BLACKWELL'S

UNDERGROUND CLINICAL VIGNETTES

BIOCHEMISTRY, 3E

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PREFACE TO THE 3RD EDITION

We were very pleased with the overwhelmingly positive student feedback for the 2nd edition of our *Underground Clinical Vignettes* series. Well over 100,000 copies of the UCV books are in print and have been used by students all over the world.

Over the last two years we have accumulated and incorporated **over a thousand "updates"** and improvements suggested by you, our readers, including:

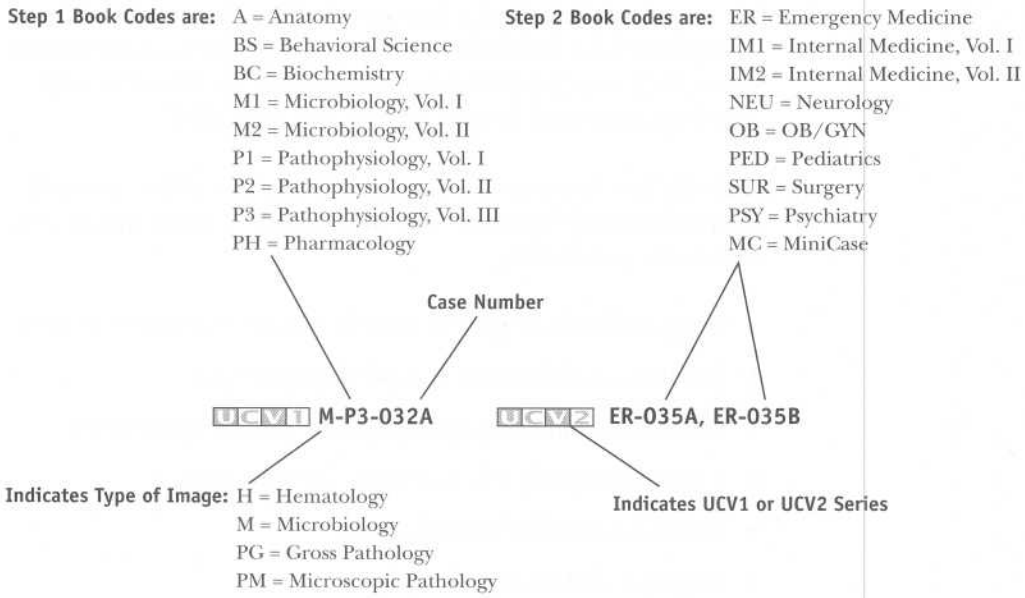
- many additions of specific boards and wards testable content
- deletions of redundant and overlapping cases
- reordering and reorganization of all cases in both series
- a new master index by case name in each Atlas
- correction of a few factual errors
- diagnosis and treatment updates
- addition of 5–20 new cases in every book
- and the addition of clinical exam photographs within *UCV—Anatomy*

And most important of all, the third edition sets now include two brand new **COLOR ATLAS** supplements, one for each Clinical Vignette series.

- The *UCV–Basic Science Color Atlas* (*Step 1*) includes over 250 color plates, divided into gross pathology, microscopic pathology (histology), hematology, and microbiology (smears).
- The *UCV–Clinical Science Color Atlas* (*Step 2*) has over 125 color plates, including patient images, dermatology, and funduscopy.

Each atlas image is descriptively captioned and linked to its corresponding Step 1 case, Step 2 case, and/or Step 2 MiniCase.

How Atlas Links Work:



- If the Case number (032, 035, etc.) is not followed by a letter, then there is only one image. Otherwise A, B, C, D indicate up to 4 images.

Bold Faced Links: In order to give you access to the largest number of images possible, we have chosen to cross link the Step 1 and 2 series.

- If the link is bold-faced this indicates that the link is direct (i.e., Step 1 Case with the Basic Science Step 1 Atlas link).
- If the link is not bold-faced this indicates that the link is indirect (Step 1 case with Clinical Science Step 2 Atlas link or vice versa).

We have also implemented a few structural changes upon your request:

- Each current and future edition of our popular *First Aid for the USMLE Step 1* (Appleton & Lange/McGraw-Hill) and *First Aid for the USMLE Step 2* (Appleton & Lange/McGraw-Hill) book will be linked to the corresponding UCV case.
- We eliminated UCV → First Aid links as they frequently become out of date, as the *First Aid* books are revised yearly.

- The Color Atlas is also specially designed for quizzing—captions are descriptive and do not give away the case name directly.

We hope the updated UCV series will remain a unique and well-integrated study tool that provides compact clinical correlations to basic science information. They are designed to be easy and fun (comparatively) to read, and helpful for both licensing exams and the wards.

We invite your corrections and suggestions for the fourth edition of these books. For the first submission of each factual correction or new vignette that is selected for inclusion in the fourth edition, you will receive a personal acknowledgment in the revised book. If you submit over 20 high-quality corrections, additions or new vignettes we will also consider **inviting you to become a "Contributor" on the book of your choice**. If you are interested in becoming a potential "Contributor" or "Author" on a future UCV book, or working with our team in developing additional books, please also e-mail us your CV/resume.

We prefer that you submit corrections or suggestions via electronic mail to **UCVteam@yahoo.com**. Please include "Underground Vignettes" as the subject of your message. If you do not have access to e-mail, use the following mailing address: Blackwell Publishing, Attn: UCV Editors, 350 Main Street, Malden, MA 02148, USA.

Vikas Bhushan
Vishal Pall
Tao Le
October 2001

HOW TO USE THIS BOOK

This series was originally developed to address the increasing number of clinical vignette questions on medical examinations, including the USMLE Step 1 and Step 2. It is also designed to supplement and complement the popular *First Aid for the USMLE Step 1* (Appleton & Lange/McGraw Hill) and *First Aid for the USMLE Step 2* (Appleton & Lange/McGraw Hill).

Each UCV 1 book uses a series of approximately 100 **"supra-prototypical" cases as a way to condense testable facts and associations**. The clinical vignettes in this series are designed to incorporate as many testable facts as possible into a cohesive and memorable clinical picture. The vignettes represent composites drawn from general and specialty textbooks, reference books, thousands of USMLE style questions and the personal experience of the authors and reviewers.

Although each case tends to present all the signs, symptoms, and diagnostic findings for a particular illness, **patients generally will not present with such a "complete" picture either clinically or on a medical examination**. Cases are not meant to simulate a potential real patient or an exam vignette. All the **boldfaced "buzzwords" are for learning purposes** and are not necessarily expected to be found in any one patient with the disease.

Definitions of selected important terms are placed within the vignettes in (SMALL CAPS) in parentheses. Other parenthetical remarks often refer to the pathophysiology or mechanism of disease. The format should also help students learn to present cases succinctly during oral "bullet" presentations on clinical rotations. The cases are meant to serve as a condensed review, not as a primary reference. The information provided in this book has been prepared with a great deal of thought and careful research. This book should not, however, be considered as your sole source of information. Corrections, suggestions and submissions of new cases are encouraged and will be acknowledged and incorporated when appropriate in future editions.

ABBREVIATIONS

5-ASA	5-aminosalicylic acid
ABGs	arterial blood gases
ABVD	adriamycin/bleomycin/vincristine/dacarbazine
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
AFP	alpha fetal protein
AI	aortic insufficiency
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphocytic leukemia
ALT	alanine transaminase
AML	acute myelogenous leukemia
ANA	antinuclear antibody
ARDS	adult respiratory distress syndrome
ASD	atrial septal defect
ASO	anti-streptolysin O
AST	aspartate transaminase
AV	arteriovenous
BE	barium enema
BP	blood pressure
BUN	blood urea notrogen
CAD	coronary artery disease
CALLA	common acute lymphoblastic leukemia antigen
CBC	complete blood count
CHF	congestive heart failure
CK	creatine kinase
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CSF	cerebrospinal fluid
CT	computed tomography
CVA	cerebrovascular accident
CXR	chest x-ray
DIC	disseminated intravascular coagulation
DIP	distal interphalangeal
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DTRs	deep tendon reflexes
DVT	deep venous thrombosis

ID/CC A 68-year-old obese male is rushed to the ER after he was found **unconscious** on the floor of his office.

HPI He had been on medication for coronary artery disease.

PE On admission, he is found to be in an acute state of tissue **hypoperfusion** (SHOCK) with a barely palpable pulse, hypothermia, and bradycardia. Immediate treatment for cardiac shock is begun.

