Chapter 1

Medical Brevities

In this chapter, I try to challenge your traditional thinking. The "brevities" are designed to inform, to suggest common denominators in seemingly varied medical conditions, and to provoke your thinking. You will never diagnose a disease if you do not think of it.

Brevity 1: A Deficiency in a Hematinic Agent May Cause Illness While the Blood Count Is Still Normal

Iron Deficiency

Clinical vignette: A 36-year-old woman presents with a feeling of weakness, listlessness, and easy fatigability. The patient works part-time while raising her three children. Physical examination is normal. Hemoglobin is 12.0 g/dL, and the other blood elements are in the normal range. The clinician tells the patient, "Your physical examination is normal and your blood count is normal. I think you may well be depressed from your arduous workload. I suggest that you start this medication." A selective serotonin receptor inhibitor (SSRI) is prescribed.

The clinician must recognize that iron deficiency without anemia can cause the patient's symptoms. In this patient, a low serum ferritin (< 30 ng/mL) would document decreased iron stores while the hemoglobin, serum iron, and iron binding capacity are still in the normal range.

Iron deficiency occurs most often in the patient with increased blood loss, for example, from menstrual loss or from blood loss secondary to gastrointestinal bleeding, gross hematuria, trauma, or intravascular hemolysis (caused by loss of iron from hemoglobinuria and hemosiderinuria). Further, iron deficiency may occur with deficient oral intake or with impaired intestinal absorption of ingested iron. Impaired iron absorption is common in

celiac disease and *Helicobacter pylori* gastritis and, less frequently, in autoimmune atrophic gastritis.

As the body deficiency in iron becomes more pronounced, the patient will develop the characteristic microcytic anemia.

Additionally, iron deficiency may cause other clinical illnesses. First, iron deficiency is one cause of restless leg syndrome (RLS). This disorder, twice as common in females than in males, is characterized by spontaneous, continuous leg movements associated with unpleasant paresthesias only when the patient is at rest. The symptoms, which are usually bilateral, are relieved by leg movement. Reduced levels of serum or spinal fluid ferritin are diagnostic of iron deficiency–related RLS. In these patients, the neurologic examination is normal. Other diseases and conditions known to be associated with RLS include end-stage renal disease, Parkinson's disease, venous insufficiency, and pregnancy. In pregnancy, the symptoms are most common in the third trimester; incidence drops quickly after delivery. Some patients with RLS have no recognized pathogenesis and are considered to be idiopathic or primary.

Second, iron deficiency may cause breath-holding syncope in children. This condition typically affects children who are 5 months to 6 years of age. (Ninety percent have the first episode before age 18 months.) The episodes are triggered by even mild emotional insults, anger, fear, or pain. The origin is considered to be a variant of vasovagal syncope. The syncopal episodes may be associated with a pallid or cyanotic skin hue. During syncopal episodes, the patient is limp and may exhibit seizure activity. Consultation with a pediatric neurologist is generally indicated to differentiate breath-holding syncope from a true seizure disorder.

Vitamin B_{12} (Cobalamin) Deficiency

Clinical vignette: A 54-year-old man has progressive dementia of 7 months duration. Examination shows cognitive impairment. Propriception and vibratory sensation could not be adequately tested because of the patient's distractibility. Hemoglobin is 14.2 g/dL; other blood elements are normal. Red blood cell indices are normal.

The clinician must be aware that vitamin B_{12} deficiency may cause severe neurologic manifestations while the hematocrit and red blood cell indices are normal. Intrinsic factor, produced in the gastric mucosa, is essential for cobalamin absorption in the distal ileum. Cobalamin deficiency is present in the autoimmune disease pernicious anemia because these patients have anti-intrinsic factor antibodies and, less commonly, anti-parietal cell anti-

bodies. The anti-intrinsic factor antibodies prevent the vitamin absorption in the ileum. Other patients who do not have autoimmune disease may develop vitamin B_{12} deficiency. These include patients who have undergone gastrectomy and who do not produce intrinsic factor; patients who have inflammatory disease involving the terminal ileum and are unable to absorb cobalamin, for example, in Crohn's disease; patients with intestinal blind loop syndromes in which bacterial overgrowth competes for cobalamin; and those who follow a strict vegan diet without intake of dairy products, meat, and fish. Vitamin B_{12} is found only in food of animal origin.

Vitamin B_{12} deficiency causes a macrocytic and megaloblastic anemia as a result of impaired DNA formation in the premature erythrocyte. The vitamin deficiency impairs myelination of nerve fibers, resulting in neurologic deficits. The earliest neuropathic symptoms are paresthesias and ataxia. Early on, neurologic examination shows loss of vibratory sensation and proprioception due to degeneration of the posterior (dorsal) and lateral spinal columns. Higher nervous center impairment follows, with the patient exhibiting dementia or irritability.

Folic acid (folate) deficiency can produce the same megaloblastic anemia seen in cobalamin deficiency. However, folate deficiency does not cause neurologic impairment. Here is the key clinical element: In the patient who has vitamin B_{12} deficiency with anemia and neurologic deficit, the folate ingestion *will reverse the anemia but not the neuropathy*. To the question, How does vitamin B_{12} deficiency cause dementia and spinal cord degeneration while the blood count is normal, *the answer is that the cobalamin-deficient patient is ingesting adequate amounts of folate to prevent anemia*. (Dietary folate is found in green leafy vegetables in addition to multivitamin supplements.)

In the patient who has peripheral neuropathy or dementia while the hemoglobin and red blood cell indices are normal, vitamin B_{12} deficiency may be diagnosed by a low serum cobalamin level. If the cobalamin level is borderline low, an elevated serum methylmalonic acid level supports the diagnosis of vitamin B_{12} deficiency. If the vitamin B_{12} deficiency neuropathy is diagnosed at an early stage, it is reversible with cobalamin therapy.

You must remember:

1. Iron deficiency may cause significant symptoms of fatigue and lassitude while the hemoglobin level is still normal. A decreased level of serum ferritin is diagnostic of iron deficiency.
2. Vitamin B_{12} deficiency of any etiology may produce neurologic impairment (loss of proprioception and vibratory sensation) or dementia while the hemoglobin is normal. Ingestion of adequate folate will prevent the B_{12}-deficiency anemia but not the neuropathy.

Brevity 2: Not All Dementia Is Irreversible. The Clinician Must Always Look for a Treatable Cause of the Cognitive Disorder

Essentially irreversible causes of dementia include Alzheimer's disease, vascular (multi-infarct) dementia, Parkinson's disease, Huntington's chorea, and Lewy body dementia. Yet, there are potentially *treatable and reversible* causes of dementia. These patients may exhibit memory loss, impairment in calculation and judgment, and impaired problem solving. Patients who have the following disorders may improve with treatment:

- Depression
- Vitamin B_{12} (cobalamin) deficiency
- Medications
- Niacin deficiency
- Chronic subdural hematoma
- Normal pressure hydrocephalus (NPH)
- Hypothyroidism
- Bismuth poisoning
- Central nervous system tumors
- Whipple's disease

Depression often masquerades as dementia with memory loss and impaired judgment ("pseudodementia"). Appropriate treatment of the psychiatric disorder improves the patient's cognitive function. As noted earlier (see medical brevities 1), a neurologic manifestation of vitamin B_{12} deficiency may be dementia. If therapy with cobalamin is initiated early in its course, the dementia is reversible. Patients who have NPH will have dementia in addition to gait disorder and urinary incontinence. A ventricular shunting operative procedure can improve cognition in half of the patients operated on.

Particularly in the patient with impaired renal function, intake of bismuth, as in treatment of *Helicobacter pylori* gastritis, can cause confusion and dementia. Hypothyroidism can cause memory loss and depression, in addition to other classic manifestations, including weight gain, cold intolerance, and constipation. Serum thyroid stimulating hormone (TSH) levels are elevated in primary hypothyroidism, but are typically low in secondary hypothyroidism. Niacin deficiency, most commonly noted in the patient suffering from chronic alcohol abuse, can cause dementia. The patient may not exhibit the classic symptom triad of niacin deficiency in pellagra, namely, dermatitis, diarrhea,

and dementia. Some patients with chronic subdural hematoma or primary brain tumor may present with dementia; in these patients motor signs may be subtle or absent. Many medicines may cause memory loss and cognitive dysfunction, including tranquilizers, sedatives, anticholinergic agents, and antidepressants. Whipple's disease is a rare bacterial illness. Patients commonly have arthralgia (or arthritis), abdominal pain, lymphadenopathy, fever, and dementia. Prolonged antibiotic therapy results in dramatic clinical improvement.

You must remember:
1. Though uncommon, the clinician must carefully search for a treatable cause in the patient who has dementia.

Brevity 3: Remember the "Acey-Ducey" Rule: In Paired Structures in the Body, *Recurrent* Involvement of One of the Pair Suggests a "Local" Disorder Whereas Involvement of Both Strongly Suggests Systemic Disease

Many years ago I was conscripted (physicians' draft) into the military and assigned to the Navy. I quickly learned of the Acey-Ducey clubs, the social clubs for first- and second-class petty (noncommissioned) officers. (No need to go into details of my social initiation to the clubs, including my introduction to the Salty Dog cocktail.) Thus, in my mind, *Acey* became "one" and *Ducey*, "two." Such is the provenance of my Acey-Ducey rule in medicine.

Clinical vignettes:

"Acey"

Over a 3-year-period, a 35-year-old man has had three attacks of renal colic related to kidney stones; all stones have been in the right kidney.

"Ducey"

A nurse at the hospital where I attended patients approached me one morning and anxiously told me that her son, a 20-year-old college student, just had a second episode of renal colic due to a kidney stone. I immediately asked her whether both attacks

involved one kidney, or whether both kidneys were involved. She answered that she did not know but would immediately inquire. A few minutes later, after speaking with her son, she informed me that the first stone was in the left kidney and the most recent attack involved the right kidney. I said to the nurse, "Ducey."

What is the important clinical difference?

"Acey"
A 47-year-old man has had three episodes of pneumonia in the past 4 months.

In each case, the infection was in the right lower lobe.

"Ducey"
A 33-year-old woman has had three episodes of pneumonia in the past 4 months. One episode of illness involved the left lower lobe, another involved the right middle lobe, and the most recent episode was pneumonia involving the left upper lobe.

What is the important clinical difference?

Two more vignettes:

"Ducey"
Three months ago, a 47-year-old man had carpal tunnel syndrome (CTS) involving his left wrist; he now has the disorder affecting his right wrist.

"Acey"
A 51-year-old woman who works as a secretary had CTS affecting her right wrist 2 years ago. With conservative therapy and nerve gliding exercises under the direction of an occupational therapist, she has had no recurrence.

