Chapter 2

The Most Important Word in Diagnosis: *And*

A medical student, bearing a puzzled expression, approached me and related that she had just encountered a patient whose chief complaint was fatigue. The student declared, "I didn't know where to start because so many diseases can cause fatigue." I softly responded, "And." The student was nonplussed; finally, she faintly asked, "What does 'and' mean?"

The practice of medicine is not easy. Despite bountiful advances in investigative technology, the clinician continues to be challenged by the fact that common symptoms may be indicative of disease in many organ systems. Fatigue may be due to anemia, neoplasia, endocrine, cardiovascular, musculoskeletal, and infectious disease. Breathlessness (dyspnea) may result from disorders in the chest, abdomen, nervous system, and psyche.

It is most reassuring when the patient's symptom suggests a specific pathophysiologic mechanism that is confirmed by a physical sign that demonstrates a functional or structural abnormality. For example, a patient has weakness. Physical examination reveals that the apical impulse is in the sixth intercostal space in the anterior axillary line. Weakness *and* a dilated left ventricle that signifies increased ventricular volume (preload) quickly leads to an accurate diagnosis of systolic heart failure (HF).

Unfortunately, not all illnesses are so easily diagnosed. You, as the clinician, must be a medical detective. The detective in a criminal investigation searches for material or chemical evidence. You, the clinician, seek *ands*.

And Is the Most Important Element in Medical Diagnosis

What are some *ands?*

- *And* may link a symptom to a physical examination sign:
  Weakness *and* a dilated left ventricle = systolic heart failure
- *And* may link a symptom to another symptom:
  Sudden weakness of the right arm and leg *and* febrile sweats = endocarditis

- *And* may link a symptom to an abnormal laboratory or imaging result:
  Shortness of breath *and* elevated serum brain natriuretic peptide = heart failure
- *And* may be the link to a geographical location:
  Fever *and* recent global travel to sub-Saharan Africa suggest malaria

Global travel and immigration, increasingly, represent the *And* in the patient whose symptom complex is related to helminth (worm) infection or a zoonotic disease, such as malaria.

The astute clinician must be prepared to use *And* in different pathways. If the symptom does not easily link to a sign in forming the diagnosis, the clinician may start in another direction. For example, in the patient whose symptoms are entirely nonspecific, an abnormal laboratory value often challenges the physician to think "backward" to arrive at the diagnosis.

Let us begin our clinical linkages, our *Ands*.

In the following, *And* links a symptom to a sign.

Fatigue *And*

The patient presenting with weakness and fatigue represents a common, and often perplexing, problem for the clinician. It is because of its many causes that fatigue, an impaired response to effort, represents a challenge. Fatigue may be caused by infectious, cardiac, neoplastic, endocrine, autoimmune, neuromuscular, psychiatric, and pulmonary disorders. But, first, before getting more specific, *the clinician should always think of the patient's medications as the cause of fatigue, or in fact, any symptom!*

1. Fatigue *and* Fever

Any febrile infectious disease may cause transient fatigue. In the patient with persistent fever, consider the following:

- AIDS-related illness
- Endocarditis
- Myxoma in the heart
- Sarcoidosis
- Toxoplasmosis
- Neoplasia, particularly, lymphoma and leukemia

HIV infection leads to CD4 cell depletion and impaired cellular immunity. Ultimately, the immune dysfunction from the HIV type 1 human retrovirus infection leads to the appearance of clinical AIDS. The virus is transmitted

sexually and parenterally. Virtually every organ can be involved in this disease. However, the clinician should recognize that fatigue, fever, weight loss, and night sweats are common presenting features.

Toxoplasmosis infects both immunocompetent and immunocompromised patients. Toxoplasma infection in 80% of immunocompetent patients is asymptomatic. When symptomatic, patients most frequently have bilateral, nontender cervical adenopathy. The course of the illness is self-limited. In contrast, immunocompromised patients infected with the protozoan organisms may have encephalitis with headache and confusion, chorioretinitis with eye pain and reduced visual acuity, or pneumonitis with cough and dyspnea.

Sarcoidosis is a disease of unknown etiology that commonly targets the heart, lungs, liver, kidney, eyes, and skin. It is three to four times more common in black patients than white patients. Enlargement of lymph nodes and the parotid gland is frequently noted. The disease most commonly involves the lungs. Thus, initial symptoms of the disease are often pulmonary, for example, cough or dyspnea. The initial radiographic pulmonary involvement is bilateral hilar node enlargement (similar to Hodgkin's disease). As the pulmonary disease progresses, diffuse interstitial fibrosis occurs, causing the patient to have restrictive pulmonary functional impairment. Restrictive lung disease results in hyperventilation resulting in low system $PaCO_2$ and hypoxemia due to impaired transfer of oxygen from alveoli to pulmonary capillaries.

Sarcoidosis may affect any portion of the central or peripheral nervous system. Half of sarcoidosis patients will develop cranial nerve VII palsy. Approximately 75% of patients with untreated sarcoidosis will have elevated serum levels of angiotensin converting enzyme. Calcium metabolism is often abnormal in these patients due to extrarenal production of calcitriol. Hypercalciuria occurs in approximately 50% of cases and hypercalcemia in 10–20%. As a result, nephrocalcinosis and renal failure may occur.

Many neoplasms can present with fever. Hodgkin's disease has a bimodal age distribution, 20 to 30 years and 50 to 60 years. Fever and night sweats are common (20%); these symptoms are less frequently noted in the patient with non-Hodgkin's lymphoma. HIV infection is associated with a fivefold increase in the incidence of Hodgkin's disease.

Renal carcinoma and tumors of the liver (primary and metastatic) are associated frequently with fever. Atrial myxoma is often confused with endocarditis and lymphoma because it may present with fever, malaise, and weight loss. Tumor obstruction at the mitral valve, causing a diastolic murmur, may precipitate pulmonary edema. Additionally, fragments of tumor may cause peripheral embolization or, in the case of a right atrial myxoma, pulmonary embolism.

2. Fatigue *and* Elevated Central Venous Pressure

There are four cardiac disorders associated with fatigue in which the central venous pressure is elevated:

- Right HF resulting from chronic left HF (biventricular failure) due to valvular, hypertensive, or ischemic heart disease
- Pulmonary hypertension due to pulmonary vascular or parenchymal disease
- Cardiac tamponade
- Constrictive pericarditis

The common denominator causing fatigue in these disorders is a reduced cardiac output, particularly, a diminished cardiac output related to effort.