Labs ECG: acute anteroseptal myocardial infarction. **Increased serum lactate**; hyperphosphatemia. ABGs: **severe metabolic acidosis** (pH 7.27); bicarbonate 14 mEq/L (low). **Increased anion gap** (19) with no ketoacids; BUN and creatinine normal.

Treatment Treat precipitating cause of acidosis; administer bicarbonate if pH is < 7.2. Treat shock.

Discussion A state of increased levels of lactic acid in blood (LACTIC ACIDOSIS) may be due to a number of causes, including **shock** and **sepsis** (both of which increase lactic acid production due to hypoxia), methanol poisoning, metformin toxicity, and liver failure (due to failure of lactic acid to be removed from blood by its transformation to glucose). The anion gap is an estimation of the total unmeasured plasma anions, such as proteins, organic acids, phosphate, and sulfate. Increased anion-gap metabolic acidosis is due to salicylate poisoning, alcohol (e.g., methanol, ethanol, propylene glycol) intoxication, lactic acidosis, renal failure, and diabetic ketoacidosis.

ID/CC A 1-year-old female is taken to the emergency room because of **persistent vomiting** (20 times in 24 hours) that has been unresponsive to intramuscular antiemetics.

HPI While on a family vacation to Florida, she was given vanilla ice cream that was being sold on the street (dairy and meat products may harbor staphylococcal enterotoxins that produce food poisoning).

PE VS: tachycardia; mild fever; hypotension. PE. low urinary volume; **eyes sunken; poor skin turgor** with dryness of skin and mucous membranes; **lethargy and proximal muscle weakness** (due to hypokalemia).

Labs CBC: increased hematocrit (due to hemoconcentration); increased BUN. Lytes: **hypokalemia**; hypochloremia. UA: proteinuria; **high specific gravity**. ABGs: **metabolic alkalosis**. ECG: ST-segment and T-wave depression; U waves (hypokalemia).

Treatment Fluid and electrolyte replacement.

Discussion Dehydration may be isotonic, hypotonic, or hypertonic. When caused by protracted vomiting, it leads to metabolic alkalosis due to a decrease in hydrogen ion concentration with a compensatory rise in P_{CO_2} (due to diminished alveolar ventilation). The contraction of volume stimulates the proximal renal tubular cells to reabsorb bicarbonate in spite of alkalosis.

ID/CC A 56-year-old man who is a known non-insulin-dependent **diabetic** (NIDDM **type II**, maturity onset) and who has been receiving an oral hypoglycemic agent is brought to the emergency room in a **stuporous state**.

HPI For approximately 2 weeks, he had been treated for a **URI** with oral antibiotics and bronchodilators.

PE VS: **tachycardia**; hypotension. PE: severe **dehydration** with dry oral mucosa and low urinary volume; patient **semiconscious** and **confused**; pupils react bilaterally and normally to light; evidence of proliferative diabetic retinopathy on funduscopic exam; no focal neurologic deficit found.

Labs CBC: mild leukocytosis (12,600). **Markedly increased blood glucose** (900 mg/dL); **increased serum and urinary osmolality** (> 350 mOsm/kg). Lytes: hypernatremia; mild hypokalemia. **Normal anion gap**. ABGs: normal serum bicarbonate (no acidosis). Elevated BUN and serum creatinine (suggestive of prerenal azotemia). UA: **glycosuria with no ketonuria**.

Treatment Hypotonic (one-half normal) saline. Insulin infusion (e.g., lower dose than in ketoacidosis). Potassium and phosphate supplement as needed.

Discussion Hyperosmolar, hyperglycemic nonketotic coma occurs mainly in older NIDDM patients and is usually associated with an episode of physical or mental stress (check for silent MI); it is not associated with ketosis or ketoacidosis. Volume depletion is severe (average fluid deficit 25% of total body water), and the mortality rate is high.

ID/CC A 44-year-old male is admitted to the orthopedic department because he sustained a **femoral neck fracture when he fell from a small stool**; the type and magnitude of the fracture are not compatible with the patient's age and impact.

HPI The patient recently emigrated from Somalia and states that he has been suffering from increasing **leg weakness** and persistent **lower back pain**.

PE VS: normal. PE: complete right femoral neck fracture; on palpation, **tenderness of lumbar vertebrae** and pelvic rim.

Labs Mild anemia (Hb 10 g/dL). Lytes: normal. **Increased alkaline phosphatase; decreased levels of 25-OH-D_3; hypocalcemia; hypophosphatemia**; increased PTH.

Imaging XR, hip: surgical neck femoral fracture. XR, lumbar spine: **collapse of lumbar vertebrae; generalized osteopenia; pseudofractures** (appearance of nondisplaced fractures representing local bone resorption).

Micro Pathology Excess osteoid but poor mineralization.

Treatment Vitamin D, calcium (and sometimes phosphate) supplements; surgical treatment of fracture, physiotherapy.

Discussion A poor diet in vitamin D and calcium, **lack of sunlight exposure, intestinal malabsorption, renal insufficiency**, or target organ resistance may lead to osteomalacia in the adult (or rickets in children), with defective calcification of osteoid.

25 OSTEOMALACIA

ID/CC A 40-year-old male visits his internist for an evaluation of sudden (PAROXYSMAL) **attacks of headache, perspiration, and anxiety**; attacks are precipitated by exercise, emotional stress, postural changes, and, at times, urination.

HPI **Very high blood pressure** has been recorded at the time of previous paroxysms. The patient has a good appetite but looks cachectic; blood pressure recorded between paroxysms is normal. The patient has no history suggestive of renal disease.

PE VS: **hypertension** (BP 180/120). PE: hypertensive retinopathy changes on funduscopic exam.

Labs **Elevated blood sugar** (due to increased catecholamines). Lytes: normal. **Increased** 24-hour urinary free **catecholamines** and **vanillylmandelic acid (VMA)** levels.

Imaging CT/MR: 5-cm left **adrenal mass**; very high signal on T2-weighted MR. Nuc: MIBG localizes to tumor and metastases.

Gross Pathology Encapsulated, **dusky-colored**, round tumor mass with compressed adrenal gland remnants at periphery and foci of necrosis and hemorrhage.

Micro Pathology Nests of pleomorphic large cells with basophilic cytoplasm and **chrome-staining granules** in vascular stroma; argentaffin stains positive; membrane-bound secretory granules on electron microscopy.

Treatment Treat hypertensive crises with pharmacologic alpha and beta blockade (pretreat with alpha blockers prior to beta blockers); resection of tumor.

Discussion Pheochromocytoma is the most common **tumor of the adrenal medulla** in adults; its symptoms are produced by **increased production of catecholamines**. Of these tumors, 10% are extra-adrenal, 10% bilateral, 10% malignant, and 10% familial; 10% occur in children, and 10% calcify. May be associated with multiple endocrine neoplasia (MEN) IIA or IIB syndromes.

Atlas Links UCVI **PM-BC-026, PG-BC-026A, PG-BC-026B**

ID/CC A **9-year-old** female is brought to her pediatrician because of **breast enlargement**.

HPI Her mother also reports **cyclical vaginal bleeding** and the appearance of **pubic and axillary hair** since the age of 4; an older cousin developed similar signs and symptoms.

PE Fully developed breasts; axillary and pubic hair present; normal mental development; height and weight greater than average for her age; no focal neurologic signs.

Labs **Increased plasma FSH, LH**, and estradiol; pubertal pattern of increased gonadotropins after infusion of GnRH.

Imaging XR: **advanced bone age**. US: ovary enlarged to pubertal size with cyst formation. CT/MR: no pituitary lesion.

Gross Pathology **Ovarian cyst** formation (luteal); in idiopathic variety, no structural abnormality found.

Treatment GnRH agonists; psychiatric support; continuous search for possible cause.

Discussion The most common cause of precocious puberty is idiopathic or constitutional; less common causes include hypothalamic-pituitary tumors (pinealomas, hamartomas, gliomas) or lesions causing gonadotropin-dependent precocious puberty.

ID/CC A 5-year-old **boy** is brought to the pediatrician because of intermittent **numbness and leg cramps**.

HPI His father is also concerned about the fact that his child is **shorter** than his classmates.

PE **Full, round face**; short neck; flat nasal bridge; right convergence squint and left **cataract; delayed dentition**; positive Chvostek's and Trousseau's signs.

Labs CBC: normal. Lytes: **hypocalcemia** (< 8.8 mg/dL); **hyperphosphatemia** (> 5 mg/dL). **Increased** plasma **PTH; no increase** in renal **cAMP** and phosphate clearance **with PTH infusion**.

Imaging XR: **fourth and fifth metacarpals** are **short; premature physeal closure**; thickening of cortices with demineralization.