What is the important clinical difference?

The Answer: First, consider that the kidneys, lungs, and wrists are paired structures in the body.

"Acey": Recurrent Involvement of One of the Paired Structures Suggests a "Local" Condition

Recurrent kidney stones involving *one* kidney suggest an underlying congenital anomaly or, perhaps, scarring from trauma or infection. Recurrent carpal tunnel involving *one* wrist suggests prior wrist trauma or Colles fracture or radiculopathy. Recurrent pneumonia in *one* lung (or *one* lobe) suggests an

endobronchial lesion such as bronchogenic carcinoma, or, less often, a broncholith, or a local inflammatory disorder such as bronchiectasis.

"Ducey": Recurrent Involvement of Both of the Paired Structures Suggests a Systemic Disorder

Recurrent pneumonia that involves *both* lungs suggests a systemic disorder, most commonly, an immunocompromised state, such as HIV-AIDS or multiple myeloma. In myeloma, impaired lymphocyte function and hypogammaglobulinemia predispose to recurrent pulmonary infections that can be present in any locus in the lungs ("Ping-Pong ball" pneumonia). HIV type 1 is a human retrovirus that infects lymphocytes and other cells that bear the CD4 surface protein. The resultant immune dysfunction results in recurrent pulmonary infections that involve both lungs.

Recurrent CTS that involves *both* wrists over a short time period (few months) suggests a systemic disorder. Approximately 30% of patients who have end-stage renal disease will have CTS. Commonly, patients who have hypothyroidism (7% of cases) and diabetes mellitus (6% of cases) have median nerve dysfunction. Seven percent of pregnant women have CTS; there is prompt resolution after delivery. Other systemic disorders that cause CTS are rheumatoid arthritis, acromegaly, and amyloidosis.

Recurrent kidney stones that involve *both* kidneys suggest a systemic disorder such as hypercalcemia, idiopathic hypercalciuria, hyperuricemia, or cystinuria. Patients with gout have hyperuricemia and, therefore, are most susceptible to uric acid calculi in the kidneys. Cystinuria is a rare hereditable disease with autosomal recessive transmission that should be considered when a child has a renal calculus.

It is useful to separate hypercalcemia into two categories: hypercalcemia with low serum phosphate, and hypercalcemia with normal serum phosphate.

In the patient who has *hypercalcemia with a low serum phosphate*, think first of primary hyperparathyroidism, most commonly resulting from a solitary parathyroid adenoma (80% of cases) and, in the remaining 20% of cases, hyperplasia of the gland. Remember that primary hyperparathyroidism may, in selected patients, be part of a multiple endocrine neoplasia (MEN) syndrome. Lithium therapy may result in increased serum parathyroid hormone secretion with similar serum chemical abnormalities.

Hypercalcemia in malignancy may be caused by three mechanisms. First is nonmetastatic tumor secretion of parathyroid-related protein resulting in hypercalcemia with low serum phosphate. T-cell lymphoma and B-cell non-Hodgkin's lymphoma are examples.

In contrast, *hypercalcemia may occur in association with a normal serum phosphate*. Examples include prolonged immobilization, myeloma, milk

alkali syndrome, hyperthyroidism, thiazide diuretic therapy, malignancy, and sarcoidosis. Hypercalcemia occurs in 5% of sarcoidosis patients, but hypercalciuria is noted in 20%.

The other two mechanisms of malignancy-induced hypercalcemia include osteolytic metastases, most commonly resulting from breast and non-small cell lung cancer, and tumor production of calcitriol. Hodgkin's disease and, less commonly, non-Hodgkin's lymphoma are tumors that may produce calcitriol. In the body, vitamin D is activated to calcitriol, which increases intestinal absorption of calcium, increases parathyroid hormone bone resorption, and reduces urinary calcium and phosphate excretion. As a result, malignant disease related to these two mechanisms produces hypercalcemia with a normal serum phosphate concentration.

Milk alkali syndrome was common years ago when ingestion of milk and cream, in addition to bicarbonate compounds, was the mainstay of ulcer therapy. The syndrome now occurs in a different patient population. Patients now take calcium carbonate in the prevention or treatment of ostoporosis and, additionally, as part of a therapeutic program in eradication of *Helicobacter pylori* gastritis or ulcer. Milk alkali syndrome is characterized by hypercalcemia, elevated plasma bicarbonate, and azotemia. The serum phosphate level is most frequently normal, but may be slightly elevated in some patients.

You must remember the Acey-Ducey rule:
1. Think of paired structures in the body.
2. Recurrent involvement of one of the pair points toward a "local" disorder.
3. Recurrent involvement of both structures suggests systemic disease.

Brevity 4: Young Adults Can Suffer Acute Stroke. In These Patients, You Must Consider Patent Foramen Ovale, Factor V Leiden Mutation, and Antiphospholipid Antibody Syndrome as Causative Factors

Clinical vignette: I received an urgent phone call from one of my former medical students. With great anxiety, she stated that she was in a hospital emergency department with her 28-year-old firefighter husband who just spontaneously recovered from a

30-minute episode of weakness in his right arm and right leg. "What could it be?" she urgently inquired.

I first asked about his pulse. She responded that the pulse was normal in rate and was perfectly regular in rhythm. Immediately, it did not appear to be a cerebral embolus from a dislodged left atrial clot related to atrial fibrillation (AF). I then quickly probed about his general health. Her response was that he was robustly well.

Of course, I suggested immediate consultation, but volunteered that the three most likely causes, in descending order of frequency, were paradoxical embolus in a patent foramen ovale (PFO), antiphospholipid antibody syndrome (APS), or Factor V Leiden mutation. (One week later, he underwent percutaneous device closure of a PFO. After an appropriate period of anticoagulation, he returned to his work as a professional firefighter and has suffered no recurrent neurologic event.)

When attending the young adult who has had a transient ischemic attack or ischemic stroke, the clinician must consider cryptogenic stroke related to a PFO or to a hypercoagulable state in association with APS or Factor V Leiden mutation.

Cryptogenic stroke is the term applied to those patients, usually under the age of 50 years, who have suffered an acute ischemic cerebral event without an identifiable embolic source and without an identifiable large arterial atherosclerotic source. Recent clinical investigation has demonstrated that many of these ischemic events originate in an embolus that arises in a *systemic vein* in the leg or pelvis that travels to the right atrium, across a PFO into the left atrium, and ultimately, from the left ventricle to the brain.

A PFO is a flaplike valve between the right and left atria. It plays an important role in fetal development because oxygenated blood from the umbilical vein enters the right atrium. Fetal lungs are not inflated, causing a high pulmonary vascular resistance. As a result, oxygenated blood in the right atrium moves through the PFO into the left atrium and then, ultimately, into the systemic arterial circulation. After birth, hemodynamic changes in the atria close the flap and, normally, adhesions form at the site. However, in 25% of individuals the foramen ovale remains patent. PFO is common.

Because there is normally an equal blood pressure in the two atria, what might cause a venous clot moving from a leg vein into the right atrium not to move into the right ventricle, but rather, to traverse a PFO and enter the systemic circulation?

A Valsalva maneuver appears to be the most frequent explanation. During the Valsalva strain period, right atrial pressure is transiently greater than left atrial pressure. The clot in the right atrium then moves from right to left into the left atrium. In the course of daily activity, a person frequently performs a

Valsalva maneuver as he or she strains to defecate, lifts or pushes a heavy object, or has a vigorous, repetitive coughing episode. Consequently, it is thought that the ischemic cerebral event occurs when the patient, inadvertently, performs a Valsalva strain maneuver that enables a clot that happens to be in the right atrium to move through the PFO into the systemic circulation.

PFO may play an important role in the genesis of migraine headaches. Although the number of patients is small, there is suggestive data that PFO closure in migraineurs who have associated aura will significantly reduce the frequency, or even end, migrainous attacks.

Diagnosis of PFO is confirmed via transesophageal echocardiography. Agitated saline is injected into the femoral vein and the patient performs a Valsalva strain maneuver. The echocardiogram documents right to left shunting at the atrial level.

Consider the following interesting questions:

- A PFO is noted in 25% of the adult population; yet, cryptogenic stroke is very uncommon. Why?

No one knows the answer.

- The source of the paradoxical embolus is thought to be a venous clot forming in the leg. In a patient suspected of having an ischemic cerebral event caused by paradoxical embolism, how often does imaging reveal a clot in a leg vein?

The answer is that seldom is the source of embolism found in a leg or pelvic vein. Nonetheless, imaging of the veins is thought to be appropriate in the patient.

- In a patient who has a venous clot that moves to the right atrium and *no PFO* in the atrial septum, what happens to the clot?

The clot moves to the right ventricle and finally into the lung. The endothelium of the lung has an active fibrinolytic system that dissolves the clot without clinical illness. Only if the venous clot is large, or multiple, will the patient have symptoms and signs of pulmonary embolism.

Other less common causes of an ischemic brain event in a young person include hypercoagulable states associated with APS or Factor V Leiden mutation. In APS there are antibodies to plasma proteins bound to phospholipids. These antibodies are also referred to as lupus anticoagulant and anticardiolipin antibodies. APS may be primary, of unknown cause, or secondary, related to systemic lupus erythematosus. Medicines that are associated with antiphospholipid antibody production include hydralazine, quinine, amoxicillin, thiazides, propranolol, phenytoin, procainamide, oral contraceptives, and phenothiazines. (These medications are associated with the drug-induced lupus syndrome.)

The clinical presentation of APS includes venous thrombosis, arterial thrombosis, recurrent fetal loss, and thrombocytopenia. APS is associated with thrombosis in deep veins of the legs, and axillary, subclavian, and retinal veins. Approximately 10% of patients who have deep vein thrombosis (DVT) have these antibodies. Pulmonary embolism is a frequent complication. APS should be suspected in any young person who has an ischemic stroke but does not have the common risk factors. In the woman who has recurrent fetal loss (spontaneous abortion) after 10 weeks gestation, APS is an important underlying cause. Livedo reticularis, a netlike pattern of macular violaceous erythema involving legs, feet, and abdomen, is noted in 20% of APS patients. It must be recognized that livedo reticularis may be entirely benign, occurring in young women aged 20 to 40 years. In these patients, the erythema is most pronounced during cool temperature exposure and disappears with warming.

