

**INTERMEDIATE MEDICAL  
LIFE INSURANCE UNDERWRITING**

**ALU 201 TEXTBOOK**

**Eight Edition – 2022**

**THE ACADEMY OF LIFE UNDERWRITING**



## **GUIDING PRINCIPLES FOR THE UNDERWRITER**

Act promptly, while exercising sound, objective, and consistent judgment, in making underwriting decisions.

Follow established risk classification principles that differentiate fairly on the basis of sound actuarial principles and/or reasonable anticipated mortality or morbidity experience.

Treat all underwriting information with the utmost confidentiality, and use it only for the express purpose of evaluating and classifying risk.

Comply with the letter and spirit of all insurance legislation and regulations, particularly as they apply to risk classification, privacy, and disclosure.

Avoid any underwriting action which is in conflict with the obligation to act independently and without bias.

Act responsibly as an employee with scrupulous attention to the mutual trust required in an employer/employee relationship.

Provide information and support to sales personnel to help them fulfill their field underwriting responsibilities in selecting risks and submitting underwriting information.

Strive to attain Fellowship in the Academy of Life Underwriting, maintain a high level of professional competency through continued education, and help promote the further education of all underwriters.

Maintain the dignity and sound reputation of the Underwriting Profession.

Increase the public's understanding of underwriting by providing information about risk classification.

**These Guiding Principles are presented, not as specific standards for others to measure individual performance, but for the self-guidance of all those who are striving to understand and meet the responsibilities of an underwriter.**

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The pronouns "he, his, him" are to be interpreted as pertaining to both male and female genders wherever appropriate in context.

### **Laws**

Laws and regulations discussed in the ALU text series are those of the United States of America, unless specifically noted as applying to other countries.

### **Acknowledgements**

The Academy of Life Underwriting thanks all the authors who contributed to the ALU textbook series. We are grateful for their professionalism, dedication, and commitment to the future of quality underwriting. Their efforts are integral to the continuing success of the ALU education and examination program.

### **Special Appreciation**

The Academy of Life Underwriting also wishes to express its gratitude to all the volunteers who have contributed to the revision of the ALU curriculum over the years. The members of the ALU Curriculum group, medical consultants, authors, and editors work diligently to develop, review, and update the curriculum each year. Without their knowledge, support, and enthusiasm, maintaining the integrity of the curriculum would not be possible.

### **Endnotes and Bibliography**

Endnotes, references, and bibliographies have been removed from the end of each chapter and can be found on the ALU Website, under the Curriculum section at [www.alu-web.com](http://www.alu-web.com).

**ALU EXAM 201**  
**ASSIGNED READINGS FROM**  
**ESSENTIALS OF ANATOMY AND PHYSIOLOGY**

**Required Text**

Scanlon, Valerie C. and Sanders, Tina, Essentials of Anatomy and Physiology, Eighth Edition, Philadelphia, PA, F. A. Davis Company, 2019. (The Seventh Edition of the text can also be used.)

Essentials of Anatomy and Physiology, Seventh or Eighth Edition is no longer available from the ALU. It can be purchased from an online bookseller such as Amazon.com or from the publisher.

**The ALU 201 student will be responsible for the material in the following chapters. The contents of each chapter, including the material in the boxes, tables, and figures, will be tested.**

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## **CHAPTER 1**

### **THE GASTROINTESTINAL SYSTEM**

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**Revised 2022**



# THE GASTROINTESTINAL SYSTEM

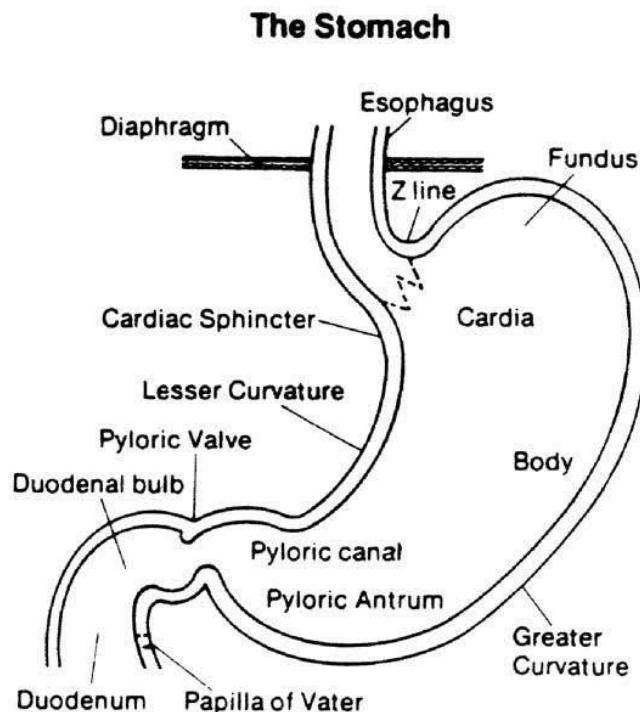
## Introduction

The gastrointestinal system consists of the alimentary food tract, pancreas, and hepatobiliary system. This chapter will address the alimentary tract and the pancreas; the hepatobiliary system is covered in the next chapter. The alimentary tract is one continuous tube, beginning at the mouth and progressing through the esophagus, stomach, small intestine, large intestine, and ending with the anus. Digestion, the breakdown and absorption of nutrients, electrolytes, and water, occurs in a series of mechanical and chemical processes as food passes through the alimentary tract. The gastrointestinal system can be affected pathologically by ulceration, inflammation, infection, tumors (both benign and malignant), neurologic dysfunction, and mechanical obstruction.

## Digestion: Anatomy and Physiology

The mouth is the site of initial digestion. Here, food is mechanically broken down by chewing and is lubricated by saliva produced by the salivary glands. There is some breakdown of starch in the mouth, but this is of minimal digestive importance. After food is chewed, it is passed to the esophagus through the neurologically mediated process of swallowing. Once food enters the esophagus, it is forced downward by gravity and the rhythmic contractions (peristalsis) of the muscles that make up the outer two layers of the esophagus. Food passes from the esophagus into the stomach through the lower esophageal sphincter, located just below the level of the diaphragm. This gastroesophageal junction (GE junction) is also known as the Z-line because of its zigzag appearance.

**Figure 1.**



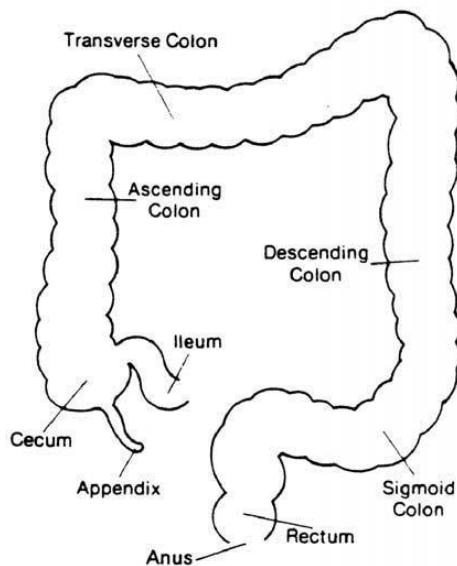
The stomach is anatomically divided into several areas (Figure 1). The major function of the stomach is to continue the mechanical grinding of the food bolus and to enhance the chemical process of digestion. This is done through the secretion of hydrochloric acid (HCl) and pepsin. For the most part, the stomach does not absorb nutrients, though it is the main site of alcohol absorption. The stomach's other role is the production of intrinsic factor, a protein that is necessary for the absorption of vitamin B<sub>12</sub>.

The food is passed from the stomach through the pylorus, a muscular channel, into the first part of the small intestine, the duodenum. Digestive enzymes, produced in the pancreas, and bile, produced in the liver, empty into the duodenum through a common opening known as the ampulla or papilla of Vater. This fluid, along with locally produced pH neutralizing bicarbonate, mixes with the food, allowing for the major chemical breakdown of protein, carbohydrates, and fats into smaller, simpler, absorbable forms. As the nutrients pass through the rest of the small intestine (the jejunum and finally the ileum), they are absorbed through multiple projections of the mucosa called the villi. The terminal ileum is critical for the absorption of vitamin B12 and the reabsorption of bile salts. The small intestine on average is 22 feet long, and the villi produce many more feet of absorptive surface.

The residual solution that is not absorbed by the small intestine passes through the ileocecal valve, located in the right lower quadrant of the abdomen, into the cecum, the first part of the large intestine (colon) (Figure 2). The appendix, a long, non-functional, narrow tube, also opens into this area of the large intestine. The colon extends up the right side of the abdomen (the ascending colon), takes a bend to the left at the liver (the hepatic flexure), and crosses the upper abdomen (the transverse colon). At the level of the spleen (the splenic flexure), the colon turns downward (the descending colon). It is configured into an S-shape towards the lower left quadrant and therefore is referred to as the sigmoid colon. The last 15 centimeters of the colon is called the rectum. The structure that controls the fecal outflow is called the anus.

**Figure 2.**

**The Large Intestine**



The major function of the large intestine is to reabsorb water and electrolytes passing from the small intestine and to control the elimination of the digestive waste material. To accomplish this process, the transit time (forward motion) slows greatly in the colon. The large bowel is also host to many bacteria that aid in the production of vitamin K.

## Oral Diseases

As mentioned earlier, the gastrointestinal tract can be subject to many pathologic processes. The mouth can be affected by cancer, infection, and inflammation. Oral cancer is usually squamous cell carcinoma, which tends to recur and has a high mortality rate. Many systemic diseases have associated oral lesions. For example, aphous ulcers (flat erosions of the mouth) can be associated with Crohn's disease and systemic lupus erythematosus. A candida fungal infection of the mouth (i.e., thrush) can be a sign of an immune deficiency state such as acquired immunodeficiency syndrome (AIDS) or the result of inhaling steroid medication. Glossitis (an inflammation of the tongue) is seen with vitamin B12 deficiency. These mouth lesions and other oral lesions are of little underwriting importance, but the underlying disease can have a significant impact on morbidity and mortality.

## Esophageal Disease

Esophageal disorders can occur because of primary esophageal motor abnormalities, central nervous system diseases, strictures, or masses. Dysphagia (i.e., difficulty swallowing) can be caused by any of these processes. The pain associated with dysphagia (i.e., odynophagia) is described as retrosternal and occurs while swallowing. Treatment requires first determining the underlying etiology. When a primary motor disorder (e.g., esophageal spasm) is diagnosed through esophageal manometry (i.e., pressure monitoring of the esophagus) and barium x-ray studies, the treatment often consists of the promotility medication metoclopramide (Reglan<sup>®</sup>) or antispasmodic agents such as nifedipine (Procardia<sup>®</sup>) and nitroglycerin. Strictures of the esophagus require dilatation that is usually performed by the passage of tubes or balloons through the mouth with the use of special fiberoptic instruments (i.e., upper endoscopes). Achalasia is the failure of the lower esophageal sphincter to relax. This results in significant dilation of the esophagus. It is treated with endoscopic balloon dilatation or surgery. Achalasia is associated with an increased risk of esophageal cancer, both squamous cell carcinoma and adenocarcinoma.

### Gastroesophageal Reflux Disease and Complications

Gastroesophageal reflux disease (GERD), the reflux of gastric contents back into the esophagus, is a common disorder of the esophagus. GERD can occur idiopathically or in association with a hiatal hernia (see below). Reflux most often causes retrosternal burning pain, commonly referred to as heartburn (i.e., pyrosis), though it can cause a pressure-like sensation in the chest that can radiate into the neck, jaw, and arms. This pain syndrome can mimic cardiac angina and must, therefore, be distinguished from this life-threatening disease.

Pathologically, reflux can induce inflammation that is usually mild but can occasionally be more severe, causing ulceration, bleeding, and the formation of strictures. In a minority of individuals, chronic inflammation can cause a transition of the normal squamous esophageal

mucosa into glandular gastric mucosa. Further changes to the mucosa (i.e., metaplasia) causing it to resemble intestinal cells (i.e., intestinalization) is Barrett's esophagus. Barrett's can be detected visually using upper endoscopy. The instrument can be passed through the mouth to the duodenum allowing visualization, as well as biopsy, and the performance of therapeutic procedures (therapeutic esophagogastroduodenoscopy [EGD]). Endoscopically Barrett's esophagus appears as pink areas of mucosa in an esophagus that ordinarily is a pearly white color. Confirmation, however, must be done microscopically on a biopsy specimen.

Barrett's esophagus is significant because it is a premalignant process. Over time, the newly transformed, intestinalized cells can become dysplastic (premalignant). The dysplasia is described as either low-grade or high-grade. Both grades have a high incidence of developing into an overt adenocarcinoma, with high-grade dysplasia being more ominous with a high mortality rate. Both grades require close follow up with frequent surveillance endoscopy and biopsies. Barrett's can be treated with endoscopic therapies, such as radiofrequency ablation and photodynamic therapy, but, even after treatment, close surveillance to check for recurrence is required.

Another complication of reflux is the aspiration of gastric contents into the respiratory tract causing bronchospasm and, in severe cases, pneumonia.

GERD is usually diagnosed by history and confirmed by endoscopy, x-ray studies, and/or pH monitoring of the esophagus. GERD is treated with anti-reflux measures including:

1. avoidance of citrus fruits, tomatoes, fats, coffee, alcohol, chocolate, and cigarettes
2. restricting food intake for several hours prior to reclining
3. raising the head of the bed
4. weight loss.

Acid-reducing medications and promotility drugs are frequently used to treat GERD. Surgery is undertaken when the GERD is severe and not responsive to the above measures. The most common surgery, in which the stomach is wrapped around the lower esophagus, is a Nissen fundoplication performed with a fiberoptic surgical instrument (laparoscope).

### Esophageal Squamous Cell Cancer

Esophageal cancer, unrelated to reflux and Barrett's esophagus, is usually squamous cell carcinoma (SCC). In the United States, there is a significant correlation between smoking and alcohol abuse and esophageal squamous cell carcinoma. In the past, SCC was the most common form of esophageal cancer, but now adenocarcinoma associated with Barrett's esophagus is more common. All esophageal cancers have a high mortality rate.

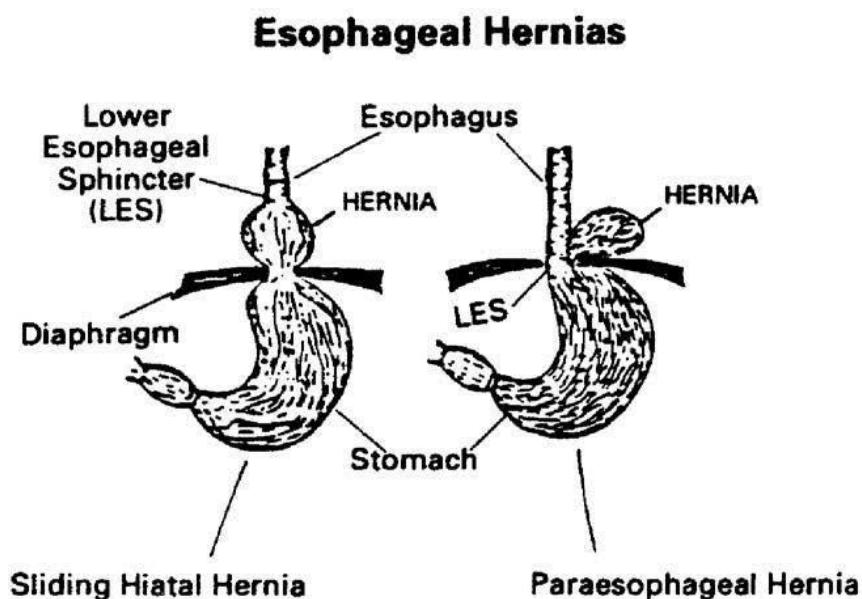
### Esophageal Hernias

As mentioned earlier, the stomach normally lies in the abdominal cavity with the gastroesophageal junction being just below the level of the diaphragm. When the stomach pushes up through the diaphragm into the chest, it is called an esophageal or hiatal hernia. There are two

types of hiatal hernias – a sliding or axial hiatal hernia and a paraesophageal hernia (Figure 3). The former hernia results in the gastroesophageal junction being above the level of the diaphragm.

Hiatal hernias are very common and usually do not result in symptoms; however, the abnormal position of the lower esophageal sphincter can allow the gastric contents to reflux into the esophagus more readily. A paraesophageal hernia occurs when part of the stomach folds back upon itself and gets trapped in the diaphragmatic ring. This hernia occurs with much less frequency than hiatal hernias. With this hernia, the gastroesophageal junction stays below the diaphragm. Strangulation of the stomach can occur with paraesophageal hernias, causing necrosis. This can be life threatening and often requires surgical repair. Esophageal hernias are detected by x-ray studies or endoscopy.

**Figure 3.**



### Gastric and Duodenal Inflammation and Ulcer Disease

The stomach and duodenum are both subject to inflammation and ulceration of the mucosa. Burning mid-epigastric pain, relieved by food or antacids, is the most common presentation. For years, the mechanism was felt to be strictly related to the acid content of the stomach and duodenum. Therefore, these ulcers are also referred to as peptic ulcers. The cause is now understood to be multifactorial and, in some instances, different for the stomach and the duodenum. There can be a genetic predisposition to ulcer disease. Stress has not been proven to induce or exacerbate ulcers. One of the most common causes of gastric and duodenal inflammation and ulceration is aspirin and the group of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). These include medications such as ibuprofen (Motrin®, Advil®) and naproxen (Naprosyn®, Aleve®). Alcohol is another common irritant to the gastric and duodenal mucosa causing inflammation, erosion, and ulceration. Cigarette smoking inhibits the healing of ulcers.

Ulceration of the stomach can also be secondary to a gastric cancer. Approximately 1% of gastric ulcers are malignant. To rule out malignancy, it is standard practice to biopsy all significant gastric ulcers via endoscopy and to perform a follow-up endoscopy of large ulcers to verify that complete healing has occurred.

The main complications of inflammation and ulceration of the stomach and duodenum are bleeding and, more rarely, perforation. Duodenal ulcers and pyloric channel ulcers can cause gastric outlet obstruction because of swelling. Gastritis, duodenitis, and ulcer disease are all treated with medications aimed at reducing the acid content of the stomach, no matter what the causative agent. These medications include liquid or tablet antacids (Maalox<sup>®</sup>, Mylanta<sup>®</sup>), H<sub>2</sub> blockers (cimetidine/Tagamet<sup>®</sup>, ranitidine/Zantac<sup>®</sup>, famotidine/Pepcid<sup>®</sup>), and proton pump inhibitors (omeprazole/Prilosec<sup>®</sup>, esomeprazole/Nexium<sup>®</sup>, pantoprazole/Protonix<sup>®</sup>, lansoprazole/Prevacid<sup>®</sup>, rabeprazole/Aciphex<sup>®</sup>). Diagnosis is made by endoscopic or x-ray evaluation. There is some suggestion that PPIs are associated with a small increased risk of coronary artery disease and renal insufficiency. These findings are still controversial, but the degree of increased risk is very small and not likely a significant insurance risk.

### Helicobacter Pylori

In the early 1980s, it was determined that a small bacterium, Helicobacter pylori (H. pylori), was one of the causes of antral gastritis. It was later determined that H. pylori also plays a major role in duodenal and gastric ulcer disease that is not caused by aspirin or nonsteroidal anti-inflammatory agents. Ulcers and gastritis can be healed with traditional acid reducing agents but if H. pylori is present and not treated with antibiotics, there is a high likelihood of recurrence. Atrophy of the stomach lining (atrophic gastritis) and a small increased risk of gastric adenocarcinoma have also been linked to the bacteria. H. pylori also causes mucosa-associated lymphoid tissue (MALT) lymphoma, a type of gastric lymphoma. This tumor can regress with antibiotic treatment of the H. pylori.

H. pylori can be detected directly by microscopic examination of a biopsy specimen. It can be detected indirectly through serum antibody testing, stool testing, or biopsy testing to detect urea produced by the bacteria (CLO-test or Pyloritek) or by a breath test to detect the urea.

## **Pancreatic Disorders**

### Pancreatitis

The pancreas produces insulin and digestive enzymes. Inflammation of the pancreas, or pancreatitis, can be acute or chronic. It can be caused by alcohol, blockage by gallstones (gallstone pancreatitis), medications, infection, autoimmune disease, hypertriglyceridemia with triglyceride levels >1000, and idiopathically. Acute pancreatitis has a high mortality rate.

The diagnosis is based on elevated serum amylase and lipase levels and imaging studies (e.g., ultrasound, CT scan, MRI, and/or magnetic resonance cholangiopancreatography [MRCP]). The inflamed pancreas can cause fluid and debris to collect adjacent to the pancreas, which over time can form into a cyst-like mass—a pseudocyst. Once resolved, the mortality risk of acute

pancreatitis is determined by the underlying cause and the likelihood of recurrence. Chronic pancreatitis can cause inadequate insulin production (diabetes) and inadequate digestive enzyme production (pancreatic insufficiency) leading to malabsorption and weight loss. Diabetes often requires insulin injections. Pancreatic insufficiency requires oral digestive enzymes with meals (Creon®, Pancrease®).

## Pancreatic Tumors

### *Solid Lesions*

The pancreas can be affected by tumors. These are categorized as benign, malignant, or hormone-producing (endocrine) tumors. The most common tumor of the pancreas is pancreatic adenocarcinoma, which has a very high mortality rate. The most common endocrine tumors are:

1. gastrinomas (Zollinger-Ellison syndrome) that cause refractory stomach and duodenal ulcers
2. insulinomas that cause precipitous low blood sugar (hypoglycemia)
3. vasoactive intestinal peptide-producing tumors (VIPomas) that cause watery diarrhea.
4. glucagonomas that cause hyperglycemia, diabetes, necrolytic migratory erythema and thromboembolic complications.

These conditions cause disease by their mass effect, the effect of the excess hormone, and the spread to lymph nodes or the liver. They are often multiple and difficult to identify on imaging studies, thus making treatment difficult.

### *Cystic Lesions*

Pancreatic cysts are fluid filled lesions that are often found incidentally at the time of imaging for other reasons. They present a diagnostic dilemma as to whether they are benign or malignant. Determination of the nature of the lesion and the risk it represents is made through various techniques including endoscopic retrograde cholangiopancreatography (ERCP), CT scan, MRI, MRCP and endoscopic ultrasound-guided biopsy or fine needle aspiration (FNA). Fluid withdrawn from cysts can be sent for cytology, measurement of CEA and amylase and DNA analysis. Worrisome features include size > 3 cm, any solid component, dilated pancreatic duct and rapid growth. Cysts with no worrisome features require surveillance and can be monitored with follow-up imaging studies at 1, 3 and 5 years. Those with worrisome features require FNA and, if suspicious for malignancy (e.g. elevated CEA, high risk DNA analysis, malignant cells on cytology), require surgical resection. The management of these lesions is complicated and still evolving. These lesions are characterized as follows:

No malignant potential	Malignant potential	Malignant
Pseudocyst	Intraductal papillary mucinous neoplasm (IPMN)	Cystic ductal adenocarcinoma
Lymphoepithelial cyst		Cystic neuroendocrine tumor
Retention cyst	Mucinous cystic neoplasm	Solid pseudopapillary neoplasm
Congenital cyst	Intraductal tubular tumor	Cystic pancreaticoblastoma
Endometrial cyst		Cystic acinar cystadenocarcinoma
Cystic lymphangioma		
Cavernous hemangioma		
Serous cystic adenoma		

### Malabsorption and Diarrhea

Abnormal or inadequate absorption of nutrients occurs because of insufficient breakdown of food, disruption of the intestinal lining, loss of absorptive surface area or the too rapid passage of food through the intestines. Insufficient breakdown of food can occur because of the inadequate production of pancreatic digestive enzymes (i.e., pancreatic insufficiency) or the blockage of the flow of pancreatic fluid into the duodenum. Blockage can be caused by tumor, stones, or a stricture of the pancreatic duct or ampulla of Vater. The blockage of the bile flow into the duodenum by tumors, stones, or strictures can interfere with the absorption of fats and fat-soluble vitamins. Other digestive enzymes produced in the intestine can also be inadequately produced, causing maldigestion and thus malabsorption. A common example of a mild form of insufficient intestinal enzyme production is lactase deficiency, causing the inability to digest the milk sugar, lactose (i.e., lactose intolerance).

Disruption or destruction (i.e., blunting) of the villous surface of the small intestine, resulting in a decreased absorptive surface area, is another cause of malabsorption. This can occur due to infection, such as viral or bacterial gastroenteritis, or an immune- or allergen-mediated destruction, such as celiac sprue (gluten-sensitive enteropathy). Clinically, malabsorption manifests with bloating, diarrhea, weight loss, abdominal pain, anemia, low serum albumin, osteoporosis, and other symptoms of vitamin deficiency.

Celiac sprue is the most common cause of small bowel mucosal blunting. Diagnosis is initially assessed with serum antibody tests. Elevated IgA tissue transglutaminase (IgA tTG) with normal total serum IgA levels is the most reliable test though often other tests – anti-gliadin antibodies and endomysia tissue antibodies are also done. Definitive diagnosis is usually made with a biopsy of the duodenum performed during an upper endoscopy. All patients with celiac disease are HLA-DQ2 and/or HLA-D8 positive so a negative genetic marker rules out celiac sprue. Conversely, 30% of people without sprue can be HLA-D8 positive without having sprue. Celiac sprue is associated with a small risk of lymphoma and adenocarcinoma of the small intestine especially in those with poorly controlled disease. A lifelong gluten free diet is usually sufficient to treat celiac sprue, but, in rare cases, steroids can be needed.

If food and water are not absorbed in the small intestine, the excess volume is presented to the large intestine. When this volume overwhelms the colon's absorptive capacity, diarrhea (defined as greater than 200 grams of stool per day) occurs. Diarrhea can also occur as the result of infection of the large intestine, either by bacteria or viruses, which can inhibit absorption of water, cause increased secretion of water, or stimulate too rapid transit through the large intestine.

### **Inflammatory Bowel Disease – Crohn's Disease and Ulcerative Colitis**

In addition to ulceration and malabsorption, the small intestine can be affected by Crohn's disease. Crohn's disease, also known as granulomatous or regional enteritis, is an inflammatory process that can affect any part of the gastrointestinal tract, but most frequently affects the distal third of the small intestine (ileum) and the colon. The etiology is unclear but is felt to have an autoimmune basis. Crohn's disease needs to be distinguished from the other inflammatory bowel disease (IBD), ulcerative colitis (UC). Ulcerative colitis affects only the large intestine.

The evaluation of inflammatory bowel disease often includes endoscopic evaluations (usually colonoscopy but occasionally upper endoscopy), lab tests for anemia, infection, markers of inflammation (ESR – sed rate, CRP) and various imaging studies. Standard CT scanning is the most used imaging modality. A small bowel x-ray series is sometimes done to look for disease beyond the colon when Crohn's disease is suspected. Beyond the initial diagnosis, small bowel evaluation is often done with either CT enterography or MRI enterography. Both studies can evaluate mucosal changes, strictures, fistulas, and abscesses. MRI has the advantage of not using radiation.

In addition to location, there are other significant differences between these two disease entities (Table 1). Crohn's disease can affect the bowel in a non-continuous pattern, creating what is known as skip lesions. With this, affected individuals can have areas of severe inflammation with intervening normal mucosa. Ulcerative colitis, conversely, always involves the rectum and is continuous to some proximal part of the large intestine. Crohn's disease affects all layers of the bowel and can, therefore, be complicated by strictures, fistulas, and abscesses. The inflammation of ulcerative colitis is limited to the mucosa; therefore, the former complications do not occur unless there is a concomitant malignancy. Microscopically, Crohn's can reveal granulomas (aggregates of giant cells). This does not occur in ulcerative colitis.

In Crohn's disease involving the colon (Crohn's colitis) and in UC, there is an increased risk of colon cancer. It is well established that eight to ten years after the initial onset of the disease, there is a steady, significant, increased risk of developing cancer. This risk increases with the extent of the disease, i.e., how far up the colon the disease has spread and with the severity of the inflammation. Ulcerative colitis that is limited to the rectum (the distal 15 centimeters of the colon) is called ulcerative proctitis. Ulcerative proctitis and ulcerative proctosigmoiditis (up to 25 centimeters) have a small, increased cancer risk.

Appropriate management of individuals with ulcerative or Crohn's colitis for more than 10 years consists of full colonoscopy every one to two years, looking for overt cancer and performing multiple random biopsies looking for microscopic patches of dysplasia. Once dysplasia has been found, total colectomy (i.e., removal of the colon) is necessary to avoid future malignancy.

The treatment goal for Crohn's disease is to put the individual into remission. This is done with antibiotics, steroids (e.g., prednisone, budesonide/Entocort EC<sup>®</sup>), immunosuppressive agents (e.g., 6-mercaptopurine or 6MP, azathioprine/Imuran<sup>®</sup>), and/or sulfasalazine (Azulfidine<sup>®</sup>). Once remission is achieved, the medications can be tapered. Maintenance of the medications does not prevent relapse.

Ulcerative colitis is treated with antibiotics, sulfasalazine or one of its derivatives (olsalazine/Dipentum<sup>®</sup>, balsalazide/Colazal<sup>®</sup>, mesalamine/Pentasa<sup>®</sup>, Asacol<sup>®</sup>, Lialda<sup>®</sup> and Canasa<sup>®</sup> or Rowasa<sup>®</sup> enemas), and/or steroids. Sulfasalazine is often used to maintain remission and prevent relapse.

Infliximab (Remicade<sup>®</sup>), Adalimumab (Humira<sup>®</sup>), Certolizumab pegol (Cimzia<sup>®</sup>), Golimumab (Simponi<sup>®</sup>), Natalizumab (Tysabri<sup>®</sup>), Vedolizumab (Entyvio<sup>®</sup>) and the recently approved Ozanimod<sup>®</sup> (Zeposia) are in a class of drugs known as biologic disease modifying agents (DMARDs). These drugs are used to avoid the prolonged need for steroids. They can be used in difficult to treat cases as well to maintain remission. They are associated with an increased risk of infections and a small risk of lymphoma and possibly other malignancies. Most of these medications are given intravenously or by injection every two to eight weeks, however Ozanimod is an oral treatment.

Surgery for Crohn's disease is often palliative and required to treat a complication of the disease (e.g., a fistula). Surgery for ulcerative colitis with a total colectomy, including the rectal mucosa, is curative. The simplest operation consists of creating an ileostomy, a procedure that requires connecting the terminal ileum to an opening in the skin in the right lower quadrant of the abdomen, with an external bag to collect the fluid. A more complicated procedure, ileoanal anastomosis, involves attaching the ileum to the anus with the creation of an internal pouch. This allows for normal evacuation, though usually with five to six bowel movements a day. Inflammation of the pouch (pouchitis) is a complication of this surgery and can be refractory to treatment.

From an underwriting perspective, Crohn's disease mortality is associated with bleeding, malabsorption, complications of the medications used to treat the disease, and late cancer risk, as well as obstructive, infectious, and surgical complications.

With ulcerative colitis, there is the risk of acute disease-causing bleeding, acute dilation (i.e., toxic megacolon), and perforation of the colon. When acute symptoms of ulcerative colitis are not severe, mortality is most significantly affected by the increased risk of cancer.

Both Crohn's disease and ulcerative colitis are associated with extraintestinal complications including ankylosing spondylitis, arthritis, iritis, pyoderma gangrenosum, and erythema nodosum. Liver tests can be affected by Crohn's disease, causing elevated AST, ALT, and GGT. This is felt to be secondary to nonspecific inflammation around the microscopic bile ducts and is of little clinical significance. Abnormal liver enzymes in ulcerative colitis, predominantly alkaline phosphatase and GGT, can be the result of primary sclerosing cholangitis (PSC). In this poorly understood disease, the bile ducts throughout the liver become scarred and narrowed, causing obstruction of bile flow. This eventually leads to cirrhosis and death. It is also associated with an increased risk of bile duct cancer. PSC persists even after colectomy.

**Table 1.**

<b>Differences between Ulcerative Colitis and Crohn's Disease</b>		
	<u>Ulcerative Colitis</u>	<u>Crohn's Disease</u>
Rectal bleeding	Common	Occasionally
Abdominal pain	Uncommon	Common
Rectal involvement	Almost 100%	50%
Fistula formation	No	Common
Stricture, obstruction	Only with malignancy	Common
Perianal, perirectal abscesses	Uncommon	Common
Type of involvement	Continuous	Discontinuous (skip areas)
Depth of involvement	Mucosa & submucosa	Transmural
Small bowel involvement	Not involved	Often involved
Risk of malignancy	Greatly increased	Moderately increased

### **Irritable Bowel Syndrome**

Inflammatory bowel disease (IBD) must be distinguished from the more common entity, irritable bowel syndrome (IBS). IBS is believed to be a disorder of the motor function of the gastrointestinal tract, creating areas of spasm and pain. This entity does not cause inflammation, bleeding, or obstruction. Several common lay terms used for this syndrome – spastic or mucous colitis – are, therefore, misnomers.

Individuals present with symptoms of diarrhea, abdominal pain, bloating, and/or constipation. There is almost never any weight loss and symptoms usually do not occur during sleep. It is believed that psychological stress can influence this syndrome, unlike Crohn's or ulcerative colitis, neither of which is affected by stress. Thus far, no diagnostic test has been devised to diagnose IBS. It is usually a diagnosis of exclusion based on the history and the absence of findings on endoscopic or x-ray tests. Treatment usually consists of fiber products, antispasmodics, antidiarrheal agents, and/or laxatives. There is no mortality risk from IBS but there can be significant morbidity issues.

### **Tumors and Intestinal Polyps**

The large intestine is the part of the gastrointestinal tract that is most often affected by neoplasms. Neoplasms begin as outgrowths of the luminal surface of the colon and are called polyps. These can be broad-based (sessile) or on a stalk (pedunculated). They generally are slow growing. The histology of the polyp determines the malignancy potential. Pre-malignant polyps can be adenomas – tubular adenomas, villous adenomas, or tubulovillous adenomas. By definition, these polyps are low-grade dysplastic polyps. The larger or more villous the polyp is, the higher the malignant potential. Serrated polyps or serrated adenomas are other premalignant polyps. Benign polyps with no malignant potential include hyperplastic, inflammatory, or isolated juvenile polyps. Juvenile polyposis syndrome, on the other hand, is associated with a high risk of colorectal cancer (see Table 2 below). Most polyps tend to be multiple in number and frequently new polyps

arise over time. Several inherited syndromes have been identified in which numerous polyps occur. These polyposis syndromes are outlined in Table 2.

**Table 2. Polyposis Syndromes.**

Syndrome	Polyp type/Predominant location	Other intestinal lesions	Extraintestinal lesions
Familial Adenomatous Polyposis (FAP) and Attenuated FAP	Adenoma/Colon	Possible Gardner's or Turcot Syndrome	Possible Gardner's or Turcot Syndrome
Gardner's Syndrome – FAP plus other lesions	Adenoma/Colon	Ampulla of Vater tumors Small intestinal tumors	Osteomas Congenital hypertrophy of the retinal pigment epithelium (CHRPE) Mesenteric desmoid tumors
Turcot Syndrome – FAP plus brain tumors	Adenoma/Colon	See above	Brain tumors
MYH Polyposis	Adenoma, serrated/Colon	Duodenal cancer	Ovary, bladder, skin, papillary thyroid cancer. Sebaceous gland tumors thyroid nodules. ? increased risk for breast and endometrial cancer.
Hereditary Non-Polyposis Colon Cancer (HNPCC or Lynch Syndrome)	Adenoma/Colon	Stomach, small intestine, and biliary cancer	Endometrial, ovarian, prostate, ureter, and kidney cancer
Peutz-Jeghers Syndrome	Hamartoma/Small intestine	Polyps: Stomach, colon Cancer: Stomach, colon	Polyps: Renal pelvis, bronchus, gall bladder, nasal passages, bladder, and ureter. Cancer: Pancreas, breast, and ovary, cervix Dark spots on lips, inside cheeks, fingers
Juvenile Polyposis	Hamartoma/Colon	Entire GI tract polyps - benign with malignant transformation risk	Pancreas

Treatment of non-inherited benign polyps consists of polypectomy. This is usually performed by colonoscopy, during which a fiberoptic flexible tube is passed through the anus to the cecum. Follow-up with periodic colonoscopy is essential for all pre-malignant and malignant polyps to monitor for new lesions and recurrence of prior cancers. Colon polyps and cancer occur more

frequently after the age of 50. Screening with fiberoptic colonoscopy beginning at age 50 in average risk individuals and at age 40 (or ten years before the age at diagnosis of the youngest affected relative, whichever is earlier) in those with a family history of colon polyps or cancer has become routine. The American Cancer Society recently changed their guidelines to recommend that colorectal cancer screenings begin at age 45, instead of 50, because colorectal cancer cases are on the rise among young and middle-aged people. Repeat colonoscopy in three to five years in those individuals with premalignant polyps or a family history is recommended. In all others, the current recommendation is a repeat colonoscopy in eight to ten years.

Virtual colonoscopy (CT colonography) is a noninvasive, radiographic technique for colon polyp/cancer screening. It is not as reliable as standard colonoscopy and still requires a colonoscopy to biopsy or to remove any lesions found. Other, less sensitive methods of screening for colon polyps include stool testing for blood (guaiac, occult blood, or Hemoccult® cards, FIT testing), barium enema, flexible sigmoidoscopy, and/or stool testing for cancer DNA (Cologuard).

Colon cancer spans the spectrum from carcinoma in situ, which is confined to the superficial layer of the bowel, to invasive cancer. Colon cancer spreads locally to adjacent lymph nodes and organs. Most frequently, it metastasizes to the liver, lung, and brain. Prognosis is determined by the extent of the disease.

### **Diverticular Disease of the Colon**

Diverticula are outpouchings of the colon. They occur most commonly on the left side of the colon but can be located throughout the large intestine. Diverticulosis, the existence of these pockets, is a very common finding but is usually asymptomatic and found incidentally. When diverticulosis does present with symptoms, it does so in one of two ways: lower intestinal hemorrhage or diverticulitis.

Lower intestinal hemorrhage can spontaneously occur from a bleeding diverticulum. The diverticulum is almost never inflamed when hemorrhage occurs. The bleeding usually stops spontaneously but can require surgery or an angiographic embolization procedure.

Diverticula can also become inflamed and infected, causing the condition diverticulitis. This presents with abdominal pain and often fever. There may be an intra-abdominal abscess. Occasionally, an infected diverticulum can perforate, causing a life-threatening abdominal cavity infection (i.e., peritonitis). Treatment for diverticulitis without perforation usually consists of bowel rest (i.e., nothing ingested by mouth) and antibiotics. Surgery can be required for recurrent episodes of diverticulitis and for perforations.