Treatment Calcitriol and calcium supplementation.

Discussion Also called Seabright-Bantam syndrome, pseudohypoparathyroidism is an **X-linked dominant** disorder in which there is **resistance to PTH action on the renal tubule** and bone with resulting hypocalcemia. Two types exist according to the response of cAMP to PTH. In type I (as in this case), patients fail to exhibit a phosphaturic response or increased cAMP after administration of PTH. Type II is associated with Albright's hereditary osteodystrophy.

ID/CC A **15-month-old Eskimo** boy is brought to the pediatric clinic by his parents because of **delayed dentition, poor growth and development**, frequent crying, and weakness.

HPI The infant's **diet** is **deficient in** eggs and **dairy products**, and he spends most of his time indoors (i.e., he has **no exposure to sunlight**).

PE Irritability; poor muscular development and muscle tone; abdominal distention; hypotonia of all muscles; anterior fontanelle open; **softening of occipital and parietal bones with elastic recoil** (CRANIOTABES); frontal bossing; enlargement **of costochondral junctions** (RACHITIC ROSARY); **bowing of legs; lineal chest depression along diaphragm** (HARRISON'S GROOVE).

Labs **Serum calcium normal or slightly low; decreased serum phosphorus**; increased alkaline phosphatase; low $1,25(OH)_2$-vitamin D level.

Imaging XR: **widening of growth plates**; osteopenia of cranial and long bones; irregularity and cupping of distal ends of long bones; pseudofractures in metaphysis (LOOSER'S LINES).

Gross Pathology Excess amount of **uncalcified bone** at junction of cartilage; bone stretched and pulled out of shape by gravity; increased osteoid seams; osteopenia; frontal bossing of skull; **pigeon breast deformity**.

Micro Pathology Defective mineralization of osteoid in epiphysis and diaphysis.

Treatment Increase calcium and vitamin D in diet.

Discussion Rickets is a disease of infancy and childhood involving **defective mineralization of osteoid** in bone skeleton and the neuromuscular system because of **low vitamin D** or calcium in the diet; it can also be due to low sunlight exposure (vitamin D conversion in skin) and chronic renal failure (BUN and phosphorus levels are high).

Atlas Link UCV2 MC-308

ID/CC A 61-year-old male smoker presents with headache, weakness, **fatigue**, and **decreased urinary output** (OLIGURIA).

HPI He was recently diagnosed with **oat cell carcinoma of the lung**.

PE Cardiac sounds normal; no murmurs; no arrhythmias; no pitting edema; no hepatomegaly; no jugular plethora (no evidence of cardiac disease); no asterixis, jaundice, spider nevi, or parotid enlargement (no evidence of hepatic disease).

Labs **Decreased serum sodium** (HYPONATREMIA); **decreased serum osmolality** (< 280 mOsm/kg); normal or low BUN and serum creatinine; no proteinuria (no renal disease); adrenal and thyroid function tests normal. UA: **urine osmolality markedly increased** (versus psychogenic polydipsia where osmolality is decreased); hypernatriuria (urinary Na > 20 mEq/L). **Diminished blood uric acid level** (HYPOURICEMIA).

Treatment **Water restriction** plus a high-salt diet. **Demeclocycline**.

Discussion **Syndrome of inappropriate** (increased) secretion of **antidiuretic hormone** (SIADH) occurs with either increased hypothalamic secretion (e.g., CNS disease, postoperative states) or ectopic secretion (e.g., tumors such as oat cell carcinoma of the lung). There may also be increased sensitivity to the effect of ADH (as occurs with chlorpropamide, fluoxetine, and carbamazepine).

ID/CC A 37-year-old man presents with **dark, blackened spots in his sclera and ear cartilage** as well as **back pain** and restriction of motion with **pain and swelling of both knee joints**.

HPI Directed questioning reveals that his **urine turns black** if left standing.

PE **Increased pigmentation** in ears, conjunctiva, nasal bridge, neck, and anterior thorax (OCHRONOSIS); arthritis of spine, both knee joints, and fingers.

Labs UA: **elevated urine homogentisic acid** (causes urine to darken upon standing or with addition of alkaline substances).

Imaging XR: calcification in cartilage of knee menisci and wrist; premature arthritic changes.

Treatment Symptomatic treatment of arthritis.

Discussion Also called **ochronosis**, alkaptonuria is an autosomal-recessive disorder of tyrosine metabolism characterized by the **absence of homogentisate oxidase** due to a defective gene on chromosome 3 with accumulation of homogentisic acid in cartilage, giving a dark blue discoloration to the tissues and leading to degenerative joint disease.

ID/CC An **11-year-old white** female is brought to the ER by her parents because of fever, **difficulty breathing, and a productive cough with greenish sputum**.

HPI Her parents are of northern European descent. She has a history of **recurrent UTIs and foul-smelling diarrhea** since infancy.

PE VS: tachycardia; tachypnea (RR 45). PE: mild cyanosis; malnourishment; **nasal polyps**; hyperresonance to lung percussion with **barrel-shaped chest**; scattered rales; hepatomegaly.

Labs **High sodium and chloride** concentrations in **sweat test**; *Pseudomonas aeruginosa, Haemophilus influenzae* and *Staphylococcus aureus* in sputum culture. PFTs: increased RV/TLC ratio. Increased **fecal fat**. ABGs: hypoxemia; hypercapnia.

Imaging CXR: few dilated bronchi (BRONCHIECTASIS) filled with mucus; emphysema; XR, paranasal sinuses: opacification of sinuses.

Gross Pathology Atrophic pancreas with almost complete disruption of acini and replacement of exocrine pancreas with fibrous tissue and fat; mucous plugging of canaliculi.

Micro Pathology Inflammatory change.

Treatment Antibiotics, low-fat diet, and supportive measures; recombinant human DNase (cleaves extracellular DNA from neutrophils in sputum); inhaled amiloride, nasal corticosteroids, systemic corticosteroids, decongestants; consider lung transplant.

Discussion Cystic fibrosis is an **autosomal-recessive** disease that is due to a mutation in the long arm of **chromosome 7** (band q31) in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. If CFTR function is deficient, **chloride** and water transport is slowed and secretions are inspissated.

ID/CC A 15-year-old female is brought to the emergency room from school following the sudden development of **severe, intermittent right-flank pain** together with nausea, vomiting, and **blood in her urine** (a picture typical of renoureteral stone).

HPI Her medical and family history is unremarkable.

PE VS: tachycardia; normal BP; slight fever. PE: short stature (due to lysine deficiency); in acute distress; **constantly switches positions in bed** (due to renal colic); abdominal tenderness; no peritoneal irritation; costovertebral angle tenderness.

Labs **Increased urinary excretion of cysteine, ornithine, arginine, and lysine** on urine amino acid chromatography (due to intestinal and renal **defect in reabsorption**). UA: hematuria; hexagonal crystals (CYSTEINE) upon cooling of acidified urine sediment.

Imaging KUB/IVP/CT urography: radiopaque stone in area of right kidney.

Treatment **Low-methionine diet**; increase fluid intake; alkalinize urine; penicillamine.

Discussion Cystinuria is an **autosomal-recessive** disorder of dibasic amino acid metabolism (due to impaired renal tubular reabsorption); it leads to increased cysteine urinary excretion and **kidney stone formation**.

ID/CC A 9-year-old boy is brought to the emergency room with pain, inability to move his left shoulder, and flattening of the normal rounded shoulder contour (SHOULDER DISLOCATION) that occurred when he tried to hit a ball with his bat at a local baseball field.

HPI He has **dislocated his left shoulder nine times before and his right shoulder three times before**. He also has a history of **easy bruising**.

PE **Hyperelastic skin; "cigarette paper"** scars in areas of trauma; **hyperextensibility of joints**; left shoulder dislocated; multiple bruises over skin.

Labs Clotting profile normal.

Imaging XR: left shoulder dislocated.

Micro Pathology Collagen fibrils of dermis of skin larger than normal and irregular in outline on electron microscopy.

Treatment Supportive.

Discussion Ehlers–Danlos syndrome is also known as cutis hyperelastica. **Faulty collagen synthesis** produces 10 types of Ehlers-Danlos syndrome, some of which are autosomal recessive (type VI), others autosomal dominant (type IV), and others associated with X-linked recessive transmission (type IX). Prone to aneurysm and dissection in the great vessels.

ID/CC A 17-year-old **male** presents with episodes of **painful, burning paresthesias along his palms and soles** along with markedly **diminished vision** in his right eye.