Factor V Leiden is a common mutation and is considered to be the most common cause of inherited thrombophilia, increasing the tendency to venous thromboembolism. Less commonly, prothrombin gene mutation and a deficiency in proteins C and S and antithrombin cause venous thrombosis. The major clinical manifestation of Factor V Leiden mutation is DVT and pulmonary embolism. It appears that the mutation has the greatest associated risk of venous thrombosis in those who have additive factors, including oral contraceptive intake, or who have had recent surgery, are immobilized, are pregnant, or who smoke. In children, more frequently than in young adults, this mutation may cause stroke as a result of cerebral artery thrombosis. It also is associated with recurrent fetal wastage. The screening test for Factor V Leiden mutation is the activated partial thromboplastin time.

In addition to the *inherited thrombophilias causing venous thrombosis*, note that there are two important *acquired* disorders that promote venous clotting. These include nephrotic syndrome, in which deep vein and renal vein thrombosis are relatively common, and malignancy. Oftentimes, the DVT and pulmonary embolism associated with malignancy precede the diagnosis of the neoplastic disorder. The most common malignancies associated with venous thrombosis are carcinoma of the lung, colon and rectum, pancreas, kidney, and prostate.

You must remember:

1. In the young patient who has an ischemic stroke (and is in normal sinus rhythm), consider PFO, APS, and Factor V Leiden mutation.
2. In the older patient who has DVT, consider occult malignancy as the underlying cause.

Brevity 5: Consider a Metabolic Disorder in Any Patient Who Presents with Psychiatric Disturbances. In Many Cases, the Emotional Manifestations Are Very Early Signs of the Underlying Metabolic Abnormality

Clinical vignette, Patient A: A 22-year-old woman has a 1-month history of anorexia and depression. Diligent interviewing of the patient reveals that she also has mild constipation and recurrent, vague abdominal discomfort. Laboratory evaluation shows a serum calcium concentration of 12 mg/dL. The patient is diagnosed with hyperparathyroidism, and a solitary parathyroid nodule is excised. Two months after surgery the emotional symptoms are no longer present.

The symptoms of hypercalcemia are most commonly nonspecific and include weakness, fatigue, anorexia, and depression. These emotional disturbances frequently precede the classic complications of hypercalcemia, such as nephrolithiasis and peptic ulcer. It is important to note that the emotional disturbances associated with hypercalcemia may be present while the serum calcium concentration is only mildly elevated.

Clinical vignette, Patient B: A 55-year-old woman has a 2-month history of impaired memory and depression, general apathy, loss of interest in her grandchildren, loss of libido, and 3-pound weight loss. Serum sodium concentration is 129 mEq/L and serum potassium is 5.3 mEq/L. Endocrine evaluation results in a diagnosis of chronic adrenal insufficiency (Addison's disease). Appropriate replacement with glucocorticoid and mineralocorticoid replacement was associated with resolution of the symptoms.

Psychological symptoms are ubiquitous in chronic adrenal insufficiency as in this patient. The emotional complaints occur early in Addison's disease and often predate the classic symptoms of nausea, weakness, postural lightheadedness, and the appearance of hyperpigmentation.

Clinical vignette, Patient C: A 24-year-old woman has a 3-week history of anxiety, irritability, and 3-pound weight loss, without associated tremulousness or heat intolerance. She is now 9 weeks

postpartum. Laboratory studies show a serum TSH concentration of 0.03 mcU/mL and total thyroxine (T4) level of 12 mcg/dL. A diagnosis of postpartum thyroiditis (PPT) was confirmed.

PPT is considered to be a variant expression of chronic autoimmune (Hashimoto's) thyroiditis. PPT typically starts 1 to 4 months after delivery and is associated with a hyperthyroid state that lasts 2 to 8 weeks. At this time, serum thyrotropin concentration is low and serum thyroxin (T4) concentration is elevated. The disorder then progresses to a hypothyroid state that lasts 2 weeks to several months. Ultimately, the patient returns to a euthyroid status.

Subacute thyroiditis (de Quervain's) is of suspected viral etiology. Most common in young women, it is associated with painful enlargement of the thyroid gland. A hyperthyroid state occurs in half of the patients, lasts several weeks, and finally, a euthyroid status is regained. A hyperthyroid state is found in Graves' disease, toxic solitary thyroid nodule, toxic multinodular goiter, and exogenous intake of excessive thyroid hormone.

The important clinical point is that psychiatric complaints are extremely common in all disorders associated with hyperthyroidism. Anxiety, emotional lability, and worsening memory are common early symptoms for which the patient may delay seeking medical attention. Further, these symptoms often result in delayed diagnosis of the increased thyroid metabolic state.

Other metabolic disorders are associated with psychiatric disturbances. Included are chronic hypocalcemia, hypercortisolism (Cushing's disease and Cushing's syndrome), Wilson's disease, pheochromocytoma, hypothyroidism, and intermittent porphyria.

Hypercortisolism is very commonly associated with obesity, hypertension, and hyperglycemia. Of course, there are many patients who have obesity, hypertension, and hyperglycemia, but do not have hypercortisolism with its excess glucocorticoid state.

Psychiatric disturbance occurs in more than half the patients with Cushing's disease or syndrome. Common complaints include anxiety, depression, emotional lability, and panic attacks. Depression occurs in two-thirds of patients. Unlike most patients with depression who have decreased appetite, depressed patients with hypercortisolism have *increased appetite* and weight gain. An important clinical point is that the psychiatric symptom is frequently the presenting complaint to the clinician.

Chronic hypocalcemia is associated with decreased production or action of vitamin D (as in malabsorption syndrome), hypoparathyroidism, or hypomagnesemia (as occurs in chronic alcohol abuse, malabsorption syndrome, or with cisplatin therapy). Hypocalcemic patients may exhibit anxiety or depression

before the neurologic manifestations of circumoral paresthesias, tetany, or positive Chvostek sign are evident. Hypoalbuminemia, as is noted in chronic, severe liver disease or in nephrotic syndrome, is associated with a decrease in total serum calcium concentration but not in ionized calcium concentration. Therefore, hypoalbuminemic patients do not have symptoms or signs of hypocalcemia.

Hypothyroid patients often have poor mental concentration, depressed mood, apathy, or social withdrawal. However, it appears that these psychiatric expressions occur when the patient has other clear manifestations of the decreased thyroid state, such as cold intolerance, pallid complexion, and dry skin. However, patients with *subclinical hypothyroidism*, defined as normal serum free thyroxine (T4) concentration with a slightly elevated serum thyrotropin (TSH) concentration, appear to have increased frequency of neurotic depression or anxiety when other clinical features of hypothyroidism are not evident.

The classic presentation of pheochromocytoma is episodic hypertension in association with profuse sweating, palpitations, and headache. Anxiety often occurs during the paroxysmal release of catecholamines from the sympathetic ganglia or adrenal medulla. During the acute anxiety, the patient will have tachycardia and hypertension.

Wilson's disease is an autosomal recessive heritable disease of cellular copper transfer. The incidence is approximately 1 case in 30,000 live births. Pathologically, copper is deposited in the liver, kidney, and brain. The clinical manifestations almost always start between the ages of 6 and 30 years. Liver involvement ranges from asymptomatic hepatic dysfunction to acute liver failure to cirrhosis with portal hypertension. Young patients whose diagnosis is not made because of liver dysfunction often present with psychiatric disturbances ranging from personality change to worsening academic performance to extrapyramidal signs, such as rigidity and bradykinesia. Serum ceruloplasmin concentration is low in most patients with Wilson's disease.

Acute intermittent porphyria (AIP) is an autosomal dominant heritable disorder in which an enzyme deficiency results in impaired heme synthesis. It is more common in women; symptoms appear to be exacerbated during the premenstrual period. Approximately 90% of persons with the inherited enzyme deficiency are clinically normal throughout life. The clinical presentation of the inherited disorder starts after puberty and is neurologic, with involvement of the peripheral, autonomic, and central nervous system. The neurologic pathophysiology causes acute abdominal pain, either generalized or local, which is the most common symptom in AIP. The pain may be severe and may be associated with nausea, vomiting, diarrhea, and ileus. Peripheral neuropathy may present with proximal muscle weakness, cranial or motor

neuropathy, bulbar paralysis, or sensory neuropathy. Central nervous system neuropathology may cause seizure in acute attacks of AIP.

Many medications may precipitate acute attacks of AIP. These include angiotensin converting enzyme inhibitors, barbiturates, calcium channel blockers, ergot preparations, ketoconazole, sulfonamides, and sulfonyureas.

Here is the key clinical point germane to this topic: Psychiatric disturbances may be prominent in AIP and may be the sole expression of the inherited disease. Anxiety, hysteria, depression, agitation, delirium, and psychosis may be evident. It is estimated that as many as 1 in 500 psychiatric inpatients has AIP.

You must remember:
1. Psychiatric complaints are very common reasons for patient visits.
2. Before prescribing a psychotropic medication, the clinician must studiously consider the presence of an underlying metabolic disorder as the cause of the patient's distress.
3. Many medications may precipitate the symptoms in AIP.

Brevity 6: Always Seek a Common Denominator in Medicine

The Common Denominator in Syncope Is Cerebral Ischemia

Clinical vignette, Patient A: During venipuncture in a medical clinic, a burly 31-year-old man has sweating, nausea, and then faints. Heart rate during syncope is 44/min. The patient spontaneously awakens within 1 minute.

Clinical vignette, Patient B: A 77-year-old man with known coronary heart disease and stable angina pectoris faints during a heated, vociferous argument in a condominium association meeting. He spontaneously regains consciousness in 30 seconds.

Clinical vignette, Patient C: While running on the soccer field, an 18-year-old man suddenly collapses and faints. He quickly regains consciousness and is transported to the emergency department of the closest hospital.

Three patients; three patients who have syncopal episodes; yet, three patients with totally different medical conditions. Is there a common denominator?

Indeed, the common denominator in syncope is transient, generalized cerebral ischemia. The decreased cerebral perfusion may be caused by several different pathophysiologic mechanisms. Cardiovascular etiologies of syncope include the following:

- Arrhythmia
- Obstruction to blood flow
- Reflex mechanisms
- Orthostatic hypotension

Let us consider each of these mechanisms.

A. Syncope Resulting from Arrhythmia

Bradycardia

1. In sick sinus syndrome (brady-tachy syndrome) including sinus arrest or sinus pauses
2. Second- or third-degree atrioventricular (AV) block resulting from disease of the cardiac conduction system
3. Adverse effects of medicine, for example, calcium channel blockers, beta adrenergic blockers, digoxin

Tachycardia

1. Ventricular tachycardia
2. AF in preexcitation syndrome

   Acute myocardial ischemia is a common cause of ventricular tachycardia that results in decreased cerebral blood flow and syncope. The pathophysiologic mechanism is considered to be ischemia-induced reentry circuits in the ventricle. *Fainting in the older patient during physical exertion or during a heated argument suggests myocardial ischemia-induced arrhythmia*.