### **Gastrointestinal Bleeding**

Gastrointestinal bleeding spans the spectrum from small amounts of bleeding to massive hemorrhage. Signs and symptoms often depend on the acute or chronic nature of the bleeding, as well as the volume of blood lost. Small volume and infrequent bleeding episodes often go undetected. Individuals are often asymptomatic. An evaluation for small volume gastrointestinal bleeding can be prompted by the discovery of iron deficiency anemia on routine complete blood

count (CBC) or microscopic quantities of blood detected using Hemoccult® cards. The clinician will pursue a work-up using patient history, physical exam, and eventually endoscopic and/or x-ray testing. The causes of slow gastrointestinal bleeding include esophagitis, gastritis, duodenitis, inflammatory bowel disease, vascular anomalies, gastric and duodenal ulcers, and malignant and benign tumors throughout the gastrointestinal tract. Hemorrhoids (i.e., dilatation of the rectal veins) rarely cause iron deficiency anemia though they can cause positive Hemoccult® cards. Attributing significant gastrointestinal blood loss to hemorrhoids should only be done after an extensive work-up has revealed no other source and the hemorrhoids bleed frequently and profusely.

Large volume acute gastrointestinal blood loss can be caused by any of the entities that can cause slow blood loss. Clinically, acute gastrointestinal bleeding is divided into upper and lower gastrointestinal sites.

Upper gastrointestinal bleeding (above the jejunum) usually presents with vomiting of blood (i.e., hematemesis) and/or melena (i.e., black, tarry stools). The most common sources of large volume upper gastrointestinal bleeding are:

1. esophageal varices (distended veins secondary to portal hypertension)
2. ulcers
3. severe gastritis
4. Mallory-Weiss tear (tear of the lower esophagus usually after vomiting).

Lower gastrointestinal bleeding usually presents with bright red blood per rectum. Large volume lower gastrointestinal bleeding (hematochezia - bloody stools) is most caused by:

1. diverticulosis
2. arteriovenous malformations (AVMs)
3. polyps
4. cancers.

Mortality is associated with the underlying cause, the acute complications associated with rapid blood volume loss (i.e., syncope, shock, and myocardial infarction), and the risks of the therapy needed to control and treat bleeding (i.e., surgery and transfusions). For underwriting purposes, the cause of the bleeding is the key to determining the mortality risk. In older age groups, colon cancer is the major impairment of concern in view of its high incidence and high mortality risk. In younger age groups, inflammatory causes and their concomitant mortality risk are the concern.

## **Intestinal Obstruction**

Intestinal obstruction can be caused by:

1. blockages within the small or large intestine by tumors, polyps or foreign bodies
2. bowel twisting on itself (i.e., volvulus)
3. adhesions from prior surgery or prior intrabdominal infection causing tethering of the bowel and obstruction.

4. telescoping of the bowel on itself (i.e., intussusception)
5. herniation of the bowel through the abdominal wall, inguinal ligament, or diaphragm.

The last four conditions also cut off the blood supply to the intestine and can result in ischemia or infarction with gangrene and risk of perforation. Volvulus, obstruction due to adhesions, herniation and even intussusception can resolve on their own with “bowel rest” – gastric suction and not taking anything by mouth. If this is not successful, then surgery is required.

### **Intestinal Ischemia**

Any disruption of blood flow to the intestines can cause ischemia. In addition to obstruction cited above, blood flow can be diminished by clotting of the intestinal arteries. This can occur due to gradual narrowing due to atherosclerosis, a clot due to a hypercoagulable condition, or an acute embolism. A sudden drop in blood pressure can also result in ischemia of the bowel. Decreased blood flow causes damage to the mucosa and bleeding. Prolonged ischemia can result in necrosis and gangrene with perforation. Ischemic colitis of the left colon can often mimic colitis due to infection or inflammatory bowel disease. Often, the cause of ischemia is unknown. It can resolve on its own with bowel rest but can require surgery.

### **Bariatric Surgery**

Obesity has become an epidemic in the United States. Surgery to induce weight loss has become more common with newer, easier surgical techniques. The most common operations performed in the U.S. are gastric bypass (also known as a Roux-en-Y bypass), sleeve gastrectomy, and an adjustable gastric band (i.e., lap banding). These procedures are most performed laparoscopically rather than through an open incision. Gastric bypass involves dividing the stomach so that a smaller reservoir is created and connecting it to a part of the small intestine so that it empties further down the intestine. This causes intentional partial malabsorption. A sleeve gastrectomy involves removing the pouch-like portion of the stomach, creating a narrow “sleeve-like” shaped stomach. The lap band is a silicone ring that is placed around the outside of the upper stomach. It is connected to an injectable port that is placed under the skin. This allows for the injection of saline into the band to adjust the tightness. Obsolete or rarely performed procedures are vertical banded gastroplasty and biliopancreatic diversion with or without a duodenal switch. These have fallen out of favor due to the associated structural and metabolic complications of these procedures.

The goal of bariatric surgery is to facilitate weight loss to improve overall health with decreased morbidity and mortality. Weight reduction varies between 45-80% of excess weight corresponding to an approximately 60-120-pound loss. This occurs over the first 12-18 months with gastric bypass and sleeve gastrectomy and 24 months with the lap band. Once individuals attain their desired body weight, over time they can be expected on average to regain about ten percent of the weight lost.

There is a small amount of 30-day post-operative mortality (<0.5%) associated with these operations as well as long-term complications. The long-term problems include esophageal reflux,

stenosis of the anastomosis sites, ulceration and bleeding, vitamin and mineral deficiencies, and intestinal obstruction.

Obesity related illnesses including diabetes, hypertension, hyperlipidemia, nonalcoholic fatty liver disease, and obstructive sleep apnea all improve or resolve often within the first 12 months following surgery. Cancer rates also decrease long-term after surgery. Generally, the improvement in obesity-related illnesses corresponds to the degree of maintained weight loss. Long-term overall mortality improves 40% by 7 years and persists up to 20 years when compared to those who did not have surgery.

## **Review Questions – ALU 201, Chapter 1**

1. The failure of the lower esophageal sphincter to relax is:
    1. hiatal hernia
    2. pyrosis
    3. achalasia
    4. odynophagia
  2. All the following are causes of ulcers EXCEPT:
    1. gastric cancer
    2. nonsteroidal anti-inflammatory drugs (NSAIDs)
    3. alcohol
    4. proton pump inhibitors (PPIs)
  3. Causes of Crohn's disease mortality include which of the following?
    - A. intra-abdominal infections
    - B. medication-related side effects
    - C. cancer
- Answer Options:
1. A only is correct.
  2. B only is correct.
  3. B and C only are correct.
  4. A, B, and C are correct.
4. Describe the causes of acute and chronic pancreatitis and what types of diseases can be triggered by pancreatitis.
  5. Describe the different types of colon polyps, the inherited syndromes, and their treatments.

6. Which of the following statements regarding pancreatitis are correct?
- It can be caused by heavy alcohol use.
  - It can cause diabetes.
  - It is frequently associated with elevated amylase and lipase levels.
- Answer Options:
- A and B only are correct.
  - A and C only are correct.
  - B and C only are correct.
  - A, B, and C are correct.
7. The transformation of normal esophageal mucosal to tissue resembling intestinal mucosa is:
- hyperplasia
  - Barrett's metaplasia
  - achalasia
  - gastroesophageal reflux disease (GERD)
8. Define GERD and describe the potential complications of this disease.
9. Compare and contrast Crohn's disease and ulcerative colitis. Include etiology, symptoms, complications, and treatment.
10. Identify the most common forms of bariatric surgery, the goal of these procedures, potential complications, and any associated extra mortality.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 3: achalasia – page 3.

### *Review Question 2*

Answer 4: proton pump inhibitors (PPIs) – pages 5-6.

### *Review Question 3*

Answer 4: A, B, and C are correct – page 10.

### *Review Question 4*

Refer to pages 6-7.

### *Review Question 5*

Refer to pages 11-13.

### *Review Question 6*

Answer 4: A, B, and C are correct – pages 6-7.

### *Review Question 7*

Answer 2: Barrett's metaplasia – page 4.

### *Review Question 8*

Refer to pages 3-4.

### *Review Question 9*

Refer to pages 9-11.

### *Review Question 10*

Refer to page 15.



## **CHAPTER 2**

### **LIVER AND BILE DUCT DISORDERS**

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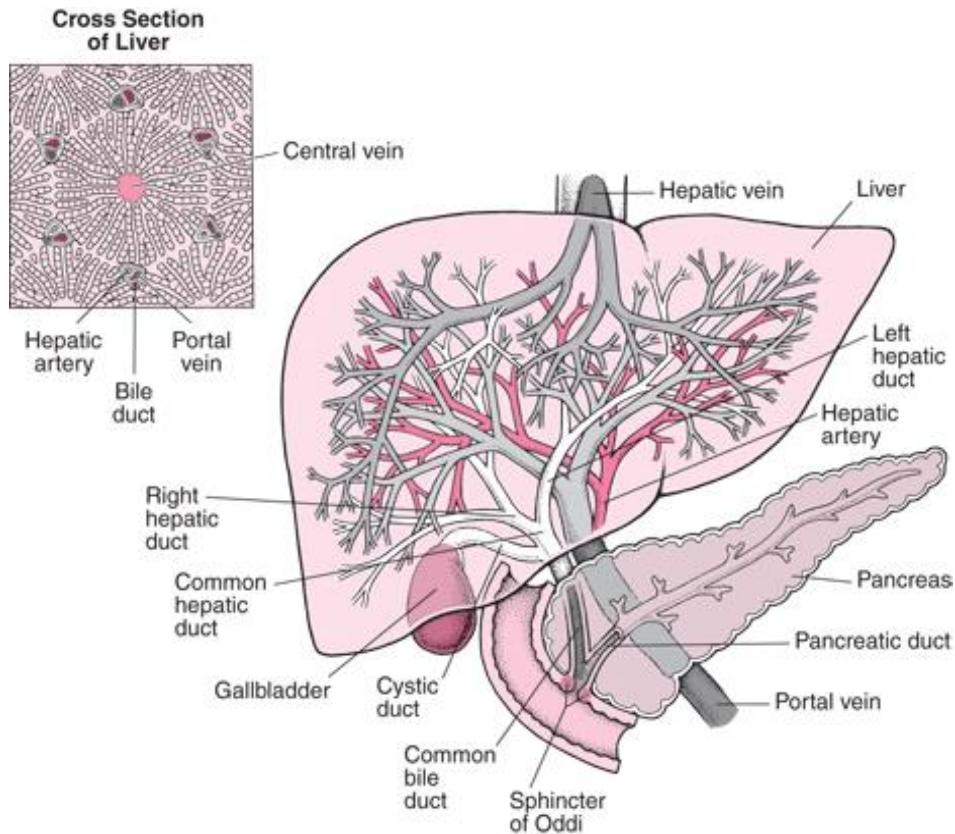
## LIVER AND BILE DUCT DISORDERS

### Introduction

The study of the liver can be traced back to ancient times. As early as 1550 BC, *The Egyptian Papyrus Ebers*, one of the oldest known medical documents, contained the first description of the liver in both a medical sense and as the seat of inner emotions.<sup>1</sup> Crude hepatoscopy provided the foundation for many of the Greek, Babylonian, and Mesopotamian theories regarding the importance of the liver for physical, emotional, and religious health. Fast forward to the current millennium and there is no doubt that the liver plays a crucial role in many of the most vital functions in the body to sustain life.

According to the CDC, 4.5 million American adults have liver disease.<sup>2</sup> The purpose of this chapter is to help the underwriter determine the mortality implications associated with disorders of the liver and biliary tract.

**Figure 1. Anatomy of the liver and biliary tract.<sup>3</sup>**



## **Anatomy of the Liver**

Located in the right upper quadrant of the abdomen, the liver is the largest solid organ in the body. It is one of the few organs capable of self-repair and regeneration. As little as 25% of healthy liver tissue can regenerate into an entire liver; however, repeated injury to the liver results in loss of its tissue regeneration capability. The structural and functional integrity of the liver is essential to the health of the human organism. The structure of the liver can be broken down into three categories: the hepatic vascular system, the biliary tree, and the hepatic lobules.<sup>4</sup>

### Hepatic Vascular System

Unlike other organs in the body, the liver has a dual blood supply, making it an extremely vascular organ. At any one time, approximately 500 ml of blood, or 13% of blood volume, is contained in the liver.

Arterial (oxygenated) blood is supplied to the liver by the hepatic artery, while the portal vein brings to the liver all the blood that has previously passed through the small intestine and spleen. This venous blood supply, which accounts for approximately 75% of the blood entering the liver, contains the nutrients that have been absorbed from the small intestine.

Terminal branches of the hepatic portal vein and hepatic artery empty together and mix as they enter *sinusoids* in the liver, which are vascular channels lined with highly fenestrated endothelial cells and surrounded by hepatocytes (i.e., liver cells). As blood flows through the sinusoids, plasma is filtered into the space between the endothelium and hepatocytes, providing a major portion of the body's lymph. The blood flows through the sinusoids and empties into the central vein of each lobule. The central veins coalesce into hepatic veins, which leave the liver and empty into the inferior vena cava.

### Biliary System

The biliary system is a series of channels and ducts that transport bile from the liver into the small intestine. Hepatocytes produce and secrete the bile, which flows into the bile ducts.

Bile is secreted from each lobe of the liver through the right and left hepatic ducts, which join to form the common hepatic duct. The latter meets the cystic duct from the gallbladder to form the common bile duct. After reaching the gallbladder, bile is concentrated and stored until it is needed for the digestive process. Bile re-enters the common bile duct through the cystic duct, which enters the duodenum after combining with the pancreatic duct to form the ampulla of Vater. The ampullary opening into the duodenum is controlled through the muscular sphincter of Oddi.

### Hepatic Lobules

The hepatic lobule is the structural unit of the liver. It consists of a hexagonal arrangement of plates of hepatocytes radiating outward from a central vein. It encompasses the liver tissue that is served by a single branch of the central vein, which is a branch of the hepatic vein. At the corners

between adjacent lobules are the portal triads, which are regions of connective tissue that include branches of the bile duct, portal vein, and hepatic artery. There are approximately 100,000 hepatic lobules in a normal liver. The adult liver provides a scaffold for many complex cell-to-cell interactions that allow for effective, coordinated organ function.

## **Functions of the Liver**

The liver's primary purpose is to maintain homeostasis, which is essential for survival of any living organism. It is estimated that the liver has more than 200 functions, although many of the specific processes involved within this organ's multiple functions are not yet understood. This section describes some of the most important functions.

### Detoxification

The liver transforms potentially dangerous metabolites, toxins, and excess hormones into biologically harmless water-soluble compounds. These substances enter the blood supply either as a result of the digestive process or from the ingestion of drugs or other foreign compounds. Enzymes in the liver alter some toxins so they can be more easily excreted in urine.

### Metabolism

The hepatic cells assimilate carbohydrates, fats, and proteins. They convert glucose to its stored form, glycogen, which is reconverted into glucose as the body requires it for energy. Glucogenesis, the production of glucose from sources other than carbohydrates, is also carried out by the liver. Excess carbohydrates and protein are also converted into fat by the liver.

### Synthesis of Lipoproteins and Cholesterol

The end products of fat digestion, fatty acids, are used to synthesize cholesterol and other substances needed by the body.

### Synthesis of Plasma Proteins

Many essential blood components are manufactured by the liver, including approximately 95% of the plasma proteins and blood clotting substances. These plasma proteins produced by the liver include:

1. albumin, which binds many water-insoluble substances and contributes to osmotic pressure
2. fibrinogen, which is key to the clotting process
3. certain globulins that transport substances such as cholesterol and iron.

### Synthesis of Immune Factors

The phagocytes in the liver produce acute-phase proteins in response to microbes. These proteins are associated with the inflammatory process, tissue repair, and immune cell activities.

## Digestive Functions

The liver synthesizes and secretes bile, which is necessary for adequate digestion and absorption of fats. It then secretes into the bile a bicarbonate-rich solution of inorganic ions, which helps neutralize acid in the duodenum.

## Excretion of Bilirubin

Bilirubin is one of the few waste products excreted in bile. Macrophages in the liver remove worn-out red blood cells from the blood. Bilirubin is formed by the breakdown of the hemoglobin in these red blood cells and is excreted into bile by hepatocytes. Jaundice results when bilirubin cannot be removed from the blood quickly enough due to hepatic duct obstruction (such as from gallstones), liver disease, or the excessive breakdown of red blood cells.

## Storage

The liver stores enough glucose in the form of glycogen to provide about a day's worth of energy. The liver also stores fats, iron, copper, and many vitamins, including vitamins A, D, K, and B12.

## **Blood Tests**

Liver function tests (LFTs) are widely accepted in both clinical and insurance settings as the basis for screening for underlying liver pathology. Yet, while they are the standard for screening, there are several issues that affect the usefulness of these tests when trying to determine the presence and extent of liver disorders. Some of the primary issues are:

1. Many of these tests are nonspecific for the liver, and abnormal results can be associated with other pathologic disorders.
2. Liver function tests have low sensitivity and specificity.
3. Results can be affected by several factors such as food intake, fasting status, physical activity, medications, sample collection technique, specimen transport/stability, and hemolysis.
4. Due to the liver's large functional reserve capacity, as well as its regenerative capability, structural or functional damage can evade detection using blood testing.<sup>5</sup>

While there is no ideal study or battery of studies to evaluate the liver's diverse functions, routine liver function tests are used to evaluate specific aspects of the liver. They can be categorized based on their ability to:

1. detect injury to hepatocytes (i.e., determine cellular integrity)
2. determine hepatic biosynthetic capacity (i.e., ability to synthesize proteins)
3. measure excretory function
4. detect chronic inflammation in the liver, altered immune regulation, and viral hepatitis
5. serve as tumor markers.

## Aminotransferases

Serum aminotransferases are enzymes that are sensitive indicators of hepatic injury. The most frequently used markers are alanine aminotransferase (ALT, also known as serum glutamic pyruvic transaminase or SGPT) and aspartate aminotransferase (AST, also known as serum glutamic oxaloacetic transaminase or SGOT). AST is found in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes. The highest level of ALT is found in the liver, with only small amounts found in cardiac and skeletal muscle, making it a more specific for liver injury.

These enzymes catalyze the reversible transformation of  $\alpha$ -ketoacids into amino acids.<sup>6</sup> When injury to hepatocytes occurs, ALT and AST leak out of the damaged cells into the serum. Aminotransferases are elevated in all types of acute and chronic hepatitis, and in cirrhosis, infectious mononucleosis, heart failure, malignancy, and alcoholic liver disease. There is poor correlation between the degree of liver-cell damage and the level of the aminotransferase elevations.<sup>7</sup>

## Lactate Dehydrogenase

Measurement of lactate dehydrogenase (LDH) adds little to the evaluation of suspected hepatic dysfunction. LDH is present in most tissues of the body. In the insurance setting, elevated LDH levels serve to determine the presence of a hemolyzed specimen, which is helpful in determining the validity of other results.

## Gamma Glutamyl Transpeptidase

Gamma glutamyl transpeptidase (GGT) is an enzyme involved in the transfer of amino acids across cellular membranes. It is found in high concentrations in the cell membranes of the liver, bile duct epithelia, and kidney but is also present in smaller amounts in many other tissues, including the pancreas, heart, epididymis, small intestine, bone marrow, spleen, and brain. Since there is no GGT found in the bone, it is helpful in confirming the hepatic origin of an elevated alkaline phosphatase.

Elevations in GGT can occur even with minor subclinical hepatocellular damage, usually in association with elevations in ALT. Although GGT is a very sensitive indicator of hepatobiliary disease, it is not specific. It can be elevated in other conditions including renal failure, cardiovascular disease/coronary artery disease, myocardial infarction, pancreatic disease, and diabetes mellitus.<sup>8</sup> Abnormal GGT levels can also be induced by alcohol and medications, such as phenytoin (Dilantin®), non-steroidal anti-inflammatory drugs (NSAIDs), warfarin (Coumadin®), and HMG-CoA reductase inhibitors (statins). GGT elevations due to alcohol abuse are present with steady, heavy drinking over time, but not with binge drinking. GGT is unaffected by exercise, muscle injury, or bone growth.

GGT elevations are common in the following conditions: alcohol abuse, alcoholic liver disease, hepatic tumors, hepatic congestion, acute and chronic hepatitis, biliary obstruction, sclerosing cholangitis, primary biliary cirrhosis, renal disease, pancreatitis, diabetes, and fatty liver disease.

## Bilirubin

Bilirubin is the main bile pigment that is formed from the breakdown of hemoglobin in red blood cells. It travels to the liver, where it is secreted into the bile. Serum bilirubin levels reflect the liver's ability to take up, process, and secrete bilirubin into the bile.

Almost all the bilirubin produced is excreted as one of the components of bile salts. Bilirubin is the pigment that gives bile its characteristic bright greenish-yellow color. When the bile salts reach the intestine via the common bile duct, the bilirubin is acted on by bacteria to form chemical compounds called urobilinogens. Most of the urobilinogen is excreted in the feces; some is reabsorbed and goes through the liver again, and a small amount is excreted in the urine. Urobilinogen gives feces their dark color. An absence of bilirubin in the intestine, such as can occur with bile duct obstruction, blocks the conversion of bilirubin to urobilinogen, resulting in clay-colored stools.<sup>9</sup>

Because bilirubin is chemically different after it goes through the conjugation process in the liver, lab tests can differentiate between the unconjugated (indirect) and conjugated (direct) bilirubin. The terms "direct" and "indirect" reflect the way the two types of bilirubin react to certain dyes added to the blood specimen. In the clinical setting, total bilirubin, direct bilirubin, and indirect bilirubin levels are measured. The ability to differentiate between direct and indirect levels of bilirubin assists in determining the cause of abnormal values.<sup>10</sup>

Unconjugated hyperbilirubinemia is caused by:

1. increased production of bilirubin – e.g., hemolytic anemia
2. decreased conjugation – e.g., familial hyperbilirubinemia (Gilbert's disease).

Conjugated hyperbilirubinemia is caused by:

1. decreased secretion of bilirubin by the liver – found in cirrhosis, hepatitis, primary biliary cirrhosis, or drug-induced (steroids, oral contraceptives, antibiotics, barbiturates)
2. cholestasis – found in biliary obstruction, choledocholithiasis, stricture, neoplasm, biliary atresia, sclerosing cholangitis.

## Alkaline Phosphatase

Alkaline phosphatase (AP) comprises a group of enzymes present in many tissues. It is primarily found in the liver and bone, but it is also present in the kidney, intestine, lung, and placenta. In the liver, increased AP levels are stimulated by a rise in bile acids. A rise in bile acids is the earliest marker of cholestasis, which results in increased synthesis and secretion of alkaline phosphatase into the blood.<sup>11</sup> In general, if the AP is elevated due to hepatic pathology, GGT and/or bilirubin will also be elevated

Alkaline phosphatase levels are commonly elevated in conditions that impair excretion of bile, restrict bile production, or cause bone growth. The most common causes of AP elevations include:

1. liver – biliary obstruction, cholestasis, cholecystitis, cholangitis, cirrhosis
2. bone disease – Paget’s disease, osteosarcoma, bone metastases from prostate cancer, other bone metastases, fractures
3. malignant tumors
4. renal disease (secondary hyperparathyroidism)
5. primary hyperthyroidism
6. polycythemia vera
7. pregnancy.
8. normal bone growth in children and adolescents.

### Albumin

Albumin, which is the most important plasma protein, is synthesized exclusively in the liver. With progressive hepatocellular injury, hepatic synthetic capacity decreases and albumin levels fall. Heavy alcohol abuse and chronic inflammation inhibit albumin synthesis. Hypoalbuminemia is not specific for liver disease and can occur in protein malnutrition of any cause as well as in nephrotic syndrome, in which protein is lost through the urine.<sup>12</sup>

### Alpha-Fetoprotein

Alpha-fetoprotein (AFP) is a glycoprotein synthesized in the yolk sac, liver, and gastrointestinal tract of the fetus; it is the major protein in fetal serum. As the fetal liver matures, it gradually starts producing albumin instead of AFP, and AFP levels begin to decline. Following birth, AFP levels rapidly decrease, reaching low circulating levels before age one. AFP has no known function in healthy adults. A normal liver in a non-pregnant adult does not produce AFP.

AFP is used as a tumor marker for hepatocellular carcinoma. Elevated serum levels occur as a result of increased production of AFP by abnormal cell proliferation in the liver. It is also produced by other tumors including hepatoblastoma and nonseminomatous germ cell tumors of the ovary and testis. Moderately elevated AFP levels can also be found in the presence of cirrhosis and viral hepatitis. Most studies report that elevated AFP concentrations are present in approximately 70% to 80% of individuals with hepatocellular carcinoma; however, a normal value does not rule out the diagnosis.

### Prothrombin Time

Most coagulation factors are synthesized by the liver including factors I, II, V, VII, IX, and X. The prothrombin time (PT) measures the rate of conversion of prothrombin to thrombin after activation of the extrinsic coagulation pathway. Deficiency of one or more of the liver-produced coagulation factors results in a prolonged PT. Measurement of prothrombin time is useful in assessing the severity and prognosis of acute liver disease.

Non-hepatic causes of prolonged prothrombin times include vitamin K deficiency, coagulopathies, inherited deficiency of a coagulation factor, or medications that antagonize the prothrombin complex (e.g., warfarin).<sup>13</sup>

## Carbohydrate-Deficient Transferrin

Carbohydrate-deficient transferrin (CDT) is a blood test used to help detect heavy alcohol consumption. Transferrin is a plasma protein that carries iron through the bloodstream to the liver, spleen, and bone marrow for red blood cell production. Changes to the makeup of the transferrin protein can occur in individuals who consume significant quantities of alcohol (usually more than four to five alcoholic beverages per day for two weeks or more). When CDT is used with other tests, such as GGT, AST, and ALT, it can be a useful tool in identifying alcohol abuse.

## Hemoglobin-Associated Acetaldehyde

Acetaldehyde is a metabolite of alcohol and hemoglobin-associated acetaldehyde is the chemical combination of hemoglobin and acetaldehyde. It can be used to assess for alcohol abuse as its elevation is a direct result of alcohol ingestion. Its use is limited by false positives and it may not detect binge drinking.

## **Imaging Studies**

### X-rays

Plain abdominal x-rays add little to the evaluation of liver disease. On occasion, calcification due to gallstones, cysts, or scarring can be detected. Calcified tumors or vascular lesions can also be identified.<sup>14</sup>

### Ultrasound

The initial radiological study of choice for many hepatobiliary disorders is the ultrasound. It depicts interfaces in tissue of different acoustic properties. It is inexpensive, non-invasive, and portable. It is better at detecting focal lesions than parenchymal disease and is the initial test of choice to detect biliary dilatation. Ultrasound is useful for detecting stones in the gallbladder and bile duct. Ultrasound is also used to facilitate percutaneous biopsy of solid hepatic masses, drainage of abscesses, and paracentesis of ascites.<sup>15</sup>

### Computed Tomography

Computed tomography (CT) is becoming the preferred technique for imaging the hepatobiliary system, with perhaps the exception of the gallbladder, which is better imaged with ultrasound. CT with intravenous contrast is an excellent way to identify and characterize hepatic masses. This technique can distinguish between cystic and solid masses and identify abscesses. It can also identify cavernous hemangiomas as well as neoplastic vascular invasion. CT scanning can also suggest the presence of cirrhosis and portal hypertension as well as changes consistent with fatty liver or hemochromatosis.<sup>16</sup>

The latest generation of CT scanners uses a technology called helical or spiral CT scanning. This technique optimizes detection and characterization of lesions that can be missed by

conventional incremental contrast-enhanced CT. It is also better at identifying hemangiomas and vascular metastases.

### Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has rapidly become an important tool in the investigation of hepatobiliary disease, particularly for the characterization and staging of liver lesions seen on other imaging tests. It is considered the study of choice for confirming the presence of vascular lesions, particularly hemangiomas.<sup>17</sup>

### Liver Biopsy

Despite all the other diagnostic testing available, liver biopsy remains the most accurate test to confirm the diagnosis of specific liver diseases. The biopsied tissue can provide information that is otherwise unavailable regarding the structural integrity of the liver, as well as the type and degree of injury.

There are several methods of obtaining liver tissue: percutaneous, transjugular, laparoscopic, and ultrasound or CT-guided fine needle aspiration. The percutaneous liver biopsy is the simplest and most performed approach. A transjugular biopsy is preferred for patients with a coagulopathy, ascites, or a vascular tumor. Laparoscopic liver biopsy is likely to have a higher diagnostic yield in individuals with cirrhosis compared to percutaneous liver biopsy and is excellent for staging the extent of disease in those with various intra-abdominal malignancies. A fine needle biopsy with imaging, either ultrasound or CT, is used to evaluate a focal liver lesion and provides a small number of cells for cytologic examination.

Indications for liver biopsy include:

1. evaluation of abnormal diagnostic findings and hepatomegaly
2. confirmation of a diagnosis and determination of prognosis
3. confirmation of a suspected hepatic neoplasm
4. diagnosis of cholestatic liver disease
5. evaluation of infiltrative or granulomatous disease
6. evaluation and staging of chronic hepatitis
7. identification and staging of alcoholic liver disease
8. evaluation of effectiveness of treatment of liver disorders.

Because it is an invasive procedure, there is a very small risk of complications associated with liver biopsy. These include pain, hemorrhage, biliary peritonitis, and bacteremia. The major limitation of liver biopsy is sampling error due to the adequacy and/or location of the specimens obtained.

### Surrogate Tests

Although liver biopsy is the gold standard to evaluate liver pathology, it is an invasive procedure that has risk of complications. Surrogate tests are now being used more frequently in

place of a liver biopsy. The two types of surrogate tests are serologic and radiologic. A person can have both tests performed to improve the accuracy.

### *Serologic Tests*

Proprietary serologic tests, such as FibroSure, use indirect markers of fibrosis, which reflect alterations in hepatic function. The various tests use lab results such as AST, ALT, platelet count, glucose, and albumin, in addition to BMI, age and diagnosis of DM. The tests can differentiate between patients with significant fibrosis (F2 to F4) and cirrhosis from those without significant fibrosis (F0 to F1) but cannot identify the specific degree of fibrosis.

### *Radiologic Tests*

Elastography, such as FibroScan, estimates liver stiffness by applying mechanical waves and measuring their speed through the liver using imaging. The imaging can be with ultrasound or MRI. The liver stiffness correlates with the degree of fibrosis. These tests are good at detecting cirrhosis and advanced fibrosis (fibrosis state 2 or greater) but are not good at distinguishing between minimal and no fibrosis (fibrosis stage 1 or 0.)

## **Major Disorders**

### Fatty Liver

Fatty liver is defined as a liver where more than 5% of the liver mass is made of fat, usually triglycerides. It is traditionally classified as either alcoholic or nonalcoholic fatty liver and encompasses a range of severity from mild steatosis (fatty liver) to inflammation (steatohepatitis), to fibrosis and cirrhosis.

### Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is a group of disorders that presents as a spectrum of disease ranging from simple hepatic steatosis to steatosis with necroinflammatory changes leading to progressive fibrosis and cirrhosis. Steatosis alone is a benign condition, while nonalcoholic steatohepatitis (NASH) can be associated with progressive fibrosis, cirrhosis, and liver failure.

Hepatic steatosis can be caused by one or more of the following defects in the movement of fatty acids through the liver:

1. increased peripheral mobilization of fatty acids into the liver
2. increased hepatic synthesis of fatty acids
3. impaired hepatic catabolism of fatty acids
4. impaired synthesis and excretion of VLDL from the liver
5. necroinflammatory changes, which occur as a result of hepatocellular toxicity of free fatty acids, oxidant stress, and impaired mitochondrial function and hepatocellular depletion of ATP (an organic compound that releases energy necessary for most important biochemical processes).

The most advanced stages of NAFLD are marked by the deposition of collagen in the liver, resulting in progressive fibrosis and eventually the architectural distortion that signifies cirrhosis.

The etiology of NAFLD is unknown but is believed to be associated with insulin resistance. The risk factors include central obesity, DM II, increased BMI, dyslipidemia, and metabolic syndrome. It is also associated with hypertension and obstructive sleep apnea. NAFLD is one of the most common causes of liver disease worldwide and is the most common liver disease in Western countries, where there is a prevalence of 27-38%. As the obesity rates in Western nations increase, the number of people affected by NAFLD will also increase.

Most individuals with NAFLD are asymptomatic and are first identified by abnormal liver transaminase levels on routine screening, although fatigue and discomfort in the right upper quadrant of the abdomen can be reported. Liver enzyme levels fluctuate, with normal levels being present in up to 78% of individuals at any one time. When levels are elevated, the AST and ALT are typically 2 to 5 times the upper limit of normal, with an AST to ALT ratio < 1. Liver enzyme levels do not reliably correlate with liver histology, and the full range of disease can be seen in individuals with NAFLD who have normal transaminase levels.

The serum ferritin concentration and transferrin saturation may be elevated and a serum ferritin greater than 1.5 times the upper limit of normal is associated with advanced hepatic fibrosis.

Ultrasonography and CT and MRI scanning are reliable for detecting moderate to severe fatty changes in the liver. Hepatic fat causes increased echogenicity on ultrasound. In non-contrast CT scans, the fatty liver is hypodense and appears darker than the spleen. Hepatic vessels give the appearance of being relatively brighter and can be mistaken for contrast injection. No imaging method can distinguish between simple steatosis and NASH or indicate the stage of fibrosis. The sensitivity and specificity of ultrasound for detecting fatty infiltration decreases as BMI increases and thus varies from 49% to 100% and from 75% to 95%, respectively.<sup>18</sup>

Liver biopsy is the most accurate way to diagnose the presence and extent of NAFLD. In addition to confirming the clinical diagnosis, liver biopsy is valuable for excluding other liver diseases and for monitoring disease progression. Liver biopsy performed on individuals who have persistently elevated liver enzyme levels, and no viral serologic markers of chronic liver disease will reveal NAFLD 66% to 90% of the time.<sup>19</sup>

A liver biopsy report should specify the stage and grade of disease. The stage indicates the degree of fibrosis and the grade indicates the severity of the disease. There are various staging systems, but the following is a common 5-point scale:

- F0 – no fibrosis
- F1 – portal fibrosis without septa
- F2 – a few septa
- F3 – numerous septa without cirrhosis
- F4 – cirrhosis

Significant fibrosis is a stage F2 or higher.

Other information that may be found on a liver biopsy report is the degree of steatosis, defined as the presence of intracellular fat in more than 5% of hepatocytes. The percentage of hepatocytes with intracellular fat determines the degree of steatosis: mild 5-33%, moderate 34-66% and severe >66%.

The treatment of NAFLD is primarily focused on the modification of risk factors to prevent progression of the disease. These measures include weight loss, dietary modifications that reduce carbohydrate and fat intake, and tighter control of hyperlipidemia and diabetes/insulin resistance.

Risk factors for disease progression are:

1. histologic evidence of hepatic inflammation
2. older age
3. DM
4. heavy alcohol use
5. elevated serum transaminases
6. presence of ballooning degeneration plus Mallory hyaline or fibrosis on liver biopsy
7. BMI >28
8. higher visceral adiposity index, which is determined by assessing the waist circumference,
9. BMI, TG and HDL.

There is some controversy regarding the mortality risk of NAFLD. Some studies show an increase in cardiovascular mortality while others show no increased risk of all-cause mortality. People with NASH are at increased risk of liver-related deaths compared to those without NASH.

### Alcoholic Liver Disease

Alcohol use is widespread in the U.S. with approximately 75% of the population consuming alcohol at least occasionally. Approximately 10% of this group abuse alcohol or are alcohol dependent. Chronic and excessive alcohol ingestion is one of the major causes of liver disease in the western world. The spectrum of alcoholic liver disease ranges from alcohol-associated fatty liver (steatosis) to alcohol-associated steatohepatitis and eventually to alcohol-associated cirrhosis, which may lead to hepatocellular carcinoma.<sup>20</sup>

Fatty liver is present in over 90% of binge and chronic drinkers. It is estimated that a third of people with steatosis will progress to steatohepatitis if they continue to drink. Cirrhosis is more likely to develop in someone with steatohepatitis than steatosis. Although alcohol is considered a direct hepatotoxin, only 10% to 20% of alcoholics will develop alcoholic hepatitis. While quantity and duration of alcohol intake are the most important risk factors involved in the development of alcoholic liver disease, the roles of beverage type and pattern of drinking are less clear. Progression of hepatic injury beyond the fatty liver stage seems to require additional risk factors that remain incompletely defined.<sup>21</sup>

Risk factors for alcoholic liver disease include:

1. quantity of alcohol consumed
2. female gender
3. hepatitis C (HCV)
4. genetic variability in alcohol-metabolizing enzymes
5. malnutrition
6. co-exposure to drugs or toxins
7. immunologic dysfunction.<sup>22,23</sup>

Continued alcohol ingestion results in fat accumulation throughout the entire hepatic lobule. Despite extensive fatty change and distortion of the hepatocytes with macrovesicular fat, the cessation of drinking results in normalization of the hepatic architecture and fat content within the liver.

### Cirrhosis

The World Health Organization defines cirrhosis as "...a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules that lack normal lobular organization."<sup>24</sup> It results in irreversible chronic injury of the hepatic parenchyma and includes extensive fibrosis in association with the formation of regenerative nodules. The following criteria are used to determine a diagnosis of cirrhosis:

1. pronounced, insufficiently repaired necroses of the parenchyma (with or without inflammatory processes)
2. diffuse connective tissue proliferation
3. varying degrees of nodular parenchymal regeneration
4. loss and transformation of the lobular structure within the liver as a whole
5. impaired intrahepatic and intra-acinar vascular supply.<sup>25</sup>

Cirrhosis is classified based on etiology of the disease because (1) morphologic classification is more difficult to determine due to the overlap of findings among different etiologies, and (2) treatment and prognosis are based on etiology. The major causes of cirrhosis in the U.S. include alcohol, chronic infection (hepatitis B, C), autoimmune hepatitis, and NASH.

The structural changes in the liver cause impairment of hepatic function, resulting in jaundice, portal hypertension, esophageal varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, and coagulopathy.

### *Jaundice*

Serum bilirubin levels reflect the liver's ability to take up, process, and secrete bilirubin into the bile. Excessive levels of bilirubin stain the fatty tissues of the skin yellow, resulting in jaundice. Jaundice, or *icterus*, is a yellowish discoloration of skin, conjunctiva, and mucous membranes that occurs as a result of hyperbilirubinemia.

There are three classes of causes for jaundice:

1. pre-hepatic or hemolytic jaundice – a result of increased breakdown of red blood cells
2. hepatic jaundice
3. extrahepatic jaundice (obstructive jaundice).