HPI His maternal **uncle died of chronic renal failure** at the age of 40.

PE Clusters of **purplish-red, hyperkeratotic lesions** on skin around umbilicus, buttocks, and scrotum (ANGIOKERATOMAS); **right corneal leukomatous opacity**; neurologic exam normal except for painful paresthesias along arms and soles; pitting edema in lower extremities.

Labs **Elevated serum creatinine and BUN** (patients usually die of renal failure). UA: proteinuria; broad casts. PBS: leukocytes reveal deficiency of α-galactosidase.

Micro Pathology Lipid deposition in epithelial and endothelial cells of glomeruli and tubules (FOAM CELLS) on renal biopsy; **lysosomal accumulation of glycosphingolipid (ceramide trihexoside)** in the form of "myelin bodies" on electron microscopy of skin, heart, kidneys, and CNS.

Treatment Treat pain crises symptomatically; renal failure may require renal transplantation.

Discussion Fabry's disease, a sphingolipidosis, is a **rare X-linked recessive disorder** of glycosphingolipid metabolism caused by a **deficiency of α-galactosidase A** and by the consequent accumulation of ceramide trihexoside.

ID/CC A **28-year-old** white male complains of severe **retrosternal pain** radiating to his left arm and jaw.

HPI He has not had a physical exam in a long time. He adds that his **father died at a young age of a myocardial infarction**.

PE Anguished, dyspneic, diaphoretic male with hand clutched to chest (indirect sign of myocardial pain); soft, **elevated plaques on eyelids** (XANTHELASMAS); arcus senilis; painful **xanthomas of Achilles tendons** and patellae.

Labs Elevated CK-MB; elevated troponin T and I. ECG: MI. Extremely **high levels of LDL**.

Imaging Angio: coronary artery disease.

Gross Pathology **Premature atherosclerosis** in large arteries.

Micro Pathology Foam cells with lipid characteristic of atherosclerotic plaques.

Treatment Diet, exercise and cholesterol-lowering drugs (althought HMG-CoA reductase inhibitors are ineffective in homozygous FH patients due to complete lack of LDL receptors). Consider portocaval anastamosis or liver transplantation.

Discussion Familial hypercholesterolemia is also called type II hyperlipoproteinemia; it is an **autosomal-dominant defect in LDL receptor** with a gene frequency of 1:500. Homozygotes may have an LDL count eight times that of normal.

ID/CC A 16-year-old white female complains of sudden **midepigastric pain and nausea** after eating french fries.

HPI Her history reveals that **she and a sibling** have had similar episodes of abdominal pain in the past. Careful questioning discloses that she experiences **flushing** every time she **drinks alcohol**.

PE **Nonpainful, yellowish papules on face, scalp, elbows, knees, and buttocks** (ERUPTIVE XANTHOMATOSIS); lipemia retinalis on funduscopic exam; hepatosplenomegaly; abdominal muscle guarding and palpable tenderness.

Labs **Elevated serum amylase** and lipase; **very high triglycerides**; moderate elevation of serum cholesterol and phospholipids.

Micro Pathology Lipid-laden foam cells.

Treatment **Low-fat diet**; avoidance of alcohol; exercise; **fibric acid** and **niacin** in selected cases.

Discussion Familial hypertriglyceridemia is an autosomal-dominant disorder. Abdominal pain stems from **recurrent acute pancreatitis**.

ID/CC An 8-year-old boy is referred to the pediatric clinic for evaluation of **anemia and multiple developmental anomalies**.

HPI His parents report that he **bleeds easily**.

PE Pale and **mentally retarded;** small head (MICROCEPHALIA); low height and weight for age; hyperpigmentation of torso and thighs with café-au-lait spots; **decrease in size of penis**; decrease in size of eyes (MICROPHTHALMIA); **absence of both thumbs**.

Labs CBC: decreased WBCs (LEUKOPENIA), platelets (THROMBOCYTOPENIA), and RBCs (ANEMIA) (PANCYTOPENIA). Increased levels of HbF. Bone marrow chromosomes show diverse alterations (breaks, constrictions, and translocations).

Imaging XR: **bilateral absence of radii**. IVP/CT: **hypoplastic kidneys**.

Treatment **Marrow transplantation**, androgens, corticosteroids.

Discussion Fanconi's anemia is a congenital, autosomal-recessive disorder characterized by constitutional **aplastic anemia due to defective DNA repair**, presumably as a result of viral infection causing hypersensitivity to DNA cross linking agents. It is associated with multiple musculoskeletal and visceral anomalies, proximal renal tubular acidosis, and a higher incidence of leukemia.

ID/CC A 10-year-old **male** is referred to a genetic evaluation clinic by his pediatrician because of **mental retardation**.

HPI His mother did not take any drugs during her pregnancy, did not suffer from any major illnesses, was seen by an obstetrician periodically, and was monitored intrapartum.

PE Patient well developed physically with grade I mental retardation; no evidence of cardiovascular, genitourinary, or hepatic disease.

Labs Patient has been subjected to basic and endocrinologic lab profiles, all of which have yielded normal results. Karyotype: **"fragile gap" at end of the long arm on X chromosome**.

Treatment Supportive.

Discussion The **second most common cause of mental retardation** after Down's syndrome **in males** (women are carriers), fragile X syndrome should be suspected in any male patient whose mental retardation cannot be explained by other disease processes. It is often associated with macro-orchidism, large ears and jaw, a high-pitched voice, and connective tissue abnormalities and demonstrates genetic **anticipation** (worsening of the disorder in successive generations) owing to the expansion of **trinucleotide repeats**.

ID/CC A 2-month-old white male is taken to his family doctor because of lethargy, **feeding difficulties**, and yellowish skin (JAUNDICE).

HPI The child has been **vomiting** on and off since birth.

PE Irritability; **jaundice; cataracts; hepatomegaly**; growth and development in fifth percentile; edema.

Labs UA: **galactosuria**; aminoaciduria; albuminuria. **Hypoglycemia**; increased ALT and AST; elevated direct and indirect bilirubin; prolonged PT; erythrocytes have **markedly reduced galactose-1-phosphate uridyl transferase activity** and elevated galactose-1-phosphate.

Imaging US/CT: enlarged fatty liver.

Gross Pathology Early hepatomegaly and fatty change with giant cells leading to cirrhosis; gliosis of cerebral cortex, basal ganglia, and dentate nucleus of cerebellum; cataracts.

Micro Pathology Liver, eyes, and brain most severely affected by **deposits of galactose-1-phosphate and galactitol**; kidney, heart, and spleen also involved.

Treatment Limit intake of milk and other galactose- and lactose-containing foods.

Discussion Galactosemia is an **autosomal-recessive** lack of enzyme galactose-1-phosphate uridyl transferase; the presence of **cataracts** differentiates it from other causes of jaundice in the newborn.

ID/CC An 11-year-old **Jewish** male presents with weakness, **epistaxis**, and a left-sided abdominal mass.

HPI He has a history of **bruising easily** and sustaining fractures following minimal trauma.

PE Mental retardation; multiple **purpuric patches**; skin pigmentation; mild hepatomegaly; **massive splenomegaly**; marked pallor; no lymphadenopathy or icterus.

Labs CBC: normocytic, normochromic anemia; thrombocytopenia; low normal WBC count. LFTs normal; bone marrow biopsy characteristic; isolated WBCs demonstrate reduced β-glucosidase activity; elevated serum acid phosphatase.

Imaging XR, spine: biconcave (H-shaped) vertebral bodies. XR, knee: Erlenmeyer flask deformity of distal femur; osteopenia. CT/US: enlarged spleen with multiple nodules.

Micro Pathology Bone marrow biopsy shows myelophthisis; replaced by Gaucher's cells 20 to 100 μm in size; characteristic **"wrinkled paper" cytoplasm** due to intracytoplasmic glucocerebroside deposition; PAS stain positive.

Treatment Symptomatic, enzyme replacement with purified placental or recombinant acid β-glucosidase, splenectomy.

Discussion Gaucher's disease is an **autosomal-recessive deficiency of glucocerebrosidase** with accumulation of glucosyl-acylsphingosine in bone marrow, spleen, and liver.

ID/CC A 5-month-old male is brought to the doctor because of frequent nausea, **vomiting**, night sweats, tremors, and **lethargy**.

HPI When the patient was exclusively breast fed (i.e., during the initial four months after birth), he was well; the **onset of symptoms coincided with** the occasional **addition of fruit juices** to the baby's diet.

PE Lazy-looking, slightly **jaundiced** baby; mild growth retardation; **hepatomegaly**.