A Structurally Normal Heart

There are three conditions, all associated with a *structurally normal heart*, that are associated with syncopal attacks. They are long QT interval syndrome, preexcitation syndrome, and Brugada syndrome. Long QT interval syndrome may be a heritable (genetic) disorder or acquired; related to an electrolyte abnormality, such as hypokalemia, hypocalcemia, or hypomagnesemia; or caused by the direct effect of medication on the myocardial action potential.

This syndrome places the patient at risk for the heart rhythm to suddenly catapult into ventricular tachycardia, causing syncope or, worse, sudden cardiac death. *The key clinical point is that sympathetic nervous system stimulation appears to be the trigger for development of the life-threatening tachycardia.* Fainting in a child or adolescent during physical exertion or during a heated argument suggests congenital long QT interval. Of course, acquired long QT interval may occur at any age, but again, the paroxysmal ventricular tachycardia is triggered by sympathetic nervous system stimulation.

Preexcitation syndrome is a congenital disorder in which accessory conduction fibers (Bundle of Kent) connect the atria to the ventricles, bypassing the AV node. The electrocardiographic manifestations are short PR interval, delta wave, and wide QRS complex. Conduction of action potentials through the accessory pathways bypassing the AV node predisposes the patient to AF with very fast ventricular rates, even 300/min. The patient may then have a sudden syncopal episode. However, if the AF degenerates into *ventricular* fibrillation, sudden cardiac death occurs.

Brugada syndrome is a heritable disorder (autosomal dominant) in which there is an abnormality in sodium transport in the myocardial action potential. As a result, the patient is at risk of developing ventricular tachycardia. If self-limited, the tachyarrhythmia may cause syncope; if not, sudden cardiac death results. In most cases, Brugada syndrome clinically is expressed in persons ages 20 to 65 years, though it has been reported in a child of 3 years.

A Structurally Abnormal Heart

Let us turn our attention to syncope associated with *structural heart abnormalities*. The most common and the most important condition, because of its association with sudden cardiac death, is hypertrophic cardiomyopathy (HCM). HCM is a disorder of the sarcomere in the myocardium that is clinically characterized by inappropriate left ventricular hypertrophy, hyperdynamic left ventricular contraction, increased stiffness (or reduced compliance) of the left ventricle, and, in some cases, left ventricular outflow obstruction. To the clinician, the most significant feature of hypertrophic cardiomyopathy is its *variability*: variability in genetic mutation, anatomy, clinical features, and hemodynamics.

Many genetic mutations have been identified in HCM; it appears that most mutations involve cardiac myosin or troponin. In the majority of cases, autosomal dominant inheritance can be demonstrated. Other HCM cases are sporadic. A genetic mutation found in HCM is thought to be present in 1 in 500 persons. The frequency of this mutation does not mean that HCM is a common clinical condition. Rather, it is thought that many persons with a genetic mutation of HCM live normal or near-normal lives.

Anatomically, any portion of the left ventricle may be disproportionately hypertrophic. In some patients the hypertrophy is generalized; in others, the hypertrophy may be limited to the anterior portion of the ventricular septum, or limited to the anterior and posterior septum, or limited to the septum and lateral free wall, or, predominantly, limited to the apical area. It is puzzling, but the degree of hypertrophy does not appear related to the severity of the patient's symptoms.

The full anatomic expression of HCM may not be evident until the end of adolescent growth. Let me explain the clinical importance of this statement. For example, an 18-year-old has just been diagnosed with HCM. His siblings should undergo evaluation, including history and physical exam, electrocardiography, and echocardiography. If a 13-year-old sibling has a normal echocardiogram, the diagnosis of HCM cannot be dismissed. That sibling should have an *annual echocardiogram performed through age 18 years* and at 5-year intervals as an adult. Rarely, HCM may present clinically after age 60 years. Approximately 90% of patients diagnosed with HCM are asymptomatic and are diagnosed through family screening of diagnosed HCM patients.

The classic pathophysiologic abnormality in HCM is increased stiffness (decreased compliance) of the left ventricle. The resultant increase in left ventricular end-diastolic pressure causes elevation of the mean left atrial pressure. In turn, the elevated left atrial pressure is transmitted back to the lungs, causing interstial fluid accumulation and increased lung stiffness. The patient, then, has dyspnea. Further, some HCM patients have left ventricular outflow obstruction resulting from a combination of anatomic septal hypertrophy in conjunction with abnormal mitral leaflet motion, namely, systolic anterior motion of a mitral leaflet. This anatomic and functional disturbance impairs ejection of left ventricular blood into the aorta. This patient will have a bisferiens, or a double, carotid arterial pulse.

The three cardinal symptoms in HCM are as follows:

- Dyspnea related to the stiff left ventricle
- Angina pectoris caused by increased oxygen demand of the hypertrophic myocardium
- Syncope

Syncope in HCM may be related to three different mechanisms, all resulting in generalized cerebral ischemia. First, left ventricular outflow obstruction, as described earlier, may decrease cardiac output and cerebral blood flow. Second, the hypertrophic myocardium may become ischemic with a resultant induced ventricular tachycardia causing syncope (or sudden cardiac death). Finally, some HCM patients have inappropriate peripheral

vasodilation during exertion. In these patients, exercise is not associated with the expected, normal increase in blood pressure. Rather, there is a drop in blood pressure thought to be caused by inappropriate vasodilation in nonexercising muscles. The drop in blood pressure causes cerebral ischemia and syncope.

HCM is the most common cause of sudden cardiac death in high school and college athletes. Sudden death is often the *initial clinical manifestation* of the disorder, for many of these patients did not, earlier, have any of the classic symptoms. However, in those diagnosed with HCM, identified risk factors for sudden cardiac death include family history of HCM-related sudden death, syncope not related to any other specific cause, massive (> 30 mm) ventricular hypertrophy, asymptomatic ventricular tachycardia, and abnormal blood pressure response to exercise.

Syncope and sudden cardiac death in HCM are not necessarily correlated with physical exertion. Syncope may occur with or without vigorous physical exertion. Further, only about 20% of HCM patients who die suddenly were engaged in moderate to vigorous physical activity at the time of death.

Typically, syncope due to arrhythmia is not associated with prodromal symptoms prior to the sudden loss of consciousness. (An exception is the bradycardia associated with vasovagal fainting, which is described later in the section titled "Syncope Due to Reflex Mechanisms").

Brady-tachy syndrome (sick sinus syndrome) may be intrinsic or extrinsic, the latter related to medication intake or coexisting noncardiac disease. The syndrome is characterized by alternating periods of tachycardia (usually AF or atrial flutter) and bradycardia (typically related to marked sinus bradycardia or sinus arrest). The tachyarrhythmia presents with heart failure (HF), palpitations, or angina pectoris; the bradyarrhythmic episodes are associated with syncope, near-syncope, and weakness.

Pathologically, *intrinsic* brady-tachy syndrome is associated with degeneration and fibrosis of the sinoatrial node and adjacent atrial tissue. *Extrinsic* causes include intake of medications (beta adrenergic blockers, the calcium channel blockers verapamil and diltiazem, and lithium), hypothyroidism, sleep apnea, and increased intracranial pressure.

AV block is a common cause of syncopal episodes. Second-degree AV block is characterized by intermittent failure of sinoatrial impulses to depolarize the ventricle and excite ventricular contraction. It is classified as Mobitz type I (Wenckebach) in which the conduction block occurs at the level of the AV node, or Mobitz type II in which the block is infranodal. In Mobitz I block, progressive lengthening of the PR interval occurs until a sinus beat is not conducted to the ventricle. The electrocardiographic appearance of Mobitz II block is a fixed PR interval (usually > 0.20 sec) with intermittent failure of the atrial

impulse to reach the ventricle. Mobitz I AV block is temporary and reversible when related to acute inferior wall myocardial infarction (the artery to the AV node is derived from the right coronary artery), heightened vagal tone, and medications (beta adrenergic blockers, the calcium channel blockers verapamil and diltiazem, lithium, and digoxin). Infrequently, infectious diseases such as endocarditis and Lyme disease may produce Mobitz I AV block. Mobitz II block is not reversible and is not related to medication intake. These patients generally have a poor prognosis because of associated extensive myocardial damage.

Complete AV block (third degree) may be a result of the previously mentioned medications and, even transiently, of increased vagal tone. Degenerative disease of the conduction system (Lev disease) is a common underlying etiology of complete AV block. Infiltrative disease of the myocardium, particularly, amyloidosis and sarcoidosis, is a much less common cause of third degree block. Rarely, endocarditis and Lyme disease may be the underlying cause.

In second- and third-degree AV block, the inability of some or all atrial impulses to reach the ventricles causes bradycardia, decreased cardiac output, generalized cerebral ischemia, and resultant syncope.

B. Syncope Due to Obstruction to Blood Flow

- Aortic valve stenosis
- Hypertrophic cardiomyopathy
- Pulmonary embolism
- Left atrial myxoma

The classic triad of symptoms in severe aortic stenosis includes dyspnea (resulting from diastolic HF), angina pectoris (even in the absence of coronary artery stenosis), and syncope.

The syncope is typically *associated with exertion*. With the fixed outflow obstruction at the aortic valve, the cardiac output cannot increase as would be expected during effort. At the same time, exercise induces peripheral vasodilation that lowers blood pressure. Vasodilation in the presence of fixed cardiac output causes the syncopal episode.

Signs and symptoms of DVT in the legs may be obvious, subtle, or absent. Examination of the patient whose DVT is complicated by pulmonary embolism may reveal erythema or edema of the leg and a palpable venous cord. The most common symptoms of the pulmonary embolism are acute, pleuritic chest pain and dyspnea. Not infrequently, apprehension, hemoptysis, sweating, and cough are associated symptoms. However, if the embolus (or multiple emboli) is large enough to obstruct pulmonary blood

flow, then a sudden decrease in left ventricular stroke volume results and syncope occurs.

A myxoma is an atrial tumor often attached by a stalk to the left side of the atrial septum. The myxoma may move into the mitral orifice during ventricular diastole, thereby obstructing blood flow from left atrium to ventricle. A sudden drop in stroke volume results, thus provoking syncope. At other times, the tumor may fragment, leading to systemic embolism. Echocardiography provides clear imaging of these intracardiac masses.

C. Syncope Due to Reflex Mechanisms

- Parasympathetic (neurocardiogenic or vasovagal)

Vasovagal syncope includes the common faint in which the patient, often in a disquieted state, such as during venipuncture, while experiencing body pain, or with prolonged, motionless standing, has a prodrome of nausea, sweating, and warmth immediately followed by loss of consciousness.