### *Portal Hypertension*

The liver has a dual blood supply: arterial blood (25%) from the general circulation and venous blood (75%) supplied by the portal circulation in the liver. The portal vein receives venous blood from the intestine, spleen, pancreas, and gallbladder. In a normal liver, this system allows blood to flow through the hepatic lobules to be filtered so that nutrients can be metabolized, and toxins excreted. Once this is completed, blood flows through the hepatic vein into the inferior vena cava, which transports the venous blood back to the right side of the heart.

Normal pressure in the portal vein is low. Portal hypertension is defined as abnormally high pressure in the portal circulation. Clinically significant portal hypertension is present in >60% of those with cirrhosis because of increased resistance to blood flow through the liver.<sup>26</sup> This increased resistance leads to the development of collateral veins that divert blood flow to the general circulation, bypassing the liver.

Major sites of collateral flow involve the veins around the cardioesophageal junction (between the lower esophagus and upper part of the stomach), the rectum, retroperitoneal space, and the falciform ligament of the liver. At these sites, the vessels develop varicosities, becoming engorged and dilated, while the vessel walls become thin and fragile. Also, because the collateral blood vessels bypass the liver, detoxification of the blood does not occur. As toxins build up in the systemic circulation, hepatic encephalopathy develops, resulting in significant neurologic changes. Increased pressure in the portal blood vessels can cause protein-containing (ascitic) fluid from the surface of the liver and intestine to leak into the abdominal cavity (ascites). The major clinical manifestations include hemorrhage from gastroesophageal varices, splenomegaly with hypersplenism, ascites, and acute and chronic hepatic encephalopathy.<sup>27</sup>

Portal hypertension occurs in the presence of cirrhosis after considerable irreversible injury to the liver has significantly impaired its functional capacity. It is consistent with end-stage liver disease.

### *Esophageal Varices*

Approximately 50% of those with alcoholic cirrhosis will develop esophageal varices within two years of diagnosis, and 70% to 80% will do so within ten years. In individuals with cirrhosis secondary to hepatitis C, the risk is lower, in that 30% develop esophageal varices within six years of the initial diagnosis of cirrhosis. Individuals with cirrhosis who develop large esophageal varices because of portal hypertension have a 25% to 35% risk of variceal hemorrhage and a 30% to 50% mortality rate associated with each bleeding episode.<sup>28</sup>

Esophageal varices are dilated blood vessels within the wall of the esophagus that develop because of portal hypertension. This dilation can be profound. The original diameter of the blood vessels is measured in millimeters while the esophageal varices can be 0.5 to 1.0 cm or larger in diameter.

As the blood vessels dilate, the walls of the vessels become increasingly stretched and thin, making them extremely fragile and at risk of rupture. Variceal bleeding usually occurs spontaneously without obvious precipitating factors. The individual typically presents with painless but massive hemorrhage, which accounts for the high mortality rate associated with a variceal bleed. Each episode of hemorrhage is life threatening and requires immediate medical attention.

### *Ascites*

Ascites is defined as the pathological accumulation of fluid within the peritoneal cavity. In the United States, 85% of cases of ascites occur in the setting of cirrhosis. The presence of ascites in an individual with cirrhosis represents advanced progression of disease — 50% of those with ascites will die within two years. Other causes of ascites include other liver diseases, malignancy, heart failure, infection, and pancreatitis.<sup>29</sup>

Ascitic fluid infections develop primarily in individuals with pre-existing ascites in the setting of cirrhosis and, less commonly, in those with subacute liver disease. Those with ascites and cirrhosis carry a 10% annual risk of developing an ascitic fluid infection without an apparent primary source of infection. The most common is spontaneous bacterial peritonitis.

### *Hepatorenal Syndrome*

Hepatorenal syndrome (HRS) refers to the development of acute renal failure in individuals with advanced chronic liver disease and fulminant hepatitis, who have portal hypertension and ascites.<sup>30</sup> Estimates indicate that at least 40% of individuals with cirrhosis and ascites will develop HRS within five years of the development of their disease. It is characterized by:

1. marked decrease in glomerular filtration rate (GFR) and renal plasma flow in the absence of other identifiable causes of renal failure
2. marked abnormalities in systemic hemodynamics
3. activation of endogenous vasoactive systems.

Although the exact cause is unknown, the pathology involved in the development of HRS is thought to be an alteration in blood flow and blood vessel tone in the *splanchnic circulation*, which is the circulation that supplies the intestines, and in renal circulation. It is an extreme manifestation of circulatory dysfunction and is usually indicative of an end-stage of perfusion to the kidneys due to deteriorating liver function.

### *Hepatic Encephalopathy*

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that occurs in the setting of significant liver disease. The specific cause of HE is unknown. It is characterized by disturbances in consciousness and behavior, personality changes, fluctuating neurologic signs, asterixis or “flapping tremor,” and distinctive electroencephalographic changes. Encephalopathy can be acute and reversible or chronic and progressive. In severe cases, irreversible coma and death can occur.<sup>31</sup>

### *Coagulopathy*

Individuals with cirrhosis demonstrate a variety of abnormalities in both cellular and humoral clotting function. Thrombocytopenia can result from hypersplenism. In the alcoholic individual, there can be direct bone marrow suppression due to the alcohol. Diminished protein synthesis can lead to reduced production of fibrinogen, prothrombin, and factors V, VII, IX, and X. In cirrhosis, factor VII is the first of the factors to be depleted. Bleeding generally occurs when the prothrombin time becomes elevated and the platelet count drops to <50,000/mm<sup>3</sup>. In the presence of bleeding esophageal varices, the already significant mortality risk increases due to impaired clotting function.

### Hepatitis

Hepatitis is a general term that refers to inflammation of the liver. This condition can result from various infectious and noninfectious agents. Infectious etiologies include viral, bacterial, fungal, and parasitic organisms. Medications, toxins, and autoimmune disorders can cause noninfectious hepatitis.

Viral hepatitis is a systemic infection affecting the liver. Almost all cases of viral hepatitis are caused by one of five viral agents: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), and hepatitis E virus (HEV). All the viruses are RNA viruses, except for hepatitis B, which is a DNA virus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses.

The agents of viral hepatitis can be broadly classified into two groups: viruses that spread via enteric (oral-fecal) transmission and blood-borne agents. The enterically-transmitted hepatitis viruses (HAV and HEV), in general, are self-limiting infections, but severe hepatitis can develop in some cases. The blood-borne hepatitis viruses (HBV, HCV, and HDV) are associated with persistent infection, prolonged viremia, and the development of chronic liver disease.<sup>32</sup> Further classification is made based on the duration of the illness. Acute hepatitis is a self-limiting inflammation of the liver which does not lead to fibrosis. Chronic hepatitis is defined as persistent infection for at least six months, which can lead to long-term disease.

## *Hepatitis A*

Acute viral hepatitis A is caused by an RNA virus and transmitted via the oral-fecal route. Prevalence correlates with sanitary standards and large household size. HAV occurs rarely in the U.S. but is quite prevalent in developing countries. It is generally a self-limiting disease; over 85% of people recover within three months, and 99% recover by six months. HAV very rarely leads to fulminant (acute onset) liver disease. It also does not transition into chronic hepatitis and there is no carrier state. There is no correlation between HAV and primary liver cell carcinoma. The mortality rate associated with HAV is 0.1% and usually occurs among the elderly, those with chronic liver disease, and the immunosuppressed. A vaccine is available to prevent hepatitis A in those at high risk of exposure.

## *Hepatitis B*

In the U.S., an estimated 200,000-300,000 people become infected each year with HBV; the prevalence of chronic HBV infection in the U.S. is 0.35%. Approximately 5% of the world's population has chronic HBV infection. It is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma worldwide.<sup>33</sup>

Transmission of HBV results from exposure to infectious blood or body fluids. Possible forms of transmission include (but are not limited to) unprotected sexual contact, blood transfusions, re-use of contaminated needles and syringes, and vertical transmission from mother to child during childbirth.

The stages of HBV include:

1. incubation period – ranges between 15-180 days, with an average of 60-90 days
2. prodromal stage – lasts from a few days up to 2-4 weeks; non-specific symptoms gradually develop, including malaise, myalgia, and gastrointestinal and influenza-like symptoms
3. clinical stage – defined by the presence of jaundice (icterus) and hepatomegaly; lab values vary significantly, depending on the degree of severity and the course taken by the hepatitis; this stage lasts 3-6 weeks
4. convalescence phase – a natural course of the disease; all lab values normalize within 4-6 months.

Chronic hepatitis is a late complication of acute HBV, occurring in a small percentage of individuals. Chronic HBV infection can be either asymptomatic or associated with chronic inflammation of the liver, leading to cirrhosis over a period of years. Although hepatocytes can regenerate, the recurrent injury to the cells, over time, eventually leads to scarring and fibrotic changes in the liver, resulting in loss of the ability to regenerate tissue. Over time, liver function begins to decline; fibrosis develops, followed by cirrhosis, and liver failure.

The presence of chronic HBV significantly increases the risk of developing hepatocellular carcinoma. Co-infection with hepatitis C or D further increases the risk of both cirrhosis and liver cancer. Infection with HBV at birth is associated with a clinically silent, acute infection, and a 90% chance of chronic infection.

Factors that suggest progression to chronic infection include:

1. lack of complete resolution of clinical symptoms and persistence of hepatomegaly
2. presence of bridging or multi-lobular hepatic necrosis on liver biopsy during protracted, severe acute viral hepatitis
3. failure of the serum aminotransaminase, bilirubin, and globulin levels to return to normal within 6-12 months after the acute illness
4. persistence of HBeAg beyond three months or HBsAg beyond six months after acute hepatitis.<sup>34</sup>

### Hepatitis B Serology

1. HBV surface antigen (HBsAg)
  - a. earliest marker of acute infection
  - b. appears before the onset of symptoms and the elevation of serum transaminases
  - c. should clear by convalescence stage of acute infection
  - d. persistence for more than six months indicates progression to carrier state or chronic HBV.
2. HBV e antigen (HBeAg)
  - a. marker for highly infectious state and active viral replication
  - b. found only in presence of HBsAg
  - c. should clear by convalescence stage of acute infection
  - d. persistence for more than 10 weeks suggests progression to chronic state.
3. HBV core antibody (HBcAb or anti-HBcAb)
  - a. indicates exposure to HBV and viral replication
  - b. appears shortly after HBsAg in acute infection and persists for life
  - c. not a good marker for acute disease or cure.
4. HBV surface antibody (HBsAb or anti-HBsAb)
  - a. a protective antibody that neutralizes HBV
  - b. if present with negative HBsAg, it represents cure from acute infection and immunity from future infection
  - c. if present with persistent positive HBsAg, but negative HBeAg, it represents a chronic carrier state
  - d. if present with a negative HBcAb, it represents immunity as a result of vaccine
5. HBV e antibody (HBeAb or anti-HBeAb) - indicates decreasing infectivity
6. HBV DNA
  - a. measures the viral load
  - b. useful for the assessment of those with chronic HBV as candidates for antiviral treatment and to track response to treatment.

Goals of therapy for chronic hepatitis B include achieving sustained virologic suppression, reducing the rate of disease progression, and decreasing the risk of complications, including cirrhosis, liver failure and hepatocellular carcinoma. The antiviral agents currently being used are lamivudine, adefovir, tenofovir, entecavir, telbivudine, interferon alfa (IFN-a) and pegylated interferon alfa (PEG-IFN-a 2a). Treatment responses are evaluated based on biochemical

(normalization of serum ALT level), virologic (sustained clearance of HBeAg and HBV DNA), and histologic (decreased inflammation on liver biopsy) parameters. There can be significant adverse responses to these agents such as intolerance to the medication, viral resistance to treatment, development of a viral mutation, and relapse after completion of treatment. Liver transplantation with adjuvant use of antiviral agents to prevent recurrence of disease can be appropriate in individuals with liver failure and end-stage liver disease.

Histologic features in those with chronic hepatitis B are of significant prognostic importance. In one long-term study of individuals with chronic HBV, investigators found a 5-year survival of 97% for individuals with mild chronic hepatitis, 86% for those with moderate to severe chronic hepatitis, and 55% for those with chronic hepatitis and post-necrotic cirrhosis. The 15-year survival for these groups was 77%, 66%, and 40%, respectively.<sup>35</sup>

**Table 1. Grading of disease activity in chronic hepatitis.<sup>36</sup>**

Grade	Descriptive	Lymphocytic piecemeal necrosis	Lobular inflammation and necrosis
0	Portal inflammation	None	None
1	Minimal	Minimal, patchy	Minimal; occasional spotty necrosis
2	Mild	Mild; involving some or all portal tracts	Mild; little hepatocellular damage
3	Moderate	Moderate	Moderate; with noticeable hepatocellular change
4	Severe	Severe	Severe; with prominent diffuse hepatocellular damage

**Table 2. Staging of fibrosis.<sup>37</sup>**

Stage	Descriptive	Criteria
0	No fibrosis	Normal connective tissue
1	Portal fibrosis	Fibrous portal expansion
2	Periportal fibrosis	Periportal or rare portal-portal septa
3	Septal fibrosis	Fibrous septa with architectural distortion; no obvious cirrhosis
4	Cirrhosis	Cirrhosis

### *Hepatitis C*

The hepatitis C virus is an RNA virus that was discovered in 1989. It is transmitted via blood and body fluids. The natural targets of the virus are hepatocytes. HCV can produce at least 10 trillion new viral particles each day, generating many mutant viruses. These represent minor molecular variations of the virus and pose a major challenge to immune-mediated control of HCV. They can also explain the variable course of the disease and the difficulty in developing a vaccine for HCV.<sup>38</sup>

Six distinct HCV genotypes and 13 subtypes have been identified, but the major HCV genotype worldwide is genotype 1, which accounts for 40% to 80% of HCV. Genotypes 1a and 1b are

prevalent in the U.S. Genotype 1, particularly 1b, does not respond to therapy as well as genotypes 2 and 3 do. Genotype 1 can also be associated with more severe liver disease and a higher risk of hepatocellular carcinoma.

Most infected individuals fail to clear the virus; viremia persists and is accompanied by variable degrees of hepatic inflammation and fibrosis. Findings from recent studies suggest that at least 50% of hepatocytes can be infected with HCV in individuals with chronic hepatitis C.

In the U.S., HCV infections account for 30,000 new infections and 8,000-10,000 deaths each year. Of new infections, 60% occur in individuals who use intravenous drugs; less than 20% are acquired through sexual exposure. An estimated four million people are infected with HCV, and 2.7 million have chronic infection.

The stages of hepatitis C include:

1. incubation period, which lasts for approximately 6-12 weeks – Anti-HCV cannot be detected for four to six weeks after infection, but polymerase chain reaction (PCR) is positive within the first week. Current serological tests fail during the incubation phase, which is the reason that individuals who are asymptomatic can unknowingly transmit HCV (e.g., blood donors).
2. acute phase, which is characterized by a continuous rise in the detection of anti-HCV – Only 5% to 10% will still test negative, because some individuals will have a delayed immune response to the virus. Any symptoms that occur during this stage are very mild; 80% of those in the acute phase have no symptoms, which make it difficult to define the onset of disease. Approximately 20% to 30% of individuals will clear the virus during this stage.
3. chronic HCV, which will develop in 70% to 80% of those infected with the virus – The disease progression is largely silent; infection is often identified on routine lab screening or prior to blood donation. Symptoms are typically absent until substantial scarring of the liver has occurred.

Pathogenesis of chronic HCV ranges from minimal periportal inflammation to active hepatitis with bridging fibrosis, hepatocyte necrosis, and cirrhosis. Steatosis, lymphoid aggregates, and bile duct damage are frequently found on liver biopsy. Grading and staging of chronic HCV is the same as for HBV.

There are three mechanisms that cause the pathology associated with HCV:

1. direct damage to hepatocytes
2. immune-mediated hepatocyte inflammation and destruction
3. viral-induced autoimmunity.

Virtually all people with chronic HCV have evidence of inflammation on liver biopsy; however, the rate and progression of fibrosis vary significantly among individuals. Recent data suggest that among untreated individuals, approximately one-third progress to cirrhosis in less than 20 years; another third progress to cirrhosis within 30 years. The remainder progress so slowly that they are

unlikely to develop cirrhosis within their lifetimes. Factors reported to influence speed of progression include age (increasing age is associated with more rapid progression), gender (males have more rapid disease progression than females), alcohol consumption, HIV co-infection, insulin resistance, metabolic syndrome, and fatty liver.

Anti-HCV antibodies indicate exposure to the virus but cannot determine if ongoing infection is present. HCV RNA by PCR is used to measure the presence of the virus (i.e., viral load), and to measure the effectiveness of treatment. Genotype testing is useful in order to determine the most appropriate treatment.

Current treatment utilizes a combination of pegylated interferon alpha and the antiviral drug ribavirin for a period of 24 or 48 weeks, depending on genotype. Sustained viral response to treatment, 75% or better, occurs in those with genotypes 2 and 3 after 24 weeks of treatment. About 50% of those with genotype 1 will show evidence of sustained response with 48 weeks of treatment; 65% of those with genotype 4 after 48 weeks of treatment.<sup>39,40</sup>

### *Hepatitis D*

The delta hepatitis agent, or HDV, is a defective RNA virus that co-infects with, and requires the helper function of, HBV for its replication and expression. Transmission of HDV can occur either via simultaneous infection with HBV (co-infection) or via infection of an individual previously infected with HBV (superinfection). Both superinfection and co-infection with HBV result in more severe complications when compared to infection with HBV alone. These complications include a greater likelihood of liver failure in acute infections as well as a higher risk of liver cancer in chronic infections. In combination with HBV, HDV has the highest mortality rate of all the hepatitis infections at 20%.

### *Hepatitis E*

Hepatitis E is an acute viral hepatitis that is prevalent in most developing countries, with only rare occurrence in the U.S. It is spread primarily through fecal contamination of water supplies or food and blood transfusions in endemic areas. Mortality rates are generally low, 0.5 to 3%. However, in pregnant women, the disease is often more severe and is associated with fulminant hepatic failure. The mortality rate for pregnant women who contract HEV, especially those in the third trimester, is approximately 20%.

### *Autoimmune Hepatitis*

Autoimmune hepatitis (AIH) is defined as a chronic disorder characterized by continuing hepatocellular necrosis and inflammation, usually with fibrosis, which commonly progresses to cirrhosis and liver failure. The criteria for AIH include hepatocellular inflammation and necrosis, hypergammaglobulinemia, and liver-associated autoantibodies.

The disease is often associated with other autoimmune diseases. Autoimmune hepatitis cannot be explained based on chronic viral infection, alcohol consumption, or exposure to hepatotoxic

substances. Autoimmune reactions lead to a chronic inflammatory process, which appears on biopsy as periportal piecemeal necrosis and inflammation of portal zones.

Evidence suggests that the progressive liver injury in individuals with autoimmune hepatitis is the result of a cell-mediated immunologic attack directed against hepatocytes.<sup>41</sup> While predisposition to autoimmunity is inherited, the specific injury to the liver is triggered by environmental (chemical or viral) factors. Autoimmune hepatitis accounts for 11% to 23% of chronic hepatitis in the U.S. If left untreated, AIH progresses rapidly with transition to cirrhosis; the mortality rate for untreated AIH is 50% by five years.

Autoimmune hepatitis is initially treated with prednisone, with or without azathioprine (Imuran®). Approximately 65-80% of individuals respond to initial therapy and enter histological remission; however, 80% of these individuals' relapse within 12 months of drug withdrawal. People who relapse after drug withdrawal may need life-long therapy.

#### *Drug-induced liver injury (DILI)*

Drug-induced liver injury, sometimes referred to as toxic hepatitis, is defined as liver injury following the inhalation, ingestion, or parenteral administration of several pharmacologic and chemical agents. These include industrial toxins, prescription and over-the-counter medications, and herbal or alternative medications. Agents producing DILI are generally systemic poisons or are converted in the liver to toxic metabolites. Depending on the agent involved, DILI can result in a clinical and morphologic presentation like that of viral hepatitis or can simulate extrahepatic bile duct obstruction with evidence of cholestasis. There are over a 1000 medications and herbal products that are associated with the development of DILI, but in the United States the most common drug is acetaminophen followed by antibiotics.

The latent period between exposure and liver injury is usually short (often several hours); the clinical manifestations occur within 48 hours. Treatment of DILI is largely supportive and includes discontinuation of the suspected agent. Symptoms generally subside after removal of the agent, and liver function returns to normal. Although liver failure can occur because of DILI, this is a rare complication.

#### Hereditary Hemochromatosis

Hereditary hemochromatosis (HH) is an impairment that results in the abnormal accumulation of iron in parenchymal (tissue) organs, leading to toxicity and fibrosis. It is the most common inherited liver disease in Caucasians and one of the most common genetic disorders in the world.

The average adult male loses approximately 1 mg (10%) of iron daily. Normally, this loss is offset through the absorption of an adequate amount of dietary iron to maintain a constant level of iron in the body, approximately 1 mg./day eating a typical Western diet. A person with HH will absorb 2 – 4 mg/day of iron. Regulatory mechanisms in the body prevent the excessive absorption of iron once sufficient levels of iron are restored. There are three important mediators that regulate iron absorption:

1. transferrin, the major transporter of iron
2. the transferrin receptor
3. ferritin, the intracellular storage form of iron.<sup>42</sup>

In HH, a mutation of the HFE gene disrupts the regulation of the intestinal absorption of iron. As a result, the intestinal absorption of iron increases, leading to excessive accumulation of iron in the body. The two mutations of the HFE gene associated with hemochromatosis are C282Y and H63D. More than 80% of HFE-related hemochromatosis is caused by either the homozygous C282Y mutation or the C282Y/H63D compound heterozygous mutation. HH is an autosomal recessive disorder with low penetrance, which means that not everyone with the gene mutation will develop HH and iron overload.

The excessive iron is deposited into several organs, including the heart, pancreas, skin, joints, and endocrine organs, but the major site of excess iron deposition is the liver. In the liver, the accumulated iron is stored in the hepatocytes in the form of ferritin and hemosiderin. This accumulation is toxic to the liver. Hepatic damage and/or fibrosis occur because of the following mechanisms: the production of free radicals that cause injury to hepatocytes; direct damage to DNA that leads to hepatocellular mutations and carcinogenesis; and increased collagen synthesis that causes hepatic fibrosis.<sup>43</sup>

The development of liver disease in HH is directly related to iron concentration in the liver; it is characterized by progressive fibrosis and development of cirrhosis. The risk of hepatocellular carcinoma in those with HH is up to 200 times greater than that of the normal population. Similar damage occurs in the other organs affected by excessive iron accumulation, including the pancreas, heart, skin, joints, and endocrine organs.

The primary causes of death from HH include:

1. hepatocellular carcinoma (30%)
2. complications of cirrhosis (25%), including liver failure, portal hypertension, and bleeding esophageal varices
3. cardiomyopathy (30%), congestive heart failure, and arrhythmias
4. complications of diabetes mellitus
5. bacterial and viral infections.

The prognosis associated with HH is directly related to early diagnosis and compliance with treatment to prevent iron deposition in target organs. Survival is improved by removal of the excessive stores of iron and maintenance of iron levels at slightly below normal levels. If diagnosis and treatment begin before the development of fibrosis or cirrhosis, a normal life expectancy can be anticipated, and morbidity risk due to complications of the disease is significantly minimized. The five-year survival rate with treatment increases from 33% to 89%. The 10-year survival rate is 93% when there is no evidence of cirrhosis. In those with cirrhosis, the 10-year survival rate is only 62%.<sup>44,45</sup>

Hereditary hemochromatosis should be suspected in any individual with an unexplained elevation in serum ferritin levels or iron saturation. The following tests are useful in the diagnosis of HH:

1. serum ferritin level – An elevated ferritin level, which is the main intracellular iron storage protein, can be associated with hemochromatosis but can also be elevated in the presence of infection, inflammation, and liver damage due to other disorders
2. transferrin saturation – This test determines how much iron is bound to transferrin, which is the protein that transports iron in the blood
3. genetic testing for HFE mutations
4. MRI is a noninvasive test that can estimate the iron stores in the liver and/or heart
5. liver biopsy.

The goal of therapy for those with HH is to remove the iron before it causes irreversible tissue damage. Treatment consists of regular phlebotomy to mobilize and remove excess iron stores and to prevent accumulation of iron in target organs. The frequency of phlebotomy is determined based on serum ferritin levels. If end-stage liver disease develops, liver transplantation can be performed; however, one- and five-year survival rates are only 58% and 42%, respectively, which is significantly lower than survival rates for liver transplants done for all other indications.

### Benign Solid Tumors of the Liver

Benign tumors of the liver are being detected with increasing frequency and are often identified incidentally. This is a result of the common use of imaging studies of the abdomen, as well as technical advances in imaging modalities, which have led to the identification of very small lesions. The most common benign solid tumors are hepatocellular adenoma, hemangioma, and focal nodular hyperplasia.

#### *Hepatocellular Adenoma*

This is a rare tumor that develops in women using estrogen-containing medications. Complications of a hepatocellular adenoma include bleeding and malignant transformation. Women will have any estrogen-containing medication discontinued as this can lead to regression of the adenoma. Management is determined by the size of the adenoma and if it is causing symptoms. Women with adenomas < 5 cm can be observed with serial imaging to monitor for stability. Women with adenomas > 5 cm or who are experiencing symptoms should undergo surgical resection. Men have an increased risk of malignant transformation and should undergo surgical resection, regardless of the size of the adenoma.

#### *Hemangioma*

Hemangioma is the most common benign tumor of the liver. Due to vascular malformation, thin-walled spaces, which are filled with blood and lined with endothelium, develop. Most often, they are found incidentally and have no major clinical implications. The estimated prevalence ranges from 0.4% to 20%.

In most cases, hemangiomas are small and asymptomatic. When symptoms are present, right upper quadrant abdominal pain is common. Less commonly are nausea, anorexia, and early satiety. Infrequently, they can grow to a large size and can press or displace adjacent structures.

In an asymptomatic individual, no treatment is recommended, and the person is observed for the development of symptoms. The follow up imaging surveillance is determined by size. A lesion  $< 5$  cm does not require any follow up imaging. A lesion  $> 5$  cm should be imaged in 6 to 12 months and if it found to be stable, no further imaging is recommended. Bleeding from a ruptured hemangioma is rare and is not related to the lesion size. Although hemangiomas can increase in size over time, they have no potential to become malignant. They usually do not require treatment; there is no additional mortality risk associated with hemangiomas.

### *Focal Nodular Hyperplasia*

Focal nodular hyperplasia (FNH) is the second most common benign solid tumor of the liver found predominantly in women. Diagnosis is often made based on specific tumor characteristics found on CT. The lesions are often stable or regress and do not require any treatment or surveillance. The risk of bleeding is minimal and there is no risk of malignant transformation. If diagnosis cannot be made, liver biopsy or surgical resection may be indicated to rule out hepatocellular carcinoma.

### Hepatic Cysts

Most liver cysts are found incidentally on imaging studies and tend to have a benign course. However, a minority can cause symptoms and rarely can be associated with serious morbidity and mortality. Larger cysts are more likely to cause complications, such as spontaneous hemorrhage, rupture into the peritoneal cavity, compression of biliary ducts, and rupture into the biliary tree. Specific types of cysts can have unique complications such as malignant transformation.

The most common hepatic cysts are simple cysts. They are cystic formations that contain clear fluid and do not communicate with the intrahepatic biliary tree. The presence of a liver cyst does not cause elevation of liver enzymes. Their size ranges from a few millimeters to massive lesions of 30 cm or more. Simple cysts are usually solitary, but occasionally multiple cysts can be found. Only a small minority cause symptoms and complications are rare. Most simple cysts do not require treatment.

### Hepatocellular Carcinoma

Primary hepatocellular carcinoma (HCC) is the most common non-metastatic malignancy of the liver, and the second most lethal tumor after pancreatic cancer. HCC is less common in most parts of the developed western world; its incidence is increasing. It is the most common cause of death in individuals with cirrhosis.

Risk factors for development of HCC include cirrhosis, chronic hepatitis B and/or C, NASH, alcohol and tobacco usage, obesity, and DM. Although the prognosis of primary HCC is

determined by the tumor grade and stage, the average survival is only five months from time of diagnosis.

Metastatic tumors of the liver are common, ranking second only to cirrhosis as a cause of fatal liver disease. In the U.S., the incidence of metastatic carcinoma is at least 20 times greater than that of primary carcinoma. At autopsy, hepatic metastasis occurs in 30% to 50% of individuals dying from malignant disease. The most frequent sites of origin for hepatic metastases are lung, breast, gastrointestinal, and genitourinary tracts.

### Portal Vein Thrombosis

Portal vein thrombosis is a form of venous thrombosis that affects the portal veins in the liver; it is the most common cause of non-cirrhotic portal hypertension. The most common causes of portal vein thrombosis include cirrhosis, malignancy, pancreatitis, hypercoagulable disorders, and sepsis.<sup>46</sup>

When blood flow through the portal vein is impeded, it causes hepatic inflow obstruction and increased pressure in the vascular bed. This leads to portal hypertension and its associated complications, including variceal bleeding, hepatic encephalopathy, and ascites. In cases where there is no associated cirrhosis, the primary complication that appears as a result of portal hypertension is variceal bleeding.

The overall prognosis for portal vein thrombosis can be quite favorable in those individuals who do not have cirrhosis or a malignancy as an etiologic factor. In adults with portal vein thrombosis, the 10-year survival has been reported to be 38% to 60%, with most of the deaths occurring secondary to the underlying disease (e.g., cirrhosis, malignancy). In the absence of cirrhosis, the two-year bleeding risk from esophageal varices is reported to be 0.25% and of those that bleed the mortality rate is approximately 5%. Those with cirrhosis and varices have a 20% to 30% two-year bleeding risk with a mortality rate of 30% to 70%. This difference is primarily a consequence of the normal hepatic function in the non-cirrhotic individual.<sup>47</sup>

### Wilson's Disease

Wilson's disease is a rare, autosomal recessive inherited disorder of copper metabolism. It primarily affects the liver, brain, kidneys, eyes, and joints. Copper is an essential co-factor for many enzymes, and the maintenance of normal copper homeostasis depends on the balance between gastrointestinal absorption and biliary excretion.

Copper is known to be hepatotoxic at excess levels. As a result of these toxic changes, three major patterns of liver damage can occur: cirrhosis, chronic hepatitis, or fulminant hepatic failure.

When the storage capacity of the liver for copper is exceeded, or when hepatocellular damage results in the release of cellular copper into the circulation, levels of non-ceruloplasmin-bound copper in the circulation become elevated. Once this occurs, copper is deposited in extra-hepatic organs, primarily the brain. The primary complications associated with progressive disease include hepatitis leading to cirrhosis and destruction of basal ganglia in the brain.

The areas of the brain affected by Wilson's disease are those that coordinate movement. The three main neurologic problems are dystonia, incoordination, and tremor. Psychiatric features can also be present including behavioral, affective, schizophrenic-like, and cognitive abnormalities.

The prognosis depends on the severity of disease at diagnosis and its appropriate management. If discovered early, recovery during the first two years of treatment is substantial. However, approximately 40% to 50% of individuals present with liver disease, and 35% to 50% present with neurologic or psychiatric symptoms. Early recognition is critically important since untreated Wilson's disease is always fatal. Diagnosis is made using a scoring system that assesses specific biochemical tests, such as ceruloplasmin, urine copper and hepatic copper, clinical manifestations, and genetic mutation testing.

Treatment of Wilson's disease is done in two phases. The first removes or detoxifies the accumulated tissue copper and the second prevents re-accumulation. Chelating agents enhance excretion of copper and inhibit absorption of copper by the body. Oral zinc salts may be used to prevent copper absorption. A low copper diet needs to be followed and copper-rich foods avoided. Other measures include management of complications from the disease. Treatment of Wilson's disease is life-long and crucial to improving life expectancy associated with the disease.

### Glycogen Storage Disease

Glycogen storage disease (GSD) is a group of disorders that develop because of any one of several inborn errors of metabolism. These occur because of enzyme defects that affect the process of glycogen synthesis or its breakdown within the liver, muscles, and other cell types. The most common glycogen storage disease is type 1 disorder, glucose-6-phosphatase deficiency. The onset of symptoms usually occurs early in childhood but can manifest in infancy.

Since individuals with type 1 GSD can store glucose as glycogen but not able to release it normally, over time, the stores of glycogen in the liver build up, causing hepatomegaly as well as enlargement of the kidneys. Levels of hormones, lactic acid, triglycerides, lipids, uric acid, and other metabolic by-products increase in the blood as the body attempts to raise blood sugar. Fats get stored in the liver along with the glycogen, causing further enlargement of the liver. The acute and rapid episodes of hypoglycemia can lead to seizures, cyanosis, and apnea. The continued presence of low blood sugar can eventually lead to delayed growth and development.

Significant long-term complications of type 1 GSD include hepatic adenomas, hepatocellular carcinoma, progressive renal insufficiency, severe hypoglycemia, coma, brain damage, and severe anemia. These individuals can also develop chronic pancreatitis and inflammatory bowel disease.

Treatment of type 1 GSD is aimed at maintaining normal blood glucose levels, maximizing growth and development, and preventing complications of the disease. Individuals who are promptly identified and properly treated should have reasonable life expectancy.

## Disorders of the Biliary Tract

### *Gilbert's Syndrome*

Gilbert's syndrome is the most common hereditary cause of unconjugated hyperbilirubinemia and is found in approximately 5% of the population. This condition is characterized by intermittent jaundice in the absence of hemolysis or underlying liver disease. The hyperbilirubinemia is mild with considerable variation in bilirubin levels at any given time. Aminotransferases and alkaline phosphatase concentrations are normal.

Hyperbilirubinemia can be precipitated by dehydration, fasting or stressors, such as vigorous exercise or illness. Individuals can report symptoms such as vague abdominal discomfort and general fatigue for which no cause is found. These episodes resolve spontaneously, and no treatment is required. Gilbert's syndrome is a benign condition with no associated mortality risk.

### *Cholangitis*

The term cholangitis refers to localized or diffuse inflammatory changes affecting the intrahepatic and extrahepatic bile ducts. Cholangitis can be acute or chronic. It can originate as a primary disease in the bile ducts or develop as a secondary consequence of another underlying disease.

#### *Acute Cholangitis*

Acute cholangitis is a syndrome that is characterized by fever, jaundice, and abdominal pain. While viral, parasitic, and mycotic organisms can cause acute cholangitis, bacterial infection is the most common cause.

Acute cholangitis is a result of stasis and infection of the biliary tract. The most frequent causes of biliary obstruction are biliary stones, biliary stricture, and malignant obstruction, due to a tumor in the gallbladder, bile duct, ampulla, duodenum, or pancreas. Acute cholangitis can also be a complication from endoscopic retrograde cholangiopancreatography (ERCP).

The incidence of complications is based on the severity of the disease as well as the underlying cause of the bacterial cholangitis. Treatment includes antibiotics, supportive care and biliary drainage or decompression. The complications that occur with this disease include liver failure, sepsis with septic shock, disseminated intravascular coagulopathy (DIC), infected portal thrombosis, acute renal failure, hepatic abscesses, metastatic abscesses, and catheter-related complications related to treatment.

Mortality has improved with advances in treatment to a fatality rate of 11% but remains high in those with severe acute cholangitis at 20 to 30%. Prognosis depends on several factors, including early recognition and treatment, response to therapy, and elimination of underlying obstruction.

### *Primary Sclerosing Cholangitis*

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology whose incidence is higher in males with a median age at diagnosis of 41 years. It is frequently found in association with inflammatory bowel disease.

Although the mechanisms responsible for the development of PSC are unknown, alterations in the immune system are thought to cause the disease. An autoimmune response, causing damage to the biliary tree, is the most likely etiology. PSC is characterized by fibrosing inflammation of both the intrahepatic and extrahepatic biliary tree. It is a progressive disease that results in irreversible damage to the bile ducts and ultimately leads to cholestasis, cirrhosis, and liver failure. Long-term follow up of those with PSC has revealed a high frequency of colon and bile duct cancers, both of which are probably related to the chronic inflammation of those structures.<sup>48</sup> Medical therapies are not effective in preventing progression of the disease, and liver transplantation is the only effective therapeutic option for individuals with end-stage liver disease from PSC. A statistical model is used to predict survival and determine the timing of a liver transplant. The components of the model include age, serum bilirubin, serum albumin, serum AST and a history of variceal bleeding.

### *Primary Biliary Cholangitis*

Primary biliary cholangitis (PBC), previously called primary biliary cirrhosis, is a rare form of liver disease caused by destruction of the bile ducts. It is characterized by cholestasis and progressive liver disease.

Primary biliary cholangitis is a chronic and progressive cholestatic liver disease that predominantly affects middle-aged females. The etiology is unknown, although it is presumed to be autoimmune in nature. There also appears to be a genetic component, as familial occurrences have been observed.

The major pathology of the disease is the continuous destruction of small and medium bile ducts, resulting in chronic cholestasis. After the loss of intrahepatic bile ducts, a disruption of the normal bile flow occurs with retention and deposition of toxic substances, which are normally excreted in bile. The retention of toxic substances, such as bile acids and copper, can cause a further secondary destruction of the bile ducts and hepatocytes, resulting in liver damage and eventual cirrhosis.

The prognosis of PBC has improved with ursodeoxycholic acid (UDCA) treatment, leading to a normal life expectancy if treated in the early stage. Factors that are associated with a worse prognosis include the presence of symptoms at time of diagnosis, elevated alkaline phosphatase and bilirubin levels, advanced histological stage, presence of antinuclear antibodies, cigarette smoking and certain genetic mutations.

### *Hepatic Sarcoidosis*

The liver is involved in most people with sarcoidosis but is only symptomatic in 5 to 15% of those diagnosed. If symptoms are present, they are commonly abdominal pain and pruritis. Hepatomegaly may be present. Most people will have elevation of the alkaline phosphatase and GGT. Rare complications include cirrhosis, cholestatic liver disease resembling sclerosing cholangitis and hepatic vein thrombosis.

### *Alpha 1-Antitrypsin Deficiency*

Alpha 1-antitrypsin deficiency is a genetic disorder caused by a variety of mutations to the alpha 1-antitrypsin (A1AT) gene, leading to decreased A1AT activity in the blood and lungs, and deposition of excessive abnormal A1AT proteins in the liver. There are several forms and degrees of deficiency based on the type of gene mutation.

The A1AT protein is produced in the liver; one of its functions is to protect the lungs from enzymes that can damage connective tissue and destroy alveoli. Deficiencies in normal A1AT production result in failure of this protective mechanism, with the development of significant pulmonary disease, primarily emphysema. This occurs in 75% to 80% of individuals with this deficiency. Damage to the liver is thought to be caused by accumulation of the mutant A1AT molecule in hepatocytes with subsequent hepatotoxicity, leading to cirrhosis and liver failure. People who develop end-stage liver disease are candidates for a liver transplant. The donor's liver will correct the A1AT deficiency by producing and secreting the normal protein, slowing the progression of the lung disease in some recipients.