Labs **Marked hypoglycemia; fructosemia**. UA: fructosuria; urine test for reducing sugar positive; dipstick for glucose negative; fructose tolerance test not advisable (may cause severe hypoglycemia).

Micro Pathology Liver biopsy reveals **low aldolase B activity** (confirmatory test).

Treatment Return to breast feeding as sole food; avoid fruit juices, fruits, and sweets.

Discussion Any food containing fructose or sucrose (fructose + glucose) may cause symptoms in patients with fructose intolerance, an **autosomal-recessive deficiency of aldolase B** (enzyme used to split fructose-1-phosphate into glyceraldehyde and dihydroxyacetone phosphate), resulting in accumulation of fructose-1-phosphate within liver cells. This inhibits glycolysis, gluconeogenesis and glycogenolysis. If long-standing, it may lead to cirrhosis and kidney failure. Differential diagnosis is galactosemia.

ID/CC A 9-year-old male is referred to the pediatric clinic because of progressive **mental retardation, diminished visual acuity**, and **bone deformity** in the thorax.

HPI The boy was born in Malaysia and never had any prenatal screening.

PE Tall and thin with elongated limbs (Marfanoid appearance); fine hair; **abnormally long fingers** (ARACHNODACTYLY); **pectus excavatum; lenticular dislocation** (ECTOPIA LENTIS); malar flush; high-arched palate; genu valgum; cardiovascular exam normal.

Labs **Increased serum methionine; increased urinary homocystine**.

Imaging XR: generalized **osteoporosis**.

Micro Pathology Brain gliosis; fatty liver; arterial intimal thickening without lipid deposition; degeneration of zonular ligaments of lens.

Treatment High-dose pyridoxine (cofactor for cystathionine synthetase; effective only in some forms of disease); methionine-restricted diet; cysteine and folate supplements.

Discussion Homocystinuria is an autosomal-recessive **disturbance of methionine metabolism** caused by a **deficiency of cystathionine synthetase** in liver cells with accumulation of homocystine. Major arterial and venous **thromboses** are a constant threat because of vessel wall changes and increased platelet adhesiveness due to the toxicity of homocystine to the vascular endothelium.

ID/CC An 11-year-old **male** is sent to the audiometry clinic by his pediatrician for an evaluation of **deafness**.

HPI His teachers note that he has not been paying attention at school and add that his academic performance has suffered as a result.

PE **Coarse facies and large tongue**; short stature; **corneas clear** (vs. Hurler's disease); dimpled skin in back of arms and thighs; no gibbus (acute-angle kyphosis) present (vs. Hurler's disease); nonpainful nodular lesions on left scapular area; stiffening of joints; **deafness**.

Labs UA: **increased urinary heparan sulfate and dermatan sulfate**.

Imaging Metacarpal thickening with tapering at ends.

Micro Pathology Metachromatic granules (REILLY BODIES) in bone marrow leukocytes; amniotic fluid culture during pregnancy may detect abnormality.

Treatment Supportive.

Discussion Hunter's disease, or type II mucopolysaccharidosis, is an **X-linked recessive** disease and is less severe than Hurler's syndrome (type I). Hunter's disease can be differentiated from Hurler's syndrome in that it features no corneal opacities and either no mental retardation or less severe retardation than that found in Hurler's; however, deafness is present. Caused by a **deficiency of iduronosulfate sulfatase**.

ID/CC A **2-year-old** white male is brought to the ophthalmologist for an evaluation of **eye clouding**.

HPI The child has a physical and **mental disability** very similar to that of his older **brother**.

PE **Short stature**; very **coarse, elongated facial features** (GARGOYLISM); **bilateral corneal opacities**; retinal degeneration and papilledema; saddle nose deformity; systolic murmur in second right intercostal space; **enlarged heart, liver, and spleen; kyphoscoliosis** with lumbar gibbus (acute angle kyphosis); stiff, immobile, and contracted large joints.

Labs Dermatan sulfate and heparan sulfate in urine; **α-L-iduronidase deficiency in WBCs**.

Imaging XR: dolichocephaly; increased diameter of sella turcica; deformation of vertebral bodies with scoliosis and kyphosis.

Gross Pathology Increased mucopolysaccharide (MPS) deposition in heart, eye, connective tissue, CNS, cartilage, heart, and bone.

Micro Pathology Enlarged heart; thickened endocardium; MPS infiltration in intima of coronary arteries; meningeal and neuronal deposits producing hydrocephalus; metachromatic granules in lymphocytes and histiocytes.

Treatment Supportive ophthalmologic, skeletal, and cardiovascular treatment. Consider bone marrow transplant.

Discussion Also known as gargoylism, Hurler's syndrome is the most common mucopolysaccharidosis (TYPE I). It is **autosomal recessive** and is caused by a **deficiency of α-iduronidase**. Death usually occurs by 6 to 10 years of age, usually secondary to cardiovascular complications.

Atlas Link UCM2 Z-BC-058

ID/CC A 25-year-old male visits a fertility clinic as part of an **evaluation of infertility** that he is undergoing with his wife.

HPI His medical history discloses frequent **sinus infections** (SINUSITIS) and chronic cough with sputum formation (BRONCHIECTASIS).

PE VS: normal. PE: apical impulse felt on fifth **right intercostal space**; all auscultatory foci reversed (DEXTROCARDIA); liver on left side and spleen on right (SITUS INVERSUS).

Labs CBC/Lytes: normal. Semen analysis shows **immotile spermatozoa**.

Imaging CXR: dextrocardia. KUB: situs inversus.

Discussion Kartagener's syndrome (also called immotile cilia syndrome) is an **autosomal-recessive** disorder characterized by **lack of dynein** (ATPASE) arms from the microtubules of axonemes in the cilia of the sinuses and bronchi, rendering them immotile. Sperm are also immotile (due toflagellar lack of dynein). The lack of mucus-clearing action causes frequent infections.

ID/CC A 19-year-old male visits his family physician because he is **embarrassed at having large breasts**.

HPI He also complains of frequent headaches and **impotence**.

PE **Tall, eunuchoid** body habitus; mild mental retardation; testes small and firm; breast enlargement (GYNECOMASTIA); female distribution of hair.

Labs UA: increased urinary FSH; decreased 17-ketosteroid.

Imaging XR: delayed physeal closure; short fourth metacarpal.

Gross Pathology Testicular atrophy.

Micro Pathology **Testicular fibrosis and hyalinization; lack of spermatogenesis**; Leydig's interstitial cells scarce and have foamy cytoplasmic change; **female sex chromatin bodies** (BARR BODIES) in cells.

Treatment Testosterone.

Discussion Also known as **testicular dysgenesis**, Klinefelter's syndrome is the most common cause of male hypogonadism. Alteration is due to the presence of three sex chromosomes (karyotype 47,XXY).

ID/CC A **5-month-old** child is brought to the pediatrician because of **growth retardation** and **difficulty feeding**.

HPI His parents note that the child has been **irritable** and "stiff" (SPASTICITY).

PE VS: normal. PE: patient **underdeveloped** for age; **reflexes hyperactive**; paravertebral muscles and hamstrings tense (RIGIDITY); maternal milk **sucking reflex weak** and punctuated by periods of regurgitation.

Labs Basic lab work within normal limits. LP: increased protein in CSF.

Gross Pathology Axonal and white-matter cerebral, cerebellar, and basal ganglia **demyelination**.

Micro Pathology Basophilic perivascular multinucleated globoid cells (MACROPHAGES) with cytoplasmic inclusion bodies consisting of cerebroside.

Treatment Poor prognosis, with death usually occurring rapidly.

Discussion Also called **globoid leukodystrophy**, Krabbe's disease is an **autosomal-recessive**, familial genetic disorder characterized by a **deficiency of** galactosylceramide **β-galactosidase**.

ID/CC A 2-year-old **male** is brought to the pediatrician by his mother because of repeated, **self-mutilating biting of his fingers and lips**; the patient's mother has also noticed abundant, **orange-colored "sand"** (uric acid crystals) **in the child's diapers.**

HPI The mother reports that some months ago the child's urine was red, but she took no action at the time.

PE Poor head control, difficulty walking, and difficulty maintaining an erect, seated position; **choreoathetoid movements**, spasticity, and **hyperreflexia** on neurologic exam.

Labs **Hyperuricemia** (>10 mg/dL). UA: crystalluria; microscopic hematuria (due to renal calculi).

Imaging XR: irregular amputation of several fingers.

Treatment Allopurinol. Removal of primary teeth.