Heightened vagal tone plays a key role in the syncope, for hypotension and bradycardia are typically present. (Vasodepressor syncope is a variant parasympathetic-mediated form of syncope in which hypotension is present, but the heart rate is normal.) Syncope associated with specific situations, for example, swallowing (deglutition), urination (micturition), and a vigorous paroxysm of coughing (posttussive), is, similarly, thought related to increased vagal tone.

An unusual variant of syncope related to heightened vagal tone is breath-holding syncope. This occurs in children 6 months to 6 years of age. The syncope is precipitated in most cases by emotional insult, fear, or mild trauma. The breath-holding has two clinical presentations, cyanotic and pallid. In the cyanotic form, crying precedes breath-holding. The child then becomes limp, blue, and faints. Generalized seizing may occur. In the pallid presentation, the child stops breathing, becomes pale and limp, faints, and may have clonic contractions and urinary incontinence. Consultation with a pediatric neurologist is generally indicated to differentiate breath-holding syncope from a primary seizure disorder.

D. Syncope Due to Orthostatic Hypotension

- Impaired sympathetic (adrenergic) reflexes
- Hypovolemia
- Adverse medicine response

The sympathetic reflex arc plays an integral role in regulation of blood pressure and cardiac output. *Normally*, assumption of the standing position from recumbency or sitting causes a prompt, initial drop in blood pressure. The initial

hypotension is followed by carotid baroreceptor activation that results in efferent sympathetic stimulation. The heightened sympathetic tone produces an increase in heart rate and constriction of arterioles and veins. The blood pressure increases as a result of the arteriolar constriction increasing systemic vascular resistance. At the same time, stimulation of sympathetic fibers that innervate the heart results in an increase in heart rate and contractility. Resultantly, enhanced propulsion of blood contributes to an increased blood pressure upon standing in conjunction with increased cardiac output.

Consequently, in the normal person, assumption of the standing position is associated with a slight decrease in systolic blood pressure, a slight increase in diastolic pressure, and a modest increase in heart rate. *Mean arterial pressure is the same in the standing as in the recumbent position.*

In the patient who has adrenergic insufficiency, either primary or secondary (as is common in diabetic autonomic neuropathy), assumption of the standing position does not result in arteriolar constriction or increase in heart rate. Here is a common clinical vignette:

> **An elderly patient with type 2 diabetes mellitus has lightheadedness, dimmed vision, and feeling of impending faint upon rising from bed. Blood pressure in the sitting position is 122/76 mm Hg with pulse of 78/min. Upon standing, blood pressure is 84/60 mm Hg with pulse of 80/min.**

What is the pathophysiologic mechanism that is causing symptoms and the observed hemodynamic response in the adrenergic dysfunction? Upon standing, note that both systolic and diastolic blood pressure significantly decrease (orthostatic hypotension), but heart rate does not increase—all resulting from an impaired sympathetic response to assumption of upright posture. The deficient sympathetic reflex response does not result in the expected normal compensatory response, namely, an increased heart rate and arteriolar constriction that would maintain a normal blood pressure in the standing position. Clinically, orthostatic hypotension causing syncope due to autonomic insufficiency is very common, particularly in diabetic patients.

In contrast, orthostatic hypotension is very common in patients who are hypovolemic. The decreased circulating blood volume may be a result of excessive diuresis, hemorrhage, or endocrinopathy, such as chronic adrenal insufficiency with hypovolemia related to a deficiency in mineralocorticoid hormones. Orthostatic hypotension is related to the abnormally low circulating blood volume. In these patients, the sympathetic nervous system is intact. Therefore, with assumption of the standing position, systolic and diastolic blood pressure drops, but the *heart rate significantly increases* (12 to 20 beats per minute) because the sympathetic reflexes and baroreceptor stimu-

lation are intact. Therefore, heart rate increases in an appropriate compensatory response to the orthostatic hypotension.

Note the important clinical difference: *In orthostatic hypotension related to adrenergic (sympathetic) dysfunction, the drop in blood pressure is not associated with an increase in heart rate. In orthostatic hypotension due to hypovolemia, the drop in blood pressure is associated with a compensatory increase in heart rate.*

An Important Clinical Point That Is Correlated with Syncope of Any Etiology: "All That Seizes Is Not Epilepsy"

Clinical vignette: A 48-year-old woman was walking in a mall pushing a baby stroller when she suddenly collapsed and fainted. Witnesses noted jerking of the legs bilaterally during the brief period of unconsciousness. The patient quickly awakened and was transported to the emergency department. Brain imaging studies were normal. A diagnosis of epilepsy was made. Anti-epileptic medication was prescribed. Two months later the patient had acute, fulminating hepatic failure due to the anti-epileptic medication. Liver transplantation was performed.

Careful review of the medical record revealed that the electrocardiogram taken in the emergency department after the acute event showed that the patient had normal sinus rhythm, a very long PR interval (first-degree AV block), with complete right bundle branch block and left anterior hemiblock. Clearly, electrocardiography showed evidence of markedly impaired AV and intraventricular conduction, which placed the patient at high risk for complete (third-degree) heart block.

Simply put, this patient was at very high risk of having an episode of complete heart block causing syncope, not having an epileptic attack. Appropriate cardiac evaluation would have demonstrated the need for a permanent cardiac pacemaker.

Syncope of any etiology may be associated with jerking motion of the extremities. Do not catapult to a diagnosis of epilepsy without careful consideration of whether the patient may have had a syncopal episode with secondary muscle jerking.

Let us continue on the theme "All that seizes is not epilepsy."

Clinical vignette: It occurred many years ago; I was in the very first week of my clinical practice. I happened to be seated in the physicians' lounge of the hospital having a cup of coffee. A young

man, unknown to me and in an obvious state of disquietude, sat down at the same small table. Speaking quickly, he told me his name and that he was a neurologist. "I don't understand," he cried. Clearly, I had no idea what he meant.

Without my inquiry, he volunteered that the previous day he had taken his oral examination for certification as a specialist in neurology. He had failed the examination and was distraught. Again, there was no time for me to utter a word. "Here's the case. Where did I go wrong?"

The specialty board examiner presented him with a case: A 14-year-old boy is transported to the emergency department and is having generalized seizures. The examiner asked, "How would you treat the patient?" The young neurologist, the test candidate now seated opposite me, responded that he would administer intravenous phenytoin. The examiner said that the seizures continue. "Now what would you do?" An increased dose of phenytoin; yet the seizures continue. Intravenous administration of phenobarbital; yet the seizures continue. "Now what would you do?" "I would take the patient to the operating room and have the anesthesiologist administer general anesthesia" (remember, this was 5 decades ago).

The examiner stood up, and without saying a word, slapped his hand on the table and hurriedly walked out of the room. A moment later, he returned, said, "You failed," and left.

"Where did I go wrong?" the neurologist plaintively repeated the question. Softly, I whispered, "Hypoglycemia." He threw his head back, closed his eyes, and cried.

"*All that seizes is not epilepsy*."

The Common Denominator in Cor Pulmonale Is Pulmonary Hypertension Due to Increased Pulmonary Vascular Resistance

Cor pulmonale is heart disease secondary to lung disease. The lung disease may be vascular, for example, multiple pulmonary emboli; parenchymal, for example, chronic bronchitis or interstitial pulmonary fibrosis; or pneumonioconiosis, for example, asbestosis or chronic beryllium disease. In each of these conditions, there is destruction of the pulmonary vascular bed. Massive obesity and hypoventilation (Pickwickian syndrome) are associated with alveolar hypoxia that causes pulmonary vasoconstriction.

Whether the mechanism is vasoconstriction or the physical obliteration of the pulmonary vascular bed, the common denominator is an increase in pulmonary

vascular resistance that produces an increase in pulmonary artery pressure (pulmonary hypertension) and, ultimately, right heart failure (right HF).

Right heart failure due to pulmonary hypertension from lung disease is cor pulmonale. Signs of right HF include left parasternal lift, elevated jugular venous pressure, congestive hepatomegaly (smooth, tender, enlarged liver), modest ascites, and peripheral edema.

The most common cause of right HF is chronic systolic left heart failure. This is not, however, cor pulmonale because the right HF is not due to lung disease. Finally, note that in the typical patient who has emphysema (in contrast to chronic bronchitis), pulmonary artery pressure is normal or near normal. As a result, emphysema patients do not develop cor pulmonale.

A Dilated Left Atrium Is a Common Denominator in Atrial Fibrillation

AF is the most common sustained, significant, and problematic arrhythmia in clinical practice. AF is associated with reduced quality of life, serious morbidity, and increased mortality. Left atrial dilatation (increased left atrial dimension) is commonly seen in patients with AF.

A dilated left atrium leads to AF. Oppositely, AF leads to a dilated left atrium. A dilated left atrium is common in patients who have mitral valve disease (stenosis or regurgitation), mitral annulus calcification, hypertensive heart disease, and atherosclerotic heart disease, especially in those who have sustained a myocardial infarction. In each of these conditions, there is stretching of the left atrial walls that causes left atrial dilatation that, in turn, appears to be a key factor in the genesis of AF.

There is evidence that AF itself results in left atrial dilatation. This may explain why *paroxysmal* AF commonly progresses to *chronic* AF. Further, this may explain why electrical or chemical cardioversion of AF is more difficult in patients with a longer duration of AF.

Ischemia of Muscle Is the Common Denominator in the "Claudications"

The term *claudication* is linguistically derived from the Latin word meaning "cramping." *Angina* is also derived from the Latin, meaning "strangling." Whether it be anginal discomfort in the chest or cramping in the leg, ischemia of muscle is the unifying pathophysiologic mechanism.

The key clinical point is that there are many claudications. The common denominator of muscle ischemia and claudication relate to the following structures:

- Heart

- Leg
- Arm
- Jaw
- Intestine
- Uterus

Cardiac claudication, of course, is angina pectoris. The myocardial ischemia may result from myocardial oxygen demand outstripping oxygen supply, as is typical in the patient who has atherosclerotic heart disease or left ventricular hypertrophy of any etiology. In these conditions, myocardial ischemia causes ST segment depression in the electrocardiogram.

Conversely, myocardial ischemia and angina pectoris may occur when oxygen supply is reduced at a time when myocardial demand is normal. This is typical of variant angina (Prinzmetal angina) in which coronary artery spasm is the underlying mechanism producing cardiac ischemia. Remember, during anginal discomfort in variant angina the ST segments are elevated.