### *Gaucher's Disease*

Gaucher's disease is one of the most common lipid storage diseases. It occurs as a result of mutations to the gene that regulates lipid storage and is characterized by the deposition of a glycolipid that is accumulated in the body. The severity of the disorder is extremely variable and depends upon the type of gene mutation.

Gaucher's disease exists in three clinical forms, delineated by the absence or presence of neurologic involvement and its progression:

1. Type 1 - is distinguished by the lack of central nervous system involvement and is the most common form, and onset can occur at any age. It is more common among individuals of Ashkenazi Jewish descent. Clinical features include hepatosplenomegaly, thrombocytopenia, and pathologic bone fractures. The disease is associated with an increased risk of malignancy
2. Type 2 – Infantile or acute neuronopathic commonly results in death within the first two years of life. These individuals develop hepatosplenomegaly and progressive neurologic deterioration.
3. Type 3 – Juvenile or subacute neuronopathic is a less severe form of the disease that affects children. It progresses more slowly with survival into late adolescence and early adulthood.

The abnormal accumulation of the glycolipid in the bone marrow, liver, spleen, lungs, and other organs contributes to pancytopenia, massive hepatosplenomegaly, and occasionally diffuse infiltrative pulmonary disease. The factors that contribute to neurologic involvement in types 2 and 3 disease may be related to the accumulation of cytotoxic glycolipids in the brain. Many individuals with type 1 Gaucher's disease have few manifestations and a normal life expectancy without any intervention. The prognosis for symptomatic individuals with types 1 and 3 disease who receive treatment is also favorable.

### *Reye's Syndrome*

Reye's syndrome is a rare disorder characterized by acute noninflammatory encephalopathy and hepatic failure. It occurs almost exclusively in children, although very rare cases in adults have been reported. Although the etiology of this syndrome is unknown, it typically occurs after a viral illness, particularly an upper respiratory infection, influenza, varicella or gastroenteritis, and it is associated with the use of aspirin during the illness.

Early recognition and treatment are essential to prevent death and to minimize the risk of neurologic impairment. The incidence has fallen dramatically since 1980 following the identification of aspirin use as a risk factor and the advisories against its use in febrile children. Death usually occurs because of cerebral edema or increased intracranial pressure, but death can also be due to myocardial dysfunction, cardiovascular collapse, respiratory failure, renal failure, GI bleeding, status epilepticus, or sepsis. Individuals who survive can have complete recovery, although neurologic impairment is common in children.

## **Review Questions – ALU 201, Chapter 2**

1. Functions of the liver include all the following EXCEPT:
  1. storing iron
  2. destroying damaged white blood cell
  3. removing toxin
  4. synthesizing cholesterol
2. An accumulation of excess fluid within the abdominal cavity is:
  1. icterus
  2. jaundice
  3. ascites
  4. cholestasis
3. All of the following statements regarding the hepatitis B virus surface antigen (HBsAg) are correct EXCEPT:
  1. It is the earliest marker of acute infection.
  2. It measures the viral load.
  3. It appears before onset of symptoms.
  4. It clears by the convalescence stage of acute infection.
4. Name and differentiate between the liver function tests (LFTs) that are used as the basis for screening the liver for underlying pathology.
5. Define Wilson's disease and describe its treatment options and prognosis.

6. Medical treatment for hepatitis C includes which of the following?

- A. interferon alpha
- B. methotrexate
- C. ribavirin

Answer Options:

- 1. A and B only are correct.
- 2. A and C only are correct.
- 3. B and C only are correct.
- 4. A, B, and C are correct.

7. Non-alcoholic fatty liver disease (NALFD) can be caused by all the following EXCEPT:

- 1. obesity
- 2. hypertension
- 3. metabolic syndrome
- 4. insulin resistance

8. What are the primary factors that affect prognosis in hereditary hemochromatosis?

9. Discuss the correlation between liver enzyme levels and liver histology in nonalcoholic fatty liver disease (NAFLD).

10. What are the major causes of cirrhosis?

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 2: destroying damaged white blood cells – pages 3-4.

### *Review Question 2*

Answer 3: ascites – page 15.

### *Review Question 3*

Answer 2: It measures the viral load – page 18.

### *Review Question 4*

Refer to pages 4-8.

### *Review Question 5*

Refer to pages 26-27.

### *Review Question 6*

Answer 2: A and C only are correct – page 21.

### *Review Question 7*

Answer 2: hypertension – pages 10-12.

### *Review Question 8*

Refer to pages 22-24.

### *Review Question 9*

Refer to pages 10-12.

### *Review Question 10*

Refer to page 13.

## **CHAPTER 3**

### **FOUR CANCERS:**

**Malignant Melanoma of the Skin  
Prostate Cancer  
Breast Cancer  
Colorectal Cancer**

### **CLIFTON TITCOMB, MD**

Cliff Titcomb, MD retired as Chief Medical Director at Hannover Re after 30 years in the insurance industry. He was active in AAIM, having served as President, was the Medical Consultant to “On The Risk,” contributed articles to the Journal of Insurance Medicine and “On The Risk,” and was a regular presenter at industry meetings such as AHOU, AAIM, and regional meetings. He is now a consultant medical director with International Medical Risk Consultants, Inc.

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**Revised 2019**



## **FOUR CANCERS**

### **Introduction**

This chapter presents information on cancers of the breast, prostate, colon and rectum, and malignant melanoma of the skin. These cancers were chosen because of their importance in underwriting. What makes malignancies of importance in the risk selection process is the frequency with which they are seen, their associated mortality risk, and the time course of the illness. The latter is of relevance because conditions that have a more protracted course have a longer period when an individual is alive and able to apply for insurance, while remaining at increased risk for early mortality. Proposed insureds with tumors that are rapidly fatal, such as lung cancer, infrequently survive long enough to apply for insurance. The challenge for underwriters is to appropriately assess that extra risk in the cases they do see. The best way to accomplish this is with a thorough knowledge of the cancer in question.

Tumors of the breast and prostate are the most diagnosed cancers in females and males, respectively, and the second leading causes of cancer death in each of the sexes after lung cancer. In addition, the clinical course is often prolonged with these malignancies, making it very common for underwriters to encounter proposed insureds with a history of the disease who still fall within the insurable range. Colon and rectal tumors have the third highest incidence and death rates from cancer in both males and females and are, thus, both frequently encountered and of practical importance in the risk selection process. Malignant melanoma, while far less common than the other tumors cited, has had the fastest growing incidence rate of any other cancer world-wide. It is increasingly seen in the underwriting environment and a serious mortality risk, if deeply invasive. In addition, its clinical course is often quite prolonged.

The chapter is presented in four separate sections:

- Section A - Malignant Melanoma of the Skin
- Section B - Prostate Cancer
- Section C - Breast Cancer
- Section D - Colorectal Cancer.

## **Section A**

### **Malignant Melanoma of the Skin**

Malignant melanoma has increasingly become a problem for underwriting professionals. The overall number of clinical cases of melanoma has been increasing at the annual age adjusted rate of 2-4% per year in the United States, and this increase has carried over into the insurance environment. Insurers have had to deal with a rising number of cases in their underwriting files. While most lesions are limited and have no significant extra mortality risk, a sizable subset carries a substantial probability of premature death. Thus, a thorough understanding of the tumor, its clinical parameters, risk factors, and likely outcomes is important in order to segment the risk appropriately.

Melanoma is a tumor resulting from the malignant transformation of the cells that produce the pigment melanin. These cells can be found in a variety of tissues, but this discussion will center on those found in the skin. The median age at diagnosis for malignant melanoma was 59 to 63 years in blacks and Caucasians and 52 to 56 years in other ethnic groups. It represents about 4-5% of all skin malignancies. In the United States, it is the fifth most common cancer in both males and females and it is estimated that approximately 96,480 individuals will be diagnosed with the disease and 7,230 will die from it in 2019. Incidence rates worldwide have been increasing rapidly in recent years as well. The highest rates are found in Australia and New Zealand. However, the pace at which the incidence rates have increased has diminished to some degree in the last 10 years compared to prior time periods. For non-Hispanic whites in the U.S., the lifetime risk for developing melanoma is 1 in 28 for males and 1 in 44 for females. Of note, the greatest increases in incidence rates have been in older males and in young females. Despite the increase in incidence of the disease, in the U.S. the mortality rates have followed a more irregular course and have been relatively flat over the past 20 years. To a large extent because the disease is being diagnosed at earlier stages in the U.S., 84% of melanomas are localized at time of diagnosis, with only 9% having extension to regional nodes or in-transit and 4% with distant metastases, and thus the overall prognosis is quite good.<sup>1,2</sup>

#### Risk Factors

##### *Race and Gender*

The risk for developing melanoma is highest in Caucasians. The relative risk (comparing the risk in one group to another) for the development of a cutaneous melanoma is 20:1 for whites compared to non-whites. Overall, males are more likely to develop the disease than females, and their lesion distribution pattern is different. The tumor is more likely to develop on the head and neck in males. In females, lesions on the extremities and torso are more common. However, in those under the age of 49, the disease is more common in females.

##### *Age*

Melanoma is primarily a disease of adults and is uncommon before puberty, even in those with a genetic predisposition. Fewer than 1% of lesions are diagnosed in children, although the

incidence rate in this group has been increasing. Older individuals have the highest incidence rate and poorer survival, with a more aggressive disease that is more likely to be located on the head and neck.

### *Sun Exposure*

Perhaps the most commonly recognized risk factor for melanoma is sun exposure. Intermittent, intense, recreational exposure appears to impart a higher risk than the overall time spent in the sun. For example, sunburns, both in childhood and as an adult, increase the probability of a later melanoma development (RR 2.1). Skin tone also matters. The highest risk is in fair-skinned individuals who have freckles. Compared to dark-haired individuals, the relative risk for development of melanoma is 1.8 in blondes and 2.4 in those with red hair.

The use of tanning beds has led to an increase in melanoma with a relative risk of 1.25. Younger age at exposure carries a higher relative risk of 1.69. This increased risk can explain the recently noted higher number of melanoma cases in younger females.

Ultraviolet (UV) radiation appears to be the principle culprit in producing tumors. Both UVA (wavelength 320-400 nm) and UVB (290-320 nm) rays are carcinogenic. Most sunscreens effectively block UVB rays; however, adequate cancer protection requires the use of special ingredients that also block the full spectrum of UVA radiation. These are not available in all products, and one cannot rely on a product's sun protection factor (SPF) rating alone as an indication of UVA protection.

### *Organ Transplantation and Prior History of Cancer*

The risk of developing malignant melanoma is increased three to four times in individuals with a history of organ transplantation. In addition, the prognosis is poorer in those individuals. The risk of developing melanoma is also greater in those individuals with a history of a prior melanoma or other forms of skin cancer and in those with a history of other, non-cutaneous, adult or childhood malignancies.

### *Benign Nevi*

The presence of benign nevi also increases the risk for developing melanoma. For common nevi, the probability of developing melanoma increases with the number and size of the lesions. For five or more nevi greater than 5 mm in size, or 50 or more nevi greater than 2 mm in size, the relative risk (RR) is approximately three times that of those not meeting these criteria. Congenital nevi (those present at birth) also increase the risk, again related to the size of the primary lesion. For congenital nevi greater than 20 cm in size, the lifetime risk of malignant transformation is 5-8%. The histology of the lesion is also important.<sup>3,4</sup>

### *Atypical (Dysplastic) Nevi*

Atypical nevi represent another well-recognized risk factor. These lesions are found in 2-7% of the Caucasian population, but in 25-40% of individuals with a melanoma. Development of

melanoma within a dysplastic nevus is unusual and, thus, it is not necessary to remove all atypical lesions. The real significance of atypical nevi is as a *marker* for a higher risk of developing melanoma. The risk increases with the number of atypical nevi and is up to 10 times higher in individuals with five or more lesions.

Atypical nevi are nevi characterized by a larger size ( $>5$  mm) and two or more of the following characteristics:

1. variable pigmentation
2. irregular outline
3. indistinct borders.

For those with atypical nevi, the risk of melanoma is increased further if family members also have these lesions or have had a melanoma and is increased substantially if there is family history of both. When multiple family members are affected there becomes an increasingly higher likelihood of familial atypical multiple mole and melanoma (FAMMM) syndrome, a genetic condition caused by a mutation in the CDKN2A gene that imparts a high risk of developing melanoma – approximately 30% chance by age 50 and close to an 80% lifetime risk – along with an increased risk of pancreatic and brain cancers.

Despite these associations, it should be remembered that the presence of risk factors is not a requirement for the development of a tumor. The majority of melanomas arise anew (i.e., not from a pre-existing nevus or mole). Only 20-30% of cases are the result of the transformation of a pre-existing skin lesion.<sup>5,6,7,8,9,10</sup>

### Histologic Subtypes

Definitive diagnosis of melanoma requires a skin biopsy and microscopic examination. However, clinically suspicious lesions can be identified using the so-called ABCDE criteria. In these criteria:

1. A=asymmetry of the lesion
2. B=border irregularity
3. C=color variation
4. D=diameter greater than or equal to 6 mm
5. E=evolving with changes over time (growth, color variation, itching, bleeding).

Thus, the classic melanoma will be a large, pigmented lesion that has an asymmetrical shape, an irregular, poorly-demarcated border, a varying color pattern or one that may be changing over time. However, many tumors do not follow the typical pattern. Most clinicians have learned to be cautious and frequently will biopsy lesions that meet only a few of these criteria. It has been shown that the use of dermoscopy improves diagnostic accuracy for melanoma over naked-eye examination and use of this technology suggests a better level of surveillance for those at risk. Occasionally, melanoma lesions can lack pigment. These are designated amelanotic melanoma. These lesions are very difficult to detect and require a high degree of clinical concern and acumen to diagnose.<sup>4,11,11,12</sup>

There are four major histologic subtypes of melanoma:

1. superficial spreading melanoma
2. nodular melanoma
3. lentigo maligna
4. acral lentiginous melanoma.

#### *Superficial Spreading Melanoma*

Superficial spreading melanoma is the most common subtype (60-70%) and can occur in both sun- and non-sun-exposed areas of the body. It is characterized by irregular margins and pigment variation. In these lesions, growth is initially in a radial manner along the skin surface, but it eventually enters a vertical phase in which spread is into the deeper dermal layers. As will be discussed later, risk of metastasis and, consequently, mortality risk increase as the thickness of the tumor increases.

#### *Nodular Melanoma*

Nodular melanoma is the next most common subtype (15-30%) and is characterized by a dark blue-black or bluish-red uniformly colored lesion. It has a more rapid onset than superficial spreading melanoma, and it goes more rapidly into the dangerous vertical growth phase. Nodular melanomas are more commonly found in males and on the trunk of the body.

#### *Lentigo Maligna*

Lentigo maligna occurs in about 5% of cases and is generally found in older individuals. It occurs most commonly on sun-exposed skin, especially on the face, and frequently arises from a pre-existing benign pigmented lesion known as a Hutchinson freckle. These lesions are generally thin and tend to be indolent, or more slowly progressive, in character. They usually carry a better prognosis than either superficial spreading or nodular melanomas.

#### *Acral Lentiginous Melanoma*

Acral lentiginous melanomas are the least common subtype. They frequently occur on the palm, sole, or under the nail and are more common in individuals with black or dark complexions. They are often difficult to diagnose because of their location and generally carry a poorer prognosis than the other subtypes.

#### Prognostic Factors for Mortality

The most important prognostic factors for mortality in melanoma are the depth of invasion, the presence or absence of ulceration, the mitotic rate, and if there are metastases to lymph nodes or other sites. With an increasing depth of invasion, called the Breslow level, (generally expressed in millimeters), the risk of metastasis and mortality steadily rises. The thicker the lesion, the higher the risk, and there is no critical level below which the risk is zero. It should be kept in mind that

the individual's immune system can attack the tumor, leading to some regression of the original lesion. In this case, the measured depth on pathological examination can be less than the true prognostic depth.

The presence of ulceration is also an important prognostic factor. The term ulceration does not mean that the lesion has a classic ulcer crater. Instead, it means that pathologically (i.e., under the microscope) there are no skin surface cells or epidermis overlying the tumor. Thus, the malignant cells extend through the skin surface layer. Prognostically, invasion through the epidermis is a marker for metastatic potential.

Though no longer part of the staging criteria, the presence of mitoses, or dividing cells on microscopic examination, remains an important independent prognostic factor. Individuals with one or more detectable mitoses per square millimeter have a significantly reduced survival, and that risk increases with increasing numbers of mitoses.

The presence of metastases to lymph nodes and elsewhere is a particularly adverse prognostic feature, though cures can occasionally be obtained, primarily when only a small number of lymph nodes are involved and they have only microscopic amounts of tumor. The presence of palpable lymph nodes, a thick or ulcerated primary tumor, and, especially, metastases to non-regional nodes and other sites, are particularly adverse features.<sup>13,15</sup>

A number of other prognostic factors of importance have been identified. These include:

1. Age of onset – The incidence rate of melanoma is higher in older individuals as is the number of cases with advanced disease, but increasing age is an independent risk factor as well. However, the relative risk for mortality is greater in those under age 50, due to the lower *expected* death rate in younger individuals.
2. Anatomic site – Lesions on the trunk, head, and neck have a higher relative mortality risk.
3. Vascular invasion with malignant cells produces an increase in the risk for death, similar to that seen with ulceration<sup>14,15</sup>
4. Clark level – An indicator of the level of skin (e.g., epidermis, papillary dermis, reticular dermis, and subcutaneous fat) to which the tumor has invaded:
  - a. Clark level I – epidermis only
  - b. Clark level II – upper portion of the papillary dermis
  - c. Clark level III – fills the papillary dermis
  - d. Clark level IV – reticular dermis
  - e. Clark level V – subcutaneous fat.

The Clark system is familiar to most underwriters and has been used in the past as a major prognostic indicator. However, recent data has confirmed that the Clark level of invasion is of little or no prognostic importance when the presence of ulceration and the mitosis count are taken into account.<sup>14</sup>

In addition, some other prognostic factors which have been identified include:

1. *Microsatellites* (i.e., nests of tumor cells separated from the main body of the lesion), being a marker for the ability of the tumor cells to implant and survive, are associated with a greater depth of invasion and predictive of an increased risk of relapse and reduced survival.
2. *Tumor infiltrating lymphocytes* represent an inflammatory immune response to the lesion and a greater response is associated with thinner tumors and a better outcome.
3. As with increasing age, *males* tend to present with more advanced lesions than females, but even with similar lesions, for stages I and II, they have a worse prognosis.
4. *Tumor regression* can, as previously noted, indicate that the tumor was at one time thicker than it may appear and the prognosis then worse when there is significant regression present. However, regression often reflects a more robust immune response as well, and mild regression may be a favorable factor.
5. Elevated *serum S-100 protein* is an adverse prognostic feature as is the presence of *circulating melanoma cells*.
6. *Desmoplastic melanoma* represents a unique subtype that is often very thick, but with a much lower progression risk, relative to the degree of thickness.<sup>16,17,18</sup>

It is important to recognize that melanoma (and atypical nevus) pathology interpretation and reporting can be challenging and inconsistent. It is not always easy for even an experienced dermatopathologist to always distinguish between an atypical nevus and an early melanoma, or to identify with certainty the mitotic rate, the degree of regression, or the presence of ulceration or lymphovascular invasion. When the pathology report is missing details on these prognostic factors, it is best not to assume they were all favorable, especially if not interpreted by a dermatopathologist.

#### Staging System for Melanoma: Changes by the AJCC

The staging of melanoma follows the American Joint Committee on Cancer (AJCC) TNM system. This system evaluates tumors based on:

1. local extent or, in this case, depth of the lesion, called the T category
2. presence of lymph node metastasis, designated the N category
3. existence of metastasis indicated by the M category.

The AJCC periodically modifies the staging system for melanoma to reflect these, and other, prognostic factors. This was done in 2017 with the AJCC 8<sup>th</sup> edition, with the current categories as follows:

1. T1:  $\leq 1.0$  mm
2. T2: 1.01-2.0 mm
3. T3: 2.01-4.0 mm
4. T4:  $> 4.0$  mm.

The reason these levels were chosen was primarily convenience, to allow clinicians and others to remember the cut points more easily. As noted previously, the risk associated with depth of invasion does not have discrete transition zones. However, with the recognition that tumors of 0.75 to 1.0mm have a notably worse prognosis compared to those <0.75mm, the criteria for stage T1b now includes lesions of 0.8 to 1.0 mm in depth (rounded to the nearest 0.1 mm) in addition to those where ulceration is present.<sup>14,19,20</sup>

Ulceration is used in the staging system because of its prognostic importance. The presence of ulceration, in essence, equates the lesion in question prognostically to that of a melanoma in the next greater depth category. If ulceration is present, the letter “b” is applied after the T category. Thus, a melanoma that is less than 1.0 mm in depth that has ulceration is designated T1b and has the same prognosis as a lesion that is T2a or 1.01-2.0 mm in depth without ulceration. The distinction between T1a and T1b is important from a prognostic standpoint but also from a management perspective – sentinel lymph node metastases are infrequent in T1a melanomas (<5%) but occur in approximately 10% of patients with T1b lesions. The T stage is thus often used to determine if a sentinel lymph node biopsy is performed or not.**Error! Bookmark not defined.**

The 8<sup>th</sup> edition AJCC staging no longer includes mitotic rate as a determinant of T1a vs T1b staging. This change was for simplification purposes but does not mean that mitotic rate is not important – it remains an independent prognostic factor at all T stage levels.

Finally, staging by lymph node invasion reflects the difference in prognosis by the number of involved nodes, the extent of invasion within the node, and the thickness and presence of ulceration in the primary lesion. Any size of tumor deposit present and/or any presence of melanoma-specific tumor markers (immunochemical detection) in a node as indicative of metastasis. Lymph node metastasis without a known primary lesion is staged the same as if a primary lesion were detectable; there is no difference in prognosis because no obvious primary tumor is detected.<sup>8</sup>**Error! Bookmark not defined.**

The staging system for malignant melanoma combines these various T, N, and M categories into risk groupings that correlate reasonably well with survival outcomes (see below). The entire list of combinations is outside the scope of this paper. However, in the situations without lymph node involvement (Stages I and II), representing most of the cases that are seen by underwriters, the stages can be summarized as follows:<sup>8</sup>

1. Stage 0 TisN0M0
2. Stage IA T1aN0M0, and T1bN0M0, IF a sentinel node biopsy performed and negative
3. Stage IB T1bN0M0 (clinical stage, i.e. no sentinel node biopsy was done)  
T2aN0M0
4. Stage IIA T2bN0M0  
T3aN0M0
5. Stage IIB T3bN0M0  
T4aN0M0
6. Stage IIC T4bN0M0.

Some prognostic systems use other criteria not included in the AJCC system. The Sloan-Kettering Nomogram for predicting lymph node metastasis uses age, site of involvement, and Clark level in addition to thickness and ulceration. Another prognostic system for the identification of high risk thin melanomas has been found to be more accurate than AJCC staging and uses four key factors – mitotic rate, growth pattern (radial or along the surface versus vertical), gender, and Clark level. However, these other systems have not yet found their way into most pathology reports and at this time are of limited usefulness in underwriting.<sup>21,22</sup>

### Treatment

The only effective treatment of melanoma is complete surgical resection. The disease is generally resistant to radiation therapy and response rates to chemotherapy are poor. Historically, only 1-2% of individuals have a durable or long-lasting complete response or destruction of the tumor with chemotherapeutic trials.

This may be changing however with the advent of treatment with immunotherapy, using monoclonal antibodies, vaccines and other approaches that mobilize one's individual immune system to destroy the lesion. This has now become the standard of care both for metastatic melanoma and as adjuvant therapy in higher risk melanomas after apparent complete resection. In the case of the monoclonal antibodies, specific steps in the immune process are turned on or off. Newer drugs such as ipilimumab, pembrolizumab and nivolumab, which have effects on the immune system, have shown some longer response rates in a number of individuals. Though most eventually recur with these treatments, some have had long-term responses which may prove to be curative. In the case of a unique form of immunotherapy, a modified oncolytic virus (talimogene laherparepvec) is injected directly into the tumor, destroying malignant cells through a local immune response. However, that treatment can then also have an effect on non-injected tumor sites.

Another exciting new development is the use of genetic-based understanding of cellular signaling pathways necessary for tumor advancement to develop disease-specific therapies. One important pathway is the BRAF pathway, mutations of which are found in about 40-60% of melanomas, which leads to a more aggressive tumor behavior on average. However, inhibitors of BRAF have demonstrated dramatic antitumor activity in such melanomas. The BRAF inhibitors vemurafenib, dabrafenib and encorafenib are now used primarily in conjunction with a MEK inhibitor, which also works on BRAF mutations. These treatments have yielded significantly improved outcomes compared to conventional therapy, and while many of these responses have been partial and temporary, the results provide the first indication that such targeted or “personalized” therapy can offer hope for an effective treatment of metastatic melanoma.<sup>16,17,18,19,27,28</sup>

### Mortality Risk

Mortality clearly varies by stage, and it tracks well with the AJCC staging system**Error! Bookmark not defined.** (*Figure 1*). The risk is lowest in the thinnest melanomas, with 10-year survival rates of 98% range for tumors <1.0 mm in the AJCC database. Keeping in mind too that this group contains some individuals at higher risk due to tumor ulceration, high mitotic rate, and

scalp or neck location, those without these factors should show even better outcomes (*Table 1*). This is also reflected in clinical practice data from the Surveillance, Epidemiology, and End Results (SEER) database<sup>208,29</sup> (*Figure 2*). The risk rises rapidly as lesions get deeper. Because ulceration revises the stage to the next depth category, it also significantly increases risk. Relative mortality risk also varies by the individual's age and the location of the primary tumor on the extremities or axis (trunk of the body), even in the thinnest lesions (*Figure 3*). Underwriters should account for these factors in assessing risk.

Natural regression due to immune system alteration of the tumor depth should be kept in mind in evaluating risk. If present, it will generally be noted on the pathology report.

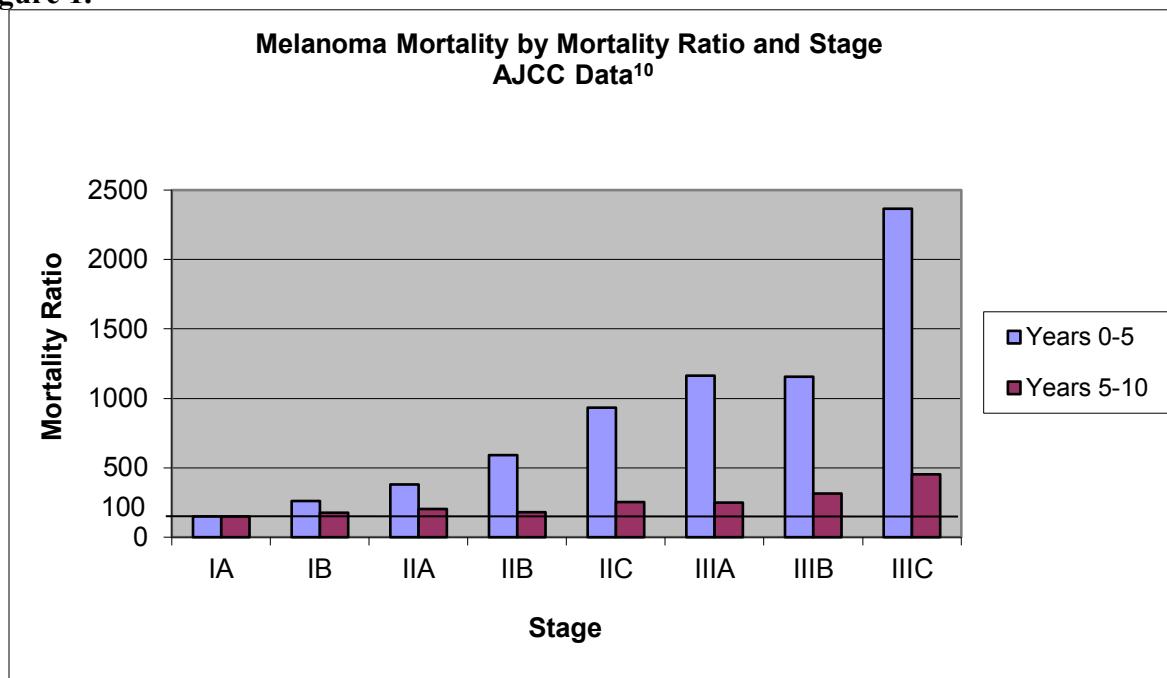
While not specifically addressed in the staging system, the occurrence of more than one melanoma in a given individual suggests either a genetic predisposition exists or that the individual in question has had a greater than usual exposure to risk factors for the development of these tumors (e.g., sun exposure). The issue is one of an ongoing increased risk that should be accounted for in mortality assessment.

Conditions that clearly predispose to the development of melanoma, such as innumerable and/or atypical nevi, a family history of melanoma, especially when occurring at a young age or in association with atypical nevi, and the presence of large congenital nevi, also warrant consideration in the course of mortality risk appraisal.

While most deaths occur within the first five years after diagnosis, late mortality is also an issue in melanoma. Recurrence and death related to melanoma is not uncommon as long as 15 years or more after diagnosis, especially with deeper lesions<sup>13,14</sup> (*Figure 4*). Although not common, recurrences after 20 years have been recorded. Thus, evidence of persistent disease (e.g., new enlarged lymph nodes, new liver or lung lesions, etc.) should not be ignored.

Local recurrences can also be problematic. A true local recurrence should have evidence of an *in situ* (i.e., malignant cellular changes without invasion) component to the lesion. Otherwise, such local lesions should be considered to be cutaneous metastasis. The presence of disease separated from the primary site and not containing an *in-situ* component carries a poor prognosis.<sup>21,22,32,33</sup>

**Figure 1.**



**Table 1.**

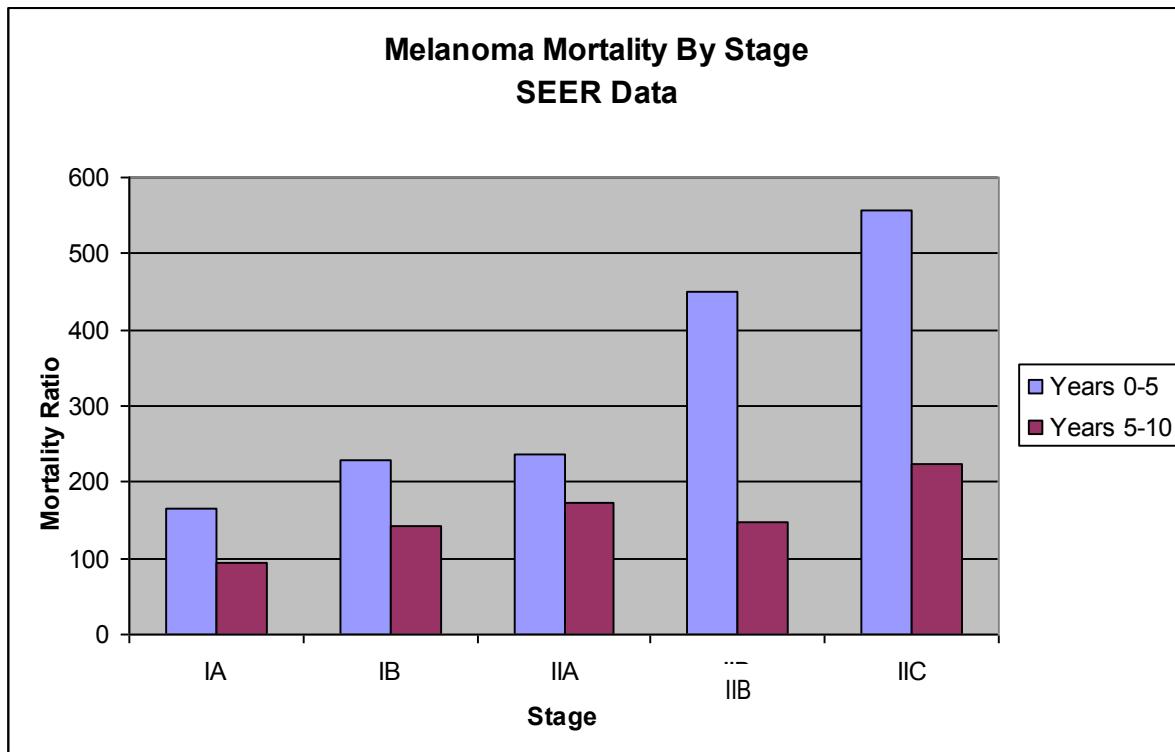
### Survival by T Classification

By pathologic staging – AJCC Database 8<sup>th</sup> edition<sup>14</sup>

Thickness Class	5 year survival %	10 year survival %
T1a	99	98
T1b	99	96
T2a	96	92
T2b	93	88
T3a	94	88
T3b	86	81
T4a	90	83
T4b	82	75

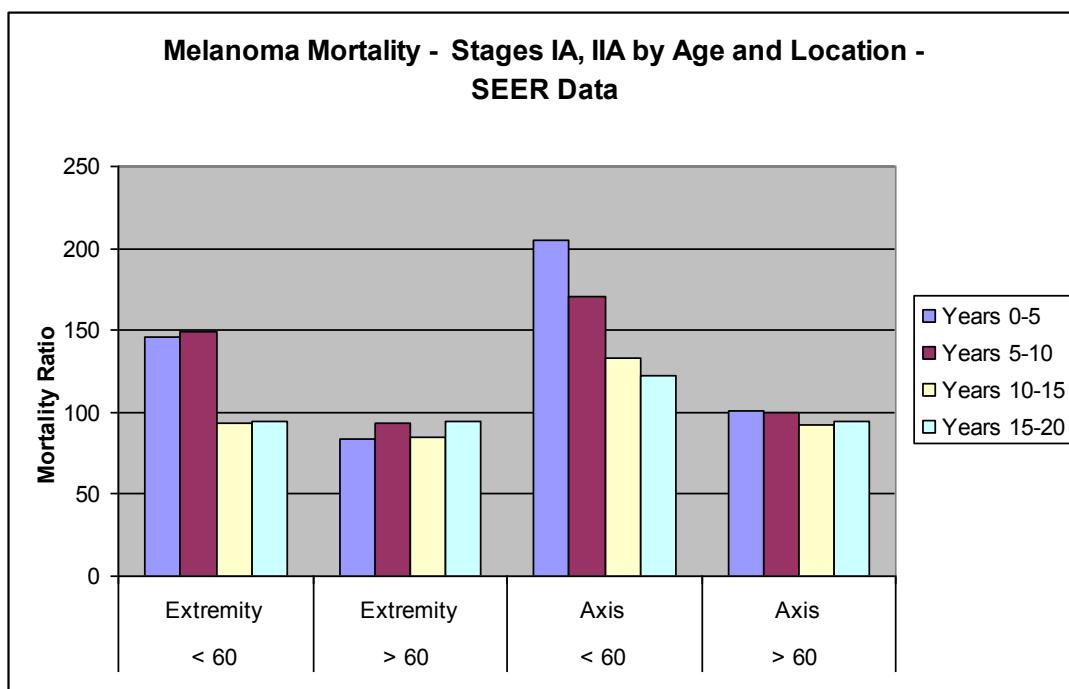
These represent important improvements from the 2009 data

**Figure 2.**



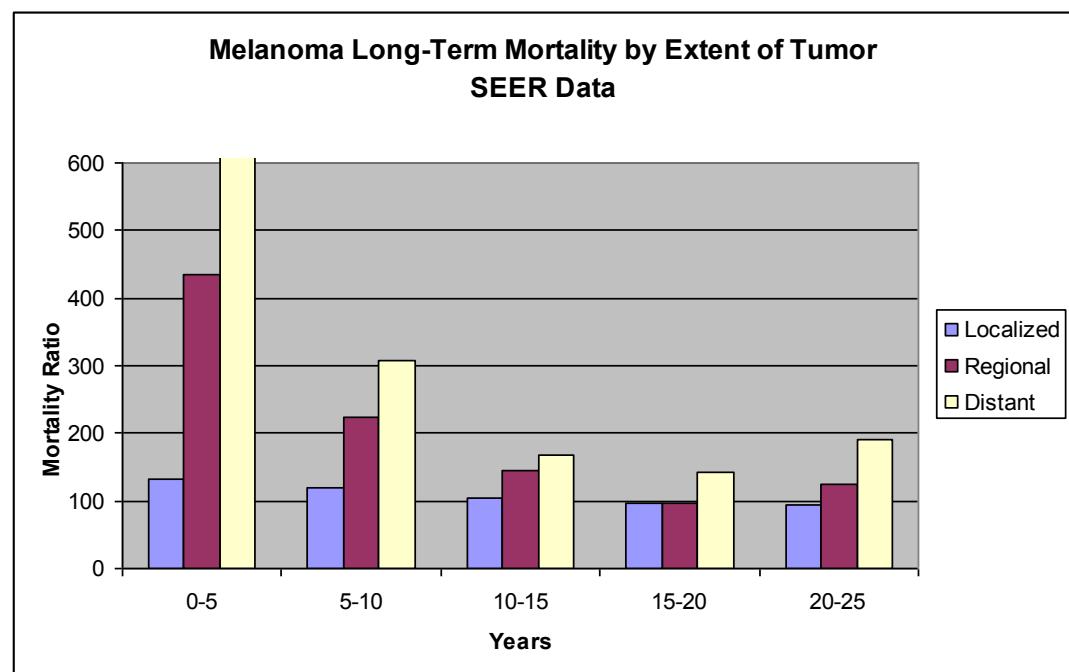
*Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.*

**Figure 3.**



Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.

**Figure 4.**



Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.

## **Section B**

### **Prostate Cancer**

#### Epidemiology

Prostate cancer is the most commonly diagnosed malignancy in males in the United States and the second leading cause of cancer death after lung cancer. It is estimated there will be 174,650 new cases in 2019 and 31,620 deaths from prostate cancer. This represents roughly 20% of all new cancer diagnoses in males, excluding non-melanoma skin cancers. In the years 2013 to 2015, a male's estimated lifetime risk for being diagnosed with prostate cancer was approximately 1 in 9; interestingly, this is down from an estimate of 1 in 6 lifetime risk just 8 years previously, due not to a true decrease in incidence but rather decreases in screening and identification of indolent prostate cancer.

Incidence rates increased dramatically in the early 1990s, peaking in 1992 at 237.4 cases per 100,000. This increase corresponded to the advent of widespread prostate specific antigen (PSA) screening. The incidence rate has subsequently diminished and was 141.0 cases per 100,000 in 2011. This number dropped significantly in 2012 with 114.1 cases per 100,000, a number close to that seen in the early to middle 1980s. This decrease may be due to the U.S. Preventive Services Task Force revised recommendations for screening for prostate cancer that appeared in May 2012, which advised against use of routine PSA testing.