Cardiac tamponade is typically dramatic and is caused by acute pericarditis of any etiology, dissection of the aorta, chest trauma, invasive diagnostic or therapeutic instrumentation, neoplasia, and, rarely, acute myocardial infarction. However, tamponade may be less dramatic, called subacute tamponade, in which the patient slowly develops hemodynamic instability over days, even weeks. These patients generally have fatigue.

The most common cause of constrictive pericarditis in the United States is prior chest irradiation, usually due to lung or breast carcinoma or to lymphoma. The constriction may be clinically evident as early as 3 months after radiotherapy, though the average duration between treatment and hemodynamic constriction is 7 years.

Superior vena cava (SVC) syndrome, due to obstruction of blood flow in the SVC, is increasing in frequency. It usually is caused by thrombosis or external compression of the vein near its entrance into the right atrium. The most common cause of SVC syndrome is malignancy, most notably small cell lung cancer and non-Hodgkin's lymphoma. (Hodgkin's disease rarely is the etiology.) Thrombosis of the vein typically is related to central venous lines attendant to chemotherapy, bone marrow transplantation, parenteral nutrition, and venous access for dialysis. An infectious cause is fibrosing mediastinitis due to histoplasmosis infection. The patient may have dyspnea. Signs include elevated central venous pressure, facial swelling (occasionally with suffusion), and dilated veins on the arms and chest wall.

In the patient younger than 50 years of age whose SVC syndrome etiology is not evident, consider an inherited hypercoagulable state such as Factor V Leiden mutation or prothrombin gene mutation causing venous thrombosis. Antiphospholipid antibody syndrome (APS), causing venous and arterial thrombosis, may be primary or related to systemic lupus erythematosus. APS is suggested in two or more pregnancy losses after 10 weeks of gestation. These hypercoagulable states are important causes of deep vein thrombosis and pulmonary embolism.

Although the central venous pressure is elevated in SVC syndrome, right HF is not present, because right atrial pressure is normal.

3. Fatigue *and* an Apical Impulse That Is Moved to the Left and Downward in the Chest

There are three cardinal determinants of ventricular function, namely, preload, afterload, and contractility. Preload is the volume of blood in a ventricle at end-diastole; thus, preload is *volume dependent*. Afterload is the pressure in the ventricular wall during ejection. Clinically, the two factors that influence left ventricular (LV) afterload are systemic arterial blood pressure and aortic valve stenosis. In each case, the left ventricle must generate increased pressure to eject blood into the aorta. Thus, afterload is *pressure dependent*.

An apical impulse that is moved to the left and downward on the precordium is indicative of LV dilatation that indicates increased preload. Increased preload is found in patients who have chronic mitral regurgitation, chronic aortic regurgitation, and dilated cardiomyopathy. The increased preload and its associated ventricular dilatation leads to systolic heart failure. Systolic HF is physiologically characterized by reduced cardiac output and ejection fraction. The classic symptom related to decreased cardiac output is fatigue/weakness.

In systolic HF, *and* links the symptom (fatigue) to the physical sign (apical impulse displaced to the left and downward) to the pathophysiology (increased preload progressing to decreased LV contractile power) that results in decreased stroke volume and cardiac output. This is systolic HF.

4. Fatigue *and* Ascites

Consider advanced liver disease of any etiology, gastrointestinal or gynecologic malignancy, and constrictive pericarditis. (You now know that constrictive pericarditis is linked to both elevated central venous pressure and ascites.) Right HF always is associated with peripheral edema, but less commonly with ascites. Left HF will not cause congestive hepatomegaly or ascites.

Cirrhosis, with its associated portal hypertension and hypoalbuminemia, is the most common cause of ascites. Ascites in pelvic malignancy is due to peritoneal seeding. Hepatocellular carcinoma and lymphoma, however, may cause ascites without peritoneal metastases. The two most important tests on ascitic fluid are, first, culture and sensitivity, and second, the serum to ascites albumin gradient. A value greater than 1.1 indicates portal hypertension. A gradient less than 1.1 indicates that portal hypertension is not present.

5. Fatigue *and* Petechiae or Purpura

Aplastic anemia, acute leukemia, and in the older male, macroglobulinemia are all characterized by fatigue and petechiae or purpura. Enlargement of the liver and spleen is common in acute leukemia, and blast cells are found upon examination of peripheral blood.

Waldenstrom's macroglobulinemia typically occurs in patients older than 60 years of age. Increased viscosity of blood due to abnormal protein production often causes visual disturbance and impaired consciousness. Lymphadenopathy, splenomegaly, and hepatomegaly are common in these patients.

Fatigue, with Two *Ands*

Fatigue with two *ands*, namely, fatigue *and* fever, and fatigue *and* petechiae, is highly suggestive of infectious endocarditis (IE). The clinical presentation of IE is very variable, depending upon the virulence of the infecting organism, the patient's age, and other important clinical factors, including the presence of indwelling vascular catheters, prosthetic heart valves, and intravenous drug abuse. The patient may appear toxic or chronically ill.

In the more classic expression of the disease, the clinical picture includes fever, night sweats, weakness, dyspnea, and weight loss. A changing heart murmur, petechiae, other skin lesions including Osler's nodes and splinter hemorrhages, and splenomegaly are found in the classic case. Clubbing may not be noted until the infection has been present for 6 weeks. Peripheral manifestations, in addition to stroke and seizure, include emboli to the gut, kidney, and spleen. Elderly patients who have IE commonly have an indolent expression of the disease. In these patients, arthralgia, weakness, low-grade fever, and anemia are more typically found.

Those patients who are infected with a virulent organism, for example, *Staphylococcus aureus*, on the aortic or mitral valve often present with high fever and chills followed by acute destruction of the valve causing acute pulmonary edema. Endocarditis of the tricuspid valve in the intravenous drug abuser is also most commonly due to *Staphylococcus aureus* infection and causes septic pulmonary emboli and lung abscess.