Discussion Lesch–Nyhan syndrome is an **X-linked recessive** metabolic disease resulting from a deficiency of an enzyme of purine metabolism, **HGPRT**. If left untreated, patients develop full-blown **gouty arthritis** and urate nephropathy as well as subcutaneous tophaceous deposits. Compulsive, uncontrollable destructive behavior is typical of the disorder. Prenatal diagnosis is possible.

ID/CC A **5-day-old** male presents with **seizures**, difficulty feeding, and vomiting; his mother reports a **peculiar, maple-sugar-like odor on his diapers**.

HPI His mother had an unremarkable full-term vaginal delivery.

PE VS: no fever. PE: full-term neonate with irregular respirations, **muscular rigidity** (SPASTICITY), and obtunded sensorium; fundus normal; peculiar odor in urine and sweat; when child's head support (hand) is suddenly withdrawn in supine position, patient fails to react with normal extension-abduction followed by flexion and adduction of arms (ABSENCE OF MORO REFLEX).

Labs **Hypoglycemia**. ABGs: metabolic acidosis. **Marked elevation in blood and urine levels of the branched chain amino acids** leucine, isoleucine, alloisoleucine, and valine as well as decreased levels of alanine, threonine, and serine.

Gross Pathology Edema of brain with gliosis and white matter **demyelination**.

Treatment **Restricting intake of branched-chain amino acids from diet**; dialysis; thiamine supplementation.

Discussion Maple syrup urine disease is an **autosomal-recessive** branched-chain α-ketoaciduria that results from defective oxidative decarboxylation of the branched-chain α-ketoacids. This decarboxylation is usually accomplished by a complex enzyme system **(α-ketodehydrogenase)** using thiamine as a coenzyme. A **deficiency** of this enzyme system causes urine to have the characteristic maple syrup odor and causes CNS symptoms in the first few weeks of life.

ID/CC A 3-year-old white male is brought to the pediatrician because of **increasing difficulty walking** due to **spasticity**.

HPI The child had been developing normally up to now, and his medical history is unremarkable.

PE **Difficulty climbing stairs; ataxia; wide-based gait**; extensor plantar response and hyperreflexia.

Labs LP: increased protein in CSF (vs. cerebral palsy). Decreased peripheral nerve conduction velocity.

Imaging MR, brain: demyelination.

Gross Pathology Generalized **demyelination** (due to deficiency of arylsulfatase A interfering with normal metabolism of myelin lipids) with gliosis.

Micro Pathology Toluidine blue staining shows brownish (METACHROMATIC) granules in oligodendrocytes and neurons of globus pallidus, thalamus, and dentate nucleus.

Treatment Poor prognosis; patients become invalids within a few years and die before puberty.

Discussion Metachromatic leukodystrophy is an **autosomal-recessive** disorder of sphingolipid metabolism that is due to a **deficiency in the enzyme arylsulfatase A** with accumulation of sulfatides in the central and peripheral nervous system as well as in the kidneys. Intrauterine diagnosis is possible.

ID/CC An 11-month-old **Jewish** male of **Ashkenazi** descent presents with globally delayed development and **diminished visual acuity**.

HPI His parents feel that the baby is not acquiring new skills and that existing ones are regressing. They also feel that their child cannot see or hear properly.

PE **Lymphadenopathy; hepatosplenomegaly; cherry-red spot on macula** on funduscopy; malnourished infant with protuberant abdomen; global developmental delay; hypoacusis.

Labs CBC: mild normochromic, normocytic anemia.

Micro Pathology Bone marrow biopsy reveals sphingomyelinase deficiency in cultured skin fibroblasts; characteristic "foam cells" containing sphingomyelin and cholesterol.

Treatment No treatment available. Carries a poor prognosis, with death occurring within a few years of birth.

Discussion Niemann–Pick disease is an **autosomal-recessive deficiency of sphingomyelinase with accumulation of sphingomyelin in the lysosomes** of histiocytes in the brain, bone marrow, spleen, and liver.

ID/CC A 2-year-old female is referred to a pediatric clinic for evaluation of **lethargy, weakness, and persistent anemia** that has been unresponsive to treatment with iron, folic acid, and vitamins C and B_{12}.

HPI She is the third-born child of a healthy white couple; her mother had an uneventful pregnancy and a eutopic delivery. Both brothers are healthy.

PE **Low weight and height** for age; **marked pallor**; flaccidity and lethargy; **sleepiness**. No focal neurologic signs; lungs clear; heart sound with slight aortic systolic ejection murmur (due to anemia); abdomen soft; no masses; no hepatomegaly; spleen barely palpable; no lymphadenopathy.

Labs CBC: **megaloblastic anemia**; elevated mean corpuscular volume. UA: increased orotic acid excretion with formation of **orotic acid crystals**.

Treatment Administration of **uridine** and cytidine. Steroids.

Discussion Orotic aciduria is an **autosomal-recessive disorder of pyrimidine synthesis**; it is caused by a deficiency of the enzyme system orotidylic pyrophosphorylase-orotidylic decarboxylase with resultant megaloblastic anemia due to impaired synthesis of nucleic acids necessary for hematopoiesis.

ID/CC A 3-year-old male presents with progressive **mental retardation, vomiting**, and **hyperactivity** with purposeless movements.

HPI The child developed normally for the first 2 to 3 months. He is fairer than his siblings and, unlike them, has blue eyes. He was born outside the United States and did not undergo any screening for congenital disorders.

PE Child is **blond with blue eyes, perspires** heavily, is mentally retarded, and has **peculiar "mousy" odor; hypertonia** with hyperactive deep tendon reflexes on neurologic exam.

Labs Guthrie test (bacterial inhibition assay method) positive (due to **increased blood phenylalanine levels**); increased urinary phenylpyruvic and ortho-hydroxyphenylacetic acid; **normal concentration of tetrahydrobiopterin**.

Imaging XR: delayed bone age.

Treatment Diet formulas low in phenylalanine. Avoid aspartame. **Tyrosine supplementation**.

Discussion PKU is an **autosomal-recessive disorder** caused by a **deficiency of the enzyme phenylalanine hydroxylase**. A neonatal screening program for the detection of PKU is in effect throughout the United States.

ID/CC A 7-year-old female presents with anxiety, **dizziness, sweating**, and nausea **following** brief episodes of **exercise**.

HPI These symptoms are **relieved by eating** and do not occur if the patient is frequently fed small meals.

PE Physical exam unremarkable.

Labs **Hypoglycemia** following brief fasting; alanine fails to increase blood sugar; fructose or glycerol administration restores blood glucose to normal.

Micro Pathology Liver biopsy for enzyme assays reveals deficiency of phosphoenolpyruvate carboxykinase, an enzyme of gluconeogenesis; **no excess glycogen storage** revealed.

Treatment Frequent small meals to prevent episodes of hypoglycemia.

Discussion Phosphoenolpyruvate carboxykinase (PEPCK) deficiency prevents pyruvate from being converted to phosphoenolpyruvate. This deficiency interferes with gluconeogenesis from 3-carbon precursors (e.g., alanine) that enter the gluconeogenetic pathway at or below the pyruvate level.

ID/CC A **2-month-old** child is brought to the pediatrician because of **failure to gain weight**, increasing **weakness**, insufficient strength to breast feed, and **lethargy**.

HPI He is the second-born son of a healthy white couple; his mother's pregnancy and delivery were uneventful.

PE Mild cyanosis; shallow respirations; increase in size of tongue (MACROGLOSSIA); moderate hepatomegaly; **significant generalized muscular flaccidity**.

Labs CBC: normal. Lytes: normal. **Glucose**, BUN, creatinine **normal**. ECG: **short P-R; wide QRS; left-axis deviation**.

Imaging CXR: **extreme cardiomegaly** and congestive heart failure.

Gross Pathology Significant increase in size and weight of heart (up to five times normal); to lesser extent, hepatomegaly.

Micro Pathology Extensive intracytoplasmic and lysosomal deposition of glycogen on myocardial fibers as well as in striated muscle fibers, kidney, and liver.

Treatment Poor prognosis; associated with early death from **cardiopulmonary failure**.

Discussion Pompe's disease is a **type II glycogen storage disease** (generalized). This fatal disorder is caused by an **autosomal-recessive deficiency in the lysosomal** enzyme (only glycogenolysis with lysosomal involvement) **α-1,4-glucosidase** (ACID MALTASE), with resulting accumulation of structurally normal glycogen in the heart, muscle, kidney, and liver.