Claudication involving the lower extremity may be due to aortoiliac occlusive arterial disease. These patients have hip and buttocks aching with walking (Leriche's syndrome). Almost always, in the male the vascular disease causes impotence. Further, atherosclerotic stenosis or occlusion of the common femoral artery causes claudication of the thigh. Superficial femoral artery stenosis typically causes cramping in the upper two-thirds of the calf; exertional cramping of the lower third of the calf is usually due to popliteal artery aneurysm or stenosis.

Claudication involving the arm occurs in one-third of patients who have subclavian steal syndrome. This disorder is due to atherosclerotic subclavian artery stenosis proximal to the origin of the vertebral artery. In these patients, there is always a significant difference in systolic blood pressure between the normal and affected arm. In my experience, the systolic blood pressure in the affected arm (the side of the arterial stenosis) is always at least 20 mm Hg lower than in the normal arm.

Patients with subclavian steal syndrome generally have *either* neurologic symptoms or arm symptoms. Neurologic symptoms that may be resulting from retrograde flow in the affected vertebral artery ("steal") include the classic symptoms of vertebrobasilar artery insufficiency:

- Dizziness or vertigo
- Ataxia
- Blurring of vision in both eyes or diplopia
- Tinnitus

Exercise involving the arm on the affected side may cause arm cramping (claudication) in addition to coolness and paresthesias or, occasionally, numbness.

A special type of subclavian steal syndrome may be termed "internal mammary-coronary steal." Note that in the following case, the development of subclavian artery stenosis presents as recurrent angina pectoris, not with arm claudication or vertebrobasilar artery insufficiency symptoms.

Clinical vignette: A patient has undergone left internal mammary artery bypass grafting for treatment of angina pectoris. Two years later, the angina pectoris recurs. The clinical impression is that the patient has developed a new coronary atherosclerotic stenosis.

Examination shows blood pressure in the right arm is 130/82 mm Hg; in the left arm, 104/82 mm Hg. What is going on in this case? The patient has developed new left subclavian artery stenosis (ipsilateral side to the graft) that is causing reappearance of angina pectoris. The new left subclavian artery stenosis is causing retrograde blood flow in the grafted internal mammary artery (steal).

A key clinical point that you must remember: It is imperative to take the blood pressure in both arms of all patients, particularly those with known atherosclerotic disease. If you do not take bilateral blood pressure measurements in the patient with prior internal mammary artery graft, recrudescence of angina pectoris will be attributed to the development of a new coronary artery atheromatous stenosis rather than the correct cause, namely, development of subclavian artery stenosis.

Claudication of the jaw is a common symptom in the patient who has giant cell arteritis, occurring in 50% of cases. Often, jaw claudication is an early symptom. It may be unilateral or bilateral. The aching discomfort is felt while chewing and is relieved in minutes by rest. This discomfort is mimicked by the discomfort noted by the patient who has temporomandibular joint pain. However, claudication is clearly differentiated from jaw fatigability without discomfort that is characteristic of myasthenia gravis.

Other symptoms of giant cell arteritis include headache, fever, visual loss, fatigue, and weight loss. Please refer to the section titled "Stroke *and* Fever" in Chapter 2, "The Most Important Word in Diagnosis: *And*."

Intestinal claudication or chronic mesenteric ischemia of the small bowel is usually due to atherosclerotic stenosis in the superior mesenteric or celiac artery. Patients have crampy, dull postprandial pain in the epigastrium and upper abdomen that starts within the first hour after eating and subsides

within 2 hours. Patients who have intestinal claudication typically have recognized atherosclerotic heart or cerebrovascular disease.

There is one more claudication, one that is termed "neurogenic claudication" or more properly, "pseudoclaudication." It is not related to ischemia; rather, it is due to osteophytic narrowing of the lumbar spinal canal. Pseudoclaudication may produce buttock or leg discomfort with walking; most commonly, it involves the calf or distal lower extremity. It resolves with rest similar to vascular claudication. In contrast to ischemia-induced leg discomfort, at times, neurogenic claudication will cause discomfort while the patient is standing still.

To differentiate vascular from neurogenic claudication, consider the following:

- Pulses are absent in vascular but are often normal in neurogenic.
- Pain with cough or sneezing occurs only in neurogenic.
- Neurogenic patients often have a dermatomal sensory deficit.
- In 30% of cases, neurogenic patients have limited straight leg raising.

Is There a Common Denominator in Clubbing? It Seems More and More Likely That There Is One

Clubbing is noted in patients who have disparate diseases that include cyanotic congenital heart disease, chronic inflammatory disorders, and malignant neoplasia. Specific diseases in which clubbing occurs include these:

- Tetralogy of Fallot
- Transposition of the great arteries
- Infective endocarditis
- Cystic fibrosis, empyema, tuberculosis, lung abscess, and bronchiectasis
- Primary and metastatic lung cancer
- Inflammatory bowel disease
- Cirrhosis
- Celiac disease

Clubbing is not associated with chronic obstructive lung disease or sarcoidosis, even when the sarcoidosis is associated with pulmonary fibrosis. *Never ascribe clubbing to chronic obstructive lung disease.*

Vascular endothelial growth factor (VEGF) is the single biologic agent that may be the common denominator that links these disorders to clubbing of fingers and toes. VEGF stimulates vascular growth in tissues as is found in clubbed digits.

VEGF is increased in conditions that are all associated with clubbing:

- Tissue hypoxia of any etiology

- Chronic inflammation
- Malignancy

In disorders in which hypoxia or inflammation is present, normal tissues produce VEGF. However, in malignancy the tumor cells produce the VEGF.

It is fascinating how such unrelated medical disorders have the same sign, clubbing, and how VEGF appears to be the common denominator linking them.

Alpha Fetoprotein: A Common Denominator in Tumor Markers

Worldwide, it is estimated that 12% of all deaths are due to cancer. Understandably, intensive research is directed toward finding serum markers that indicate the presence of a specific neoplasm or the very high likelihood of a person developing that tumor.

CA 125 and CA 19-9, carcinoembryonic antigen (CEA), and prostate-specific antigen (PSA) are well known to the public. Alpha fetoprotein (AFP) is, perhaps, less well known, but is an important common denominator in certain tumors.

Tumor markers are proteins. Cancer is essentially the unregulated growth of normal tissue; thus, both nonmalignant and malignant tissues may produce these proteins. A number of these protein markers are, in fact, tumor antigens. These antigens include CEA, AFP, and the cancer antigens CA 125 and CA 19-9.

Markers are considered to be *cancer specific*, meaning that they are directly associated with the presence of neoplasms. Cancer-specific markers include CEA, CA 19-9, and CA 125. Other markers are considered to be *tissue specific*, meaning that they are not directly related to a neoplasm, but are associated with certain tissues that are undergoing neoplastic change. AFP and PSA are tissue-specific markers. Further, AFP is considered to be an *oncofetal* antigen, meaning that it is present in normal fetal tissue and diminishes to undetectable levels in normal humans.

What Is the Common Denominator in AFP?

- Serum levels of AFP are elevated in 95% of males who have testicular germ cell gonadal tumors.
- An increasing serum AFP concentration in a patient with cirrhosis raises concern for the development of hepatocellular carcinoma.
- An elevated maternal serum AFP raises suspicion of a neural tube defect in the fetus. An ultrasound examination and amniocentesis should then be performed to determine whether the neural tube defect

is, in fact, present. I have not found an explanation why the AFP marker is elevated in neural tube defects.

Is There a Common Denominator That Links Disparate Functions and Conditions?

Are the following functions and conditions linked in some way?

- Valvular heart stenosis
- Mood and memory
- Sleep and wakefulness
- Migraine headaches
- Appetite
- Pain perception
- Bowel contractility
- Temperature regulation

Yes, there is a common denominator. It is a hormone called serotonin, also known as 5-hydroxytryptamine (5-HT).

Important clinical questions immediately come to mind. What is serotonin and what does it do? How can one hormone have such widely different physiologic effects? How does one hormone accomplish a response in so many different tissues?

The ubiquitous expression of serotonin is related to the fact that there are *at least seven major families of serotonin receptors*. Each family of receptors has its own structure, its own pharmacology, and its own functional property. The receptors all have the basic "5-HT" label, followed by a suffix (e.g., 5-HT 1, 5-HT 2). The 5-HT 1 and 5-HT 5 receptors are in the brain; 5-HT 2 receptors are in heart and stomach; the 5-HT 4 receptors are in the bowel.

Serotonin is a hormone derived from the amino acid tryptophan that has both central and peripheral physiologic effects. Serotonin is synthesized primarily (95%) in the enterochromaffin cells of the gut mucosa and to a lesser degree in the brain and in mast cells of large bronchi. The hormone synthesized in the gut mucosa is released into the circulation where it is stored in platelets.

Serotonin is a neurotransmitter (along with acetylcholine, norepinephrine, dopamine, gamma amino butyric acid, glutamate, and glycine) secreted into the parenchyma of the brain. The hormone's effect in different areas of the brain is expressed in many psychologic functions, for example, inhibiting aggressive behavior and anxiety, promoting sleep, and elevating mood. Serotonin receptors in the brain stem and in the dorsal nerve roots modulate pain perception; activation of these receptors lessens the patient's awareness of painful stimuli.

Serotonin plays an important role in migraine headaches. It appears that the final event leading to migraine pain is release of inflammatory vasodilators at the peripheral nerve endings of the trigeminal nerve (cranial nerve V) on vessels of the meninges and scalp. Release of serotonin from platelets is thought to promote this pathway. Platelet concentration of serotonin is increased before a migraine headache; during the migraine headache the serotonin concentration in the platelets is low. The action of the SSRIs (or triptans) in treatment of acute migraine is still somewhat ill defined. One beneficial action of the triptans is to stimulate 5-HT 1 receptors that reduce dural arterial vasodilation and inflammation. Additionally, the triptans stimulate the 5-HT 1 serotonin receptors in the brain stem, which reduces the awareness of pain.

Plasma concentrations of the serotonin precursor, tryptophan, are lower in patients who suffer from major depression compared to healthy, normal subjects. The beneficial pharmacologic effect of the SSRIs in treatment of depression is to potentiate serotonin's effect on brain receptors. It is clearly recognized that there is an increased prevalence of depression in children and adolescents who have type 1 diabetes mellitus. The explanation may be significantly related to the fact that plasma serotonin levels are lower in these patients compared to nondiabetic subjects.

Medications that block secretions of serotonin cause depression. In contrast, medications that increase serotonin activity in the brain lessen depression. This explains the effectiveness of SSRI medication in treatment of depression. It is clinically estimated that three-quarters of patients with depression are effectively treated with SSRIs that block the uptake of serotonin at nerve endings.