An important clinical note about petechiae:
Petechiae are found in two disorders, thrombocytopenia of any etiology (as in idiopathic thrombocytopenic purpura) and in disorders characterized by the formation of circulating antigen-antibody complexes that are not cleared by the reticuloendothelial system and, thus, deposit in the walls of blood vessels and glomeruli causing a vasculitis. The petechiae in IE result from this vasculitis. (The reticuloendothelial system is composed of phagocytic cells in the lung, spleen, liver, and lymph nodes.)

6. Fatigue *and* Adenopathy

Enlarged lymph nodes, either regional or generalized, may be found in diseases in which fatigue is a prominent symptom. Fatigue and adenopathy suggests one of the following conditions:

- Lymphoma
- Infectious mononucleosis
- Cytomegalovirus infection
- Toxoplasmosis
- Sarcoidosis
- Chronic fatigue syndrome
- Waldenstrom's macroglobulinemia

Despite a sense of marked fatigue, patients with chronic fatigue syndrome have normal muscle strength, and muscle biopsy is normal. Cervical or axillary lymph nodes are typically painful, and biopsy shows reactive hyperplasia.

Patients with infectious mononucleosis have pharyngitis, often with tonsillar exudates, and palatal petechiae. Posterior cervical adenopathy is highly suggestive of this infection. Saliva may remain infectious for 6 months from onset of symptoms. One-third of patients with mononucleosis have superimposed streptococcal tonsillitis that requires antibiotic therapy.

7. Fatigue *and* Hypertension

Antihypertensive medication is the most common cause of fatigue noted by the hypertensive patient. Fatigue and hypertension and hypokalemia suggests hypercortisolism (Cushing's syndrome) or primary hyperaldosteronism (Conn's syndrome). Patients with Cushing's syndrome typically also have round (moon) facies, buffalo hump, and ecchymoses due to easy bruising.

Patients with pheochromocytoma experience fatigue after a paroxysm of palpitation, sweating, tremulousness, and acute hypertension.

8. Fatigue *and* Jaundice

Fatigue is a symptom in the patient who has cholestasis of any etiology, particularly in those diseases associated with intrahepatic jaundice. Acute viral hepatitis is a common cause of fatigue. Primary or metastatic malignancy in the liver must be considered. Primary biliary cirrhosis, typically occurring in the female patient aged 30 to 65 years, is associated with fatigue and itching (and presence of antimitochondrial antibodies in the serum in 95% of cases). Chronic hepatitis, a common cause of fatigue, rarely causes jaundice except in acute cases of hepatic decompensation or end-stage liver disease.

9. Fatigue *and* Hepatosplenomegaly

Diseases to be suspected include acute viral hepatitis, infectious mononucleosis, alcoholic hepatitis, cirrhosis, toxoplasmosis, cytomegalovirus infection, or macroglobulinemia.

10. Fatigue *and* Weight Loss

The clinician should consider malignancy, AIDS-related illness, chronic hepatitis, and apathetic hyperthyroidism in the older patient, that is a patient older than 55 years of age.

Approximately two-thirds of older hyperthyroid patients have the typical symptoms related to increased circulating thyroid hormone, namely, tremulousness, hyperactivity, increased appetite (hyperphagia), and sweating. The remaining patients exhibit decreased appetite (anorexia), weight loss, absence of skin symptoms, and a listless disposition. Atrial fibrillation occurs in approximately 15% of patients who have apathetic hyperthyroidism. An important clinical point: Atrial fibrillation in hyperthyroidism requires anticoagulation because these patients are at significant risk of systemic embolism.

Remember, then, that fatigue and atrial fibrillation in the patient, especially one older than 55 years of age, should make the clinician think of hyperthyroidism.

11. Fatigue *and* Neurologic Signs

Multiple sclerosis, most commonly affecting the patient who is in the third or fourth decade, is associated with fatigue in addition to numbness of the face or hands, extraocular muscle abnormalities, nystagmus, abnormal papillary responses, hyperreflexia, and cerebellar ataxia. Elevated levels of cerebrospinal fluid IgG are found in many patients with multiple sclerosis.

12. Fatigue *and* Cool Skin, Periorbital Edema, Puffiness of the Fingers, and Slow Relaxation of Deep Tendon Reflexes

Fatigue accompanied by this complex of symptoms suggests hypothyroidism, either primary or secondary. Hypothyroidism of any etiology may cause macrocytosis without megaloblastic bone marrow. The most common cause of primary hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's disease). Antithyroid peroxidase enzymes are found in the serum of 90–100% and antithyroglobulin antibodies in 80% of patients. Patients with Hashimoto's disease have an increased risk of developing another autoimmune disease, such as pernicious anemia.

Medications are an important cause of primary hypothyroidism. Lithium can cause goiter and thyroiditis by inhibiting thyroid hormone secretion. Amiodarone, used in the treatment of arrhythmia, has a direct toxic effect on

the thyroid gland. The antineoplastic agent sunitinib commonly causes hypothyroidism and may cause a cardiomyopathy with decreased LV ejection fraction and bone marrow suppression.

13. Fatigue *and* Joint Tenderness or Swelling

Fatigue is common in the patient with rheumatoid arthritis who, additionally, has morning stiffness lasting more than 1 hour and bilateral peripheral polyarthritis involving the metacarpophalangeal and proximal interphalangeal joints of the fingers.

14. Fatigue *and* Heart Murmur or Systolic Click

Fatigue is common in the patient who has mitral valve prolapse with a midsystolic click and, commonly, an associated late apical systolic murmur. These patients often have sharp, jabbing noncardiac chest pain, palpitations, and dyspnea.

The rare patient with atrial myxoma typically has fatigue. Examination shows a diastolic murmur that changes in intensity with change in body position. (See the section titled "Fatigue and Fever" earlier in this chapter.)

15. Fatigue *and* Hirsutism and Acne in the Female

Hyperprolactinemia of any etiology is associated with fatigue. Prolactin is secreted only by cells in the pituitary gland. Serum prolactin concentrations increase physiologically during pregnancy.

A pathologic cause of hyperprolactinemia is prolactin cell adenoma of the pituitary gland. In the reproductive-age woman who is not pregnant, the prolactin-secreting adenoma is manifest by oligomenorrhea, infertility, and, infrequently, galactorrhea. The postmenopausal woman, already in a hypogonadal state, is more likely to present with visual disturbance due to the pituitary tumor affecting the optic nerve. In a man, hyperprolactinemia is associated with decreased libido, impotence, and gynecomastia.