ID/CC A 40-year-old **male** visits his family doctor because of a **chronic, recurrent rash** on his hands, face, and other **sun-exposed areas**; the patient's **urine turns dark brown-black if left standing**, and he has noticed that recurrences coincide with **alcohol intake**.

HPI He reports having used **hexachlorobenzene as a pesticide** for some years (a fungicide shown to be associated with porphyria cutanea tarda).

PE Skin erythema with **vesicles and bullae on sun-exposed areas**; skin at these sites is friable and shows presence of whitish plaques ("MILIA") (due to photosensitizing effect of uroporphyrin); skin of face also shows hypertrichosis and hyperpigmentation.

Labs Watson–Schwartz test negative. UA: **markedly elevated urinary uroporphyrin levels; slightly elevated urinary coproporphyrin levels**. Fecal isocoproporphyrin normal; **elevated transferrin, serum and hepatic iron**; elevated serum transaminases.

Gross Pathology Liver shows siderosis, bullae, fibrosis, and inflammatory changes.

Micro Pathology Skin biopsy demonstrates iron deposits, intense porphyrin fluorescence, and long, thin cytoplasmic inclusions.

Treatment Repeated phlebotomies; avoidance of sunlight, alcohol, iron, and estrogens. Low dose antimalarials.

Discussion Porphyria cutanea tarda (PCT), in contrast to other hepatic porphyrias, is more common among men than women. PCT is caused by partial loss of activity of **hepatic uroporphyrinogen decarboxylase**; lesions are caused by overproduction and excretion of uroporphyrin.

ID/CC A 5-year-old girl is referred to a hematologist for an evaluation of chronic **anemia that has been unresponsive to nutritional supplementation**.

HPI Both parents are clinically normal and are **first cousins** who are **Amish**. The patient has no history of passage of dark-colored urine or recurrent infections.

PE Low weight and height for age; pallor; mild **jaundice**; spleen barely palpable; liver not enlarged.

Labs CBC/PBS: **anemia; markedly increased reticulocyte count**; peripheral blood reveals macro-ovalocytosis with a few echinocytes; no sickle cells or spherocytes seen. Hyperbilirubinemia (primarily unconjugated). UA: urinary hemosiderin present. Reduced serum haptoglobin; **diminished activity of pyruvate kinase** in RBCs on spectrophotometry.

Treatment **Exchange transfusions**. Splenectomy.

Discussion Pyruvate kinase deficiency is inherited as an **autosomal-recessive** trait and usually produces mild symptoms (hemolytic anemia); **2,3-diphosphoglycerate accumulates**, shifting the hemoglobin-oxygen dissociation curve to the right (due to reduced affinity of RBCs for oxygen).

71 PYRUVATE KINASE DEFICIENCY

ID/CC A **6-month-old** male is brought to a pediatrician for evaluation of **listlessness**, lethargy, and **fixed gaze**.

HPI His parents are **Ashkenazi Jews**.

PE **Excessive extensor startle response to noise** (HYPERACUSIS); child is sleepy and hypotonic with poor head control and a fixed gaze; appears to have translucent skin; **cherry-red macular spot** found on funduscopic exam.

Gross Pathology Diffuse gliosis; cerebral and macular degeneration; up to 50% increase in brain weight (due to deposition of sphingolipid).

Micro Pathology Neuronal swelling with cytoplasmic **deposits of gangliosides** (ZEBRA BODIES).

Treatment Poor prognosis; patients usually die of pneumonia before reaching the age of 3.

Discussion Tay–Sachs disease is an autosomal-recessive disorder of sphingolipid metabolism characterized by the **absence of the enzyme hexosaminidase A**, producing excessive storage of ganglioside GM-2 in lysosomes **restricted to the cells of the central nervous system. Ganglioside GM-2** is a glycosphingolipid with sphingosine, a long-chain basic molecule, as its backbone along with an attached sugar and a terminal N-acetylglucosamine. Prenatal diagnosis can be made at the 14th week of pregnancy.

ID/CC A 7-year-old male is brought to a pediatrician for evaluation of episodes of **fatigue**, restlessness, anxiety, nausea, **lightheadedness**, vomiting, and **sweating**.

HPI The symptoms appear when he does not eat frequent meals and subside while he is eating. He also has a history of **bruising easily**.

PE Patient has **"doll-face" facies**; weight low for age; tendon xanthomas; purpuric patches over skin; **marked hepatomegaly**.

Labs Lactic acidosis; hyperlipidemia; **marked increase in serum uric acid** (patient may exhibit gout symptoms); **marked hypoglycemia**; prolonged bleeding time; **lack of rise in serum glucose following SC epinephrine** or IV glucagon but striking increase in lactate; normal urinary catecholamines.

Imaging US: hepatomegaly; kidneys also enlarged bilaterally.

Gross Pathology **Liver and kidneys enlarged** (vs. type III glycogen storage disease, or Cori's disease, in which there is no renal involvement).

Micro Pathology Hepatocytes containing variable-sized **glycogen-lipid droplets** on liver biopsy; nuclear glycogenosis seen; large glycogen deposits in kidney; skeletal and cardiac muscle not involved (vs. type V glycogen storage disease, or McArdle's disease, in which skeletal muscle is involved).

Treatment Frequent meals to prevent hypoglycemia.

Discussion Von Gierke's disease is an autosomal-recessive glycogen storage disease (type I) resulting from a **deficiency of glucose-6-phosphatase** and accumulation of structurally normal glycogen in the liver and kidneys.

ID/CC A 10-year-old girl is brought by her parents to a dermatologist because of a recent **change in color and increase in size of a warty lesion** on her face.

HPI She has been suffering from **excessive sensitivity to sunlight** and thus does her best to avoid the sun as much as possible.

PE Abundant **freckles** on all sun-exposed areas; **telangiectases**; areas of redness (ERYTHEMA) and hypopigmentation; **hyperkeratosis** on face and dorsum of hands; hard, nodular lesion on right cheek; no regional lymphadenopathy.

Labs Basic lab work normal.

Gross Pathology Generalized hyperpigmentation with desquamative spots on sun-exposed areas.

Micro Pathology Biopsy of cheek lesion reveals hyperkeratosis with melanin deposition; **squamous cell carcinoma**.

Treatment Avoidance of sunlight, protection against sunlight. Surgical removal of cancer.

Discussion Xeroderma pigmentosum is an **autosomal-recessive** disorder that is usually manifested in childhood. It is characterized by excessive sensitivity to ultraviolet light due to **impaired endonuclease excision repair mechanism** of **ultraviolet light-damaged DNA** UV light causes (cross linking of pyrimidine residues) in dermal fibroblasts. There is a marked tendency to develop **skin cancer** (squamous cell and basal cell carcinoma).

ID/CC A 40-year-old woman presents with **weakness, easy fatigability, nausea**, and **diarrhea**.

HPI She has had a long and severe course of rheumatoid arthritis for which she has been taking **methotrexate** (a folic acid antagonist).

PE VS: normal. PE: **pallor**; mild tongue inflammation (GLOSSITIS); funduscopic exam normal; chest sounds within normal limits; abdomen shows no hepatosplenomegaly; no lymphadenopathy; **no neurologic signs** (vs. vitamin B_{12} deficiency megaloblastic anemia).

Labs CBC: **hypersegmented PMNs** (> 5 to 7 lobes); **megaloblastic RBCs** (mean corpuscular volume >100); **vitamin B_{12} level normal; folate** level **in RBCs low** (vs. vitamin B_{12} deficiency megaloblastic anemia).

Treatment Folic acid supplementation.

Discussion Folic acid is found mainly in green leaves and is important for the **synthesis of DNA and RNA**. It also acts as a coenzyme for 1-carbon transfer and is involved in **methylation reactions**. Deficiency is associated with alcoholism, pregnancy (MEGALOBLASTIC ANEMIA OF PREGNANCY), dietary deficiencies, and drugs such as TMP-SMX, methotrexate, phenytoin, and proguanil.

ID/CC A 5-year-old white male is brought to the emergency room with a fracture of his right forearm that he sustained after falling off a couch.

HPI This is the **fifth bone fracture** that the child has sustained **in the past 2 years**.

PE **Bluish sclera**; right leg and right arm slightly deformed from poor healing of past fractures; mild **kyphosis and scoliosis** of thoracic spine; **hypotonia and laxity** of right leg and arm; **partial conduction deafness** in both ears.

Imaging XR: fracture of radius and ulna with evidence of osteopenia.

Micro Pathology **Marked thinning of bone cortices** (EGGSHELL CORTEX) and rarefaction of trabeculae (due to **abnormal synthesis of type I collagen**); abnormal softening of tooth enamel.

