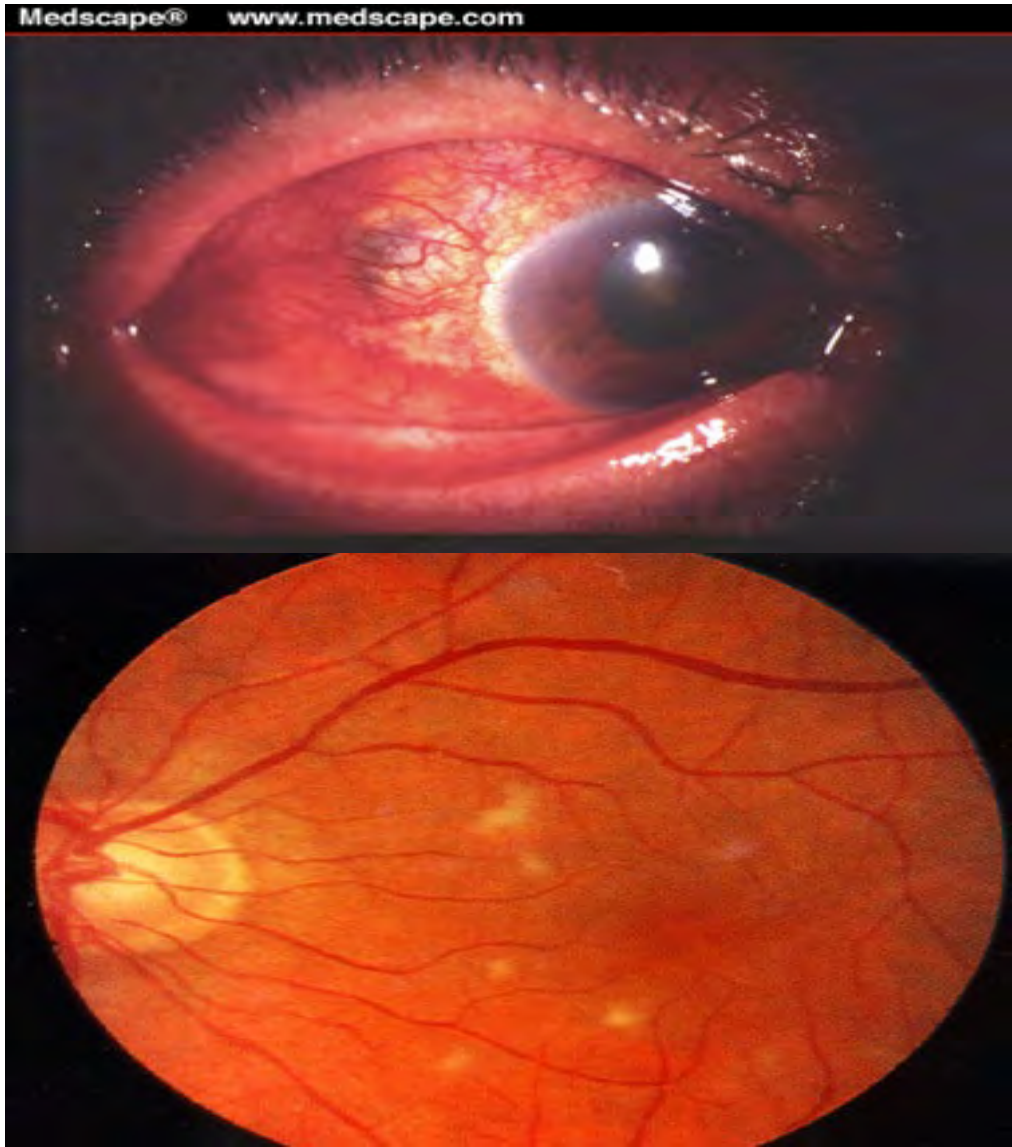


Case: Gonzalez

- 33 HF presents with a painful, red right eye
  - Started a couple of days ago, deep boring pain
  - Has tried Visine but hasn't helped the redness
- PMHx: patient reports she has been diagnosed with rheumatoid arthritis 3 years ago
  - Takes Celebrex for the joint pain
  - Patient reports she occasionally gets a skin rash when she is outdoors in the sun
- POHx: unremarkable
- PMHx: mother has rheumatoid arthritis