Many medicines cause an increase in serum prolactin concentrations. These include risperidone, phenothiazines, haloperidol, metoclopramide, butyrophenones, and domperidone.

16. Fatigue *and* a Normal Physical Examination

The clinician should think of electrolyte imbalance, for example, hyperkalemia, hypokalemia, and hypercalcemia. The physical examination is normal when the serum electrolyte abnormality is mild to moderate; more severe imbalance causes true muscle weakness. Further, marked elevation in serum calcium concentration may cause depression, stupor, and coma.

Important causes of *hypokalemia* include these:

- Respiratory and metabolic alkalosis because potassium leaves the extracellular space and enters cells as hydrogen leaves the cells to enter the circulation in an attempt to normalize pH
- Increased gastrointestinal loss of potassium that occurs with vomiting or diarrhea
- Increased urinary loss of potassium that occurs with loop and thiazide diuretic therapy

It is important to note that both gastrointestinal and urinary loss of potassium are associated with loss of magnesium. In the patient with hypokalemia, the potassium depletion cannot be corrected until the magnesium deficit is reversed.

Electrocardiographic abnormalities of hypokalemia include T wave flattening, increased amplitude of U waves, and ST segment depression. However, there is marked interpatient variability between serum potassium concentration and the electrocardiographic changes.

The most common causes of *hyperkalemia* include acute and chronic renal failure, medications, and adrenal insufficiency. Renal failure leads to hyperkalemia resulting from reduced urinary excretion of potassium. Similarly, angiotensin converting enzyme inhibitors and, less frequently, angiotensin receptor blockers, potassium-sparing diuretics (e.g., spironolactone and triamterene), and nonaspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) cause hyperkalemia resulting from impaired renal excretion of the electrolyte. Adrenal insufficiency produces elevation in serum potassium due to associated mineralocorticoid deficiency in this endocrinopathy.

Hyperkalemia is manifest by progressive electrocardiographic abnormalities, starting with peaked T waves; as serum potassium concentration increases further, a reduction in amplitude of P waves with QRS widening follows; finally, a sine wave and death occur. As in hypokalemia, there is marked interpatient variability between the serum potassium concentration and the electrocardiographic changes.

Hypercalcemia is most commonly due to hyperparathyroidism or neoplastic disease. Cancer causing hypercalcemia may be due to metastases in bone, primary tumors producing paraneoplastic endocrine syndromes in which parathyroid hormone–related proteins are secreted (e.g., ovary, kidney, and lung), multiple myeloma, and lymphoma, occasionally due to calcitriol production. Calcitriol is the active form of vitamin D and promotes renal reabsorption of calcium, increases intestinal absorption of calcium and phosphorus, and promotes calcium and phosphorus mobilization from bone into plasma.

In the following, *and* links the symptom, fatigue, to another symptom.

17. Fatigue *and* Headache

Patients with giant cell arteritis (GCA) commonly have headaches that often are associated with scalp tenderness. (If specifically asked, the patient may relate tenderness of the scalp with brushing or combing of the hair.) The headache may be in the temporal area or generalized. Headache, in conjunction with jaw claudication or acute partial visual impairment, is highly suggestive of GCA. Examination shows temporal artery tenderness and, occasionally, nodularity. (See the section titled "Stroke and Fever," which follows.)

In the following, *and* links the symptom, fatigue, to other symptoms, to signs, and to abnormal laboratory values.

18. Fatigue *and* Anorexia, Weakness, Weight Loss, Lightheadedness upon Arising, Hyperpigmentation of the Skin Creases, Hyponatremia, and Hyperkalemia

In this case, *and* leads to the diagnosis of chronic primary adrenal insufficiency (Addison's disease) that is caused, in most cases, by autoimmune destruction of the adrenal cortex. Infectious causes of this disease include tuberculosis, HIV, and disseminated fungal disease. The adrenal cortical destruction results in a physiologic deficiency in both glucocorticoid and mineralocorticoid hormones. Hyperpigmentation is due to the increased melanocyte-stimulating effect of increased plasma adrenocorticotrophic hormone (ACTH). Orthostatic lightheadedness is noted due to hypovolemia resulting from aldosterone depletion. It is important to recognize that the drop in systolic and diastolic blood pressure upon arising is associated with an increase in heart rate. (In contrast, orthostatic hypotension due to autonomic sympathetic insufficiency is not associated with a compensatory heart rate increase with the drop in blood pressure.) The mineralocorticoid deficiency results in hyponatremia being present in 90% and hyperkalemia in 65% of patients with Addison's disease. Laboratory diagnosis of chronic primary adrenal insufficiency includes abnormally low plasma cortisol and elevated plasma ACTH levels. The cosyntropin test is used to confirm the diagnosis.

Secondary adrenal insufficiency is related to a pituitary disorder, for example, a nonfunctioning pituitary tumor or postradiation or postsurgical effects. Though symptoms are the same as in Addison's disease, hyperpigmentation does not occur, plasma ACTH levels are subnormal, and the serum potassium is normal.

19. Fatigue *and* Arthralgia, Hyperglycemia, and Abnormal Liver Function Tests

In this case, *and* links the symptoms, fatigue and arthralgia, to chemical abnormalities in the body. *And* enables the clinician to recognize that the

disease causing this complex is hemochromatosis, an autosomal recessive inherited disease in which there is increased iron absorption in the intestinal tract. The excessive iron is deposited in joints, where it causes arthralgia; in the pancreas, where it causes diabetes mellitus (50% of cases); in the liver, where it causes cirrhosis; in the pituitary gland, where it causes hypogonadism in men; and in the heart, where it causes dilated cardiomyopathy. Close inspection of the skin often reveals a slate gray color, though the hemochromatosis patient is said to have "bronze diabetes."

Let us now move to other clinically important examples of the medical clue called *and*.

Stroke *and* Fever

A former student, now a medical intern, excitedly called me to tell me that one of my clinical aphorisms enabled him to make an important diagnosis that had not been considered by more experienced physicians. A young, previously healthy man had presented with an acute stroke. The cohort of senior physicians was completely puzzled as to the cause of the acute neurologic event. At the time of admission, the patient's temperature was 100.8°F. To his seniors, my former student said, "Stroke and fever equal endocarditis till proven otherwise." Indeed, this impression was confirmed with blood cultures and echocardiography.