Death rates from prostate cancer also increased in the early 1990s, but not as dramatically as did the incidence, and peaked at 39.3 deaths per 100,000. However, death rates have subsequently decreased significantly to 19.57 deaths per 100,000 in 2012, a level that is substantially below that seen in the 1980s. The prostate cancer death rates stabilized 2013 through 2016 after two decades of steep reductions (4% per year) that had been attributed to an earlier stage at diagnosis due to PSA testing and advances in treatments.<sup>1,2,3</sup> Black males have the highest incidence rates of prostate cancer in the world (237.4 cases per 100,000 in the years 1975 to 2012) and death rates that are more than double those of their Caucasian counterparts in the United States (63.37 versus 28.27 per 100,000 in that same time period). On the other hand, individuals of Asian descent have a lower risk of developing and of dying from the disease.<sup>1,2,3,4</sup>

#### Risk Factors

The most important risk factor for the development of prostate cancer is age. Whereas the probability of developing prostate cancer from birth to age 49 is 1 in 437, it is 1 in 59 at ages 50-59, 1 in 22 for ages 60-69, and 1 in 13 after age 70. Most males, if they live long enough, will eventually develop some evidence of the disease. Small foci of carcinoma can be found in 29% of males between the ages of 30 and 40 and in 64% of males ages 60 to 70 on pathologic examination, although most of these lesions are not invasive and not of clinical significance. Invasive disease is uncommon before the age of 50 but increases rapidly thereafter. About 70-75% of clinically significant tumors are diagnosed in men over the age of 65.

Family history is also an important risk factor, and hereditary disease may be responsible for 5-10% of all prostate cancers. The magnitude of the hereditary risk is similar to that seen with breast and colon cancer. The relative risk (RR) for individuals with a first degree relative (father or brother) with prostate cancer is approximately 2.0 to 3.0. However, the RR varies with the number of relatives affected and their age of onset. The RR can range up to 17 for individuals with affected brothers. The rates are higher if the index cases of prostate cancer were diagnosed at a young age.

It is estimated that as much as 57% of the risk of prostate cancer could be explained by heritable factors. Several genes have been found to be important in the development of prostate cancer. Both BRCA1 and BRCA2 are associated with increased risk and a greater chance of aggressive disease if cancer develops. The risk for tumor development appears to be increased approximately three-fold with another gene, HOXB13, but this gene has not been shown to associate with aggressive prostate cancer.

A number of other factors have been linked to the development of prostate cancer, but the association has not been as strong. Hormonal factors are thought to play a role, yet an association with serum testosterone and other androgen derivatives has not been found. Obesity and an increased waist-to-hip ratio are associated with an increased risk and also of increased disease aggressiveness. Diets high in meat and fat and low in vegetable intake have also been associated with the development of prostate cancer. Zinc supplement use may increase the risk and soy, coffee, and lycopene (e.g. from tomato products) may reduce the risk. Reduced sexual activity is associated with increased risk as is chronic inflammation in the gland; however, the degree of risk and exact mechanism by which this occurs is unclear.<sup>5,6,7,8,9</sup>

### Etiology

A number of mutations have been found within prostate tumors. The mechanism for cancer development appears to be similar to that seen with breast and colon cancers: a cascade of genetic alterations, primarily somatic (i.e., developing over the lifetime of the individual) that gradually transform normal tissue into an invasive tumor. The transition sequence appears to be a progression from normal prostatic epithelium to proliferative inflammatory atrophy (PIA) to prostatic intraepithelial neoplasia (PIN) to invasive cancer. Further genetic alterations allow the tumor to metastasize and, eventually, to escape hormonal control. The development of PIA as a precursor to PIN is one reason for the renewed interest in prostatic infection and inflammation as a risk factor for the development of cancer.<sup>5</sup>

### Screening and Diagnosis

#### *Digital Rectal Exam*

Screening for prostate cancer has involved two major approaches, digital rectal examination (DRE) with palpation of the prostate gland and blood testing for levels of the serum prostate specific antigen (PSA). DRE has been the traditional screening tool with the detection of glandular induration (i.e., a hard or firm texture), discrete nodules, or asymmetry of the gland as the hallmarks of cancer presence. However, DRE misses between 23% and 45% of prostatic tumors,

meaning that the negative predictive value is reasonably low. In addition, the positive predictive value (the likelihood that a cancer is present with an abnormal examination) is fairly low as well. The predictive value increases if physical findings are interpreted in conjunction with age and PSA level. Because not all tumors produce PSA elevations, an abnormal DRE should not be ignored even though the PSA level is in the normal range. In those situations, stability over time and the presence of negative biopsies and/or favorable MRI findings are the most important factors in ruling out a malignancy.

### *Prostate Specific Antigen Testing*

It was the introduction of PSA testing in 1987 that revolutionized the diagnosis of prostate cancer. PSA is a serine protease glycoprotein that is produced almost exclusively by the epithelial tissue of the prostate gland. It is produced by all prostatic cells, normal and malignant, and thus is not specific for cancer. Levels normally increase with age and the size of the gland. What distinguishes prostate cancer is that it produces more PSA per unit volume than does benign tissue. This increased production, and resultant higher levels, is the basis for its value in the screening process. The PSA molecule is the same in benign and malignant tissue; it is the amount produced per unit volume and detectable on testing that is different. However, it should be kept in mind that some prostate cancers will not produce significant elevations of PSA. In one study, 6.6% of males with a PSA value < 0.5 ng/ml actually had prostate cancer.<sup>10</sup>

The specificity of PSA for the diagnosis of malignancy is reduced by the fact that a number of other factors can also increase the level. These include:

1. benign prostatic hypertrophy (BPH)
2. prostatitis
3. prostatic massage
4. surgery
5. instrumentation (biopsy or resection) of the gland.

DRE probably does not affect levels significantly, but recent ejaculation can raise the value slightly, rarely more than 1.0 ng/ml. The drugs finasteride (Proscar®) and dutasteride (Avodart®), used to treat BPH, can lower PSA levels by about one-half and that should be taken into account in evaluating readings. Given these potentially confounding factors, a repeat PSA is warranted to verify the level before taking additional action. This is often done after a course of antibiotics to suppress the effects of any underlying prostatitis.

All of these factors blur the distinction between benign and malignant processes. The result is that screening for prostate cancer using PSA represents a balancing act between achieving adequate detection or sensitivity while avoiding over-diagnosis.

The upper limit of normal for PSA values in most laboratories is 4.0 ng/ml. However, this range was established in an older population, and it has been recognized that levels vary with age. With that in mind, age-dependent upper limits of normal have been often used to improve the accuracy of the screening process. These upper limits of normal (in ng/ml) are (for Caucasians):

1. 2.5 at ages 40-49
2. 3.5 at ages 50-59
3. 4.5 at ages 60-69
4. 6.5 at ages 70-79.

Readings above these limits would be considered suspicious for cancer. The values differ to a small degree for black and Asian males. However, substantial overlap occurs with benign conditions (especially BPH) in the mildly elevated ranges. Overall, in populations typically screened, the positive predictive value for a PSA >4.0 is approximately 30% (i.e., an individual would have prostate cancer found on biopsy). In addition, a significant number of individuals with cancer have PSA readings in the normal range, with a negative predictive value estimated to be around 85%. Approximately 20% of invasive cancers would be missed by using the traditional normal cutoff of 4.0 ng/ml.

#### *PSA Velocity*

To improve the accuracy of the test for screening, a number of characteristics of PSA can be used to help in the diagnosis of cancer. Although controversial in clinical circles, probably the most important for underwriting is the PSA velocity, or the rate of rise of the PSA level. PSA production by prostate cancer is out of physiologic control and levels tend to increase exponentially. A rate of rise of the PSA greater than 0.75 ng/ml per year is highly suggestive of malignancy and is useful even if the total PSA level is in the normal range. Some clinical organizations favor a lower threshold in the 0.35 to 0.40 ng/ml per year range. For optimal accuracy, one should have at least three readings spaced out over at least 18 months when assessing PSA velocity.<sup>11</sup>

#### *Controversy*

In May of 2012, the U.S. Preventive Services Task Force (USPSTF) issued a final recommendation *against* screening with PSA testing, with the committee essentially saying that the clinical benefits of detection of the usually slowly progressive prostate cancer did not outweigh the risks associated with diagnosis and treatment. This recommendation was later changed to one of supporting males to help them make informed decisions about screening that reflect their personal preferences and values, which is line with the recommendations of other professional societies. Still, the recommendation has been controversial and continues to be debated in clinical circles. The negative results of one major study reporting no mortality benefit from screening (PLCO) have been largely discounted; however other studies have only shown a small benefit to screening, owing to the fact that the PSA has limited accuracy and that so many prostate cancers are indolent and will never lead to death. Proposed insureds will likely continue to be tested for PSA by their attending physicians in the near term. This could lead to a potential asymmetry of information and the possibility of anti-selection on the part of proposed insureds.

In addition, it should be kept in mind that there is a difference in the value of PSA testing between the insurance and clinical environments. The PSA assay is a very good test for finding advanced, incurable disease with early mortality, which makes it highly valuable in the insurance arena, even when it is of limited value clinically.<sup>12,13,14</sup>

### *Improving the performance of PSA*

A number of different factors can be used in attempt to improve the diagnostic performance of PSA when levels are less than 10.0 ng/mL, though none have emerged (yet) as especially useful.

#### *Percentage Free PSA*

In a clinical setting, percentage free PSA (% FPSA) can provide additional diagnostic information. PSA normally circulates in the blood in two forms—one bound to another protein (alpha-1-antichymotrypsin) and the other unbound or “free.” Prostate cancer disproportionately produces more bound PSA and, thus, reduces the relative percentage of circulating free or unbound material. Therefore, measuring the free PSA and its relative percentage of the total PSA level can improve the diagnostic accuracy of the test. Although the cut points vary with the laboratory used, a value of 25% or higher for the % FPSA is generally suggestive of a benign cause for the elevation whereas levels less than 15% increase the suspicion for cancer. Because of some strict processing requirements needed to obtain an accurate free PSA, insurance medicine laboratory results are often falsely low, which limits their utility in underwriting.

#### *PSA Density*

The PSA density (PSAD) is another tool that has been employed, though also requires the measurement of prostate volume. It is based on the principle that cancer produces more PSA per gram of tissue than does BPH. It is determined by dividing the PSA level by the prostate volume as calculated by ultrasound or MRI. In essence, cancer produces too much PSA for the measured volume. The traditional normal value is taken as < 0.15. Values higher than this suggest the presence of a tumor. However, some authors vary the normal range by age (i.e., 0.1 at ages 40-49, 0.12 at ages 50-59, 0.14 at ages 60-69, and 0.16 at ages 70-79).

#### *PSA Isoforms*

Free PSA is comprised of 3 isoforms; pro-PSA, BPH-associated PSA, and intact free PSA. A subfraction of the pro-PSA, (-2) pro-PSA (p2PSA) has been found to be a better marker for the presence of clinically significant prostate cancer.

#### *Prostate Health Index*

The Prostate Health Index (PHI) uses a formula that combines the results of the total PSA, free PSA, and the p2PSA. This index has consistently been shown to be a better marker for the presence of prostate cancer and the presence of cancer with a high Gleason score than any of its components and any of the currently available urine markers for prostate cancer.<sup>12,15</sup>

#### *Four Kallikrein Assays*

Another testing panel which has been developed to increase detection of aggressive cancers is the 4Kscore Test which combines the total PSA, free PSA, intact PSA, and human kallikrein-

related peptidase (an enzyme similar to PSA), with age, DRE findings, and previous biopsy results. A large prospective study showed that the 4Kscore Test did a better job detecting cancers with Gleason score  $\geq 7$  than a model based on just total PSA and free PSA.

### *PCA3*

The prostate cancer antigen 3 gene (PCA3) is highly overexpressed in almost all prostate cancer tissue specimens but not in normal or hypertrophied tissue. It is measured in urine assays following a digital rectal exam. In clinical practice, it is used most commonly to evaluate the need for initial or repeat biopsy in individuals with an elevated PSA, and outperforms PSA and percent free PSA in independently predicting a positive biopsy, but as with the other predictive markers, it has not been shown to improve outcomes.<sup>13,14,15,16,19</sup>

### *Transrectal Ultrasound*

The transrectal ultrasound (TRUS) is not really a screening tool for prostate cancer but is used to evaluate the gland when the suspicion of a malignancy is increased. The hallmark of cancer on ultrasound is the presence of a hypoechoic or low density area. Prostatic calcifications, or high density areas, are suggestive of chronic infection and are *not* a sign of malignancy.<sup>5,17,18,19,20</sup>

### *Multiparametric MRI*

Multiparametric MRI is a newer technique that uses three individual imaging sequences. Though initially applied as a tool for staging males with known prostate cancer prior to radical prostatectomy or radiation therapy, it has also been found to be useful following a positive biopsy for tumor staging, for monitoring during active surveillance, to better assess the need for a biopsy in those with an elevated PSA, and especially for guiding targeted prostate biopsies. Its use results in a reduction in the number of unnecessary biopsies, a higher yield of significant cancers, and a need for fewer biopsy cores.

A prostate imaging reporting and data system (PI-RADS) system has been developed. It uses a five-point scale similar to the BiRADS system for mammography. Multiparametric MRI and MR-targeted biopsy, has led to improved detection of higher grade cancers when the PI-RADS score was 3, 4 or 5, (in 12, 60, and 63%, respectively) and can lower the need for biopsy in those with scores of 1 or 2.<sup>23,24</sup>

### *Biopsy*

Definitive diagnosis of prostate cancer depends on biopsy of the gland. Ideally, this is performed under ultrasound or MRI guidance to be sure that all abnormal areas are sampled. Any palpable abnormalities should be biopsied as well, even if the ultrasound in that area is normal. The standard of care now for biopsies is to do 10-12 or more tissue cores, unless MRI-targeted. A negative biopsy does not rule out the presence of prostate cancer. If suspicion is high, the biopsy should be repeated. The probability of detecting cancer on repeated biopsies is approximately 20-30%. Biopsy of the prostate bed can be used if there is a concern about local relapse after surgery or radiation. Prior radiation therapy makes the biopsy difficult to interpret.<sup>5,18</sup>

## Pathology

Most cancer of the prostate (>95%) is adenocarcinoma. The key features of importance on the biopsy are the:

1. presence of invasive cancer
2. grade, or the degree of malignancy of the cells
3. stage, or the extent of the tumor.

In prostate cancer, a specific system called the Gleason grading system is used to assess the degree of malignancy of the tumor. The Gleason system looks at the two most common cellular patterns on the tissue sample and classifies each on a scale of one (closest to normal tissue) to five (most deranged or malignant appearing). These values are then added to obtain the final composite Gleason score, which can range from 2 to 10.

Over the many years this system has been utilized, there have been some adjustments to how it is used. Most pathologists no longer consider histology consistent with a Gleason's grade of 1 or 2 to be diagnostic of cancer. Therefore the composite Gleason's score range is generally 6 to 10, with those of 6 (or less) being the most favorable. It has also been well recognized that Gleason 7 lesions are in a gray zone, and their behavior depends on how the score is derived. If the total is the result of a sum of 4+3 (i.e., 4 is the most dominant pattern), the behavior is more like a higher-grade lesion. If the sum results from a 3+4 (i.e., the 3 portion is more dominant in the specimen), the behavior is more like a moderately differentiated tumor.<sup>5,21,22,23,24</sup> This led to a new grading system in 2014 which has been incorporated into the staging of prostate cancer and which reflects an increasing risk of biochemical recurrence and prostate cancer mortality with increasing grade.

1. Grade group 1: Gleason score  $\leq 6$
2. Grade group 2: Gleason score  $3+4 = 7$
3. Grade group 3: Gleason score  $4+3 = 7$
4. Grade group 4: Gleason score = 8 (including 4+4, 3+5, or 5+3)
5. Grade group 5: Gleason scores 9 to 10 (4+5, 5+4, or 5+5).

Since the prostate cancer grade is so closely tied to prognosis, it is imperative to pay close attention to how the Gleason's score is presented. For example, is a Gleason's 4 one of the two grades used for the score (such as Gleason's 4+3), is it the full Gleason's score (e.g. Gleason's grade 2+2=4), or is it the Gleason Grade group (i.e. a Gleason's score of 8)?

In some cases, a tumor can contain a small component of higher grade tumor in addition to the two predominant patterns; the grade of this minor component is referred to as the tertiary Gleason grade. Though the tertiary Gleason grade has previously not been felt to be part of the overall Gleason score in biopsy specimens, it is recognized that those with biopsy Gleason score 3+4 or 4+3 prostate cancer and a tertiary pattern 5 should have their cancers classified as Gleason score 8 or 9, respectively because they have an increased risk of biochemical and clinical recurrence compared with those who have Gleason score 7 disease without a tertiary grade 5 component.

At times, high-grade prostatic intraepithelial neoplasia (PIN) can be found on a biopsy. Pathologically, high grade PIN has malignant changes in the ductal cells, but no invasion, and is considered a precursor to prostate cancer. The risk of finding cancer in a patient with isolated high-grade PIN, however, is only slightly higher than that in a patient with a benign prostate biopsy. Additional biopsies are thus not routinely indicated and only close follow-up is done. Low grade PIN is not of clinical or underwriting significance and generally not reported.<sup>21,25</sup>

### Staging

The current staging of prostate cancer uses the TNM system. The T designates the extent of the tumor, the N represents the presence of lymph node metastasis, and M refers to the presence of distant metastasis. Pathologic staging is determined whenever a total prostatectomy is performed and uses microscopic examination of the actual surgical specimen. All others are staged clinically using the biopsy findings along with the results of DRE, ultrasound, and MRI or CT scans. This includes those individuals treated with radiation where a definitive pathologic specimen is not received. Clinical staging is less accurate than pathologic staging and frequently underestimates the extent of disease. The small letters c or p are placed in front of the staging categories to designate whether the categories were clinically or pathologically derived.

The T portion of the system is the most important for insurance purposes (T1-T3), as the presence of lymph node or distant metastasis indicates that the cancer is incurable and cannot be eradicated using presently available treatments.

1. T1 lesions (T1a, T1b, or T1c) indicate clinical staging only when the cancer is not palpable and is found incidentally. The final designation depends on the extent of the tumor (T1a or T1b) or whether the diagnosis was made via PSA testing alone, without clinical findings (T1c).
2. T2 lesions are confined to the prostate. When clinically determined, the designation is cT2a if confined to less than half of one lobe, cT2b if unilateral but more than half the lobe, and cT2c if there is involvement of both lobes. For pathological staging, only pT2 is used, indicating the tumor was confined to the prostate.
3. T3 lesions indicate extension outside of the prostatic capsule without (T3a) or with (T3b) seminal vesicle invasion.
4. T4 lesions are fixed or invade adjacent structures.

Tumors that are located in the apex or that invade the prostatic capsule without penetration through the capsule are considered T2, not T3 lesions.<sup>26</sup>

### Prognostic Factors

The most important prognostic factors in prostate cancer are those used in the AJCC 2017 prognostic staging groups:

1. stage of the tumor
2. gleason grade group
3. pre-treatment PSA level.

Prognostic stage group I includes the lowest risk individuals: those with cT1, cT2a, and pT2 lesions, Gleason grade group 1, and pre-treatment PSA level of < 10 ng/ml. The intermediate risk stage group II includes those with a T2b or T2c lesion, a Gleason score of 7 or 8, or a pre-treatment PSA level of 10-20 ng/ml. Individuals with T3 or T4 lesions, a Gleason score of 9-10, or a PSA > 20 ng/ml and those with metastatic disease are considered high risk<sup>5,28</sup>. Current staging for those without metastases to the lymph nodes (Stage IA) or elsewhere (Stage IVB) is as follows:

T stage	Grade group	PSA	Stage Group
cT1, cT2a, pT2	1	<10	I
cT1, cTa, pT2	1	10-<20	IIA
cT2b, cT2c	1	<20	IIA
T1-2	2	<20	IIB
T1-2	3	<20	IIC
T1-2	4	<20	IIC
T1-2	1-4	≥20	IIIA
T3-4	1-4	Any	IIIB
T any	5	Any	IIIC

A major advantage of regular PSA screening is detection of a rising level, one often still in the normal range, and the subsequent diagnosis of more individuals with lower stage lesions with lower pre-treatment PSA values.

Additional tumor features that appear to have prognostic significance for males who have not undergone a prostatectomy are the number and percentage of positive core biopsies and the presence of tumor perineural and/or lymphovascular invasion.

## Treatment

### *Active Surveillance*

Most prostate cancers are now diagnosed while clinically localized. Taking into account the indolent nature of many of these cancers, and considering the patient's age and life expectancy, standard management is often to monitor the course and postpone definitive therapy until and unless there are signs of progression. This is known as active surveillance (AS) and has often become the preferred option for those with very low-risk prostate cancer (Stage Group I), as well as for older males with low-risk groups. The aim of this approach is to avoid the morbidity of therapy in individuals with non-aggressive disease. If the tumor does show signs of significant progression during the regular follow-up, the intent is to institute curative therapy with surgery or radiation. Data are accumulating on use of other modalities, in addition to staging criteria, to determine the suitability of AS vs more active therapy. At present, gene expression assays and multiparametric MRI are the most useful.<sup>9,29</sup>

The accepted strategy for surveillance with AS is not fully delineated. PSA testing is generally done every 6 months and a repeat biopsy, or MRI scan is advised within 1-2 years and then every

two years. With long-term stability, this timeframe can be lengthened. A rising PSA (doubling in <3 years), progression of MRI changes, or a new digital rectal exam finding, requires a follow-up biopsy or going directly to definitive treatment.<sup>30</sup>

### *Surgery and Radiation*

The two major forms of curative treatment for presumed organ-confined prostate cancer are surgery and radiation therapy. Either of these is usually the initial choice for those not meeting the criteria for AS, those wishing a more definitive approach rather than AS, and those who show progression during AS. Surprisingly, there are no good studies that directly compare the outcomes of each form of treatment, especially with the more modern techniques employed for each.<sup>5</sup> In general, overall long-term outcomes have been better with surgical therapy. However, there are a number of factors that complicate the analysis of treatment results.

First, individuals chosen for surgery are generally felt to be healthy enough to tolerate a radical prostatectomy. Males who are frail or who have significant comorbid medical conditions are more likely to be treated with radiation. The result is that the surgically treated group tends to be, in general, a younger and healthier population. One way that researchers have tried to adjust for this phenomenon is to report findings in terms of disease-specific survival, instead of overall survival.

Second, individuals treated with radiation are, of necessity, staged clinically so that the precise extent of their tumor is uncertain. Surgical cases are staged pathologically. Thus, the precise extent of the tumor can be tied to the clinical outcomes. The result is that a clinical stage T2 and a pathologic stage T2 can be substantially different lesions and have different outcomes that have nothing to do with the form of therapy used.

Finally, the dose of radiation that must be delivered to the prostate to ensure eradication of the cancer and the techniques for doing so have been evolving over time. Surgical techniques have not changed to such a large extent. This makes comparisons between surgery and radiation and among the various forms of radiotherapy difficult, especially over long-term follow-up.

Radical prostatectomy involves the removal of the entire prostate gland and is primarily reserved for males who are otherwise reasonably healthy and have a projected life expectancy of at least 10 years. Long-term results with prostatectomy have been good with extended long-term survivals. Results are best with organ-confined disease and Gleason scores less than 8. Because the prostate has been completely removed, the PSA levels should be essentially non-detectable, beginning shortly after surgery. Different labs use different reference points for undetectable levels of PSA, therefore use caution when comparing results from different labs. According to the most widely accepted criterion, that of the American Urological Association, a biochemical recurrence following radical prostatectomy is defined as a serum PSA  $\geq 0.2$  ng/mL, confirmed by a repeat testing. Rising levels even when  $<0.2$  are still potentially of concern and need to be followed closely. Though an increase in the PSA level is usually an indication that the tumor has recurred, the natural history of a PSA-only recurrence can be highly varied, and biochemical failure by itself does not necessarily predict a poor outcome. The major complications of surgery are impotence and urinary incontinence.<sup>3,5,30,31</sup>

Radiation therapy is applied in two forms: external beam radiation or radioactive seed implants (or a combination of the two). External beam radiotherapy uses a conventional radiation beam to irradiate the prostatic tissue. Newer techniques have improved the delivery of the therapy to the tumor while minimizing damage to the surrounding tissues.

1. Conformational therapy uses information from a CT or MRI to precisely locate the prostate gland within the pelvis for delivery of the radiation beam.
2. Intensity-modulated therapy provides higher doses to the prostatic bed than the surrounding normal tissue. Both modifications have allowed substantially higher doses of radiation to be delivered to the tumor. Multiple studies show improved outcomes with the higher dosages.
3. Sometimes radiation can be combined with adjuvant hormonal therapy, which is given in a short course to shrink the tumor prior to the delivery of definitive treatment in order to improve response rates.

Radioactive seed implantation (brachytherapy) is the other form of radiation therapy. In this treatment, seeds of iodine-125 or palladium-103 are implanted directly into the prostate gland in order to deliver the radiation dose directly to the tumor. This type of therapy is reserved primarily for smaller, low risk lesions. As with the external beam therapy, PSA levels drop slowly after seed implantation and generally take 18 months or longer to reach a nadir. In general, the complication rates with brachytherapy are lower than those for surgery or external beam therapy.<sup>20,21,22</sup>

Radiation does not destroy tumor cells immediately or, for that matter, destroy all prostatic tissue. Radiation causes damage to the cells, which will only lead to their death when the cells divide. Since prostate tumor cells divide slowly, this delayed necrosis can take some time to manifest itself. For this reason, post treatment PSA values decrease slowly and it can take two to three years to reach its lowest level. The nadir, or lowest level reached, and the time it takes to achieve that level are both prognostic factors for disease recurrence and mortality. Ideally, the PSA should reach a level less than 0.5 ng/ml, but a level less than 1.0 is probably acceptable if stable for an extended period of time. The longer time it takes to reach the nadir, the better the prognosis is. A rising PSA after having reached a minimum value is an indication of possible treatment failure. A biochemical recurrence is usually defined as PSA rise of 2 ng/mL or more above the nadir PSA value. A single increased level can be an aberration and not a sign of true recurrence or, when mild and very slowly increasing, can be due to the growth of residual benign prostatic tissue. The major complications of external beam radiotherapy are impotence and damage to the bladder or bowel.

*External beam radiation therapy* is occasionally used in individuals who have been treated with a radical prostatectomy but who then have a rising PSA level. In this case, the radiation is being used to treat presumed recurrent tumor in the prostatic bed. A prolonged response after irradiation, one lasting at least several years, is an indication that the rising PSA was more likely due to local disease than distant metastasis. However, despite an initial good response, an additional increase in the PSA level can occur as long as 10 years or more after treatment.<sup>29,30,31,32,33,34</sup>

### *Hormone Therapy*

Prostate cancer is very sensitive to hormonal stimulation with androgens (i.e., testosterone and its analogues). Removal of androgenic stimulation has a profound effect on the tumor and can reduce the PSA to undetectable levels. Androgen removal can be accomplished surgically via castration or medically using drugs like gonadotropin-releasing hormone analogues (e.g., leuprolide - Lupron® and goserelin - Zoladex®) that eliminate the production of testosterone. However, hormonal treatment is not considered curative and is used for localized disease only in an adjuvant setting, to improve the outcome of a primary therapy such as surgery or radiation.

Hormonal therapy is effective in the palliation of metastatic disease and can be effective for a number of years. However, most tumors eventually become androgen-independent and resistant to the treatment. Chemotherapy is used for those who fail hormonal manipulation, but it is of limited long-term benefit.<sup>35,36</sup>

### *Cryotherapy*

In some patients who are not candidates for, or who refuse, surgery and radiation therapy, cryosurgery can be used to destroy the prostatic tissue. The cooling process kills tumor cells directly, as well as via vascular damage. Cryotherapy has been used as primary treatment and as salvage therapy in individuals who have been previously irradiated. In limited follow-up, outcomes in individuals with low volume, low risk tumors have been comparable to those with radiation therapy. As with brachytherapy, the size of the gland is a limiting factor in the application of cryotherapy. There is a very high risk of impotence with this form of treatment.<sup>37</sup>

### *Watchful Waiting*

Watchful waiting is a legitimate therapeutic option in older males with a limited life span. For patients managed with watchful waiting, as opposed to active surveillance, the decision is made at the outset that the patient is not a candidate for definitive therapy and to provide palliative treatment (typically androgen deprivation therapy [ADT]) if and when symptomatic progression requires therapy

### Mortality

Prostate cancer is a slow growing tumor with a doubling time (i.e., the time required to double the tumor size) in the two to four year range. As a result, long-term survival is the rule with the disease, and survival curves are comparable to those seen with the general population. This is illustrated in data from the Surveillance, Epidemiology, and End Results (SEER) cancer database (*Figure 1*). This slow progression and good survival is a large part of the reason behind the USPSTF recommendation against PSA screening and the basis of management with Active Surveillance.

Consequently, early mortality is not generally an issue with prostate cancer. Deaths within the first five years after diagnosis are unusual except in those individuals with metastatic disease at

presentation. A prolonged clinical course is the rule and requires regular, long-term follow-up. Regular PSA testing is usually part of the regimen.

The key risk factors driving mortality are the extent of the disease or stage and the Gleason grade of the tumor. A high Gleason grade (i.e., poorly differentiated tumor) is a particularly strong marker for increased risk and tends to predict earlier recurrences and mortality. Relative mortality risk also varies by age and is higher in younger males. The pattern of mortality is summarized for surgically treated individuals in Figure 2 using disease-specific mortality data from the SEER database. The pattern is similar for radiation treatment, although with somewhat higher mortality ratios (data not shown here). As noted above, mortality peaks late and generally occurs at least 10 years after diagnosis. In older males, this frequently means that individuals will die with, rather than from, their disease. This mortality experience is supported by studies that have looked at long-term survival after radical prostatectomy.

For surgery, the risk is divided between organ-confined tumors and tumors that extend outside the prostate. For tumors extending outside the prostate, the surgical margins are important as well. This assessment is possible because surgical specimens provide the opportunity to determine the precise pathologic extent of the cancer.

In contrast, those individuals treated with radiation are evaluated by clinical staging, which employs the DRE exam and imaging studies such as TRUS and/or MRI which are less precise. Individuals treated with radiation are thus divided into low risk, intermediate risk, and high risk groups using these clinical staging parameters.

The degree and pattern of mortality with prostate cancer by extent of disease for different age groups for both surgery and radiation is illustrated in Figure 3. The mortality was studied using a Markov model, a technique that uses the probability of events to assess long-term outcomes. In this analysis, the extent of disease was organ-confined (OC), extra-prostatic extension with negative margins (EPE -) and extra-prostatic extension with positive margins (EPE +) for the surgical group, and low risk, moderate risk, and high risk (as defined by clinical stage, Gleason score, and PSA level) for the radiation treatment group. As can be noted, the mortality ratios are only mildly elevated, especially for the OC/low risk group. Although the risk is clearly higher in the radiotherapy group, for the reasons noted under the treatment section, it is difficult to do a direct comparison of the results from the treatment groups because of confounding factors. Nevertheless, the relative patterns of mortality are similar, with the highest risk in the younger individuals.<sup>38,43</sup>

What is especially important to remember is that a large number of males with prostate cancer live for an extended period of time *with* active disease. This impacts outcomes seen with those undergoing active surveillance, as well as those who have an elevation of the PSA level (referred to as a PSA or biochemical recurrence) following treatment. Progression or recurrence of the tumor is dependent on the noted prognostic factors and can occur up to 20 years or more after the initial treatment. This pattern is summarized in Figures 4 and 5.<sup>43,44</sup>

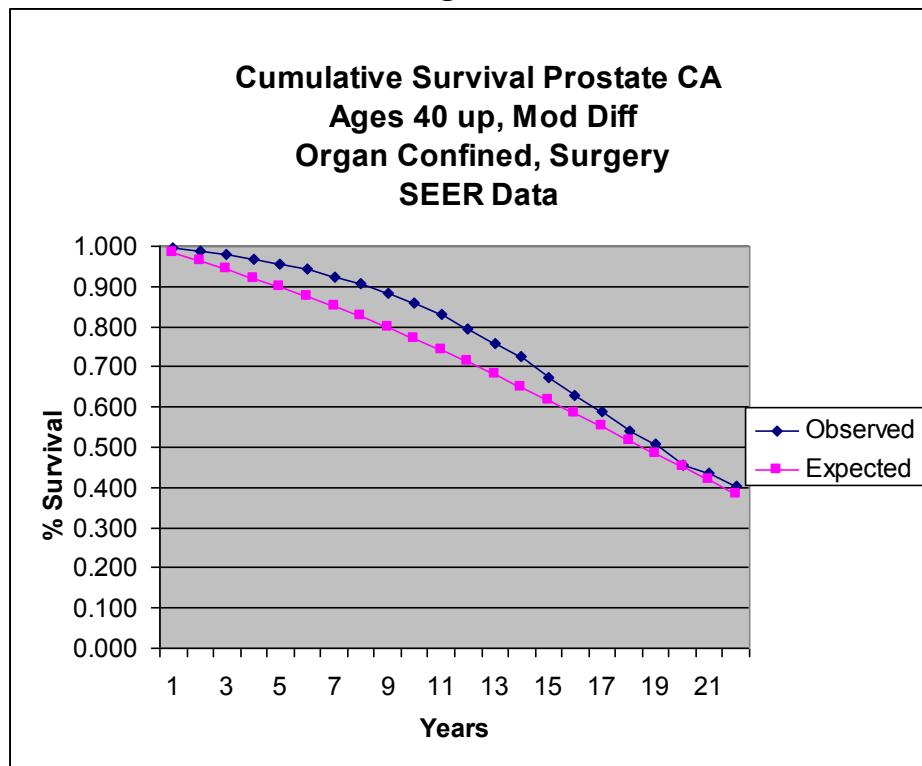
Long-term mortality risk for those undergoing active surveillance is only now being more clearly understood, since this approach is relatively new and given the protracted natural course of

the disease. For those at low risk, outcomes with AS appear to be excellent, but perhaps slightly less favorable than for those who have definitive treatment initially. One study of males randomized to receive prostatectomy vs radiation vs active monitoring, found similar 10-year survival rates (99.0, 99.6, and 98.8% respectively), but there were higher rates of clinical progression in the active monitoring group. This group however did not receive active surveillance, such as the tracking of PSA levels, as it is typically practiced. Results vary substantially between studies, based on design, but baseline risk factors for progression to metastatic disease while on AS include Gleason's score 3+4, PSA 10-20, higher number of positive biopsy cores, and older age. Roughly half of those receiving AS eventually underwent more definitive treatment. For those without the higher risk factors, long-term studies have consistently found disease-specific 10-year survivals of 99+% and 15-year metastasis-free rates of 95+%.<sup>42,45,46</sup>

Should an individual have a PSA recurrence, two studies found that the average time to the development of clinically evident metastasis was eight to ten years. From the time of clinical metastasis, there was an additional five years until death. That means that there is an average of *13-15 years from PSA recurrence to mortality*. This duration underscores the long clinical course typical of prostate cancer. However, there are certain factors that do predict a more rapid progression than that cited above. These factors include:

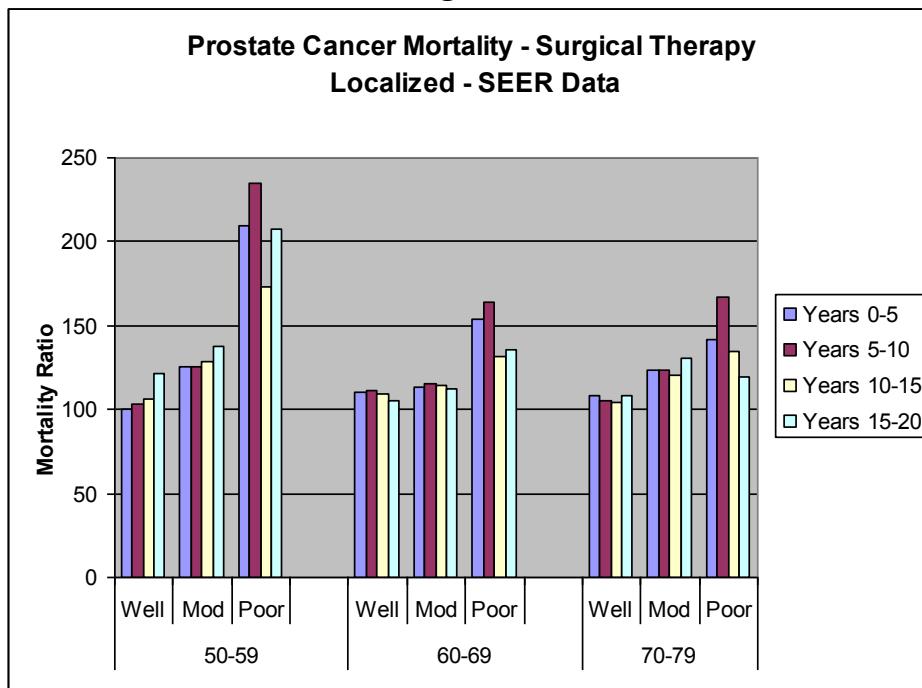
1. a shorter time from treatment to PSA recurrence
2. a higher Gleason scores
3. a short PSA doubling time (i.e., a rapidly rising PSA level after recurrence).  
See Figure 6.<sup>39,40,41,42,43,44,53,54,55</sup>

**Figure 1.**



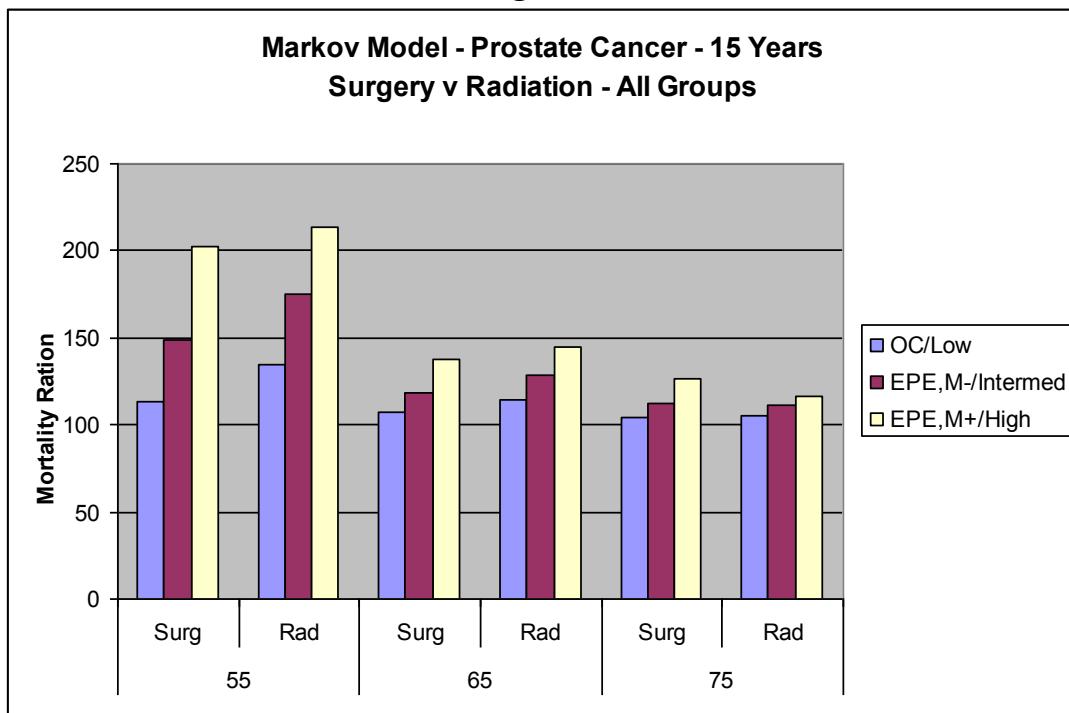
Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2006). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released April 2008. Based on the November 2007 submission.