Case: Gonzalez

- VA:
  - 6/7.5 (20/30) OD,
  - 6/6 (20/20) OS
- Pupils: PERRL –APD
- VF: FTFC OH
- EOM's: FROM OU
- BP: 130/85 mm Hg RAS
- SLE: see picture
  - 2+ cells, mild flare
- IOP's: 16, 16 mm HG
- DFE: see fundus photo



Patient Update

- Patient was worked up for lupus and diagnosed with lupus.
- Patient was already taking Celebrex which was not effective in treating the scleritis she presented with
  - upon referral to rheumatology it was discovered that she had several organs already being affected by the lupus
  - she was put on immunosuppressive agents to treat the systemic and ocular manifestations
- Patient was taken off of Celebrex and put on plaquenil (hydroxychloroquine) 400 mg po qd

Rheumatoid Arthritis (RA)

- The most common type of autoimmune arthritis
- A **bilateral, symmetric peripheral** inflammatory disease primarily of the synovial joints
- Leads to destruction of bone, cartilage, tendons, ligaments
- If untreated, can lead to deformity and disability

RA Epidemiology

Prevalence ~1% of the US population

- **Female** 3:1
  - Estrogen levels thought to play a role
  - Men who develop RA linked to low testosterone levels
- Can begin at any age but most common age of onset is in the 4^{th} or 5^{th} decade for women and 6^{th}-8^{th} for men
- Lower prevalence in African Americans & Chinese (more common in Native Americans)
- **Smoking and obesity are risk factors***
- Susceptibility is genetically determined
  - HLA-DR4 and HLA-DRB present in 50-75% of cases

Ocular manifestations of RA

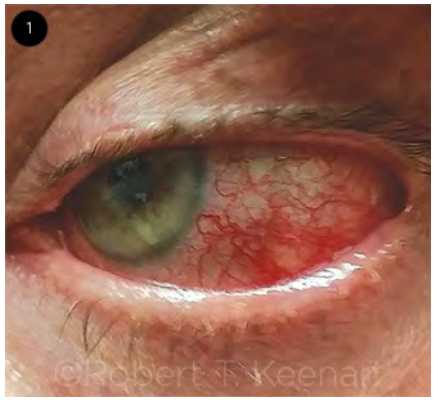
- Dry eye syndrome, also known as keratoconjunctivitis sicca, is the most common ocular manifestation of RA. It can occur as a result of meibomian gland, lacrimal gland, accessory lacrimal gland, or goblet cell dysfunction.
- Episcleritis: although the disorder is usually idiopathic, it can also be associated with RA and other systemic diseases. It is bilateral 40% of the time, and manifests with salmon-pink eyes and mild pain.

Ocular manifestations of RA

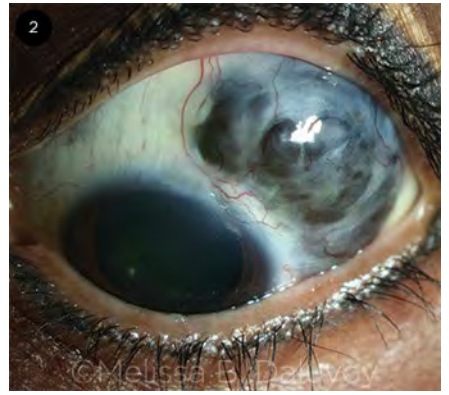
- Scleritis: RA is the most common cause of scleritis, which is an inflammation of the sclera characterized by vasodilation of the superficial and deep episcleral vessels.
  - Occasionally, scleritis may present before the onset of joint symptoms in the RA patient.
  - Scleritis occurs bilaterally 40% to 50% of the time and is classified as anterior or posterior based on its position relative to the ora serrata.

- *Scleromalacia perforans:* anterior necrotizing scleritis without inflammation
  - this condition often presents without pain, despite its ability to lead to visual loss, astigmatism, and globe perforation.

- The presence of scleritis in patients with RA is associated with increased mortality.
  - Posterior scleritis can cause serous retinal detachment or chorioretinal folds.
  - Other sequelae associated with scleritis include uveitis, cataracts, glaucoma, posterior segment damage, and peripheral ulcerative keratitis.