Stroke may be caused by thrombotic arterial occlusion, subarachnoid hemorrhage, intracerebral hemorrhage, arteritis, and embolism. Emboli, most commonly arising in the heart, may be noninfected (bland) or infected. Infected vegetations on heart valves produce the cardiogenic emboli in endocarditis.

The important clinical point is that stroke and fever equal endocarditis (till proven otherwise). Patients who present with an acute stroke and are febrile must be considered as having endocarditis. Obtaining blood cultures and performing echocardiographic imaging are essential.

In infective endocarditis, bacteremia is complicated by development of vegetations that deposit on heart valves or congenital cardiac and vascular anomalies, for example, ventricular septal defect and coarctation of the aorta. The virulence of the infecting organism determines the clinical presentation of the patient. Virulent organisms such as *Staphylococcus aureus* cause the patient to become acutely ill and present with high fever, night sweats, and rapid and severe destruction of a heart valve, which causes regurgitation. Endocarditis resulting from infection with commensal organisms of the mouth and pharynx, for example, *Streptococcus viridans*, presents in a more

insidious (subacute) character, often manifest by low-grade fever, anorexia, and arthralgia. In subacute disease, fever is low grade (< 102.5°F) and not associated with chills.

The signs associated with endocarditis involve the heart, skin, central nervous system, eye, joints, and kidney. A new or changing heart murmur is heard in approximately 80% of cases. The murmur may not be loud. Endocarditis of the tricuspid valve may not produce an audible murmur. Skin manifestations include Janeway lesions, painless and erythematous macules, and papules on the palms and soles that represent septic emboli. Petechiae, Osler's nodes (painful, violaceous nodules on the fleshy part of the toes and fingers), and splinter hemorrhages represent deposition of circulating immune complexes. Septic emboli are common because the infected valvular vegetations are friable. In addition to emboli to the brain, the first manifestation of endocarditis is often an embolus to the kidney, spleen, and with right-sided endocarditis, the lung. Tricuspid valve endocarditis, particularly common in intravenous drug abusers, causes suppurative pulmonary emboli and lung abscess formation.

Another important clinical point is not well recognized in patients who have endocarditis. Patients who have been successfully treated for the cardiac infection are at risk of suffering another type of stroke, a subarachnoid hemorrhage, due to rupture of a mycotic aneurysm. A mycotic aneurysm is a weakening and ballooning of an artery due to endocarditis-related infection in the wall of that vessel. The aneurysm in the brain may rupture weeks or even months after the end of antibiotic therapy.

In contrast to endocarditis, an important clinical point: Patients who have occlusive arterial thrombotic stroke, bland (noninfected) cerebral emboli, subarachnoid hemorrhage, and intracerebral hemorrhage *are not febrile at the time of symptom onset*. Fever may be initially noted a day or two after the vascular insult due to a "stress" response. In this case, the fever spontaneously subsides in a few days. However, fever appearing after a stroke should raise strong suspicion of secondary infection occurring in the urinary tract or lung, or infection arising at an intravenous access site. Interestingly, it is very uncommon for an acute, noninfected thrombotic stroke to present with seizure. If seizure is the presenting manifestation, a cerebral embolus or subarachnoid hemorrhage is most likely. However, seizures are very common after stroke (starting at least 2 weeks after the acute event) and account for 50% of epilepsy in older adults.

One disease closely mimics endocarditis. In fact, this condition may also present with stroke and fever. I refer to GCA. GCA is a vasculitis that affects branches of the external carotid artery, yet may involve other arteries arising from the aorta. It is a disease that affects persons older than 50 years of age;

the average age at time of onset is 70 years. GCA is not a rare disorder; the prevalence is considered to be 200 per 100,000 adults. Although GCA is not rare, the problem is that it is rarely diagnosed.

Onset of GCA symptoms may be gradual or abrupt. Systemic symptoms that mimic endocarditis include fever in 50% of cases, even spiking to 104°F, fatigue, and weight loss. Both infectious endocarditis and GCA may present with stroke and fever.

Symptoms related to narrowing or occlusion of cranial arteries that are more specific to GCA and not endocarditis include headache with temporal artery tenderness, jaw claudication (50% of cases), abrupt partial visual defect that may be transient (amaurosis fugax) or permanent, arm claudication, and polymyalgia rheumatica (PMR). Jaw claudication is caused by ischemia of the masseter muscles and is characterized by aching in the jaw with chewing. Symptoms disappear in a few minutes when chewing is discontinued.

PMR is characterized by symmetrical aching and morning stiffness in the shoulders, hip girdle, neck, and torso. It occurs in half of patients who have GCA. There is no specific laboratory test that defines GCA. The erythrocyte sedimentation rate (ESR) is usually very high, greater than 90 mm/hr, yet may be normal in 4% of cases. (The ESR in endocarditis would expectedly be elevated, but not nearly approaching levels seen in GCA.) Other common laboratory abnormalities include normochromic anemia with normal leukocyte count, increased platelet count, abnormal serum alkaline phosphatase and aminotransferase, and elevated serum C-reactive protein. GCA diagnosis is confirmed by temporal artery biopsy.

The bottom line is that any patient presenting with a stroke must have an accurate temperature measurement and ESR determination. Blood cultures must be obtained if fever is present.

Please note that diseases present with fever and acute neurologic deterioration that are not strokes. These include encephalitis, meningitis, subdural empyema, and brain abscess. Encephalitis is most commonly of viral origin; meningitis may be caused by many classes of infectious agents. Brain abscess occurs from hematogenous spread of infection from other sites in the body, such as gums or skin, or from trauma as may occur in a bullet wound in the head.

Heart Failure *and* Bounding Pulses

HF is a broad umbrella diagnosis that includes disorders with varied pathophysiology, symptoms, physical signs, and treatment. Systolic HF, for example, is characterized by weakness, dilated left ventricle, and reduced

cardiac output. Diastolic HF (DHF) is characterized by dyspnea and a noncompliant left ventricle.