**Figure 2.**



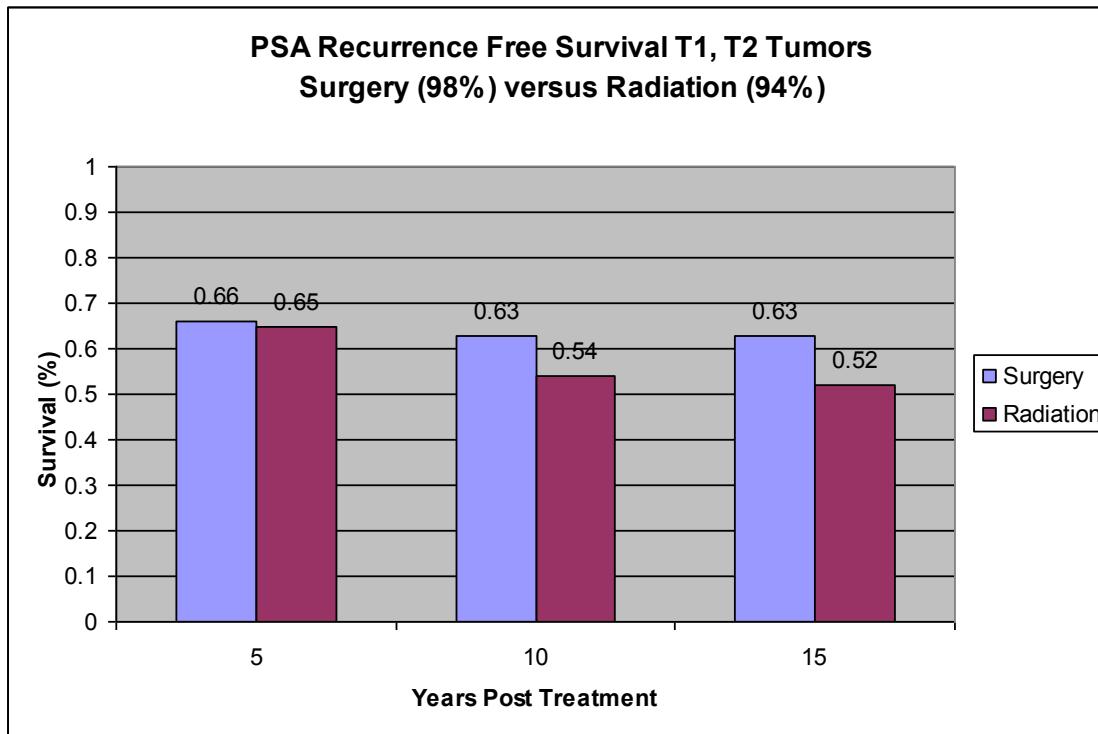
Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2006). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released April 2008. Based on the November 2007 submission.

**Figure 3.**



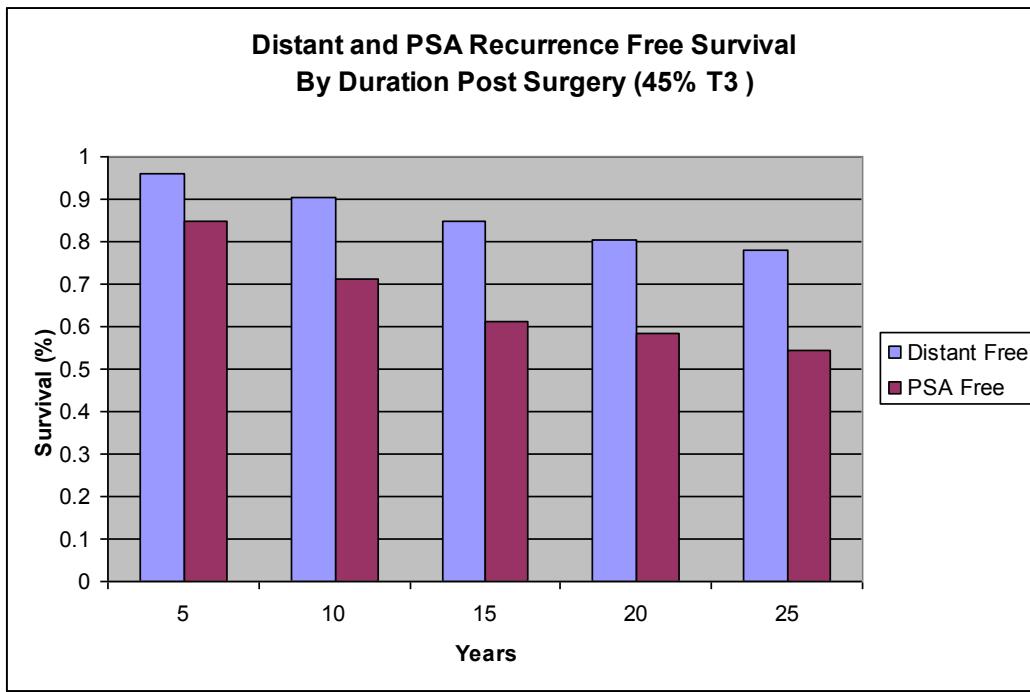
Zelefsky MJ "Long Term Results of Conformal Radiotherapy for Prostate Cancer: Impact of Dose Escalation on Biochemical Tumor Control and Distant Metastasis Free Survival Outcomes", Int J Radiation Oncology Biol Phys, 2008; 71:1028-1033.

**Figure 4.**



Uchio EM, Aslan M et al., "Impact of Biochemical Recurrence in Prostate Cancer Among US Veterans", Arch Intern Med, 2010; 170:1390-1395

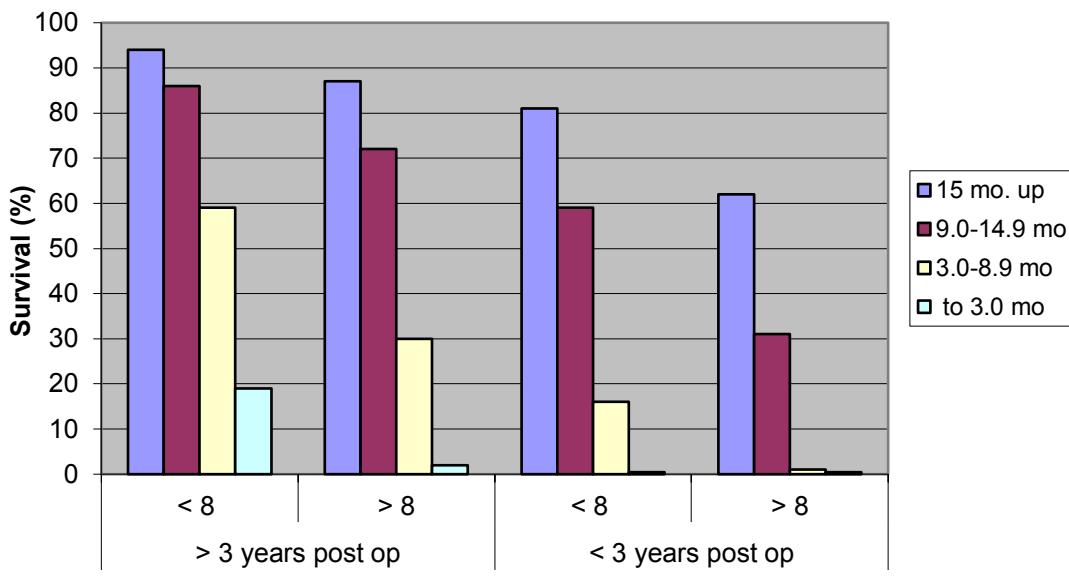
**Figure 5.**



Porter C, Kodama K, et al., "25-Year Prostate Cancer Control and Survival Outcomes: A 40 Year Radical Prostatectomy Single Institution Series", J Urology, 2006; 176:569-574

**Figure 6.**

**15-Years Cancer Specific Survival After Biochemical Recurrence - By PSA Doubling Time (mo), Duration From Surgery to Recurrence (yrs) and Gleason Score**



Freedland SJ, Humphreys EB, et al., "Risk of Prostate-Cancer Specific Mortality Following Biochemical Recurrence After Radical Prostatectomy", JAMA, 2005; 294:433-9.

## **Section C**

### **Breast Cancer**

#### Epidemiology

Globally, breast cancer is the single most frequently diagnosed malignancy. Among females in the United States, breast cancer is the most commonly diagnosed cancer and the second leading cause of death from malignancy. For middle-aged females, those between the ages of 40 to 55, it is *the* leading cause of mortality. It is clear why knowledge of breast cancer is so critical in underwriting.

The majority (80%) of the breast cancers that are diagnosed are invasive lesions. The remaining 20% are called *in situ* lesions and have cells that show malignant changes but have not invaded through the basement membrane. For the year 2019, the number of new cases of breast cancer in the U.S. is expected to be around 268,600 in females (30% of all cancers in females, excluding non-melanoma skin cancers) and 2,670 in males. It is estimated there will be 42,260 deaths from the disease (41,760 females and 500 males).

The incidence rates for breast cancer increased significantly during the 1990s. Most of that increase was in non-invasive or *in situ* lesions while the incidence rate for invasive tumors remained relatively flat. Despite this increase in incidence, the death rates from breast cancer decreased significantly during that same time in many developed countries, including the United States. The decrease has been attributed to two key factors: improved screening with mammography, with the subsequent earlier diagnosis of smaller tumors, and improvements in therapy. Most recently, incidence rates have also decreased, most likely due to the population-wide reduction in hormone replacement therapy.<sup>1,2,3,4,5</sup>

#### Risk Factors

##### *Age*

The most important risk factor for the development of breast cancer is age. The incidence rates peak in the 75-79 year age range with a modest decline in later years. Expressed another way, the odds for developing breast cancer for females is 1 in 51 from birth to age 49, 1 in 43 at ages 50 to 59, 1 in 29 from age 60 to 69, and 1 in 15 from age 70 and up, for an overall lifetime risk of 1 in 8 (12.4%).<sup>2</sup>

##### *Estrogen Exposure*

Prolonged exposure to estrogens is important in the development of breast cancer. Factors that increase exposure clearly increase risk. These factors include: early menarche, older age at first pregnancy, and delayed menopause. Current use of oral contraceptives is associated with a modest increase in relative risk (RR=1.2) that dissipates rapidly with cessation of intake. Hormone replacement therapy shows a similar increased risk (RR= 1.29) and a similar reduction when the medication is stopped. As noted above, the overall reduction in the use of hormone replacement

therapy is felt to be a major factor in the lower population incidence rates for breast cancer in recent years.<sup>1</sup>

### *Family History*

A positive family history is a well-recognized risk factor for breast cancer. About 10-20% of the females with breast cancer have a first-or second-degree relative who is also affected. The risk clearly increases with the number of affected relatives and the age at which those relatives developed a tumor. For those with a history of cancer in first-degree relatives (mother, sister, or daughter), the risk varies depending on whether the onset in the family member was premenopausal or postmenopausal and whether there was bilateral disease. With the combination of bilateral disease and early onset, the risk is increased even further. If the tumor occurred in more distant relatives, the risk for the individual is only modestly increased (on the order of that seen with hormonal therapy use) if the diagnosis was made in the family member before menopause, and not at all if the diagnosis was made after menopause. Breast cancer in a male relative also increases the risk.

About 5% of females with breast cancer have a single gene mutation that places them at high risk. Two of the identified genes whose mutations are associated with increased risk are BRCA1 and BRCA2, located on chromosomes 17 and 13 respectively. These mutations increase the lifetime risk of breast cancer to about 50-85%. The risk of ovarian cancer and selected other tumors is increased as well. However, the BRCA mutations account for only 30-40% of the familial breast cancer syndromes (conditions in which there is a well-recognized genetic defect leading to the development of cancer). The Li Fraumeni, Peutz-Jeghers, and Cowden syndromes are other examples of these conditions.<sup>1</sup>

### *Benign Breast Disease*

Some forms of benign breast disease can increase the risk of developing breast cancer. The key factors in this process appear to be the presence of proliferation, or increased cell turnover, and alterations of the normal cellular structure, or atypia, on the biopsy specimen. The risk is lowest for non-proliferative lesions, increased in those with proliferation without atypia, and highest for atypical hyperplasia (proliferation with atypia) regardless of whether it is ductal or lobular hyperplasia (RR=4.24). The risk is further modified by age and family history. The highest risk is in females under age 45 with atypical hyperplasia (RR=6.99). In contrast, for females with a strong family history and non-proliferative lesions, the relative risk is 1.62. An increased risk of breast cancer is also noted in females with increased breast density.<sup>1,6</sup>

### *Environmental Factors*

Certain environmental factors and their association with an increased or decreased risk of breast cancer:

1. Radiation to the breast significantly increases the risk, especially if it occurs at an early age. The latency period from exposure to tumor development is at least 10 years.

Clinically, the greatest risk has been in young females treated with mantle radiation for Hodgkin disease. In these individuals, the lifetime risk can be as high as 25-30%.

2. A prior history of breast cancer increases the risk of a second tumor, especially if the initial lesion occurred at a young age.
3. Alcohol consumption increases the risk of breast cancer. The greater the amount consumed, the higher the risk. The risk is highest for 10 or more drinks per week.
4. Smoking appears to increase the risk of breast cancer in younger females.
5. Obesity increases the risk of breast cancer in postmenopausal, but not premenopausal, females.
6. Selective estrogen-receptor modulator (SERM) drugs, such as tamoxifen and raloxifene, have been shown to reduce the rate of the development of breast cancer in individuals who are at higher risk. Aromatase inhibitors (AIs) such as anastrozole and exemestane are also options in postmenopausal females at high risk.
7. High levels of physical activity over a prolonged period of time can suppress estrogen levels and reduce risk to some extent. Dietary fat intake has not shown a consistent association with the development of breast cancer.<sup>1,7</sup>

#### *Prior History of Breast Cancer*

It is important to remember that breast cancer is a “field defect” which means all of the breast tissue is exposed to the same genetic and other risk factor profile for that individual. Thus, all of the remaining breast tissue remains at ongoing risk for a new primary tumor. This risk is on the order of four- to five-times the baseline risk in someone without a prior cancer.

#### Pathology

##### *In situ Carcinoma*

Ductal carcinoma in situ (DCIS) represents a group of non-invasive breast neoplastic lesions confined to the breast ducts and/or lobules. Approximately 20-25% of breast cancers in the U.S. are considered to be DCIS. As with invasive breast cancer, the risk increases with age, and it is uncommon in females younger than 30. DCIS can be diagnosed by mammography by its classic finding of clustered microcalcifications. The mortality risk from these tumors is very small. What makes DCIS important from a clinical and underwriting perspective is that it is a true precursor lesion. The initial tumor has the ability to recur if not treated appropriately, and of the DCIS lesions that do recur, about half do so as invasive cancers. The tumors at greatest risk for recurrence are those with a higher nuclear grade and those that show comedonecrosis on biopsy. Younger age at onset, a larger size, the presence of a palpable nodule, and the occurrence of multiple in situ lesions also increase the risk of recurrence.<sup>8,9,10</sup>

What has been called lobular carcinoma in situ (LCIS) is not a cancer, and many now prefer to consider it as lobular neoplasia, a designation that also includes atypical lobular hyperplasia (ALH). It is no longer included in the AJCC staging categories. Lobular neoplasia is most often an incidental finding rather than being detected by mammography. It tends to occur in younger females and to show diffuse involvement in both breasts. It is not a precursor lesion and does not progress to invasive disease, but is significant in that it is a marker for the development of invasive

cancer. Most of those invasive cancers will be ductal and can occur 15 years or more after the diagnosis of the in situ lesion. The presence of LCIS increases the lifetime risk of invasive cancer approximately 8-fold, or roughly 1% per year, which is about twice the risk incurred with ALH.<sup>11</sup>

### *Invasive Cancers*

Most invasive cancers are adenocarcinomas, and the most common of the adenocarcinomas (85%) is invasive ductal carcinoma. The next most common type (4-10%) is invasive lobular carcinoma, which tends to be multicentric and to have an increased risk of bilateral disease. Several other subtypes occur with much lower frequency; some of these, such as papillary, colloid, or mucinous tumors and tubular carcinomas, are more indolent in character and have a favorable long-term prognosis.<sup>12</sup>

### Diagnosis

Most breast cancers are asymptomatic at diagnosis. The disease is occasionally noted by the individual on self-examination as a palpable lump or nodule, new skin or nipple changes, a bloody nipple discharge, or lymph node enlargement. Clinical breast examination by medical personnel also detects some tumors.

The primary means of diagnosis of breast cancer is mammography. Mammography uses low dose x-rays to visualize the structure of the breast. It will detect about 80-90% of breast cancers in asymptomatic females. Findings suggestive of cancer are microcalcifications, nodules, or masses. Dense breasts, prior surgery, and the presence of implants reduce the sensitivity of mammography. Not all tumors are detected by mammography, so suspicious physical findings should not be ignored if mammography is negative. Technical improvements using digital mammography with breast tomosynthesis have significantly improved the sensitivity and specificity of mammography, and this diagnostic technique is the preferred choice of screening.<sup>13</sup>

Ultrasound examinations are used to evaluate suspicious lesions on mammography. Its primary value is in differentiating cysts from solid lesions and lymph nodes from nodules. It can also be used to direct needle biopsies or cyst drainage. Because ultrasound does not visualize microcalcifications, it is not an effective screening tool.

Magnetic resonance imaging (MRI) scanning is more sensitive than mammography in screening for breast cancer. It is recommended for those with dense breasts or breast implants, individuals with a high risk of developing breast cancer such as known carriers of BRCA1 and BRCA2 or other genetic high-risk conditions, and those with prior chest irradiation. Breast MRI is also sometimes useful in further assessment of high-risk proliferative breast lesions. The disadvantages of MRI are its higher false positive rate and its expense, which is about 10-times higher than a mammogram.<sup>1,14</sup>

### Staging

The staging of breast cancer relies on the TNM system. The T represents the size and/or local extent of the tumor, N represents the nodal status, and M refers to whether or not there are distant

metastases. It is useful to note that patients are typically assigned a clinical stage (designated as cTNM) prior to surgery, but what is generally more important in assessing the prognosis is the pathologic stage (pTNM) determined following surgery. In addition, for patients who undergo adjuvant therapy (chemotherapy and/or radiation treatment based on the clinical stage and given prior to definitive surgery) the subsequent pathologic staging is designated ypTNM. In such cases, from a breast cancer prognosis standpoint, what is important is the original cTNM, not the ypTNM subsequently determined.

The T stage designations are:

1. Tis – Carcinoma in situ
2. T1 –  $\leq 2.0$  cm
  - T1mi –  $\leq 1$  mm
  - T1a –  $>1$  mm but  $\leq 5$  mm
  - T1b –  $>5$  mm but  $\leq 10$  mm
  - T1c –  $>10$  mm but  $\leq 20$  mm
3. T2 –  $>2.0$  but  $\leq 5.0$  cm
4. T3 –  $>5.0$  cm
5. T4 – any size with extension to (a) the chest wall, (b) the skin, (c) both chest wall and skin, or (d) with inflammatory changes.

Since most breast cancers are less than 2.0 cm at diagnosis, the T1 category is further divided into T1mic ( $<0.1$  cm), T1a ( $>0.1$  cm - 0.5 cm), T1b ( $>0.5$  cm - 1.0 cm), and T1c ( $>1.0$  cm - 2.0 cm).

The N represents the nodal status and is evaluated either clinically or pathologically. The pathologic designation is more accurate and preferred for underwriting purposes. The pathologic N designations are:

1. pN0 – no nodal involvement
  - pN0(i+) – malignant cells in regional lymph node(s) no greater than 0.2 mm
  - pN0(mol+) – positive molecular findings (RT-PCR) only
2. pN1 – 1 to 3 nodes positive
  - pN1mi – micrometastases 0.2 to 2.0 mm
3. pN2 – 4 to 9 nodes positive
4. pN3 – 10 or more nodes positive.

Additional N subcategories can be used for the extent of involvement within the lymph nodes and the location of the positive nodes.

The M designation indicates whether distant metastasis is absent (M0) or present (M1).

The anatomic staging of breast cancer uses combinations of the TNM designations. For practical purposes, most tumors of underwriting significance fall into the stage 0 to stage II range. The staging system can be summarized as follows:

- |    |            |  |
|----|------------|--|
| 1. | Stage 0    | TisN0M0  |
| 2. | Stage IA   | T1N0M0   |
|    | Stage 1B   | T0N1miM0<br>T1N1miM0                           |
| 3. | Stage IIA  | T0N1M0<br>T1N1M0<br>T2N0M0                     |
| 4. | Stage IIB  | T2N1M0<br>T3N0M0                               |
| 5. | Stage IIIA | T0N2M0<br>T1N2M0<br>T2N2M0<br>T3N1M0<br>T3N2M0 |
| 6. | Stage IIIB | T4N0M0<br>T4N1M0<br>T4N2M0                     |
| 7. | Stage IIIC | Any T N3M0                                     |
| 8. | Stage IV   | Any T Any N M1 <sup>15</sup>                   |

The majority of breast cancers in the U.S., 62%, are diagnosed as localized (without evidence of involvement beyond the breast), with 31% showing regional, i.e. nodal, spread, and 6% with distant metastases.<sup>2</sup>

As medical and technologic advancements are made, the TNM staging systems are periodically revised. For breast cancer, the eighth edition of the American Joint Committee on Cancer (AJCC) staging became effective January 1, 2018. This introduced some significant changes with a new prognostic staging system that relies not only on the anatomic extent of disease, but also on prognostic biomarkers. These biomarkers are the histologic grade, estrogen and progesterone receptor status, HER2 expression, and, where available, the Oncotype Dx genomic assay recurrence score.

Though the anatomic staging noted above remains unchanged, it is to be used only in parts of the world where biomarkers are unavailable. Instead, a pathologic prognostic stage should be assigned as it is more aligned with the patient's prognosis – and the outcome from an underwriting perspective. The many and varied combinations that result when these factors are added to the anatomic stage leads to much complexity (122 separate possibilities not including the recurrence score) and are too extensive to include in this text, but the prognostic factors are discussed as follows. Perhaps the most useful aspect to note is that if the Oncotype Dx test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned pathological prognostic stage group IA, regardless of the grade.

## Prognostic Factors

A key principle to remember in evaluating mortality risk is the fact that invasive breast cancer is a systemic illness at the time of diagnosis. The risk of death does *not* depend on the degree of local control. *Mortality results from distant metastasis.* Thus, predictors of mortality are the factors that are associated with the distant spread of the disease.

The most important risk factor for survival is the status of the axillary lymph nodes. Mortality clearly increases with the presence of metastatic disease in the lymph nodes and the number of nodes that are affected. Although controversial, some studies show that even small deposits of tumor detected on microscopic examination or by specialized immunohistochemical testing carry an increased risk of death when compared to lymph nodes that show no evidence of malignant cells.

*Tumor size* is also critical in assessing risk, both in those with and those without nodal metastasis. The larger the size of the lesion, the greater the risk is for metastasis and mortality. This is especially the case when the tumor has grown to where it invades outside of the breast and into the surrounding tissue (T4).

*The histologic grade or degree of differentiation of the cancer* reflects how different the cancer cells look from normal cells and provides an estimate of how “malignant” the tumor is. The less differentiated the lesion is (i.e., the less the cells look like normal tissue), the greater the risk for progression and mortality. In general, well-differentiated, less malignant appearing lesions do better in the long term. The risk is especially low in older females with small, well-differentiated tumors. One problem with the use of grade in prognostic assessment is the variability of readings among different pathology departments since the readings depend upon the judgment and technical skill of the examiners, and the adequacy of the preparation of the tissue samples that are being reviewed. A more uniform grading approach is now used which should eliminate some of that variance going forward.

*The age of onset* has prognostic importance. Premenopausal females fare worse, independent of other prognostic factors, and this is most clearly shown in those less than age 35 years.

*Lymphatic or vascular invasion* on the pathologic specimen is associated with a higher risk of local and distant spread, particularly in higher grade tumors.

While the *estrogen and progesterone receptors* are predictive of response to therapy, and are prognostic for more favorable 5-year disease-free survivals, they are weak predictors of long-term mortality outcomes. In fact, over the long term, the outcome for estrogen-receptor (ER)-positive individuals and ER-negative individuals is similar. Receptor negative individuals have higher early recurrence rates, while receptor positive individuals have higher later recurrence rates. In the end, these recurrence patterns alter the time course of the illness. Thus, the receptor status has less effect on the probability of recurrences and more effect on when, during the disease course, recurrences occur. Data also supports that patients with ER-positive, but PR-negative, tumors have a more aggressive subtype of hormone receptor-positive breast cancer and somewhat worse short and long term outcomes.

Proliferative *markers* such as the S-phase fraction and Ki67 antigens have shown value as markers for outcome in some studies, primarily showing that high levels of these markers are seen with more aggressive tumor behavior.

The most promising new prognostic indicators are those that use specific genetic markers for tumors to assess risk. These assays can look for either single gene alterations or arrays that represent combinations of DNA modifications. The test for human epidermal growth factor receptor 2 (HER2) (a gene that promotes cellular proliferation) is an example of a single gene type assay. This proto-oncogene is located on chromosome 17 and its overexpression is associated with increased tumor aggressiveness. Its overexpression also predicts an increased response to the humanized antibody trastuzumab (Herceptin®), a drug that can dramatically reduce recurrence rates in these tumors. Because of the often marked response to trastuzumab in such cases, the prognosis for those with HER2 positive disease is similar to that seen with hormone receptor positive and HER2 negative disease. However, in the absence of this systemic therapy, HER2 overexpression is a marker of poor prognosis.

Recently, tumor genetic profiling using arrays of DNA markers embedded on discs has been used to segment risk of recurrence, both for determining prognosis and choice of therapy. Several multi-gene profiles are now available, with those currently considered to be validated for clinical utility to be Oncotype Dx Recurrence Score, EndoPredict, Predictor Analysis of Microarray 50 (PAM50), and the Breast Cancer Index, and, in select cases, the Amsterdam 70-gene profile (Mammaprint). Use of one of these gene expression profiles has now become the standard of care where it is available. As previously noted, the recurrence score is already incorporated into the prognostic staging criteria, and those guidelines also specifically note that future updates to the staging system may include results from other multigene panels, to assign cohorts of patients to prognostic stage groups as that evidence becomes available.

Triple negative tumors are a clinically important subset, representing about 15% of all breast cancers. They are called triple negative because they are ER-negative, progesterone-receptor negative, and HER-2 negative. They occur more commonly in females under age 40, more often in Hispanic and black females, and are seen in the majority of BRCA1 positive tumors. They are associated with a particular microarray pattern designated basal-like breast cancer. These tumors are important because they tend to be more aggressive with a poorer prognosis and are more likely to have brain and lung metastasis. Of special significance is the fact that these lesions have only limited treatment options, i.e., chemotherapy, as hormonal therapy and trastuzumab cannot be used.<sup>16,17,18,19,20,21,22,23,24,25,26</sup>

### Treatment

The treatment for DCIS is directed primarily at preventing local recurrence and generally involves either lumpectomy with local radiation or mastectomy. However, some low-risk tumors may not be treated with radiation therapy, and some high-risk lesions can require a lymph node dissection (most DCIS tumors do not).<sup>8</sup>

For LCIS, treatment of the local tumor is not necessary, as that lesion does not progress. The focus instead is on preventing the development of other invasive cancers. With that goal in mind, the usual approach is either prophylactic bilateral mastectomy, chemoprevention using hormonal therapy with SERMs (tamoxifen/raloxifene), or one of the newer aromatase inhibitor drugs (discussed below).<sup>11</sup>

Most invasive cancers of the breast can be treated with lumpectomy, with or without radiation. Individuals with large tumors, an extensive intraductal component, or in whom a lumpectomy would give an unacceptable cosmetic result can require a mastectomy. Long-term studies have shown that the outcomes in terms of survival are equivalent for mastectomy or lumpectomy. For small tumors (<1.0 cm in size) with adequate surgical margins and no lymphovascular invasion or extensive intraductal component, radiation therapy may not be necessary.<sup>8,26,28</sup>

Because of its prognostic importance and influence on choice and extent of therapy, axillary lymph node evaluation will be done for most individuals with invasive cancer. Although internal mammary or supraclavicular nodes may be involved at presentation, they rarely occur unless there is axillary node involvement. The risk for metastases to the axillary nodes is related to tumor size and location, histologic grade, and the presence of lymphatic invasion within the primary tumor. For patients without clinical evidence of axillary node involvement a sentinel node biopsy is typically performed, in which the key lymph node draining the area of the lesion is identified and removed for sectioning. If that node is negative, further evaluation is avoided, and if that node is positive, a full lymph node dissection is usually conducted (except in rare low risk situations). For those with clinically suspicious axillary lymph nodes, a needle biopsy of the node or nodes is usually performed. If positive, a complete dissection is then done at the time of surgery, and if negative, a sentinel node biopsy is performed instead. This information is important because mortality risk increases with the number of nodes that are positive.<sup>8</sup>

The major advance in the treatment of breast cancer has been the use of adjuvant chemotherapy (i.e., systemic therapy given without clinical evidence of spread of the tumor) and/or hormonal therapy employed after surgery. Nearly all females with ER-positive tumors should be offered hormonal therapy. Aromatase inhibitor drugs (Arimidex®, Femara®, Aromasin®) are now the usual choice in postmenopausal females. These drugs block the enzyme (aromatase) that converts androgens to estrogens in adipose tissue, the adrenal glands, and the breast tumors themselves (some tumors produce their own supply of estrogen), thereby cutting off the supply of this hormone to the cancer. SERMs like tamoxifen are also an option and can have a more favorable side effect profile, however they are less effective. For premenopausal females, SERMS are advised except in the case of those at high recurrence risk, for which ovarian suppression measures and an AI are often chosen.

In general, the relative risk of all-cause mortality is about 1.4-1.5 times higher for those who do *not* receive adjuvant therapy. However, the benefit of this treatment varies with many factors:<sup>29</sup>

1. The value of chemotherapy is greater in younger individuals and in those with higher grade tumors.
2. The incremental benefit of chemotherapy for older individuals is small, especially in ER-positive individuals.

3. Chemotherapy has little benefit for preventing tumors in the unaffected breast.
4. In those with ER-positive tumors, the benefit of hormonal therapy is the same whether or not chemotherapy is used.
5. The benefit of hormonal therapy does not depend on progesterone receptor status.
6. The usual duration for hormonal therapy is 5 years but can be extended up to 10 years in high-risk individuals.
7. Hormonal therapy's benefit for reduction of mortality extends out to at least 15 years.
8. SERMs and AIs reduce the development of tumors in the opposite breast by at least one-third.
9. Extra mortality caused using adjuvant therapy is minimal.<sup>27,28,32</sup>

### Mortality

As noted previously, mortality clearly varies with the three major prognostic factors:

1. lymph node status
2. tumor size
3. histologic grade.

The individual effect of each of these on survival can be seen in Figures 1-3.<sup>29,30,35</sup>

Survival in someone with a history of a small (<1.0 cm), node-negative, well-differentiated tumor is very good and can approach that of the normal population in older females.<sup>36</sup> As lesions get larger, more undifferentiated, or especially if they develop lymph node metastasis, the mortality risk increases steadily. Thus, there is a continuum of risk from small, well-differentiated tumors with no positive lymph nodes to the highest risk in large, poorly-differentiated tumors with an increased number of positive lymph nodes.<sup>29</sup> (*Figure 4*)

The mortality risk associated with breast cancer can extend out to many years after the original diagnosis. Older studies have demonstrated reduced relative survival for up to 40 years after diagnosis. Most of this excess mortality had been due to deaths related to breast cancer itself. However, some of that increase in risk is related to other malignancies and cardiovascular disease associated with older radiation techniques. With earlier diagnosis and more modern treatment techniques, especially the use of adjuvant therapy, the long-term survival has steadily improved over time. Nevertheless, mortality remains substantial in many risk groups.<sup>31,32,33,40,41</sup>

The recurrence pattern with breast cancer varies by the underlying stage and grade of the tumor. Most recurrences in higher stage and grade tumors occur within the first few years after diagnosis; consequently, the highest mortality rates are in the first five years. The recurrence, and mortality, risk with smaller and lower grade tumors is much less, but nevertheless, can extend for many years. The rate of recurrence remains elevated, and fairly consistent, even 10-20 years out, and mortality from the disease has been observed 20 years or more after diagnosis.<sup>32,34,42</sup> This long-term pattern of recurrence and mortality risk is illustrated in *Table 1* and *Figure 5*.

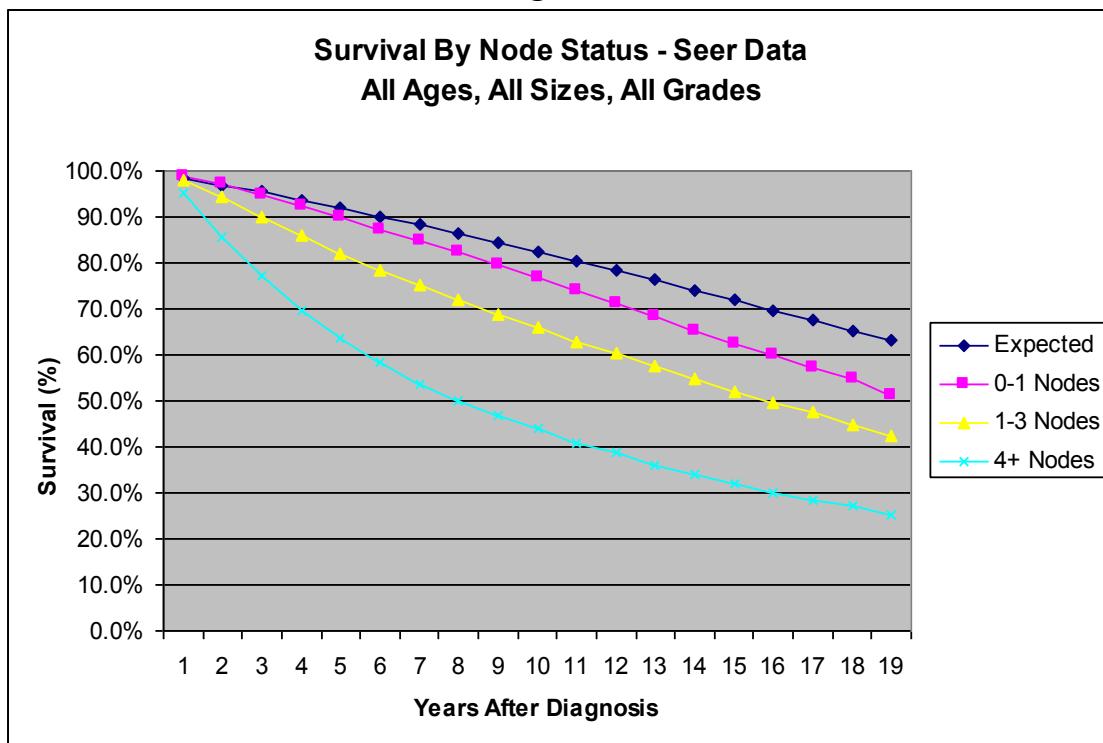
Larger and poorly-differentiated tumors tend to recur more rapidly after diagnosis and consequently have higher short-term mortality. However, for those who survive the first 10 years,

the outlook begins to approach that for lower grade lesions (*Figure 6*). Individuals with metastatic disease still show increased mortality out to 25 years or more after diagnosis (*Figure 7*).