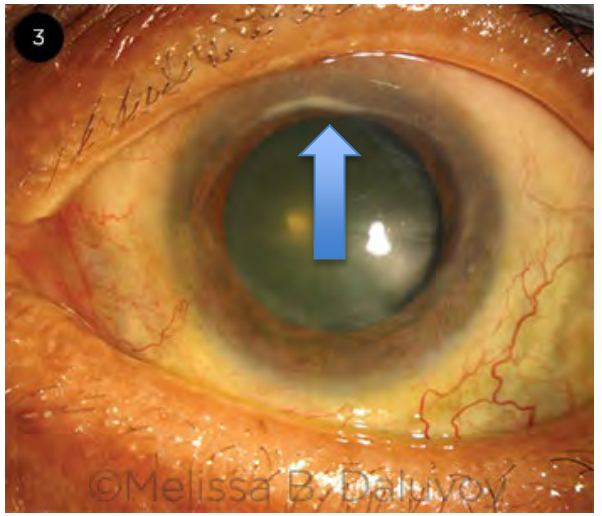
ANTERIOR SCLERITIS. Slit-lamp photo displays dilation of the episcleral vessels in a patient with underlying RA.



SCLEROMALACIA PERFORANS**.** Slit-lamp photo of the left eye shows severe superotemporal scleral thinning with visible choroid bulging anteriorly, but with minimal inflammation

Ocular manifestations of RA

- Peripheral ulcerative keratitis (PUK): is a type of corneal melt that occurs when immune complexes infiltrate the vascular arcades in the 0.5-mm corneal periphery.
  - RA is the most common etiology, accounting for 34% of cases; however, it can also be caused by other autoimmune, infectious, neurologic, and dermatologic conditions.
  - In the setting of severe RA, PUK is usually accompanied by other ocular manifestations, and it can occur secondary to scleritis, especially necrotizing scleritis
- PUK presents with stromal thinning and a secondary overlying epithelial defect and is characterized by neovascularization of the corneal periphery and crescent-shaped juxtalimbal ulcers
- It is unilateral 60% of the time.
- It can present with pain, photophobia, tearing, and decreased visual acuity due to astigmatism or corneal opacity.



Crescent-shaped ulcers are juxtaposed against the limbus (arrow pointing to the ulcer)

Laboratory Testing: Rheumatoid Factor (RF)

- RF binds to other immunoglobulins which binds to the Fc portion of IgG (autoantibody)
    - 70% of RA patients have RF
    - RF is positive in 5-20% of healthy patients over age 70
    - **"Seronegative"** means the patient does not have RF
    - RF can occur in a variety of other conditions other than RA (see table of conditions)
    - 80-97% of pts have RA if they are RF+ and ACPA+

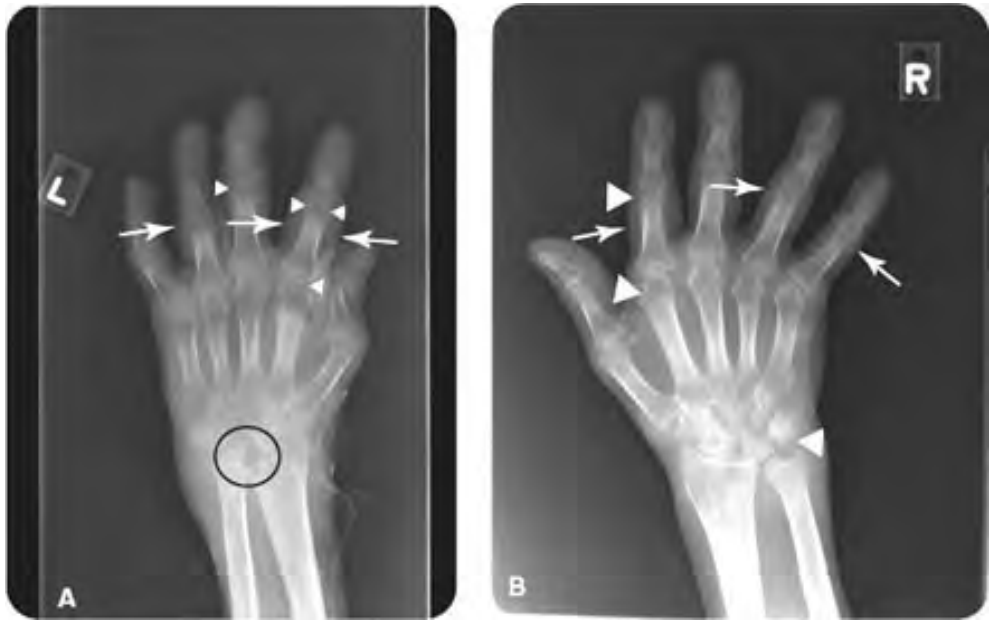
Anti-Citrullinated Protein Antibodies (ACPAs)