In the patient who has HF manifest by dyspnea, peripheral edema, gallop heart rhythm, and pulmonary crackles, and in whom examination shows bounding arterial pulses, the clinician should immediately exclude the diagnoses of systolic HF and DHF. Rather, the clinician should consider high cardiac output HF. The bounding pulses are associated with increased pulse pressure, systolic hypertension, and tachycardia, all related to decreased peripheral (systemic) vascular resistance and increased stroke volume. HF and bounding pulses are characteristic of hyperthyroidism, arteriovenous fistula, and beri beri.

Hyperthyroidism may result from an autoimmune disease (Graves' disease) in which anti-thyroid stimulating hormone receptor antibodies are present in the serum. These antibodies *stimulate* thyroid hormone synthesis, in contrast to autoimmune antibodies in other diseases that have an antagonistic effect upon the receptor organ. Other nonautoimmune causes of hyperthyroidism include toxic adenoma, toxic multinodular goiter, exogenous intake of thyroid hormone, and, causing a transient hyperthyroid state, thyroiditis.

Arteriovenous fistulas may be congenital or, more commonly, acquired. Acquired causes include surgical construction of a fistula for vascular access in patients requiring chronic hemodialysis and those patients who have suffered penetrating wounds, usually from a bullet or stabbing. Again, the bounding pulses are a result of the decreased systemic vascular resistance in these patients. Interestingly, HF from a penetrating wound tends to occur about 2 years after the injury, but may occur, infrequently, as early as 6 months after injury. High cardiac output HF in thiamine deficiency is called "wet beri beri." The *wet* form of beri beri due to vitamin B thiamine deficiency is more common in Asian countries in which the population ingests a diet high in polished rice (and low in thiamine).

In contrast to high output HF with its wide pulse pressure due to increased stroke volume in the presence of low systemic vascular resistance, many persons have increased pulse pressure related to an entirely different mechanism. Pulse pressure is simply the difference between systolic and diastolic blood pressure. Increased stiffness (or decreased compliance) of large arteries results in an increased systolic pressure during LV ejection. Then, during ventricular diastole, the reduced elasticity in the stiff aorta results in a decrease in diastolic pressure. As a result, elderly persons commonly have increased pulse pressure yet do not have the hemodynamic abnormalities, for example, increased stroke volume and low systemic vascular resistance, that are noted in high cardiac output states.

Dyspnea *And*

Dyspnea (breathlessness) is a common symptom that may be mild in character or may create fear of impending death. Of course, as in the case of many symptoms, there are many causes, including cardiac, pulmonary, musculoskeletal, neurologic, and psychiatric disorders. In the majority of patients with dyspnea, the etiology is lung disease or heart disease; so-called pulmonary dyspnea and cardiac dyspnea.

In many patients, clinical experience has taught me a very simple *and* that can help differentiate between these two disorders. *And* is the link between the symptom, dyspnea, and *the location of the point of maximal impulse (PMI)* on the precordium. The clinical principle: If the PMI is a lift or heave at the apex, think of cardiac dyspnea. If the PMI is a lift along the left sternal border, think of pulmonary dyspnea.

Let us explore the basis of this clinical point. The pathophysiology in *pulmonary dyspnea* is complex. The normal pulmonary artery pressure in the adult at rest is approximately 24/9 with a mean of 15 mm Hg. Pulmonary hypertension is defined as a mean pulmonary artery pressure greater than 25 mm Hg at rest. In those patients in whom increased pulmonary vascular resistance occurs, for example, in those with interstitial lung disease (pulmonary fibrosis), chronic bronchitis, hypoxemia and alveolar ventilation from thoracovertebral deformities, and pulmonary embolic disease, pulmonary hypertension follows.

The increased pulmonary artery pressure increases right ventricular pressure designed to preserve cardiac output. In turn, increased right ventricular pressure causes both right ventricular dilatation and hypertrophy. The clinical sign is a left parasternal lift. Therefore, if the dyspneic patient has a left parasternal lift as the PMI, the clinician knows that pulmonary hypertension is present.

The common denominator in cardiac dyspnea is an increase in left atrial mean pressure. The elevated left atrial pressure is transmitted retrograde through the pulmonary veins into the pulmonary capillaries. The lungs become stiff due to pulmonary congestion, that is, interstitial edema, and the patient experiences breathlessness. DHF is the classic cardiac disorder causing dyspnea.

Let's look closely at *cardiac dyspnea* associated with DHF. DHF is due to increased stiffness (decreased compliance) of the left ventricle. The stiff ventricle has an elevated end-diastolic pressure. Therefore, left atrial pressure must increase in an effort to propel blood forward into the ventricle during diastole. Again, this elevated left atrial pressure is transmitted backward into

the lungs, causing dyspnea. DHF is most commonly associated with left ventricular hypertrophy (LVH). LVH, in turn, is a compensatory response to systemic hypertension or aortic valve stenosis. The physical sign of LVH is an apical lift or heave and, if the patient is in sinus rhythm, an S4 gallop. LVH, then, may be *acquired*, secondary to hypertension or aortic valve stenosis, or LVH may be *related to congenital heart disease*, for example, hypertrophic cardiomyopathy.

Increased LV stiffness may be due to factors other than hypertrophy. Myocardial ischemia commonly is associated with *transiently increased stiffness*. This explains why the patient, during an attack of angina pectoris, often has associated breathlessness. After sublingual nitroglycerin use, the angina disappears and the dyspnea disappears. Further, the transient myocardial ischemia–induced stiffness of the LV explains "anginal equivalent" in which the patient has dyspnea due to transient DHF, but the patient has no associated anginal discomfort. Another cause of increased LV stiffness that can present as DHF is infiltrative myocardial disease, for example, amyloidosis.

Clubbing *And*

It is most important to recognize that clubbing of fingers and toes is not a sign of chronic obstructive pulmonary disease (COPD). If a patient with COPD develops clubbing, a careful search for another cause, especially lung cancer, must be made.

Clubbing is associated with many conditions, including primary and metastatic lung cancer, cyanotic congenital heart disease, infective endocarditis, nonmalignant pulmonary disease, cirrhosis, and inflammatory bowel disease. Clubbing may be familial and present without an associated disease.

Further, there is a related condition, hypertrophic osteoarthropathy (HO), a painful disorder in which there is subperiosteal formation of new bone. This causes pain in knees, ankles, shoulders, elbows, and wrists. HO is found in patients whose clubbing is associated with lung cancer (most commonly adenocarcinoma and least commonly with small cell carcinoma), mesothelioma, cirrhosis, and bronchiectasis.