As noted previously, the chance for developing a second primary tumor is increased in individuals who have had a diagnosis of breast cancer. Unlike the risk of recurrence, this risk is constant over time, at approximately 0.3% per year in those not known to harbor a genetic predisposition. Regular surveillance, generally with mammography, is therefore strongly indicated.<sup>34,37</sup>

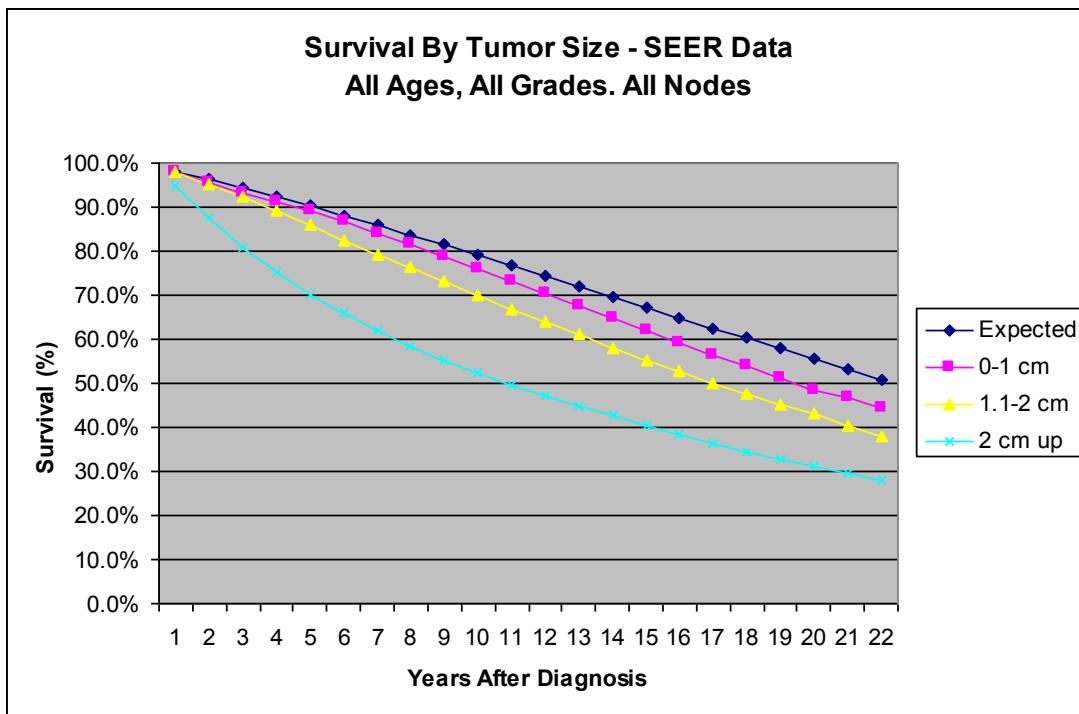
Survival patterns by stage in males are comparable to those for females. However, because the disease is less common in males, the index of clinical suspicion is lower and diagnosis is often delayed. Overall, males tend to do worse with the disease primarily because the cancer is further advanced by the time it is diagnosed.<sup>43</sup>

**Figure 1.**



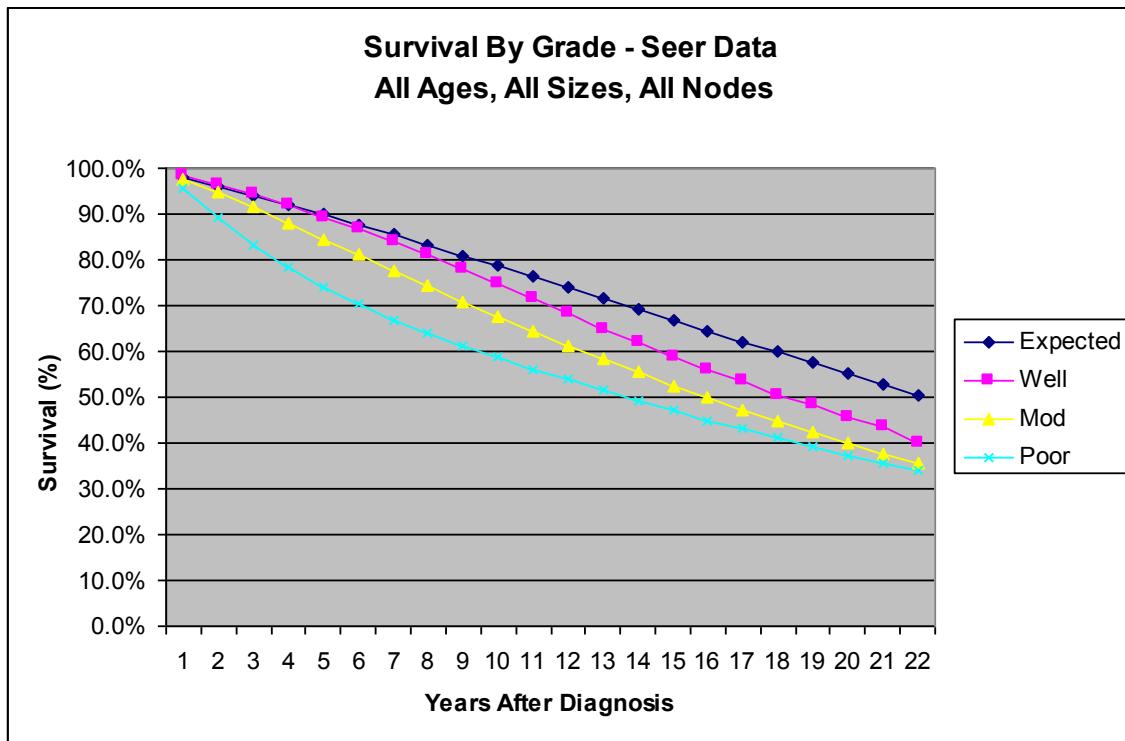
Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2006). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released April 2008. Based on the November 2007 submission.

**Figure 2.**



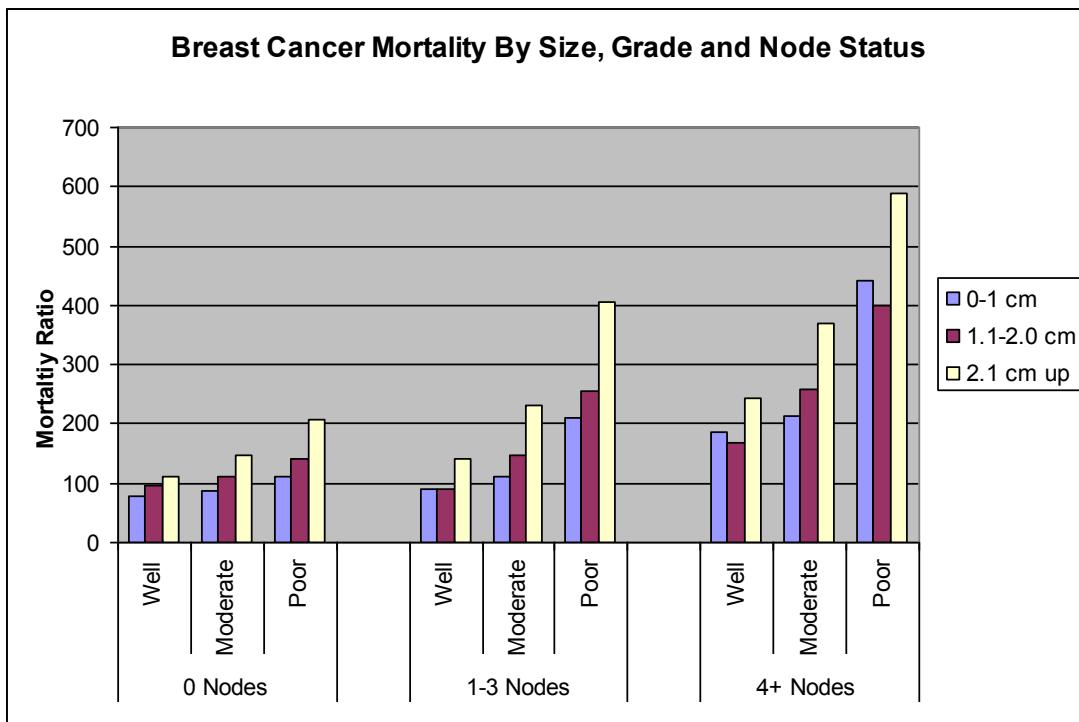
Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2006). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released April 2008. Based on the November 2007 submission.

**Figure 3.**



Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2006). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released April 2008. Based on the November 2007 submission.

**Figure 4.**

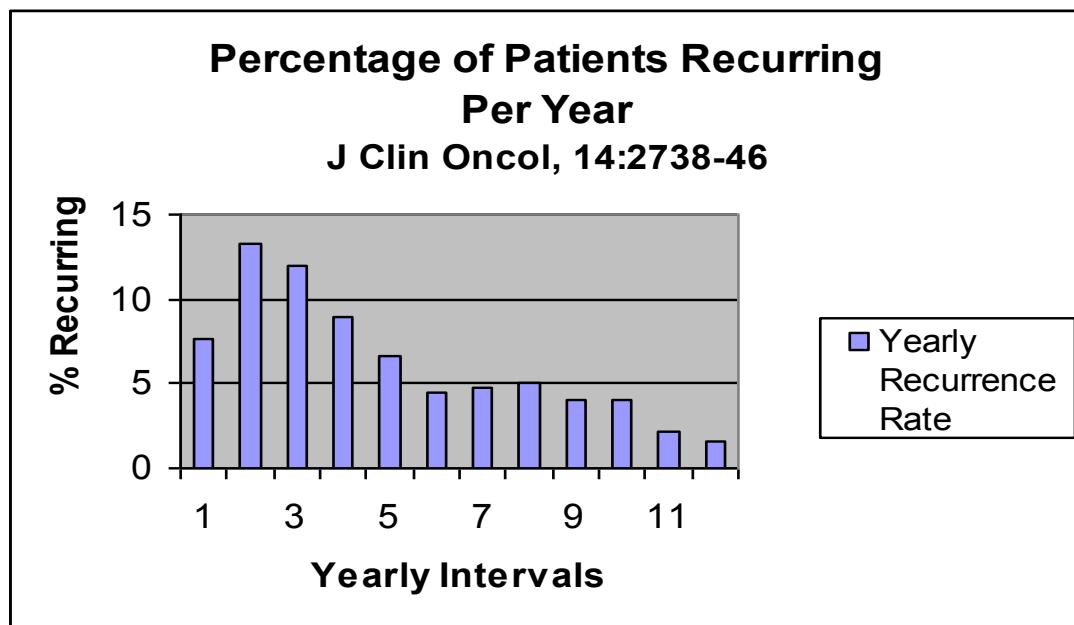


Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2006). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released April 2008. Based on the November 2007 submission.

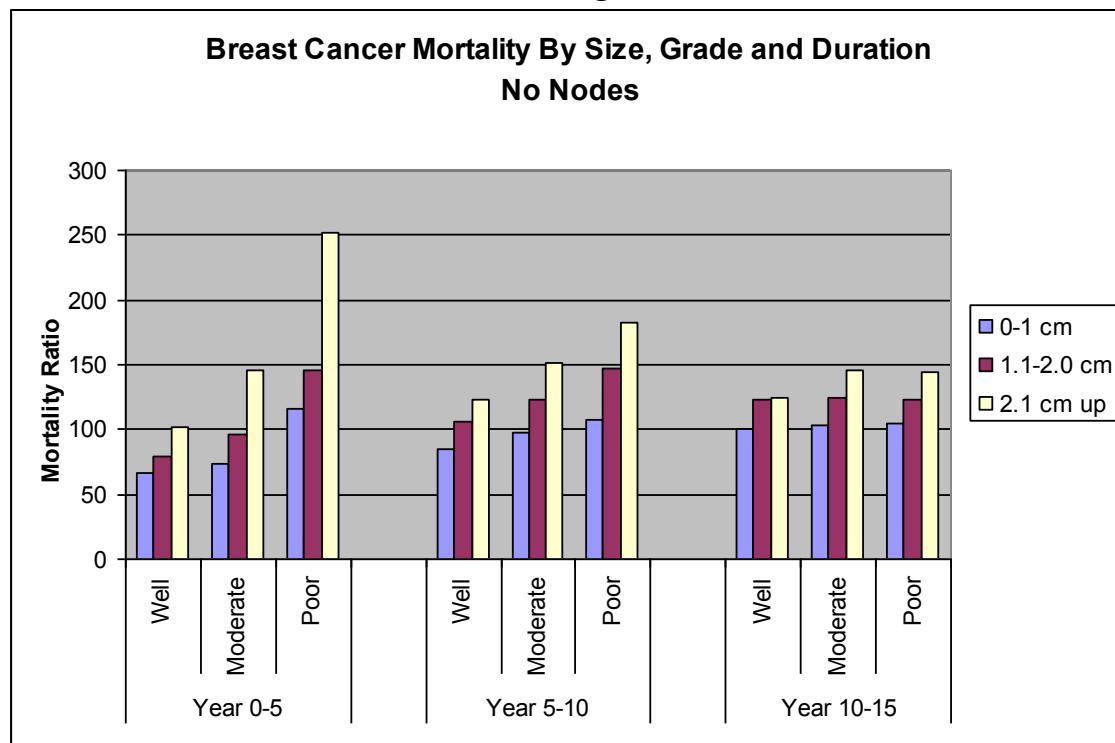
**Table 1.**

20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years										
	Nodal Involvement			Tumor Size (N0 only)			Tumor Grade (T1N0 only)			
Annual Rate of Distant Recurrence	N0 (0+ nodes)	pN1 (1-3+ nodes)	pN2 (4-9+ nodes)	T1a, T1b ( $\leq 1.0\text{cm}$ )	T1c ( $>1.0\text{-}2.0\text{cm}$ )	T2 ( $2.1\text{-}3.0\text{cm}$ )	T2 ( $3.1\text{-}5.0\text{cm}$ )	I (Low)	II (Moderate)	III (High)
5 to <10 yrs	1.0%	1.9%	3.9%	0.5%	0.8%	1.5%	1.7%	0.4%	0.7%	0.9%
10-20 yrs	1.1%	1.7%	2.8%	0.8%	1.1%	1.4%	1.4%	0.8%	1.0%	1.5%

**Figure 5.**

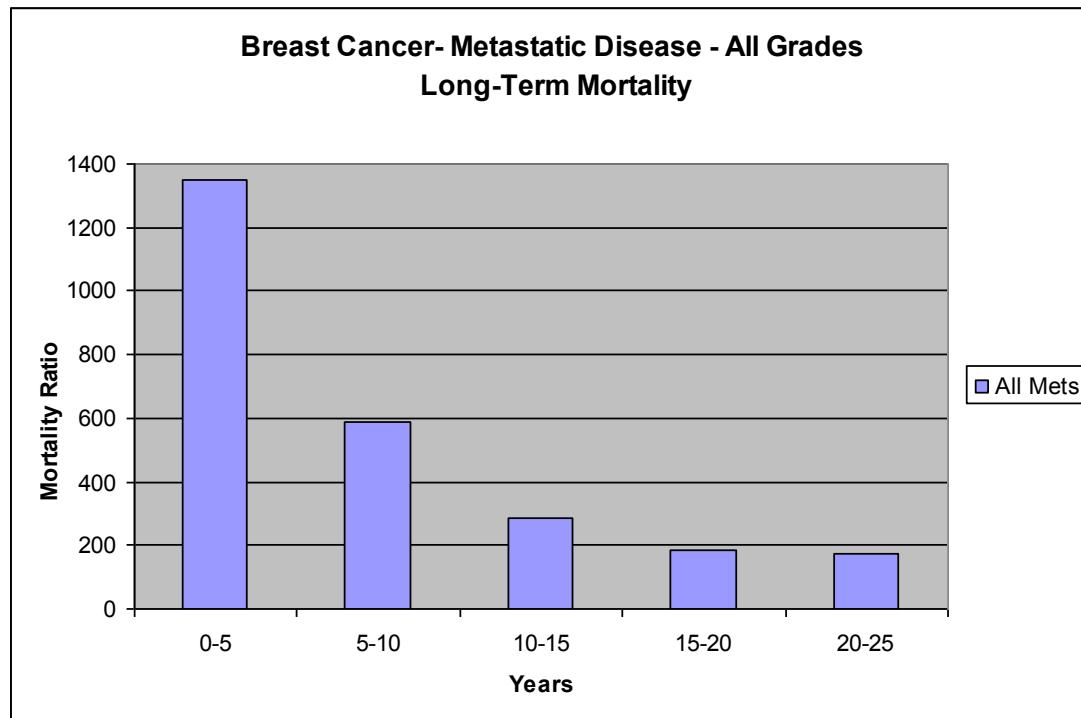


**Figure 6.**



Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2006). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released April 2008. Based on the November 2007 submission.

**Figure 7.**



Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2006). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released April 2008. Based on the November 2007 submission

## Section D

### Colon Cancer

#### Epidemiology

It is estimated that there will be 145,600 newly diagnosed cases and 51,020 deaths from colon and rectal cancer in 2019. Colorectal cancer (CRC) is the third most common cancer in the U.S. for both males and females and the third leading cause of death from malignancy for both sexes. Incidence rates for colorectal cancer have decreased in recent years from 62.8 cases per 100,000 in 1982 to 38.5 per 100,000 in 2012. The estimated probability of being diagnosed with colorectal cancer is now about 1:21 in the United States. Death rates have also decreased from 27.2 in 1982 to 14.7 per 100,000 in 2012. Increased screening, lower smoking rates, and improvements in diet are thought to be the major reasons for the decreased death rate.

Incidence rates for colorectal cancer increase with age. For the years 2008-2012, the incidence rate for colon and rectal cancer varied from 17.1 at ages 40-44, to 96.4 at ages 60-64, to 311.9 per 100,000 for ages 85 and up. Despite this age differential and the overall decrease in incidence, CRC incidence rates among adults aged <50 years increased by 22% from 2000 to 2013 and the death rate increased by 13%. The reasons for this are not entirely clear, but are felt to be due to the lack of general screening in this group and increases in obesity. The incidence and mortality rates are 30% and 40% higher in males than in females, respectively, although the lifetime risk of disease is similar (4.6% vs 4.2%) because females have longer life expectancy. Worldwide, the incidence of colorectal cancer is much higher in industrialized countries. This is attributed to differences in diet, with higher fat and less fiber consumption in the more developed areas.<sup>1,2,3,4</sup>

#### Risk Factors

About 80% of colon cancer cases are sporadic, i.e., not related to known hereditary mutations. As noted above, age is clearly a risk factor, but individuals with a younger age of onset tend to have more aggressive disease while those who are older at diagnosis tend to present at earlier stages.

Aside from the known hereditary syndromes (see below), a family history of colon cancer over age 50 in a first-degree relative increases the risk two- to three-fold. The risk increases further with a greater number of relatives affected and with an earlier age of onset in those individuals. For example, a history of colon cancer under age 45 in a single first-degree relative or disease occurrence in two first degree relatives confers a three- to six-fold risk.

Risk appears to increase with diets high in dietary fat and low in fiber. This is thought to be one of the major contributing factors to the clear geographic variation in the incidence of the disease. Weight gain is also thought to play a part in increasing risk. Individuals who are physically active have a lower risk.

Inflammatory bowel disease, including both ulcerative colitis and Crohn's disease, is a recognized risk factor for the development of colorectal cancer. An earlier age of onset and a

greater extent of inflammatory bowel disease magnify the risk. Because of this elevated cancer risk, regular surveillance is recommended in these diseases.

Some studies have shown an association of smoking and excess alcohol consumption with colorectal cancer.

Other studies have indicated a possibly reduced risk with regular use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and calcium through their effect of lowering the frequency of recurrent and advanced adenomas.<sup>1,3,5,6,7,8,9</sup>

### Etiology

About 65% of colorectal cancers arise from typical colonic polyps. About 35% arise from sessile (flat) and so-called serrated adenomas. For the most part, the development of colorectal cancer follows a logical pattern of sequential genetic mutations that transform the normal colonic mucosa into invasive cancer. The first mutation in the sequence leads to the formation of adenomatous polyps. Subsequent mutations lead to the formation of frank carcinoma. Finally, mutations in yet other genes permit the tumor to metastasize.<sup>3,8</sup>

The risk of cancer development in colonic polyps varies with the size of the lesions. Polyps less than 5 mm in size are considered diminutive and carry a negligible risk of malignancy. Growths with a diameter of 5-10 mm are considered small, and those more than 10 mm are considered large. The risk of cancer increases as the size of the polyp increases. For polyps greater than 20 mm (2.0 cm) the risk for the development of cancer approaches 50% over time.

Polyps can be hyperplastic or adenomatous. Hyperplastic polyps are generally small and do not carry a significant risk for the development of cancer, unless large in number. Among adenomatous polyps, the risk of cancer varies with the type of polyp:

1. Tubular adenomas (83%) are, by far, the most common variety and have the lowest risk of malignant transformation (4%).
2. Tubulovillous adenomas comprise only 12% of the lesions but carry four times the risk for tumor development than do tubular adenomas.
3. For villous adenomas (5%), the risk is five times higher.

About one-third of colonic polyps and about one-half of cancers develop proximal to the splenic flexure. In general, it takes about 10-15 years from polyp development to the onset of carcinoma. However, the development time varies depending on the location of the polyp in the colon and is generally more rapid in proximal lesions. In addition polyp development, and consequently cancer formation, tends to be a multicentric disease. The occurrence of multiple lesions simultaneously is a common phenomenon.<sup>5</sup>

## Inherited Colon Cancer Syndromes

About 10% of colon cancers occur as part of hereditary syndromes with a clear-cut genetic predisposition. These syndromes include conditions with and without an increase in the number of polyps. Those with an increase in the number of polyps include the familial adenomatous polyposis syndrome (FAP), juvenile polyposis, Gardner's syndrome, Turcot's syndrome, Cowden syndrome, and Peutz-Jeghers syndrome. The most important hereditary condition without a dramatic increase in the number of polyps is hereditary nonpolyposis colon cancer (HNPCC).

FAP is an autosomal dominant condition (i.e., if the individual has the gene, he has the disease) associated with a mutation in the APC gene on chromosome 5. It leads to the formation of hundreds to thousands of polyps throughout the colon. The development of cancer is inevitable, with an average age of diagnosis in the range of 35-43 years (95% by age 50). These individuals also develop a variety of extracolonic polyps or adenomas in the small intestine and stomach. Other types of growths in the skin, bone, and other areas are also possible. In addition to colorectal cancer, extracolonic malignancies can develop as well. The lifetime risk of gastric cancer is 1% and that for duodenal cancer is 4-12%.

HNPCC, also called the Lynch syndrome, is an autosomal dominant disorder that accounts for about 3-5% of colorectal cancers. Individuals with this condition have about a 70-80% lifetime risk of developing colorectal cancer. Cancer tends to occur at an earlier age (mean age 44) and multiple tumors are common. The precursor lesion is an adenoma that is flat, rather than polypoid, which tends to occur proximally. Individuals with this syndrome are at risk for a variety of other malignancies as well, especially endometrial and ovarian cancer (39% and 9% risk by age 70, respectively).<sup>3,5,6,9,10,11</sup>

## Screening and Diagnosis

Screening for colon cancer is based on the natural history of the disease and is aimed at identifying and removing colonic polyps in their premalignant phase. A number of screening options are available including stool-based testing, flexible sigmoidoscopy, colonoscopy, computed tomography colonography (CTC), and capsule colonoscopy. Recommendations for screening depend on level of risk and the availability, and acceptability, of the various options. Digital rectal examination (DRE) and barium enema are no longer advised due to lack of efficacy and the availability of better options.

Stool-based tests include guaiac-based fecal occult blood testing (gFOBT), fecal immunochemical test (FIT), and FIT-DNA. Though gFOBT has been shown to reduce mortality from colorectal cancer by 15-30%, it is limited by low specificity (only 5-10% of individuals with a positive test have a cancer) and low sensitivity (under optimal conditions, only about 85% of cancers and, at best, 50% of adenomas are detected by gFOBT). FIT or FIT-DNA are preferred choices, when feasible, due to higher sensitivity for adenomas and early stage cancers.

Flexible sigmoidoscopy is effective at detecting both polyps and cancer as well as reducing mortality, but has limited sensitivity due to its ability to visualize only the distal colon. It is generally used in conjunction with FIT.

Colonoscopy is considered the gold standard for colorectal screening. It is a highly specific test that permits direct visualization of the entire colon, removal of polyps, and biopsy of suspicious lesions. Visualization of the entire colon is especially important if a cancer is found because a synchronous lesion in another part of the colon is found in up to 5% of these cases. In addition, the ability to remove premalignant polyps avoids the subsequent development of invasive lesions and is considered preventive.<sup>3,6,7</sup>

CT colonography is nearly as sensitive as colonoscopy, and though it requires a similar bowel prep, it does not require sedation and does not risk bowel perforation if findings are negative. It is also useful in detecting lesions in individuals in whom a conventional colonoscopy cannot fully visualize the colon. However, there are major disadvantages including significant radiation exposure, the inability to biopsy or remove polyps or other suspicious lesions, and that incidental extracolonic findings often trigger further evaluation with little evidence of benefit.<sup>7,12</sup>

Capsule colonoscopy is a newer technology where the patient swallows a double-ended capsule containing a tiny wireless video device that views the colon during the device's transit. The procedure requires no sedation and does require a bowel preparation preceding the capsule's ingestion. Like CT colonography, colonic capsule endoscopy does not allow for biopsy or polyp removal. Its sensitivity and specificity appears to be less than colonography but better than FIT.

Diagnosis depends on biopsy confirmation of the presence of cancer. This is accomplished primarily at the time of colonoscopy. However, occasionally an open surgical procedure is required.<sup>6</sup>

### Clinical Presentation

Colon cancer can present as exophytic (growth extending into the lumen) or polypoid lesions, ulcerative masses, annular lesions (encircling the colon), or as infiltrative tumors extending over a length of bowel wall:

1. Polypoid lesions tend to present more commonly in the cecum and often manifest as occult bleeding with the development of iron deficiency anemia.
2. Cancers of the transverse colon can present with occult bleeding or obstruction of the bowel.
3. Tumors of the left side or descending colon and rectum are more likely to present with gross blood in the stool or symptoms related to obstruction, such as a change in bowel habits.

In general, tumors that present with symptoms are more likely to be advanced and carry a higher mortality risk. Avoiding these clinical presentation scenarios is the purpose of asymptomatic screening programs.<sup>6,9,13</sup>

## Pathology

Most colorectal cancers are adenocarcinomas and vary in their degree of differentiation or resemblance to normal tissue. These cancers are designated as well-differentiated, moderately-differentiated, poorly-differentiated, or undifferentiated or anaplastic, depending on how deranged the cells appear and the degree of gland development. Two specific subtypes of colon cancer are designated mucinous carcinomas and signet cell carcinomas and are considered variants of undifferentiated tumors.

Items of greatest importance on the pathology report are:

1. the extent of invasion of the bowel wall
2. the degree of differentiation
3. the presence of lymph node involvement.<sup>6,13</sup>

## Staging

The current staging of colon cancer uses the TNM system and looks at three key elements: the extent of the local tumor, the presence of lymph node metastasis, and the presence of distant metastasis:

1. The T system details the extent of the local tumor:
  - Tis -- carcinoma in situ, intramucosal carcinoma with no extension through muscularis mucosae
  - T1 -- invasion of the submucosa
  - T2 -- invasion of the muscularis propria
  - T3 -- invasion through the bowel wall into pericolorectal tissues
  - T4 -- direct invasion of other organs or structures either as T4a (tumor penetrates to the surface of the visceral peritoneum) or T4b (tumor directly invades or adheres to adjacent organs or structures).
2. Lymph node metastasis is characterized by:
  - N0 -- no node invasion
  - N1 -- 1-3 nodes positive, with N1a being one node positive, N1b with two or three nodes positive, and N1c without positive nodes but with tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic tissues
  - N2 -- 4 or more nodes positive for malignant cells (N2a indicates 4-6 nodes and N2b indicates 7 or more nodes)
  - In assessing nodal metastases, it is important to note that nodal micrometastases (tumor clusters >0.2 mm in diameter) are specifically designated as positive, while isolated tumor cells are not counted.
3. Distant metastases are absent (M0) or present (M1). The latter is further divided into M1a M1b, and M1c.<sup>13</sup>

The staging system for colorectal cancer combines the TNM elements into groupings that are associated with different degrees of risk (discussed below):

1. Stage 0 – TisN0M0
2. Stage I – T1N0M0  
T2N0M0
3. Stage IIA – T3N0M0
4. Stage IIB – T4aN0M0  
Stage IIC – T4bN0M0
5. Stage IIIA – T1N1/N1cM0  
T2N1/N1cM0  
T1N2aM0
6. Stage IIIB – T3N1/N1cM0  
T4aN1/N1cM0  
T2/3N2aM0  
T1/2N2bM0
7. Stage IIIC – T4aN2aM0  
T3/4aN2bM0  
T4bN1/2M0  
T1/2N2bM0
8. Stage IVA – Any T Any N M1a  
Stage IVB – Any T Any N M1b  
Stage IVB – Any T Any N M1c. **Error! Bookmark not defined.**

### Prognostic Factors

Besides the above noted indicators, there are a number of other prognostic factors of importance in colorectal cancer. The markers that suggest a worse outcome include:

1. poorly-differentiated or undifferentiated lesion
2. tumors with an abnormal DNA content
3. gross tumor perforation of the bowel wall
4. direct invasion of adjacent organs
5. lymphovascular and perineural invasion
6. high preoperative carcinoembryonic antigen (CEA) level (discussed below)
7. low total number of lymph nodes in the surgical specimen
8. infiltrating pattern of growth at the tumor border
9. KRAS, NRAS, and BRAF gene mutations.

Genetic factors also come into play in assessing the prognosis of colon cancers. Microsatellite instability refers to mutations within repetitive DNA sequences throughout the genome. Tumors with such instability (about 15%) tend to occur in the right colon and to have a better prognosis. On the other hand, tumors without this finding (85%) are more likely to be left-sided and carry a worse prognosis. Besides the verified adverse KRAS, NRAS, and BRAF activating mutations, a wide variety of other molecular markers have been studied in CRC and may prove to have some clinical applicability. Using this knowledge and information on the variety of genes mutated in colon cancer, DNA microarray analysis or genetic profiling of individual tumors can now be carried out using commercially available tests. These tests, while having prognostic significance,

have not been clearly found to impact clinical decision and as of 2019, none of those currently available (Oncotype Dx, GeneFx colon, ColoPrint, COlonPRS, and OncoDefender-CRC) are FDA approved.

Surprisingly, one factor that is not of importance prognostically, after taking other factors into account, is the size of the primary lesion.<sup>6,9,13,14,14,15,16,17,18</sup>

### Treatment

The only curative therapy for colorectal cancer is complete surgical removal of the tumor. In general, surgery requires removal of the primary lesion and all of the draining lymphatic areas. In essence, this means a hemicolectomy for colonic tumors and a permanent diverting colostomy for low rectal cancers. Chemotherapy and radiation treatment, used as adjuvant therapy, can eradicate micrometastasis and increase cure rates in individuals who have been treated primarily with surgery. In individuals with metastatic disease, chemotherapy alone is not curative but may be able to extend survival from a mean of six months to the 30-month range.

For colon polyps with malignant changes, a complete resection should be performed and is usually achieved by colonoscopy. However, in situations where unfavorable factors such as high-grade differentiation, lymphatic or venous invasion, infiltration into the submucosa below the polyp, presence of invasive cancer in a sessile polyp or involved margins of excision are present, surgical removal may be necessary.

The choice of therapy for an individual with invasive colorectal cancer depends on the stage at presentation:

1. Stage I tumors represent 15% of the lesions and are treated with surgery alone.
2. Stage II cancers represent 20-30% of all tumors and are also treated primarily with surgery. Use of adjuvant chemotherapy for higher risk stage II colonic lesions is theoretically of value. However, studies have shown mixed results, and the approach is still considered controversial. Nevertheless, adjuvant chemotherapy is commonly used for high risk stage II rectal cancers. Indicators of high risk include poor differentiation, vascular, lymphatic, or perineural invasion, tumor presentation with obstruction or perforation, T4 stage, or fewer than 12 lymph nodes sampled at the time of surgery.
3. Cancers that present in stage III already have significant local extension and adjuvant chemotherapy with several agents is generally advised. A six-month course of oxaliplatin-containing chemotherapy is recommended for most patients, in combination with either fluorouracil plus leucovorin (FOLFOX), or capecitabine (CAPOX). These regimens have been shown to yield a roughly 30% reduction in recurrence and mortality rates,
4. For stage IV cancers, the standard treatment is chemotherapy. Recently, biologic agents with monoclonal antibodies have been used with some improved response. Surgery can be employed with palliative or symptomatic, but only rarely curative, intent (e.g., bowel obstruction, perforation, bleeding). In cases where there is limited liver or lung metastatic disease, metastasis resection can lead to long-term survival in about 50% and possible cure in up to 20%.<sup>6,9,13,19,20,21,22</sup>

Carcinoembryonic antigen (CEA) is a protein typically found in the fetal or development period, but it can also be detected in the blood of individuals with colorectal cancer. While elevations are associated with colorectal cancer, the antigen is not specific for the disease, and increased levels can be found in a number of other settings, for example, in the presence of other tumors such as breast cancer, in 19% of smokers, and in 3% of normal individuals. Elevations prior to surgery are a poor prognostic indicator and are a marker for a higher risk of recurrence. If levels are abnormal before treatment, they should return to the normal range in four to six weeks after curative surgery. Failure to do so indicates persistent disease. In addition, if levels return to the normal range and then increase again, it is a powerful indicator for the presence of metastasis. Despite this fact, the CEA level has not been found helpful in choosing appropriate candidates for adjuvant therapy.<sup>6</sup>

Late recurrences in colorectal cancer are not common. Most recurrences, 80-90%, are found within the first two to three years after initial treatment. Only 5% occur more than five years after surgery. About 15% of recurrences are local and 36% are located in the liver.<sup>6,23</sup>

Because treatment is available for recurrent disease, a rigorous follow-up regimen is recommended for individuals treated for colorectal cancer with curative intent. This regimen includes regular physician visits and CEA testing every three months for two years, then every six months for an additional three years. Colonoscopy is generally done at one year postoperatively and then every three to five years. If the entire colon could not be visualized preoperatively (e.g., because of obstruction, perforation), the procedure is usually repeated relatively soon after surgery to exclude the presence of polyps or simultaneous cancers in another portion of the bowel.<sup>6</sup>

### Mortality Risk

The major risk factors for mortality are the extent of disease locally, the grade of the tumor, and the presence of lymph node metastasis. The effect of each of these for colon cancer is summarized using data from the Surveillance, Epidemiology, and End Results (SEER) database, in Figures 1-4. The most important of these are extension of the tumor through the bowel wall and into adjacent structures and the presence of lymph node metastasis. These indicate spread of tumor cells beyond the local area of origin. Of note, the mortality risk between well- and moderately-differentiated lesions is fairly small. However, the survival with poorly-differentiated tumors is considerably worse.<sup>24</sup>

The degree of mortality risk in colon cancer is represented well by the current staging system, which combines the effects of local tumor extent and presence of cancer cells in other sites. The overall pattern of mortality by stage for colon cancer can be seen in Table 1 and Figures 5 and 6.<sup>24</sup> Interestingly, it has been consistently found that stage IIB and IIC tumors (those with more advanced T stage but no nodal involvement) fare worse than those with stage IIIA tumors (one to three positive nodes but a lower T stage). This is reflected in the survival data in Table 1.

The highest mortality risk for colon cancer is in the first five years after diagnosis. Unlike breast cancer, prostate cancer, and malignant melanoma, late recurrence of disease with colon cancer is unusual. As noted above, only 5% occur more than five years after surgery. The result is that, after surviving 10 years or more after diagnosis without evidence of recurrent disease, all

individuals have about the same minimal risk of mortality going forward, regardless of their stage at presentation. This pattern can be seen recurrently in Figures 1-6. The difference between groups is the percentage of patients in each stage who actually reach that 10-year survival point. For moderately-differentiated tumors and all ages combined, those 10-year survival percentages are 53.1% for stage I, 42.7% for stage II, 33.1% for stage III, and 3.5% for stage IV.<sup>6,24</sup> This dramatic fall off in survival is the reason for the aggressive screening programs employed for diagnosing early colon cancer and its precursor lesion, the colonic polyp.

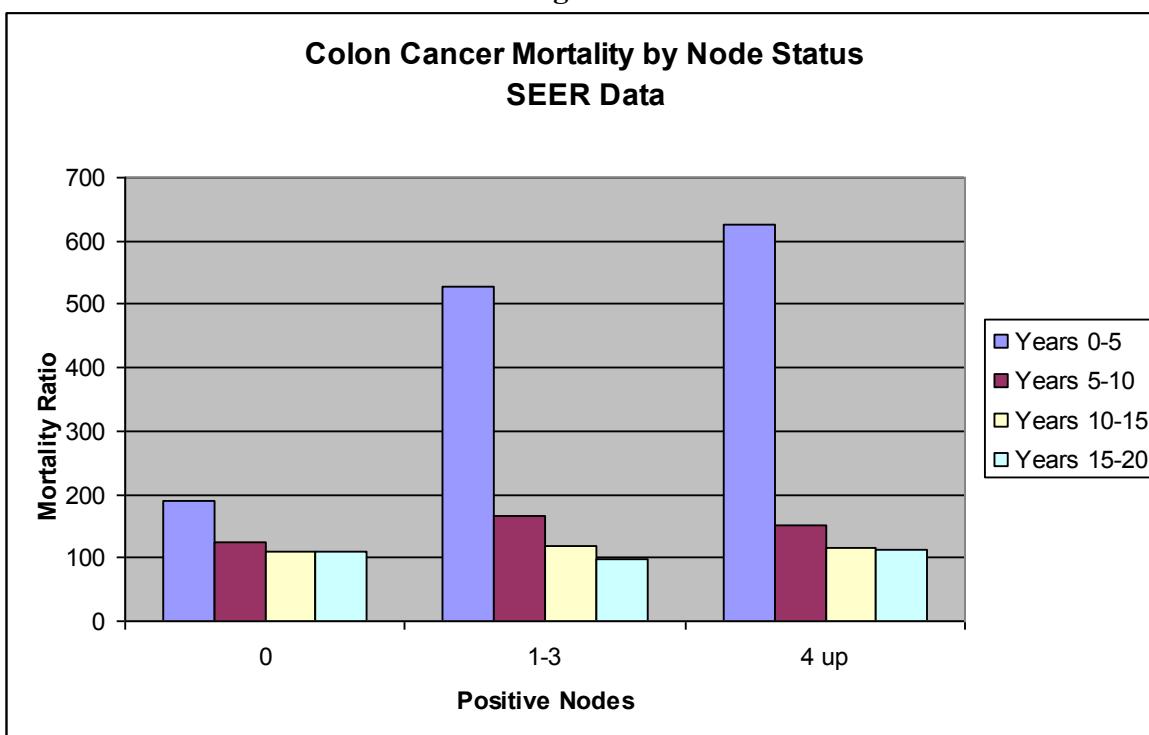
However, while the overall long-term survival for stage IV colon cancer is dismal, as noted above, isolated or limited metastasis can be amenable to surgical resection (hence the reason for new subdivision of stage IV in the new AJCC guidelines). In ideal cases, survival to 10 or more years (and, thus, probable cure) may approach 20%.<sup>6,23</sup>

Table 1  
Adjusted 5-year conditional disease-specific survival by AJCC stage

<b>Stage</b>	<b>At diagnosis</b>	<b>After 2 years</b>	<b>After 5 years</b>
I	94%	96%	98%
IIA	85%	90%	96%
IIB	71%	80%	92%
IIIA	83%	89%	95%
IIIB	64%	74%	89%
IIIC	42%	57%	80%
IV	5%	15%	48%

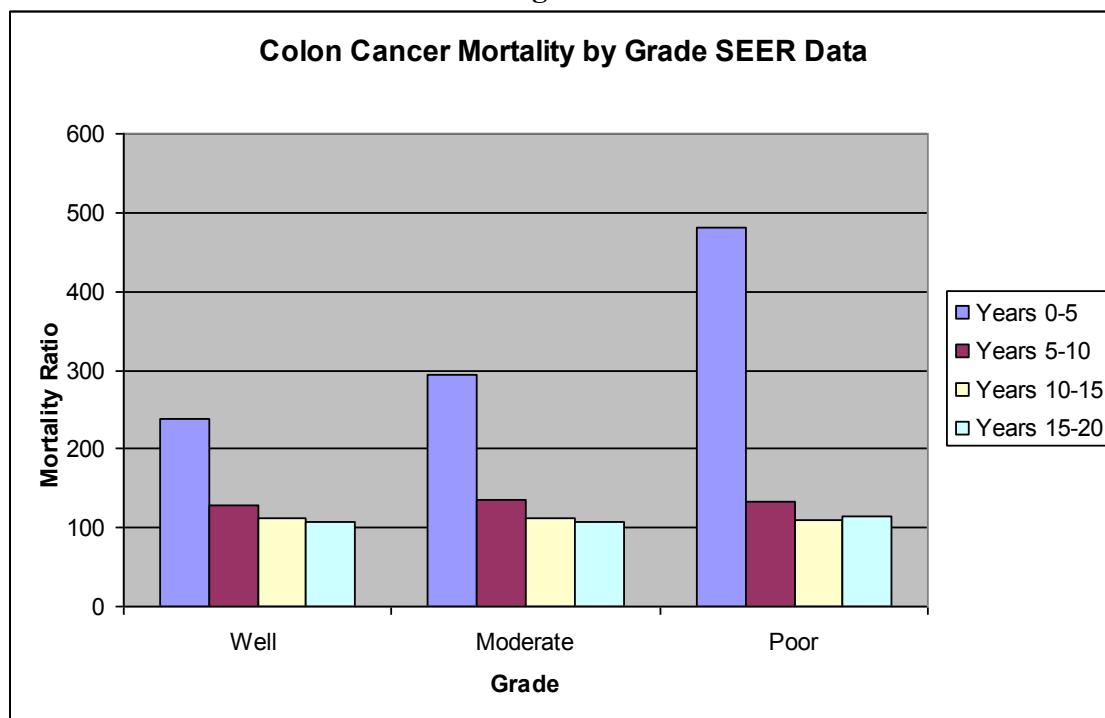
Data from the SEER17 registry. Adapted from Chang GJ, Hu CY, Eng C, et al. J Clin Oncol 2009; 27:5938.