- 50-70% of RA pts have **Anti-CCP antibodies**
- During inflammation, arginine (AA) in the synovial fluid undergoes citrullination which fits into the antigen binding site initiating an immune response
- Signals an immune response
  - If you have anti-CCP antibodies then you have an immune response
  - Need something to trigger citrullination and also need Anti CCP antibodies to be produced to induce inflammatory response
- If patient has both RF factor and ACPA then high likelihood of RA (80-97% likely)
- Poorer prognosis

RA Testing

- Complete Blood Count (CBC): Mild anemia is universal and present in chronic disease
- White cell count is normal or slightly higher
- Platelet count is often elevated
- Joint aspiration: joint fluid confirms the inflammatory nature of the arthritis

- Of all the laboratory tests, radiographic changes are the most specific for RA
  - Radiographs obtained during the first 6 months of symptoms tend to usually be normal



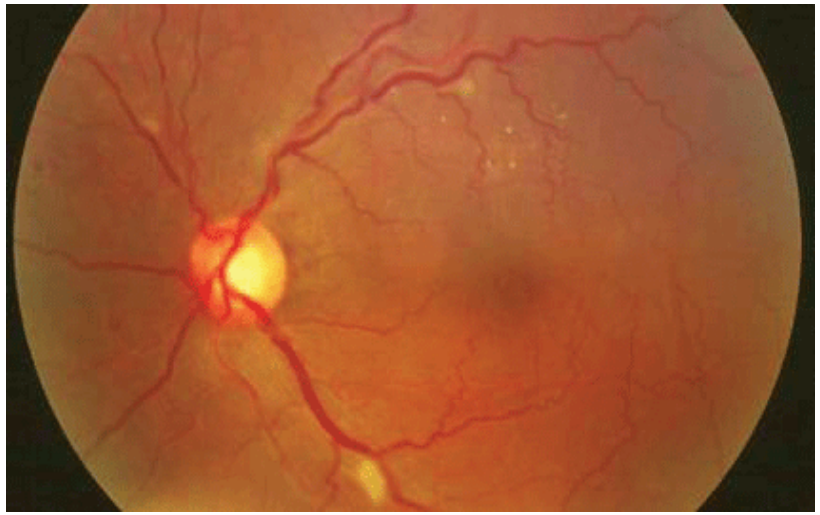
A 66-year-old man with advanced rheumatoid arthritis. Anteroposterior radiographs of the **(A)** left and **(B)** right hands demonstrate diffuse osteopenia (low bone density), proximal periarticular soft tissue swelling (*arrows*), marginal erosions (*arrowheads*), and ulnar deviation of the right fourth and fifth MCP joints.

Systemic Lupus Erythematosus (SLE)

- Autoimmune disorder characterized by autoantibodies to nuclear antigens
  - Many of its clinical manifestations are secondary to the trapping of antigen-antibody complexes in capillaries of visceral structures or to autoantibody-mediated destruction of host cells.
- Women (85%)
  - Among older individuals the sex distribution is more equal.
- Onset 20-40 years old
- African and Caribbean (1 in 250) versus white (1:1000)
- Hereditary: 3-5% chance with a primary relative
- Can be caused by medications (drug induced lupus: onset due to drugs, lupus stops if they stop taking the drug):

Ocular Involvement in Lupus

- Eyes (up to 30% of patients)
  - Dry eye syndrome (keratoconjunctivitis sicca) is the most common ocular finding in secondary Sjogren syndrome
  - most common pathologic condition involving the eye in lupus patients is retinal vasculopathy in the form of cotton wool spots.
  - Episcleritis, scleritis, conjunctivitis
  - Optic neuritis
  - Cranial neuropathies 3,6 but usually 7
  - Retinal exudates, hemorrhages, cotton wool spots (lupus retinopathy)
  - Rare: uveitis



Cotton wool spots are the most common retinopathy found in lupus.