The clinician must make the link between the clubbing and other clinical features. Here are some examples:

1. Clubbing *and* Recurrent Pulmonary Infections

Clubbing and recurrent pulmonary infections in a noncyanotic child suggests cystic fibrosis (CF). CF is an autosomal recessive hereditable disease that is

the most common cause of chronic lung disease in children and young adults. It is a disorder that affects all exocrine glands with production of viscous secretions in the respiratory, gastrointestinal, and reproductive tracts. Pulmonary involvement includes chronic bronchitis, bronchiectasis, and cor pulmonale. Pancreatic insufficiency and infertility are common. The majority of CF patients have sinus disease and nasal polyps. *Pseudomonas* infection is responsible for the majority of deaths in patients.

A common complication of CF is bronchiectasis manifest by long-standing cough, mucopurulent sputum production, wheezing, and, occasionally, hemoptysis, even massive in quantity. Bronchiectasis may occur in patients who do not have CF. Non-CF bronchiectasis is related to airway obstruction due to a foreign body in the lung (even unchewed food from aspiration), repeated pulmonary infection, presumably due to viral or mycoplasma infection, and allergic bronchopulmonary aspergillosis that may occur in the long-standing asthmatic patient. In non-CF bronchiectasis, the incidence of clubbing is directly related to the severity of the pulmonary disorder.

An important clinical point: Up to 7% of CF patients are initially diagnosed at the age of 18 years or older.

2. Clubbing *and* Lung Abscess

Lung abscess is most commonly related to two conditions, aspiration and septic embolism to the lung from tricuspid endocarditis. Lung abscess is characterized by cough, purulent (often foul-smelling) sputum, fever, and night sweats. In aspiration, the most common infecting organisms are anaerobic bacteria that are normally found in gingival crevices. These include *Peptostreptococcus*, *Bacteroides* spp, and *Fusobacterium*.

Aspiration occurs in patients predisposed to impaired consciousness, for example, those suffering from chronic alcohol or drug abuse or those who have a seizure disorder. These patients are prone to vomiting, during which time the vomitus carries gingival organisms into the lungs. The pulmonary infection typically causes abscess formation in 7 to 14 days.

It is important to recognize that, in the patient with lung abscess due to aspiration, sputum cultures and even bronchoscopy specimens are contaminated by upper airway flora. Therefore, in this patient a transtracheal aspirate is essential to obtain a sputum sample that will correctly identify the infecting organism in the lungs.

Intravenous drug abusers commonly develop lung abscess secondary to septic emboli from tricuspid endocarditis. In fact, three-quarters of patients with tricuspid endocarditis have septic emboli to the lungs. The infecting organism is most commonly *Staphylococcus aureus*. This virulent organism

causes the patient to be toxic, exhibiting high fever, chills, and night sweats. The classic murmur of tricuspid regurgitation is a holosystolic murmur in the fourth intercostal space that increases during inspiration. However, in many patients with tricuspid endocarditis, a murmur may not be heard on auscultation.

3. Clubbing *and* Cyanotic Congenital Heart Disease

Clubbing is common in cyanotic congenital heart diseases such as tetralogy of Fallot and transposition of the great arteries. In most cases, arterial desaturation must be present for at least 6 months before clubbing is evident. However, in severe cases clubbing may be noted at 3 months of age. In tetralogy, a right-sided aortic arch is present in approximately 25% of cases.

Clubbing and cyanosis are characteristic in patients who have Eisenmenger syndrome. Those who are born with noncyanotic congenital heart disease with large left to right shunts, as may occur in atrial septal defect, ventricular septal defect, and patent ductus arteriosus, are at risk of developing Eisenmenger syndrome. The pathophysiologic abnormality in this syndrome is development of increased pulmonary vascular resistance with resultant pulmonary hypertension that causes *reversal of shunt direction*. Patients then have right to left shunting that causes severe systemic arterial desaturation and clubbing formation.

4. Clubbing *and* Pulmonary Fibrosis (Interstitial Lung Disease)

Pulmonary fibrosis may be idiopathic or due to environmental disorders or to medication. Inorganic (silicon dioxide) and organic dusts (avian antigens), fumes (chlorine, isocyanates), and medications (for example, amiodarone, sulfonamides, phenytoin, cyclophosphamide, and methotrexate) are recognized agents that incite the pulmonary inflammatory process.

The pathophysiologic common denominators are decreased pulmonary compliance (or increased lung stiffness) that causes a restrictive pulmonary disorder in addition to impairment of oxygen transfer from the alveoli to the pulmonary capillaries. Restrictive lung disease is characterized by hyperventilation (without airway obstruction), hypocapnia (low $PaCO_2$), and variable hypoxemia (low PaO_2) dependent upon severity of the disease. Chest radiography shows reticulonodular infiltrates most pronounced in the lower lung fields. Clubbing occurs in 25% to 50% of patients who have pulmonary fibrosis. Pulmonary function tests in the patient with restrictive lung disease show a normal or increased forced expiratory volume 1 sec/forced vital capacity ratio (FEV 1 sec/FVC), decreased carbon monoxide diffusing

capacity, and reduced tidal volume. In contrast, the FEV 1 sec/FVC ratio is reduced in patients having obstructive airway disease, such as asthma and chronic bronchitis.

Hyperglycemia *And*

A number of diseases cause hyperglycemia and cause secondary diabetes mellitus. The clinician must look for the *and* that links the elevated plasma glucose to the correct etiology.