Serotonin increases bowel contractility and secretions; an elevated level of serotonin, as in carcinoid syndrome, causes the diarrhea characteristic of that tumor. In the heart, serotonin is released from platelets in response to a damaged endothelium as occurs in atheromatous plaque rupture. Serotonin's release from platelets increases the synthesis of thromboxane A2, whose local vascular effect is platelet aggregation and vasoconstriction, thus promoting acute thrombosis.

What Is the Link Between Serotonin and Valvular Heart Disease?

Patients who have carcinoid syndrome have a classic triad of symptoms: flushing, diarrhea, and wheezing. The flushing and wheezing are related to the tumor's release of histamine, not serotonin. It is the serotonin that causes the secretory diarrhea. Interestingly, carcinoid tumors that arise in the intestine do not cause *carcinoid syndrome* unless liver metastases are present. However, patients who have bronchial carcinoids may manifest the syndrome without metastases.

Further, it is known that patients with carcinoid syndrome often have valvular heart disease, most notably pulmonic and tricuspid stenosis. The *same fibrotic valvular disease* is noted in the following patients:

- Patients who ingest ergot alkaloid medication, such as ergotamine, methysergide, pergolide, and cabergoline (note the *ergo* in medication nomenclature)
- Patients who ingest the anorectic medicine combination fenfluramine and phentermine ("fen-phen")

Here are the key clinical points that you must know:

- The specific family of serotonin receptor called 5-HT 2 stimulates fibroblast growth and deposition of fibrous tissue on the valvular endocardium.
- The ergot medicines, the anorectic medications fenfluramine and phentermine, and carcinoid syndrome all share a single feature—they all increase serotonin levels and all stimulate the 5-HT 2 receptor. Therefore, they all cause valvular stenosis that predominantly affects the tricuspid and pulmonic valves.
- SSRIs that increase serotonin activity in the brain *do not stimulate 5-HT 2 receptors* and, therefore, do not cause valvular stenosis.
- Triptans, important medicine used in the therapy of acute migraine headaches, are serotonin agonists that increase serotonin activity in the brain. Again, triptans *do not stimulate 5-HT 2 receptors* and, therefore, do not cause valvular stenosis.

You must remember:

1. There are clinically important common denominators in patients who have syncope, cor pulmonale, AF, clubbing, and elevated serum alpha fetoprotein.
2. Serotonin is a common denominator in patients with emotional and eating disorders, right heart valvular stenosis, and the triad of flushing, wheezing, and diarrhea.

Are There Common Denominators in Heart Failure?

HF is a cardiac dysfunction manifest by an inability to achieve a cardiac output adequate to meet the metabolic demands of the body at normal ventricular filling pressures.

Why is the definition of HF so complex, combining *cardiac output* with *ventricular filling pressures*? The answer is that the single definition of HF includes:

- Different symptoms
- Different physical signs
- Different pathophysiology
- Different therapy

There are, in fact, many types of HFs. Think, for a moment, of the clinician addressing a patient in HF. The patient may indeed exhibit varied symptoms and signs associated with the following:

- Left heart systolic HF
- Left heart diastolic HF
- Combined systolic and diastolic HF
- Right HF
- Biventricular HF
- High cardiac output HF
- HF with normal circulating blood volume
- HF with increased circulating blood volume
- HF associated with arrhythmia
- HF associated with acute myocardial infarction/acute ischemia
- An asymptomatic patient with left ventricular dysfunction

We may return to the original question: Are there common denominators in heart failure? Yes.

Common denominator 1. Cardiac chambers have the ability to alter their size and configuration to a chronic change in hemodynamic load. This is called *remodeling*. Increased preload means an increase in the volume of blood in a ventricle at end-diastole, a moment before ventricular contraction begins. Increased preload leads to ventricular dilation.

Increased afterload means increased resistance to outflow of blood from a ventricle during systole. Afterload on the left ventricle, then, relates to systemic blood pressure and presence of aortic valve stenosis. *Increased afterload leads to ventricular hypertrophy.*

Common denominator 2. All patients with HF demonstrate activation of compensatory neurohumoral systems. The purpose of the neurohumoral systems is to maintain an adequate cardiac output and perfusion pressure (arterial blood pressure). These neurohumoral systems include the following:

- Sympathetic nervous system
- Renin angiotensin aldosterone system
- Tissue renin angiotensin system

- Vasopressin (antidiuretic hormone)
- Brain natriuretic peptide
- Endothelin
- Kallikrein-kinin
- Prostaglandins
- Nitric oxide

Neurohumoral systems are initially beneficial in maintaining an adequate cardiac output and blood pressure, but ultimately, they are destructive, leading to premature mortality.

Common denominator 3. Dyspnea on a *cardiac basis* is pathophysiologically due to a noncompliant (stiff) left ventricle that causes an increase in mean left atrial pressure. The left atrial pressure is transmitted back through the pulmonary veins to the pulmonary capillaries. The lungs become congested and stiff—and the patient experiences breathlessness. This is diastolic heart failure.

All patients who have diastolic heart failure have a stiff left ventricle.

Common denominator 4. Weakness on a *cardiac basis* is pathophysiologically due to impaired vigor of left ventricular contraction. Stroke volume and cardiac output are reduced. Reduced arterial flow to muscles causes the patient to sense weakness. This is systolic heart failure.

All patients with systolic heart failure have a decreased cardiac output due to reduced vigor of left ventricular power.

Common denominator 5. In any patient who presents with HF, *look for precipitating factors*. These include the following:

- Ischemia/infarction. The first question the clinician must consider in the patient with HF is, "Is the heart failure due to ischemia or infarction?" If the answer is yes, *the clinician must treat the ischemia and the HF*.
- Medications that reduce contractility
- Calcium channel blockers
- Beta adrenergic blockers
- Doxorubicin
- Discontinuation of medication
- Sodium-retaining medications
- Acute blood pressure rise in the normotensive patient

- Superimposed infection, for example, pneumonia
- Anemia
- Acidosis of any etiology (metabolic or respiratory)
- Emotional stress
- High environmental temperature

You must remember:
1. While HF has multiple pathophysiologic mechanisms, there are still common denominators.
2. Understanding these common denominators enables the clinician to better define and treat HF.

Brevity 7: Flushing

Flushing is a ubiquitous symptom in medicine. It is related to emotion, ingestion of food or medicine, neoplasia, endocrine imbalance, and dermatologic disorders. Further, its causes are age-related.

Clinical vignette, Healthy Individual A: A 22-year-old woman appears for her medical school interview. When addressing the first question, "Why do you want to be a doctor?" her face, neck, and upper anterior chest become intensely flushed without associated sweating.

Clinical vignette, Healthy Individual B: A 51-year-old woman in early menopause awakens an average of three times a night with an intense feeling of body heat, sweating, and flushing. During the daytime, she experiences very few of these episodes.

Clinical vignette, Patient C: A 34-year-old man has the sudden onset of palpitations. In the emergency department, blood pressure is 106/68, pulse 190/min/regular, and respirations 21/min. Electrocardiography reveals paroxysmal supraventricular tachycardia. Immediately after receiving intravenous adenosine, the patient becomes flushed, but normal sinus rhythm is restored.

Clinical vignette, Patient D: A 71-year-old man has a 3-week history of recurrent flushing. During the same time, he has noted that the veins on the left side of his scrotum are dilated and prominent. He now has two episodes of gross hematuria. Urologic investigation reveals a left renal cell carcinoma that has invaded the left renal vein.

Clinical vignette, Patient E: A 62-year-old man has flushing of his face that begins approximately 10 minutes after ingestion of alcohol or spicy foods. Examination shows telangiectasia and papules on the nose and cheeks. The clinical diagnosis is rosacea.

The vignettes illustrate that the cutaneous vasodilation known to lay persons and clinicians as flushing is common and has many disparate causes. Flushing may be entirely benign as in the interview candidate or may represent a fatal disease as in the patient with renal cell carcinoma whose tumor has invaded the left renal vein. (Remember that the left gonadal vein draining the scrotum empties into the *left renal vein*, so a new left varicocele should raise suspicion of left renal cell carcinoma.)

The complexity of medical practice, its richness, and its challenge relate to the fact that so many conditions have multiple causes, some entirely benign that require only reassurance of the patient, while other causes are life-threatening and require intensive intervention. Flushing is one such example; another is syncope. As has been discussed, syncope may be entirely benign as in the common vasovagal faint, or syncope may result from life-threatening, malignant ventricular arrhythmia.

Headache, snoring, and cough all may be entirely benign or related to serious illness.

Causes of Flushing

The causes of flushing are divided into *physiologic, medicine-induced, and disease states*.

Physiologic Causes of Flushing

- Emotion
- Fever
- Menopause and pregnancy
- Ingestion of hot drinks or spicy food
- Ingestion of alcohol

Medicine Causing Flushing

- Niacin
- Adenosine
- Calcium channel blockers
- Nitroglycerin and amyl nitrite
- Levodopa
- Tamoxifen
- Sildenafil
- Hydralazine

- Vancomycin
- Cyclosporine, doxorubicin, cisplatin, interferon
- Contrast media

Disease States Causing Flushing

- Anaphylaxis
- Rosacea
- Dermatomyositis
- Seborrheic dermatitis
- Carcinoid syndrome
- Medullary carcinoma of thyroid
- Renal cell carcinoma
- Mastocytosis
- Pheochromocytoma
- Migraine, cluster headache, and trigeminal neuralgia—unilateral flushing
- Brain tumors affecting the third ventricle

With so many potential causes, how does the clinician approach the patient who has flushing?

First, quickly determine whether the symptom is of physiologic origin or is due to medication.

Second, determine whether the flushing is associated with diarrhea because this symptom is characteristic of medullary carcinoma of the thyroid, mastocytosis, and carcinoid syndrome.

Third, assess for the presence of skin lesions, which should raise suspicion of mastocytosis or dermatomyositis. Seborrhea and rosacea will be clearly evident; skin biopsy may be necessary to establish the diagnosis of mastocytosis. Patients with dermatomyositis typically have muscle weakness with an associated abnormality in serum muscle antibodies, for example, creatine kinase, aldolase, and lactic dehydrogenase, in addition to the presence of antinuclear antibodies in serum.

Episodic or persistent hypertension suggests pheochromocytoma. Microscopic hematuria suggests renal cell carcinoma with flushing related to an associated paraneoplastic syndrome.

You must remember:

1. Flushing is a common symptom.
2. You must first exclude physiologic or medicine-related causes of flushing. Your history must carefully include all over-the-counter health supplements.
3. Finally, seek the less common, organic diseases associated with flushing.