SLE Testing

- The diagnosis of SLE is generally based on clinical and laboratory findings after excluding alternative diagnoses.
- Blood testing
  - CBC: Anemia
  - ESR, CRP is elevated
  - Urea and creatinine elevated with renal involvement
- ANA: anti-nuclear antibody
    - Present in in almost all patients with SLE (> 95%)
    - Very sensitive but not very specific
    - A negative test makes SLE unlikely
    - 15% of normal patients are ANA+
- If the ANA is positive, the patient should be tested for other specific antibodies, such as anti-dsDNA, anti-Smith (anti-Sm), Ro/SSA, La/SSB, and U1 ribonucleoprotein (RNP)

Diseases associated with a positive ANA

	Percent with positive ANA
Systemic autoimmune diseases	
SLE	
Active	98 to 100 percent
Remission	90 percent
Scleroderma	95 percent
Rheumatoid arthritis	45 percent
Sjögren's syndrome	60 percent
Mixed connective tissue disease	100 percent
Drug-induced LE	80 to 95 percent
Raynaud's phenomenon	40 percent
Polymyositis/dermatomyositis	35 percent
Juvenile idiopathic arthritis	15 to 40 percent
Organ-specific autoimmune diseases	
Hashimotos thyroiditis	50 percent
Graves' disease	50 percent
Autoimmune hepatitis	70 percent
Primary biliary cirrhosis	50 to 70 percent
Infectious diseases*	
Viral:	
EBV	
HIV	
HCV	
Parvovirus 19	
Bacterial:	
SBE	
Syphilis	
Malignancies*	
Lymphoproliferative diseases	
Paraneoplastic syndromes	
Miscellaneous diseases*	
Inflammatory bowel disease	
Interstitial pulmonary fibrosis	

ANA: antinuclear antibodies; SLE: systemic lupus erythematosus; EBV: Epstein-Barr virus; HCV: hepatitis C virus; SBE: subacute bacterial endocarditis.
* Although positive tests of ANA are reported in these diseases more often than in healthy controls, precise estimates vary.

Courtesy of Donald B Bloch, MD.

UpToDate®

Systemic Lupus Erythrematosis (SLE)

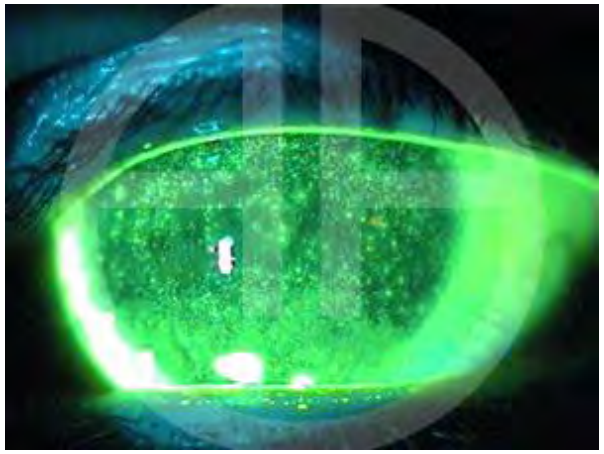
- Anti-dsDNA antibodies
  - Not very sensitive, but incredibly specific (nearly 100%)
- Anti-Sm antibodies
  - Not very sensitive, but incredibly specific (nearly 100%)
- Anti-SSa antibodies (anti-SSa/Ro) (30%)
- Anti-SSb antibodies (anti-SSb/La) (20%)
  - Sjogren's syndrome markers
- U1 ribonucleoprotein (RNP) (25%)

Sjogren Syndrome (SS)

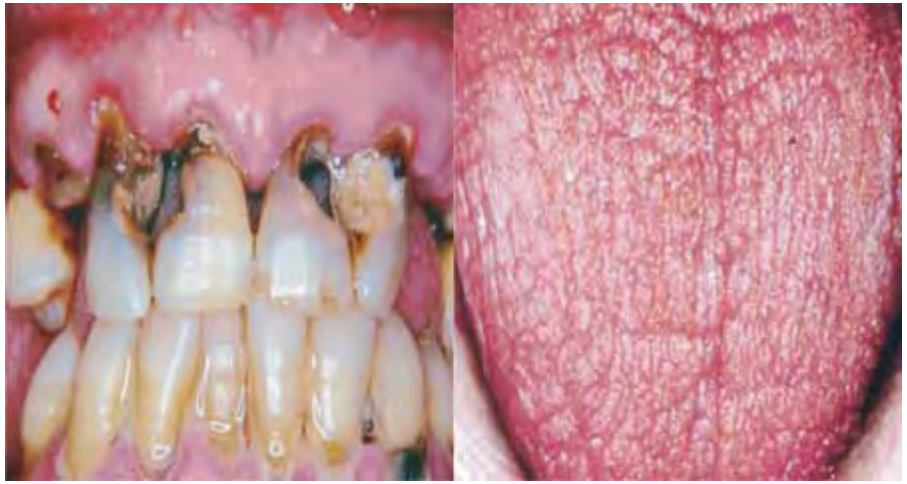
- Chronic, systemic disease in which immune cells attack and destroy the exocrine glands that produce tears and saliva
  - ***Autoimmune disease***
- Occurs mostly in women 30-65 years old
  - Peak diagnosis ≈ 53 years old
- 2 types:
  - Primary SS: not associated with other diseases
  - Secondary SS: complicates or overlaps with other rheumatic conditions
    - RA, systemic lupus erythamtosus (SLE), scleroderma
- Primary SS is the 2nd most common connective tissue disorder after SLE