1. Hyperglycemia *and* obesity, hirsutism, oligomenorrhea (or amenorrhea), and infertility is characteristic of polycystic ovary syndrome (PCO). PCO is associated with insulin resistance and hyperinsulinemia that frequently leads to type 2 diabetes mellitus. In addition to hyperglycemia, PCO patients have increased serum levels of luteinizing hormone, testosterone, and prolactin. Because of increased androgen levels, the patients have a male hair distribution.
2. Hyperglycemia *and* hypertension in a patient who has a rounded ("moon") facies and ecchymoses is indicative of hypercortisolemia. The elevated serum cortisol levels may be due to a functioning pituitary adenoma (Cushing's disease), adrenal hyperplasia or carcinoma, or to glucocorticoid medicinal therapy. Hyperglycemia is present because cortisol (and glucocorticoid medication) increases gluconeogenesis and inhibits glycogen storage.
3. Hyperglycemia *and* slowly enlarging jaw, hands, and feet in an adult patient is typical of acromegaly. Acromegaly is caused by a pituitary adenoma that secretes elevated levels of growth hormone and prolactin. Growth hormone stimulates glucagon release. As a result, insulin resistance and hyperinsulinemia are noted in 60% of patients; another 15% have diabetes mellitus. Hypertension is common, present in 50% of acromegalic patients.

   Think for a moment: Note how you can reverse the clues in the preceding two patients. Start with hypertension and add the physical signs as *and*. Now you have "hypertension *and*": Hypertension *and* a moon facies suggests hypercortisolemia. Hypertension *and* enlarging hands and feet is indicative of acromegaly.
4. Hyperglycemia *and* episodic sweats, palpitations, and headache suggests pheochromocytoma. Pheochromocytomas are tumors that secrete excessive amounts of norepinephrine or epinephrine. Most patients have

sustained hypertension; a small percentage (5–15%) have normal blood pressure with paroxysmal elevations. The hyperglycemia is due to an increase in both hepatic glycogenolysis and gluconeogenesis. Those patients with sustained hypertension often have superimposed *orthostatic hypotension* due to the hypovolemia induced by chronic elevation in plasma catecholamines. Diagnosis is made by urine assays that show increased excretion of metanephrines and catecholamines.

Approximately 15% of pheochromocytomas occur as hereditable disorders. Both have autosomal dominant inheritance. First is von Hippel–Lindau syndrome characterized by pheochromocytoma, retinal angioma, cerebellar hemangioblastoma, renal and pancreatic cysts, and renal carcinoma. The second is multiple endocrine neoplasia type 2 A (MEN 2A). In this condition the pheochromocytoma is often associated with medullary carcinoma of the thyroid and parathyroid hyperplasia that cause hyperparathyroidism.

5. Hyperglycemia *and* flushing and diarrhea suggests medullary carcinoma of the thyroid. This neuroendocrine tumor is usually sporadic; approximately 15% are part of multiple endocrine neoplasia type 2 (MEN 2) syndrome. The tumors usually secrete several chemicals, particularly calcitonin, but also serotonin, prostaglandins, and adrenocorticotrophic hormone (ACTH). The hypercortisolism induced by ACTH causes hyperglycemia in these tumors.
6. Hyperglycemia *and* azotemia. Most commonly, patients with type 1 and type 2 diabetes mellitus develop hypertension with progressive renal involvement associated with the endocrine disorder. In the type 1 diabetic, blood pressure typically begins to rise within 3 years of the onset of microalbuminuria. In the type 2 diabetic, hypertension is common prior to presence of microalbuminuria. In these patients, obesity is common, and the hypertension is likely due to the patient's weight. The mechanism by which obesity increases blood pressure is not clear. Persistent obesity not only increases blood pressure, but makes the condition more difficult to control by interfering with the effect of anti-hypertensive medication.
7. Hyperglycemia *and* acanthosis nigricans (AN) is a clinical disorder indicative of the insulin resistance found in all patients who have *non-malignancy*-associated AN. AN is found in diabetes mellitus, obesity, and Cushing's syndrome.

   Further, AN is associated with *malignancy*, especially gastric and hepatocellular carcinoma and less frequently lung cancer. AN lesions

are gray-brown to black, are rough in texture, and are most commonly found in the axillae, inguinal creases, and back and sides of the neck.

Eosinophilia *And*

Eosinophilia, defined as more than 500 eosinophiles/microL, is common in allergic (atopic) disorders such as allergic rhinitis and asthma. Diagnosis is usually quite easy. In rhinitis the *nasal secretions* demonstrate eosinophiles upon Gram stain examination. Further, in asthma the *sputum secretions* contain eosinophiles; this can be helpful in differentiation from chronic obstructive lung disease.

Eosinophilia is also noted in certain acute leukemias and neoplasms, for example, in 15% of patients with Hodgkin's lymphoma. Eosinophilia is noted in 20% of patients with systemic mastocytosis, a neoplastic disorder in which mast cells accumulate in skin, liver, spleen, bone marrow, and lymph nodes. Symptoms arise when mast cells release histamine, leukotrienes, heparin, and prostaglandins. Hypotension, flushing, diarrhea, and pruritus are typical manifestations.

Eosinphilia also may result from ingestion of many medications. Examples include NSAIDs, beta adrenergic blockers, phenytoin, cephalosporins, and the histamine H2 receptor antagonist ranitidine.

In the preceding disorders, the clinician has a clear indication of the etiology of the increased eosinophile blood count. However, there are many times, after performing a history and physical examination, when the clinician cannot determine the diagnosis. At these times, the eosinophilia may be the seminal clue in the clinical puzzle. The abnormal laboratory result may coax the clinician to search for another *and*. In the case of eosinophilia, *and* often represents international travel. Of course, international travel relates both to the immigrant as well as to the American who travels abroad, becomes infected, and then returns.

Many helminth (worm) parasitic diseases cause eosinophilia; the degree is related to the extent of parasitic invasion of the intestinal mucosa. Parasitic worms that cause human infection include nematodes (roundworms), cestodes (tapeworms), and trematodes (flukes). Trichinellosis, a nematode infection, is common in East Asia and South America. Moreover, it is not rare in the United States because human infection may be acquired by ingestion of *Trichinella* cysts from inadequately cooked pork from domestic pigs.

In trichinellosis, invasion of the intestinal mucosa causes abdominal discomfort, nausea, vomiting, and diarrhea. Hematogenous spread of the larvae

to skeletal muscle follows. Muscle pain occurs; at this point, the patient has muscle tenderness, splinter and conjunctival hemorrhages, periorbital edema, and chemosis. Eosinophilia appears approximately 1 week after the onset of muscle symptoms.

Conclusion

A patient's symptom guides the clinician's thinking toward diagnosis. It is *and* that enables the astute medical detective to quickly sort through the differential diagnosis to reach an efficient and correct diagnosis.

Always seek the *and* when searching for diagnosis.