Brevity 8: Heart Rate Is Not the Most Important Element in Cardiopulmonary Fitness

Clinical vignette: Recently, I was working out in the exercise room in the condominium in which I reside. A resident in the building came to me and said, "Isn't it true that a measure of physical fitness is getting the heart rate up high?" I nodded, but before I could fully respond, he continued, "Then, I must be healthy because I get a real fast heart rate in the sauna."

Quite simply, the role of the cardiovascular system is to maintain an adequate cardiac output and perfusion pressure. The respiratory system has two elemental goals, namely, to deliver oxygen to the tissues for cell metabolism and to remove carbon dioxide to maintain a normal chemical (i.e., pH) balance.

With physical exertion, an increase in cardiac output and in ventilation is necessary to preserve cellular oxygenation and maintain acid–base balance. The heart rate increase associated with aerobic exercise is a hemodynamic correlate of the body's oxygen uptake. However, an increase in heart rate alone is not indicative of aerobic capacity. An increase in heart rate associated with anxiety, relaxing in a heated sauna, or ingestion of a sympathomimetic or anticholinergic medicine does not impart cardiopulmonary fitness.

Most regrettably, cardiopulmonary fitness requires physical work.

There is an interesting corollary, however. Cardiovascular fitness may be reached without a significant increase in heart rate. Patients with fixed-rate cardiac pacemakers and those with blunted heart rate responses to exercise due to intake of beta adrenergic blocker medications can still achieve an exercise-induced increase in metabolic rate and state of cardiopulmonary fitness.

Brevity 9: Think of the Chronology of a Heart Murmur

The traditional and careful evaluation of a heart murmur includes the following assessments:

- Timing in the cardiac cycle
- Location
- Radiation
- Quality

- Duration
- Influence by maneuvers, such as change in body position, breathing, Valsalva strain, or squatting

Another clinically important factor in the evaluation of a murmur is what I call its "chronology." In other words, how has the murmur changed in relation to the patient's clinical status?

Clinical vignette, Patient A: A 59-year-old man has known chronic mitral regurgitation with a holosystolic murmur. Upon follow-up cardiac examination, you are now aware that the holosystolic murmur is distinctly softer than in the past and of shorter duration.

This may be an important clue signifying that systolic left ventricular function is worsening because a feebly contracting ventricle is unable to generate the same degree of turbulent flow as in the past. If, however, this patient's left ventricular function later improves with therapy, the improved hemodynamics will have an auscultatory correlation. The murmur will increase in intensity and duration.

Clinical vignette, Patient B: A 26-year-old man has acute viral myocarditis. A new murmur of mitral regurgitation is heard. What is the etiology of the murmur?

The impaired contractile strength of the myofibrils causes the left ventricle to dilate. This, in turn, causes disruption of the mitral valve apparatus, onset of mitral regurgitation, and appearance of the murmur. Clearly, the new mitral regurgitant murmur is not due to a primary defect in the valve leaflets themselves. Rather, it is the dilated left ventricle, with its secondary effect on the papillary muscles, chordae tendineae, and mitral valve ring, that is responsible for the murmur. If recovery is associated with improved left ventricular systolic function, the ventricle will reduce in chamber volume and the murmur may disappear.

Clinical vignette, Patient C: An 81-year-old woman has known calcific aortic stenosis due to degeneration of the valve cusps. You now note the murmur to be softer in intensity. What is the pathophysiologic significance of the softening of the murmur?

The murmur intensity is lessening because the hypertrophic left ventricle is now losing contractile power. Stroke volume and ejection fraction are decreasing; therefore, there is a reduction in the ability of the left ventricle to generate a turbulent flow across the aortic valve.

Clinical vignette, Patient D: A 22-year-old man has infectious endocarditis of the aortic valve. Six hours after admission, the diastolic murmur of aortic regurgitation is softer in intensity. What does this mean?

The murmur is decreasing in intensity because left ventricular function is worsening. It seems paradoxical, but the softer murmur means that the patient is sicker. The diastolic murmur is getting softer because the left ventricular end-diastolic pressure is rising. There is now a lesser gradient between aorta pressure and ventricular diastolic pressure. A reduced gradient results in less turbulent regurgitant flow and a softer murmur.

Remember this clinical point: *The intensity of a heart murmur is not simply dependent upon the anatomic severity of a valvular or congenital defect.* Rather, the murmur is dependent upon physiologic factors including ventricular function and, at times, systemic or pulmonary vascular resistance. The chronology of the murmur reflects these physiologic changes.

Brevity 10: Make It Easier to Remember

I have long believed that students expend far too much time and energy *memorizing* information. Indeed, there is so much to learn. Therefore, I always sought clues to help me remember clinically important material. I share with you a few examples of how I made remembering so much easier.

Remember That the Suffix and, at Times, the Prefix, of a Medicine's Generic Name Indicates the Class of That Medication

Here are some important suffixes:

-olol = Beta adrenergic blocker
Examples: propranolol, metoprolol, esmolol, acebutol
Note that *alol* does not indicate a pure beta blocker.
Alol, as in labetalol, is a combined beta and alpha adrenergic blocker.

-statin = HMG-CoA reductase inhibitor
Examples: simvastatin, pravastatin, atorvastatin, fluvastatin

-am = Benzodiazepams
Examples: diazepam, lorazepam, flurazepam, temazepam, midazolam, alprazolam
Exceptions: chlordiazepoxide, clorazepate

-cyclines = Tetracyclines
Examples: demeclocycline, chlortetracycline, minocycline

-cillin = Penicillins
Examples: penicillin G, cloxacillin, dicloxacillin, nafcillin, amoxicillin, ampicillin, mezlocillin, piperacillin, ticarcillin

-sartin = Angiotensin II receptor blocker
Examples: candesartan, eprosartan, olmesartan, valsartan, telmisartan, irbesartan

-pril = Angiotensin converting enzyme inhibitor
Examples: benazepril, captopril, enalapril, fosinopril, moexipril, quinapril, ramipril, trandolapril

-zide = Thiazides
Examples: hydrochlorothiazide, polythiazide, methyclothiazide, hydroflumethiazide, cyclothiazide, chlorthiazide

-romycin = Macrolides
Examples: erythromycin, azithromycin, clarithromycin, dirithromycin
Exception: troleandomycin

-phylline = Exanthine derivatives
Examples: theophylline, aminophylline, dyphylline, oxtriphylline

-vir = Antiviral medicines
Examples: acyclovir, cidofovir, ganciclovir, oseltamivir, tenofovir, zanamivir, valganciclovir, valacyclovir

-aine = Local anesthetics
Examples: benzocaine, cocaine, procaine, tetracaine, bupivacaine, etidocaine, lidocaine, etidocaine, mepivacaine, ropivacaine

-bital = Barbiturates
Examples: phenobarbital, mephobarbital

-tyline = Tricyclic antidepressants
Examples: amitriptyline, nortriptyline, protriptyline
Exceptions: amoxapine, clomipramine, despramine, imipramine

-etine = Selective serotonin reuptake inhibitors
Examples: fluoxetine, paroxetine
Exceptions: citalopram, fluvoxamine, sertraline

-quine = Antimalarials
Examples: chloroquine, hydroxychloroquine, mefloquine, primaquin
Exceptions: pyrimethamine, quinine

-acin = Fluoroquinolones
Examples: ciprofloxacin, enoxacin, levofloxacin, norfloxacine
Exception: nalidixic acid

Here are two important prefixes:

sulf- = Sulfa drugs
Examples: sulfadiazine, sulfasalazine, sulfamthizole, sulfisoxazole
Exceptions: mafenide

-ceph- or *cef-* = Cephalosporin
Examples: cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cefaclor, cefoxitin, cefuroxime, cefixime, cefoperazone, cefotaxime, cefprozil, ceftriaxone, cefonicid

Make it easier to remember by carefully considering the suffix (and prefix) in the generic name of the medication.

Remember That the "Marine in Combat" Will Explain the Effects of Sympathetic Nervous System Activation on the Body's Organ Systems

I am convinced that some things never change. With mild amusement, I have noted the annual ritual of students who are taking the physiology course and struggling to learn the effects of the sympathetic and parasympathetic nervous system (autonomic nervous system) on body organs or tissues.

It is so easy to learn if you think of the "Marine in combat."

Does the Marine want to be strong? Of course, so sympathetic stimulation dilates skeletal muscle arteries and arterioles increasing blood flow to skeletal muscle. Is blood flow to the skin and internal viscera, for example, the bowel, essential to promote the safety of the Marine? No, so sympathetic stimulation constricts skin and visceral vessels, enabling more blood to be shunted to vital organs.

Does the Marine in combat need to see clearly and as far as possible? Of course, so sympathetic stimulation dilates the pupils (mydriasis).

Will maximal oxygenation of his lungs be beneficial? Of course, so sympathetic stimulation dilates bronchial smooth muscle increasing tidal volume and alveolar ventilation.

Does the Marine want to pass urine or have a bowel movement during combat? Of course not. Thus, sympathetic stimulation relaxes the smooth muscle in the walls of the bowel and urinary bladder. Further, sympathetic stimulation causes contraction of the sphincters of the gastrointestinal and genitourinary tracts.

Will increased cardiac output be beneficial to the Marine? Of course, so sympathetic stimulation increases heart rate, myocardial contractility, and ventricular ejection fraction, all resulting in an increase in cardiac output.

Stimulation of the parasympathetic nervous system has opposite effects on organs and tissues. Heart rate slows and cardiac output is lessened; intestinal motility increases and the urinary bladder wall contracts. Bowel and bladder sphincters relax, thus promoting bowel movement and urination.

You must remember:
1. Heightened sympathetic (adrenergic) nervous system activity leads to increased cardiac output, greater physical strength, greater alertness, and improved vision—all to protect the "Marine in combat."
2. Always seek a way to make voluminous information easier to remember.

Remember That Immunoglobulin A (IgA) Is the Primary Antibody That Protects the Body from the Outside World

Immunoglobulins are antibodies that are a primary line of defense against invasion of the body by infectious organisms. They destroy or inactivate attacking organisms by blocking attachment of viruses to cells, by opsonizing bacteria, by activating complement, and by neutralizing protein toxins.

IgA is the immunoglobulin that is the primary defense against infectious organisms in the environment, the "outside world." Thus, IgA is the primary antibody in intestinal mucosa and epithelia in lungs, intestine, breast, genitourinary tracts, and female reproductive tracts. IgA is the primary antibody in external secretions, namely, tears, breast milk, bronchial secretions, vaginal secretions, and intestinal secretions.

In contrast to IgA located in the mucosal secretions, immunoglobulin G and immunoglobulin M are in the bloodstream of the host.

You must remember:
1. IgA is the immunoglobulin in secretions that protect the individual from "outside world" sources of infection.