Sjogren Syndrome

- Signs/symptoms:
  - Dry mouth (xerostomia)
  - Dry eyes (keratoconjunctivitis sicca)
  - Dryness of the skin, nose, vaginal canal
  - Superficial Punctate Keratitis (SPK), ulceration or the cornea
  - Atrophy, inflammation, and cracking of the oral mucosa
  - Joint pain, swelling, stiffness



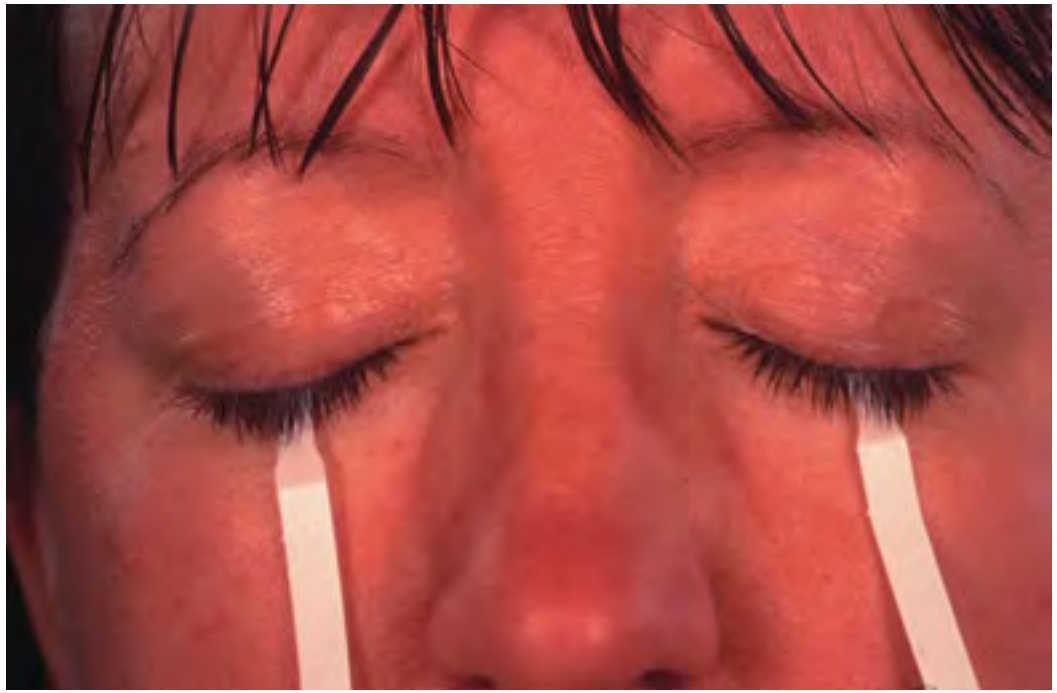
Punctate keratitis commonly seen in patients with Sjogren Syndrome



xerostomia (dry mouth) is commonly experienced by Sjogren patients which can lead to gum disease and dental caries

Sjogren Syndrome

- Diagnosis:
  - Clinical history, exam findings
    - Chronic dry mouth, eyes, among others
  - Eye exam
    - Slit lamp exam including staining of cornea and conjunctiva with NaFl and Lissamine grenn
    - Schirmer's test: A positive test occurs when less than 5 mm of the strip is wet after 5 minutes.
  - Lab tests:
    - Increased ESR, CRP
    - ANA + in 70-80%
    - Anti-SS-A (Ro) 60-70% (+)
    - Anti-SS-B (La) 50-60% (+)
    - **RF + in up to 95%**
  - Biopsy of the salivary gland or lip with increased lymphocytes



Ocular and Systemic Morbidity in Sjogren Syndrome

- 2015 published article comments on patients who were diagnosed with Sjogren Syndrome:
  - all patients had dry eye symptoms for approximately 10.4 years before presentation
  - 42% of the patients had systemic manifestations resulting from primary SS
  - **SS has been shown to be an independent risk factor for the development of non-Hodgkin’ s lymphoma.**