Treatment Supportive.

Discussion Also called brittle bone disease, osteogenesis imperfecta is an **autosomal-dominant** disorder of type I collagen synthesis in which there is deficient ossification due to inadequate osteoid formation.

Atlas Link UCV2 PED-052

ID/CC A 45-year-old male chess player is brought to the emergency room complaining of acute **nausea**; he has **vomited** five times, feels very **lightheaded**, and has a severe **headache**.

HPI He went out **drinking** last night to celebrate his victory in a chess tournament he attended last week in Mexico. While in Mexico, he contracted acute amebiasis that is currently being treated with **metronidazole**.

PE VS: marked tachycardia (HR 120); **hypotension** (BP 90/60). PE: anxious, dehydrated, and confused with severe nausea.

Labs CBC/LFTs: normal. Amylase normal. ABG/Lytes: mild hypokalemia and metabolic alkalosis (due to vomiting).

Treatment Supportive, IV fluids, antiemetics, discontinuance of alcohol.

Discussion Ethanol is degraded by alcohol dehydrogenase to acetaldehyde, which in turn is degraded to acetic acid by another acetaldehyde dehydrogenase. This **acetaldehyde dehydrogenase is inhibited** by disulfiram, resulting in the **accumulation of acetaldehyde**, which produces nausea, vomiting, headache, and hypotension (ANTABUSE EFFECT). Metronidazole, some cephalosporins, and other drugs have an Antabuse-like effect when consumed concomitantly with alcohol.

ID/CC A **premature** (32-week-old) white male infant is brought to the intensive care unit after a **cesarean** delivery.

HPI His mother had third-trimester **bleeding** and contractions that did not stop with rest and conservative treatment.

PE VS: tachypnea. PE: child weighs 3.8 lb; **cyanosis; dyspnea**; uses accessory muscles of respiration; **nasal flaring**.

Labs ABGs: hypoxemia; hypercapnia. Decreased lecithin/sphingomyelin (L/S) ratio (L/S ratio normally > 2; 1.5 to 2.0 in 40% of newborns with respiratory distress syndrome).

Imaging CXR: bilateral **reticular pulmonary infiltrates** and atelectasis.

Gross Pathology Generalized atelectasis in purple-colored lung; eosinophilic fibrinous hyaline membrane formation.

Treatment Ventilatory support, fluid, acid-base and electrolyte balance, antibiotics; administration of surfactant; steroids before birth to speed lung maturity.

Discussion **Respiratory distress syndrome** of the newborn is the most common cause of death in premature infants. It is due to a **deficiency of surfactant**, a lipoprotein produced by type II pneumocyte cells that contains the phospholipid dipalmitoyl lecithin. Fetal lung maturity may be measured by the L/S ratio. The syndrome might be prevented by giving **betamethasone** to pregnant women, since type II pneumocyte cell differentiation is dependent on steroids. Complications include patent ductus arteriosus, pulmonary air leaks, and bronchopulmonary dysplasia.

Atlas Link UCVI **PG-BC-083**

ID/CC A 36-year-old female **nonsmoker** visits her family doctor because she has become increasingly **short of breath** (DYSPNEA); her symptoms first appeared only during exercise but now occur even when she is at rest.

HPI She also complains of frequent URIs and moderate **weight loss**.

PE **Thin** female with **increased anteroposterior diameter of chest** (BARREL-SHAPED CHEST); decreased breath sounds bilaterally; **hyperresonance** to percussion; retardation of expiratory flow.

Labs CBC: increased hematocrit. PFTs: **$FEV_1/FVC < 75\%$** (diagnostic of airflow obstruction). ECG: right ventricular hypertrophy.

Imaging CXR: hyperlucent lung fields; flattening of diaphragm and decreased lung markings at periphery.

Gross Pathology Destruction of alveolar walls distal to the terminal bronchiole with hyperaeration (EMPHYSEMA); **panacinar type** (COTTON CANDY LUNG); more severe at lung bases.

Treatment Standard treatment for COPD patients. Replacement therapy with α_1-protease inhibitor.

Discussion Pollutants, cigarette smoke, and infections increase PMNs and macrophages in the lung and thus produce a number of proteolytic enzymes. Damage to lung tissue due to these enzymes is controlled by the globulin **α_1-antitrypsin**, which inhibits trypsin, neutrophil, elastase, and collagenase. A deficiency of this enzyme causes excessive lung tissue destruction and **panacinar emphysema** (cigarette smoking is associated with the centrilobular type). Patients may also develop **liver damage**.

ID/CC A 23-year-old female college student is brought to the emergency room because of **numbness** of her face and feet together with a **sensation of suffocation** and **stiff twisting of the hands** (CARPOPEDAL SPASM); these symptoms arose following an argument with her boyfriend.

HPI A friend reports that the patient has a **history of anxiety-induced colitis, gastritis, and migraine**.

PE VS: **marked tachypnea** (RR 40); tachycardia (HR 90); hypertension (BP 140/90). PE: patient **apprehensive** and anxious; physical exam otherwise normal.

Labs ABGs: **low Pco_2; respiratory alkalosis** (cause of tetany); **low bicarbonate** (to compensate for primary lowering of Pco_2).

Imaging CXR: normal

Treatment Have patient **breathe in and out of a bag** or give 5% CO_2 mixture.

Discussion Anxiety hyperventilation is a common occurrence in ERs. The anxiety state produces an increase in the frequency of respirations (HYPERVENTILATION), causing a lowering of Pco_2; the resulting respiratory alkalosis produces an unstable depolarization of the distal segments of motor nerves with symptomatic tetany. Alkalosis also sets in motion a compensatory decrease in bicarbonate level to maintain pH as close to normal as possible.

ID/CC A 36-year-old divorcee living in rural Maine is brought by ambulance to the ER with her two children, who were **all found unconscious in her home** by military personnel.

HPI A recent "El Niño" produced bad weather that resulted in a power failure; as a result, she had been using charcoal and a **wooden stove inside her house** for heating purposes.

PE **Skin bright red** (CHERRY-RED CYANOSIS); pulse arrhythmic; patient regains consciousness soon after administration of 100% oxygen but remains drowsy, **disoriented**, and nauseous and complains of a severe **headache** (due to cerebral edema); **hyperreflexia** noted as well as positive Romberg's test.

Labs **Increased carboxyhemoglobin** (> 25%). ABGs: metabolic acidosis.

Imaging CT/MR: bilateral globus pallidus lesions.

Treatment One hundred percent **oxygen**, assisted ventilation if necessary. Hyperbaric oxygen chamber.

Discussion Common sources of CO are car exhaust, pipes, and fires. Carbon monoxide has a much greater affinity for hemoglobin than oxygen (250 times more). If patient is pregnant, damage to the fetus is devastating (HbF has greater affinity to CO than HbA). Long-term side effects such as memory problems, lack of coordination, and even convulsions are common after intoxication.

ID/CC A 52-year-old obese white male comes to his family doctor complaining of severe pain in the **first metatarsophalangeal (MTP) joint** (PODAGRA) that began at **night** after an episode of binge **eating** and **drinking**.

HPI He admits to being an avid **meat** eater and drinks **red wine** every night. His history is significant for removal of **kidney stones** (uric acid stones).

PE VS: **fever** (38.2°C). PE: **right MTP joint** red, hot, and swollen; painful to active and passive motion; **tophaceous** deposits in left ear and olecranon bursitis.

Labs **Elevated serum uric acid**. UA: urate crystals. **Increased ESR**. CBC: leukocytosis with neutrophilia.

Imaging XR: punched-out erosions in right big toe at MTP joint, producing **"overhanging"** spicules.

Gross Pathology Tophi are white, soft, nodular masses of urate deposits with calcifications seen mainly in synovial membranes, tendon sheaths, and ear cartilages.

Micro Pathology Tophi and synovial fluid aspiration show characteristic negatively **birefringent, needle-shaped crystals** of uric acid salts; giant cell formation with neutrophilic infiltration.

Treatment Colchicine for acute stage; administer hourly until negatively diarrhea occurs or pain disappears; combine with aspirin or NSAIDs. Long-term treatment with allopurinol and/or probenecid.

Discussion Gout is a disorder of purine metabolism with a resulting increase in serum uric acid level and deposits in several tissues; 10% to 20% of cases may develop nephrolithiasis. In late stages, urate deposits in the kidney may lead to chronic pyelonephritis, arteriolar sclerosis, hypertension, and renal failure.

Atlas Links UCM1 **PM-BC-094** UCM2 IM2-052A, IM2-052B