**Figure 1.**



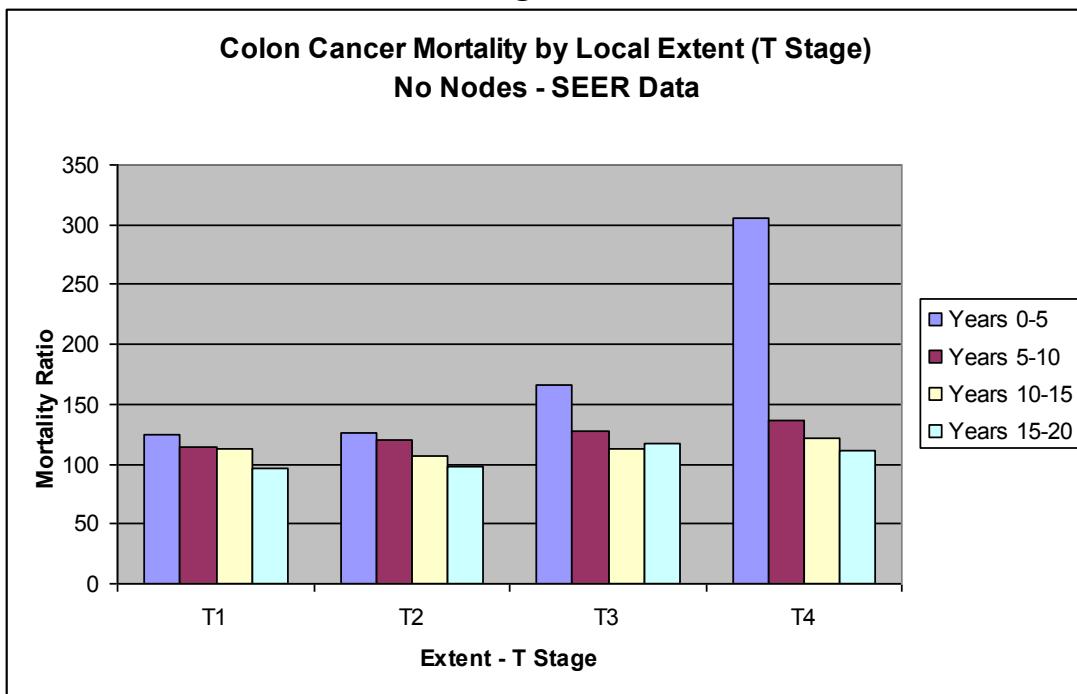
Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.

**Figure 2.**



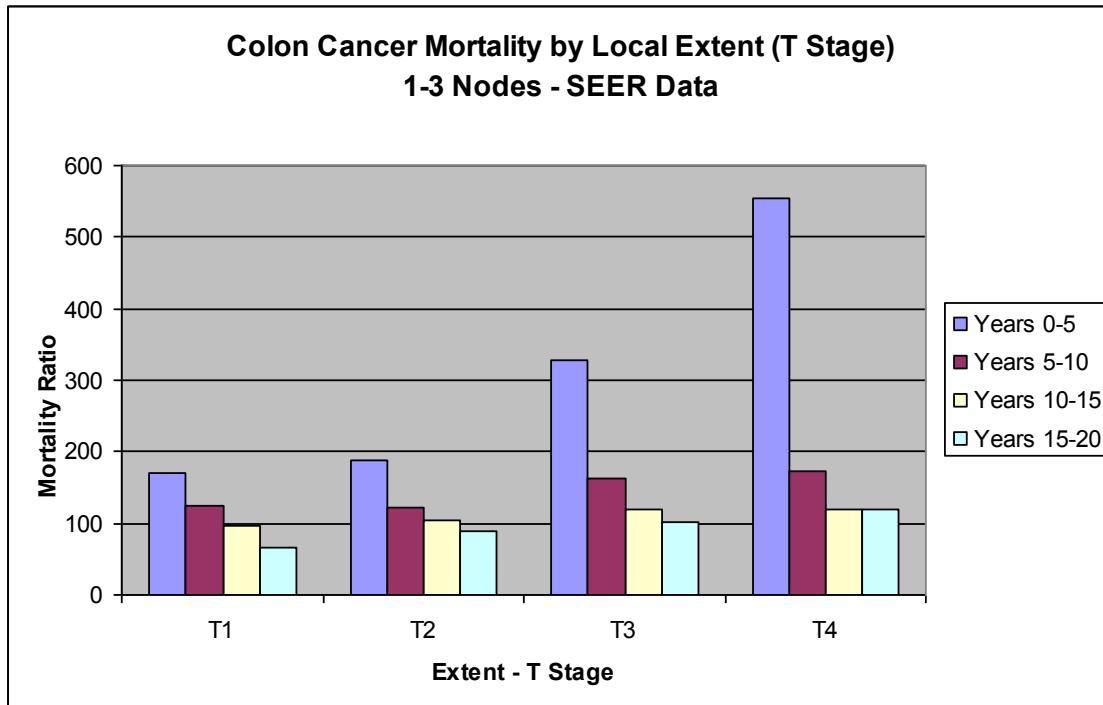
Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.

**Figure 3.**



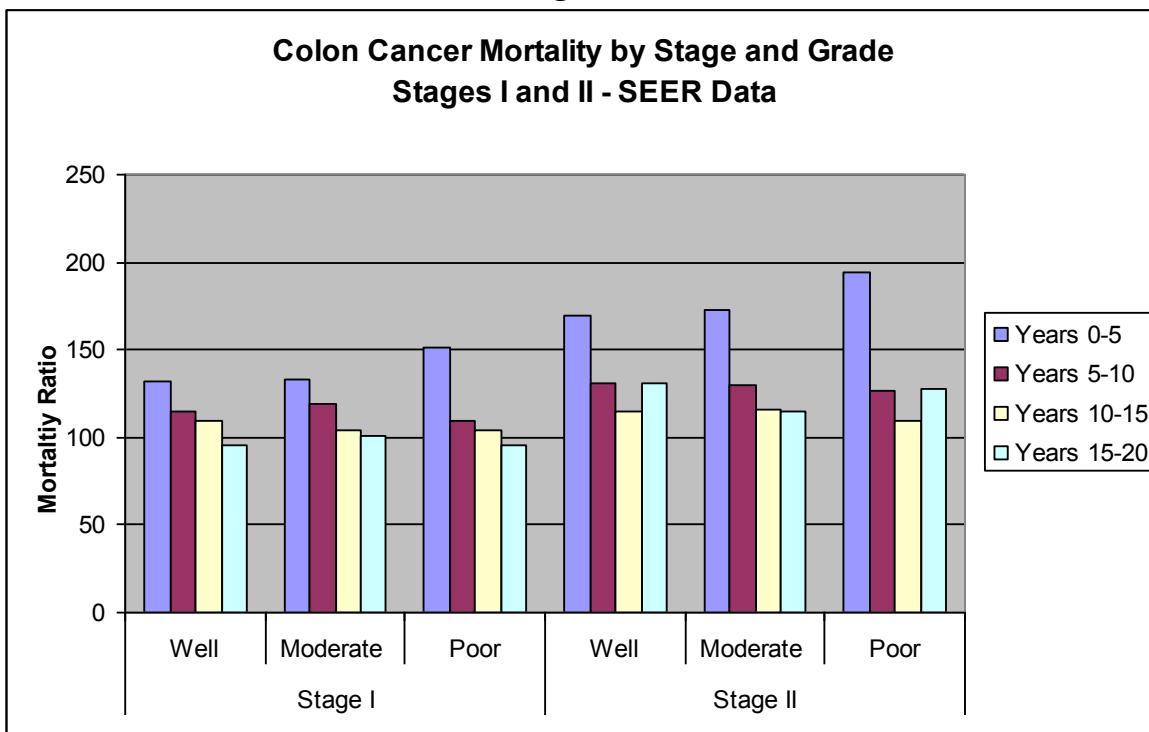
Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.

**Figure 4.**



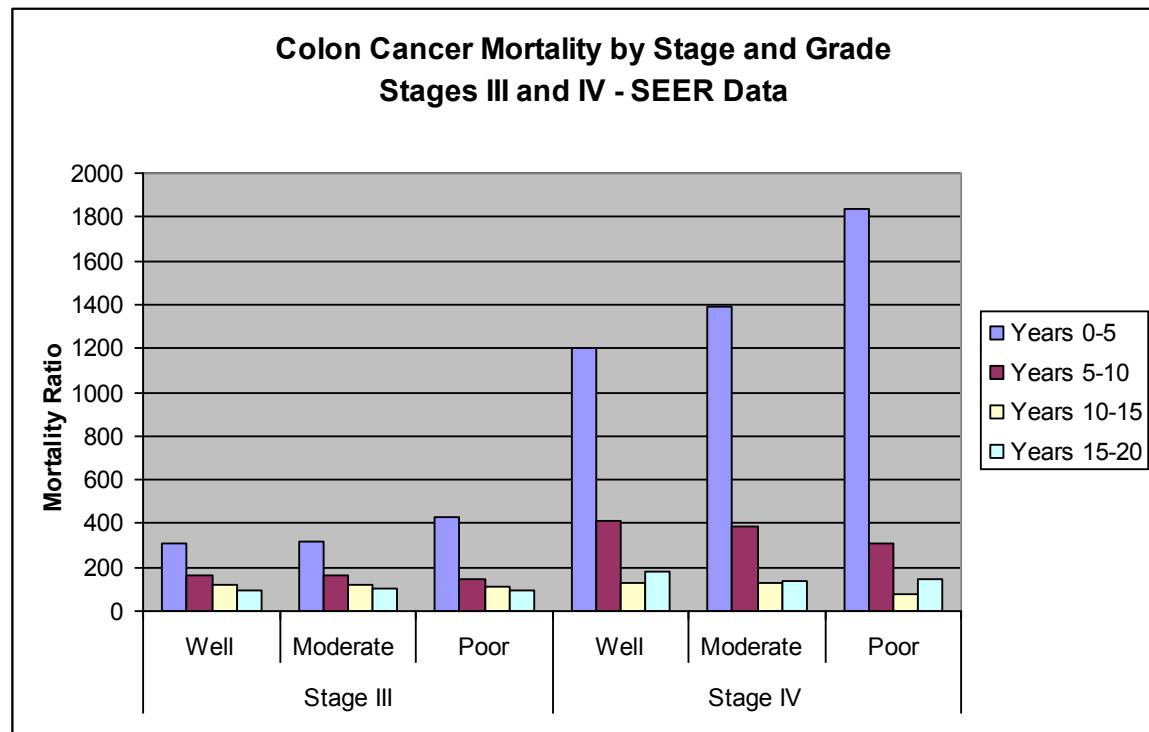
Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.

**Figure 5.**



Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.

**Figure 6.**



Adapted from the Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-2008). National Cancer Institute, DCCPS, Surveillance Research Program. Cancer Statistics Branch. Released September 2011. Based on the November 2010 submission.

### **Review Questions – ALU 201, Chapter 3**

1. Prostate specific antigen (PSA) velocity greater than 0.75 ng/ml/per year is highly suggestive of:
  1. malignancy
  2. prostatitis
  3. benign prostatic hypertrophy
  4. proliferative inflammatory atrophy
2. All of the following statements regarding cutaneous malignant melanoma are correct EXCEPT:
  1. It rarely occurs before puberty.
  2. Diagnosis is confirmed by biopsy.
  3. The immune system can cause regression.
  4. Chemotherapy significantly increases survival.
3. Which of the following statements regarding breast cancer in males as compared to females are correct?
  - A. It is often less advanced at the time of diagnosis.
  - B. It is less common in males.
  - C. Survival patterns by stage are similar.

Answer Options:

1. A and B only are correct.
2. A and C only are correct.
3. B and C only are correct.
4. A, B, and C are correct.

4. List the different types of treatment for prostate cancer and provide a short description of each treatment.
5. Describe the different types of colon polyps and their associated risk for colon cancer.

6. The most important prognostic indicator for invasive breast cancer mortality is:
1. distant metastasis
  2. degree of local control
  3. age at diagnosis
  4. tumor size
7. Unfavorable prognostic factors for colorectal cancer include which of the following?
- A. elevated preoperative carcinoembryonic antigen (CEA)
  - B. gross tumor perforation of the bowel wall
  - C. well differentiated tumor
- Answer Options: 1. A only is correct.  
2. A and B only are correct.  
3. A and C only are correct.  
4. A, B, and C are correct.
8. List the most important prognostic indicator for mortality in malignant melanoma as well as at least 2 other prognostic factors.
9. Describe the most important prognostic indicators in prostate cancer.
10. Describe the two different types of in situ breast carcinomas and compare them with the two most common types of invasive breast cancers.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 1: malignancy – page 17.

### *Review Question 2*

Answer 4: Chemotherapy significantly increases survival – page 9.

### *Review Question 3*

Answer 3: B and C only are correct – page 42.

### *Review Question 4*

Refer to pages 22-26.

### *Review Question 5*

Refer to page 48.

### *Review Question 6*

Answer 1: distant metastasis – page 38.

### *Review Question 7*

Answer 2: A and B only are correct – page 52.

### *Review Question 8*

Refer to pages 5-6.

### *Review Question 9*

Refer to page 22.

### *Review Question 10*

Refer to pages 34-35.



## **CHAPTER 4**

### **THE REPRODUCTIVE SYSTEM**

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**Revised 2022**



## **THE REPRODUCTIVE SYSTEM**

As with disorders of the rest of the body, risks presented by the reproductive system range from benign to life threatening. However, since most of the functions of the reproductive system are not critical to an individual's immediate ability to survive, problems with these organs might be ignored, minimized, or go unrecognized. Such disregard can permit a potentially treatable disorder to progress. Underwriters should be familiar with the signs and symptoms of reproductive system disorders and must understand the basics of reproductive health to evaluate them.

### **Male Reproductive Organs**

#### Anatomy

The purpose of the male reproductive organs is to produce sperm and transport them to the female reproductive system. The male reproductive organs become fully functional at puberty and, in the absence of disease, remain functional throughout life. The male reproductive organs are comprised of the:

1. scrotum
2. testes
3. epididymis
4. vas deferens
5. prostate
6. seminal vesicles
7. Cowper's glands
8. urethra
9. penis.

The scrotum is a sac composed of skin, fascia (fibrous tissue), and smooth muscle that surrounds and supports the testes outside the body, where the temperature is optimal for production of spermatozoa. There are two scrotal compartments each containing a single testis. The smooth muscle is the dartos muscle that contracts with cold or sexual stimulation.

The testicles are two oval organs about two inches (1.5-2.0 cm) long. The testicles are also called testes (singular is testis). Before birth, the testicles are located inside the body as they develop. At birth, the testicles descend from the body into the scrotum. They become mature at puberty, at which time they begin to produce viable sperm. Each testicle is divided into lobules. Within these lobules the seminiferous tubules are coiled, and it is here that spermatogenesis (i.e., production of sperm) takes place. Sertoli cells, present in the epithelial lining of the seminiferous tubules, support and nurture maturing spermatozoa. The testicles also contain the interstitial cells of Leydig, which disappear six months after birth only to reappear at the time of puberty. The interstitial cells of Leydig produce androgens (male hormones), particularly testosterone.

There are several ducts that carry the sperm from the seminiferous tubules to the exterior of the body including the following:

1. epididymis – A coiled tube that runs along the posterior side of the testis, it receives sperm from the efferent duct of the seminiferous tubules. It can store sperm for up to six weeks while they mature. During sexual excitation, smooth muscle in the walls contract to propel sperm into the vas deferens.
2. vas deferens – This is a continuation of the epididymis and is a straight tube within the spermatic cord. The spermatic cord not only contains the vas deferens but blood and lymphatic vessels, nerves, and the cremaster muscle. The vas deferens passes upward from the scrotum into the inguinal canal, passes behind the bladder, and connects with the ejaculatory duct.
3. ejaculatory ducts – These are formed by a saccular dilation at the end of the vas deferens and the duct of the seminal vesicle. The ejaculatory tubules penetrate the prostate gland and join with the urethra.
4. urethra – It is a tube that extends from the bladder to the glans penis. It has three parts including the prostatic urethra (receives secretions from the prostate gland), the cavernous urethra (surrounded by erectile tissue), and the membranous urethra (surrounded by the external urethral sphincter).

The male reproductive system also includes several accessory glands that produce fluids that serve to keep sperm viable and carry them from the body. The combination of sperm with the secretions of the accessory ducts is called semen. The accessory ducts include:

1. seminal vesicles – small sacs that are located behind the bladder and empty into the ejaculatory duct—The seminal vesicles secrete an alkaline substance that nourishes and protects sperm. These secretions constitute more than half the volume of semen.
2. prostate gland – located beneath the bladder, surrounding the urethra as it exits the bladder. It also secretes an alkaline substance that increases sperm motility and the ability of sperm to survive in the naturally acidic environment of the female reproductive system.
3. Cowper's (bulbourethral) glands – about the size of a pea—They produce an alkaline, mucous-containing secretion that lubricates, protects, and adds to the bulk of the semen.

The penis serves as an outlet for urine and as a sexual organ. The penis is extensively innervated, has thin skin, and is hairless except at the root. It is composed of three parts including the:

1. root – the point at which the penis extends below the pubis
2. body – formed by three cylindrical masses of erectile tissue—When stimulated, the arterioles dilate allowing more blood to flow into the veins than can drain away, producing an erection. This process is a response of the autonomic nervous system.
3. glans penis – the highly innervated tip of the penis—The proximal edge of the glans penis is the corona. At birth, the glans is surrounded by a loose-fitting fold of skin known as the foreskin or prepuce. Surgical removal of the foreskin is circumcision.

## Hormonal Regulation

Two hormonal systems control the male reproductive system: the testicular hormones and the pituitary/hypothalamic hormones. The principal testicular hormones are testosterone, androstenedione, and dihydrotestosterone. All three are involved in prenatal growth and differentiation of the male genitalia. At puberty and thereafter, testosterone is responsible for male secondary sexual characteristics including:

1. growth and development of male genitalia
2. male pattern hair distribution
3. enlargement of the larynx and lengthening of vocal cords, producing a lower pitch to the voice
4. increased sweat and sebaceous gland activity
5. increased muscle and bone mass, metabolic activity, red blood cell mass, and increased oxygen-carrying capacity.

Gonadotropin releasing hormone (GnRH) is produced by the hypothalamus to stimulate the production of pituitary hormones. Hormones secreted by the pituitary, in response to GnRH, control androgen production and testicular function. Follicle stimulating hormone (FSH) is produced by the pituitary gland and acts on receptors in the seminiferous tubules to produce spermatozoa. Luteinizing hormone (LH), also called interstitial cell stimulating hormone, affects receptors in the interstitial cells of Leydig to produce and secrete testosterone. Increased levels of testosterone act to inhibit the secretion of GnRH and decrease production of FSH and LH.<sup>1</sup>

## **Female Reproductive Organs**

### Anatomy

The purpose of the female reproductive organs is to support conception, growth, and development of a fetus. The female reproductive organs include the:

1. ovaries
2. fallopian tubes
3. uterus
4. cervix
5. vagina
6. external genitalia or vulva (composed of the labia majora and labia minora, urethral and vaginal openings, and the clitoris)
7. breasts.<sup>2</sup>

These organs become functional at puberty. They are sustained and regulated by a complex cycle of hormone and tissue changes that is typically about a month in duration, called the menstrual cycle. The two ovaries are in the pelvic cavity, on either side of the uterus. They are about the size and shape of almonds, are composed of connective tissue called stroma, and are covered by epithelium. The stroma has an outer cortex and an inner medulla. The cortex has ovarian follicles that are the source of oocytes (ova). Oocytes are surrounded by follicular cells to

form primordial follicles. All primordial follicles are present at birth, and one matures each month during ovulation. After puberty, under the control of pituitary gonadotropic hormones (i.e., hypothalamic gonadotropin releasing hormone [GnRH], follicle stimulating hormone [FSH], and luteinizing hormone [LH]), one oocyte continues to maturity and ovulation. The now empty follicle undergoes changes to become the corpus luteum (yellow body). The lutein cells of the corpus luteum produce estrogen and progesterone.

The fallopian tubes or oviducts receive the mature ovum released during ovulation and transport it to the uterus. They are about 4 inches (10 cm) long. The opening in the pelvis is funnel-shaped with finger-like projections, known as fimbriae that “sweep” over the ovary and catch the ova. The walls of the fallopian tubes are composed of longitudinal smooth muscle, connective tissue, and ciliated epithelium that move the ova to the uterus. Fertilization of the ova usually takes place in the fallopian tube.

The uterus is a hollow, muscular organ that is shaped like an upside-down pear. In a non-pregnant female, it is about three inches (7.5 cm) long. It lies in the pelvis between the rectum and the urinary bladder. It is composed of three layers:

1. perimetrium (serosa)
2. myometrium (smooth muscle)
3. endometrium.

The endometrium is comprised of epithelial cells and glands. It undergoes changes during the menstrual cycle and is the site of implantation of a fertilized ovum. There are several distinct parts of the uterus:

1. fundus – round portion that lies above the site of union with the fallopian tubes
2. body – thick-walled central portion
3. cervix – constricted neck that protrudes into the vagina.

These tissues expand during pregnancy and aid birth with a series of contractions that expel the fetus and supporting structures.

The cervix is the narrow neck of the uterus that contains its opening. The cervix has thick muscular walls that extend down into another muscular passage, called the vagina. Normally, the cervix and vagina are very small in diameter; however, they are distensible and expand considerably to accommodate childbirth. The opening of the vagina is shielded by the external genitalia, called the vulva.

The breasts are milk-producing glands located on the front of the chest. Male breasts are undeveloped versions of female breasts. The female breasts begin to enlarge with secretion of hormones during puberty. Each breast is divided into fifteen to twenty irregularly shaped lobes of glandular tissue that produce milk when cued by specific hormones after pregnancy. The glandular tissues, called mammary glands, secrete milk that empties into a system of ducts that combine with larger ducts that end just behind the nipple. The mammary glands are separated by dense connective tissue that supports the glands and attaches them to the chest wall.

## Hormonal Regulation

The principal female hormones are hypothalamic GnRH, pituitary FSH and LH, as well as estrogen and progesterone secreted by the ovaries. Estrogen causes growth of reproductive organs and regulates fat deposition, lipid and calcium metabolism, hypothalamic temperature, vasomotor activity, and the production of vaginal secretions.

When the female reproductive organs remain healthy, they can sustain normal menstrual cycles until late middle age, when menopause occurs. At the time of menopause, the complex hormone cycles diminish and cease. Menopause is defined as one year of amenorrhea (i.e., no menstruation) in midlife due to the final phase in the maturation of the female reproductive system (also called the climacteric). Menopause can also be caused surgically by removing the ovaries, or chemically with medication that interferes with the action of estrogen.

Physical symptoms associated with menopause include hot flashes, insomnia, night sweats, depression, vaginal dryness, and emotional irritability. These symptoms have been treated effectively with hormone replacement therapy (HRT). HRT has been a controversial subject in the medical community, with many studies claiming either mortality benefits or mortality hazards, depending on the type of HRT administered and population studied.<sup>3</sup>

## **Male Reproductive Disorders**

### Disorders of the Prostate

#### *Benign Prostatic Hypertrophy*

Benign prostatic hypertrophy (BPH), also called benign prostatic hyperplasia, is a common condition experienced by males ages 45 years and over.<sup>4,5,6</sup> There is a very low prevalence at younger ages, but prevalence increases to 50% by age 60, and over 80% by age 80. BPH occurs when the glandular tissue thickens due to stimulation by testosterone, producing nonmalignant hyperplasia, also called adenomatous hyperplasia. The extra mass of tissue can compress the bladder and urethra, causing symptoms ranging from mild discomfort to severe complications (e.g., renal insufficiency, urinary retention, recurrent infection).

The treatment of choice for BPH in those with mild symptoms is watchful waiting. Non-invasive treatment of BPH includes blocking the action of testosterone with 5 alpha-reductase inhibitor medications such as finasteride (Proscar<sup>®</sup>) and dutasteride (Avodart<sup>®</sup>). Other treatments include the alpha-adrenergic blockers/inhibitors, terazosin (Hytrin<sup>®</sup>), doxazosin (Cardura<sup>®</sup>), alfuzosin (Uroxatral<sup>®</sup>), and tamsulosin (Flomax<sup>®</sup>). Side effects of this treatment include erectile dysfunction. Finasteride and dutasteride reduce prostate specific antigen (PSA) by about 50%, which must be considered when underwriting an individual taking Proscar<sup>®</sup> or Propecia<sup>®</sup> (the same medication but used for the treatment of male pattern baldness), or Avodart<sup>®</sup>. BPH treatments that are experimental or unproven include saw palmetto and African plum tree bark.

Minimally invasive treatment of BPH includes transurethral microwave heat treatment (TUMT), transurethral incision of the prostate (TUIP), and transurethral needle ablation (TUNA). Interstitial laser coagulation (ILC) and visual laser ablation of the prostate (VLAP) are also used. Surgery using a procedure called transurethral resection of the prostate (TURP) is recommended for BPH patients with severe symptoms. Complications of surgery include erectile dysfunction and incontinence.

The American Urological Association (AUA) symptoms index is a patient-completed questionnaire that identifies and quantifies lower urinary tract symptoms. It is useful for initiating and evaluating the effectiveness of therapy. It gives a score to irritative and obstructive symptoms: mild symptoms produce a score of 0-7, moderate symptoms 8-19, and severe symptoms 20-35.<sup>7</sup>

### *Screening Using PSA*

Serum levels of prostate specific antigen (PSA) are useful in assessing the condition of the prostate.<sup>8</sup> Serum levels of PSA can be elevated by many conditions including malignancy, infection, inflammation, and BPH. Because PSA is prostate tissue specific, and not prostate-cancer specific, a high PSA level does not mean cancer is present and a normal PSA does not rule out the presence of prostate cancer. Since BPH increases in prevalence with age, the predictive value of PSA changes as well. The range for determining a normal PSA value will be lower for younger males, and higher for older males.<sup>9</sup> For example, normal values for PSA can range from 0 to 4 ng/ml for a 65-year-old male but only range from 0 to 2.4 ng/ml for a 50-year-old male. PSA levels up to 10 ng/ml can be considered borderline, and values greater than 10 ng/ml are high.

Using conventional cut-points for PSA testing will detect the majority of prostate cancers; however, a significant percentage of early prostate cancer (10-20%) will be missed by PSA testing alone.<sup>10</sup> Using a lower threshold to define an abnormal PSA level detects more cases of cancer at the cost of more false-positive results and more biopsies.<sup>11</sup> The addition of a digital rectal exam (DRE), with the PSA, increases the value of both tests. Change in PSA levels over time is called PSA velocity. This has been used to enhance detection of prostate cancer and to determine whether a repeat biopsy is indicated, particularly when the PSA levels are between 4 and 10 ng/ml and a previous biopsy was negative. Rapid and/or large increases in PSA levels, 0.75 ng/ml or greater over a period (usually one year) indicate a higher likelihood of cancer.<sup>12</sup>

In the serum, PSA circulates in two forms:

1. free PSA
2. PSA bound to other proteins.

Males with prostate cancer tend to have a lower percentage of free PSA than those without prostate cancer. The ratio of free PSA to total PSA has been used to increase the likelihood of finding cancer when considering a biopsy. There is no consensus on the optimal threshold for the ratio of free to total PSA since increasing the threshold may increase the number of cancers detected, but also the number of false positives and unnecessary biopsies. A range of 10-27% for the ratio of free to total PSA has been considered by investigators to be most useful. The higher thresholds were found to be more useful for high-risk patient groups (such as African-American males with

at least one first-degree relative with prostate cancer).<sup>13</sup> Other factors useful in assessing the prostate include the assessment of symptoms, transrectal ultrasound (TRUS), and urinary tests for pathogens.

### *Prostatitis*

Prostatitis can exhibit a variety of syndromes that reflect infection or inflammation of the prostate. Prostatitis can be acute or chronic, bacterial or nonbacterial, inflammatory or noninflammatory.<sup>14,15</sup>

Acute indicates that it is an isolated occurrence, while chronic indicates recurrent or sustained infections. Bacterial prostatitis is typically diagnosed when pathogens are detected in urine or in secretions that are extracted from the prostate. Nonbacterial prostatitis is diagnosed when no evidence of pathogens is found, yet symptoms attributed to the prostate remain, such as chronic pelvic or perineal pain. Inflammatory prostatitis is diagnosed when white blood cells (WBCs) are found in urine or prostatic secretions, while the absence of WBCs indicates noninflammatory prostatitis.

The standard treatment for pathogen-associated prostatitis is administration of antimicrobial medications.<sup>16</sup> The medications that are prescribed should be appropriate to the pathogens that are detected. Sometimes the underlying pathogens are unknown, and broad-spectrum antibiotics are prescribed on a “wait and see” basis. If there is little or no response to a reasonable variety of antimicrobial medications, anti-inflammatory agents will be prescribed.

An abscess is a severe pathogen-associated condition, which would be treated surgically. The presence of a prostate abscess is confirmed with ultrasound.

Prostatodynia is a condition that mimics prostatitis but without evidence of infection or inflammation. It can also be called chronic nonbacterial prostatitis or chronic pelvic pain syndrome. Treatment consists of symptomatic relief, including prostatic massage, hot sitz baths, and analgesics.

### *Prostate Stones*

One of the underlying causes of chronic prostatitis is prostate stones (also called calculi or corpora amylacea).<sup>17</sup> These usually can be detected with ultrasound. One cause of prostate stones is prostatic secretions that do not leave the gland due to blockage of the glandular ducts; these materials then dry out and become calcified. Another cause is products of infection that are not completely removed, which then dry out and become calcified.

Prostate stones are very common and do not always produce symptoms. However, they can harbor pathogens and give them shelter from antimicrobial medications or be a source of irritation and inflammation. Unlike the removal of kidney stones, the removal of prostate stones is very difficult. Kidney stones are continually surrounded by urine, and when broken into sufficiently small pieces, get flushed out easily. Prostate stones are not surrounded by fluid and are not easily flushed out. The removal of small prostate stones can be accomplished with prostatic massage

that breaks up stones into smaller pieces that they can pass into the urine. Stones that do not respond to this treatment can be removed surgically.

### *Solitary Prostate Nodule*

Nodules detected by DRE or ultrasound are usually followed up to determine if they are benign or malignant.<sup>18</sup> First, PSA levels are checked to see if they are elevated, and anti-microbial medications administered to see if the nodule disappears, which would indicate it is of infectious origin. However, if a nodule does not disappear or the PSA does not drop to normal with antibiotic treatment, a biopsy must be done. Pathology reports provide the assessment of the biopsy results.

### *Prostate Cancer*

Prostate cancer is covered in detail in the “Four Cancers” chapter of this text.

## Disorders of the Testicles and Scrotum

### *Testicular Cancer*

Testicular cancer is a highly treatable, often curable cancer, that usually develops in young and middle-aged males.<sup>19,20</sup> Early symptoms are nonspecific, with a heavy feeling in the testicles being the most common. Diagnosis is usually made by physical examination and ultrasound of the scrotum. If a mass is identified, a computerized tomography (CT) of the abdomen and pelvis, as well as chest x-rays, are usually performed. The following blood tests are usually done before surgery:

1. alpha fetoprotein (AFP) (normal range = <5 ng/ml)
2. beta-human chorionic gonadotropin (beta-hCG) (normal range = <5 ng/ml)
3. lactic dehydrogenase (LDH) (normal range = <200 ng/ml).

Testicular cancer is broadly divided into two histologic types: seminoma and nonseminoma. This division is particularly useful for treatment purposes because seminomas are more sensitive to radiation therapy. For individuals with seminoma (all stages combined), the cure rate exceeds 90%. Nonseminomatous tumors are more difficult to treat and tend to be more aggressive malignancies. Tumors that have a mixture of seminoma and nonseminoma components are clinically managed as nonseminomas. Nonseminoma tumors include embryonal carcinoma, teratoma, yolk sac carcinoma, and choriocarcinoma. Tumors that have seminoma histology but have elevated serum levels of AFP are also treated as nonseminomas. For stage I nonseminomas, 5-year survival is >90%. For those with small to moderate retroperitoneal lymph node involvement, 5-year survival is approximately 80%. Those with bulky tumors or metastasis achieve remission in more than 75% of the cases.

Treatment consists of orchectomy (i.e., removal of the affected testis) and, for advanced stages of the disease, radiotherapy and/or chemotherapy. A combined therapeutic approach, utilizing chemotherapeutic agents such as vinblastine, actinomycin D, and bleomycin (VAB protocol), or the introduction of one of the new platinum-based medications and/or etoposide have been

successful. Follow-up consists of lifelong periodic measurement of serum markers (including AFP, hCG, LDH), physical examinations, CT scans of the abdomen, and chest x-rays to detect lung metastasis.<sup>21,22,23</sup>

Classification of testicular cancer is done by TNM classification and histologic typing.<sup>24</sup>

TNM staging includes:

Primary Tumor (T) - classified after radical orchiectomy  
PTX - Primary tumor not assessed (no biopsy performed)  
pT0N0 - evidence of primary tumor  
pTis - Preinvasive cancer  
pT1 - Tumor limited to testis  
pT2 - Tumor invades the tunica albuginea or into the epididymis  
pT3 - Tumor invades spermatic cord  
pT4 - Tumor invades the scrotum

Regional Lymph Nodes (N)

NX - Regional lymph nodes not assessed  
N0 - No regional lymph node involvement  
N1 - Metastasis in single lymph node, 2 cm or less  
N2 - Metastasis in a single lymph node, > 2 cm but  $\leq$  5 cm  
N3 - Metastasis to a single lymph node, > 5 cm

Distant Metastasis (M)

MX - Distant metastasis not assessed  
M0 - No distant metastasis  
M1 - Distant metastasis

Stage Grouping

Stage 0	pTis	N0	M0
Stage I	Any pT	N0	M0
Stage II	Any pT	N1	M0
	Any pT	N2	M0
	Any pT	N3	M0
Stage III	Any pT	Any N	M1

### *Epididymitis and Orchitis*

Also called epididymo-orchitis, these are infections of the testes and supporting structures. The pathogens causing these infections include urinary tract bacteria, sexually transmitted diseases, and viruses, such as mumps. Treatment consists of antibiotic therapy, when appropriate, and anti-inflammatory medication to reduce inflammation. Scrotal abscess is a complication of epididymitis and can require surgery.<sup>25</sup>

### *Testicular Atrophy, Testicular Failure, and Cryptorchism*

Testicular atrophy indicates the failure of the testes to thrive, causing them to shrink or wither. Abuse of anabolic steroids is a common cause of testicular atrophy. Testicular failure indicates the inability of the testes to produce sperm, or in some cases, to produce testosterone. Both conditions can result congenitally or as the result of trauma, infection, medications, or other

adverse events. Cryptorchism (or cryptorchidism) is the failure of one or both testes to descend into the scrotum from the body. If not corrected, undescended testes can present a higher risk of testicular cancer in adult males as well as the inability to produce sperm in the undescended testicle.<sup>26</sup>

#### *Hydrocele, Spermatocele, Varicocele*

A hydrocele is a mass in the scrotum resulting from excessive accumulation of fluid. This fluid can be due to overproduction of lymph secondary to inflammation or from obstruction of lymph drainage. It can also be congenital. Treatment of a hydrocele can involve surgery (i.e., hydrocelectomy), aspiration, or injection of sclerotic medications.

Spermatocele (or spermatic cyst) is a mass or cystic structure, typically found at the top of the testis, which contains sperm. It can usually be distinguished from a hydrocele by ultrasound and is typically treated with surgery or aspiration.

Varicocele is a swelling in the scrotum caused by varicose veins. Varicose veins are caused by blood accumulating in the veins due to venous obstruction or impairment of the valves within the veins. Diagnosis is made by physical exam and ultrasound. Varicoceles can cause infertility; treatment is surgical ligation of the veins.<sup>27</sup>

#### *Erectile Dysfunction*

Erectile dysfunction, also known as impotence, is defined as the inability to initiate or maintain an erection. Erectile dysfunction (ED) increases in prevalence with age, starting around age 40. There is greater than 60% prevalence of ED among males in their 60s, and greater than 80% prevalence among those in their 70s.

Underlying causes of ED include hormonal, psychological, vascular, or neurologic impairments. Among most males with ED, the primary underlying cause is endothelial dysfunction associated with diabetes, hypertension, or atherosclerosis. ED can also be due to neurological disorders such as multiple sclerosis, or secondary to nerve damage as seen after prostate surgery or spinal fracture.

Common medications and substances that contribute to ED include alcohol, antidepressants, antihypertensives (such as beta-blockers), cocaine, estrogens, histamine<sub>2</sub> (H<sub>2</sub>) blockers, marijuana, narcotics, and tobacco. Psychosocial factors can both cause and result from ED, such as depression, anxiety, fear of failure, altered social or occupational role, and/or dysfunctional relationships.

Sildenafil citrate (Viagra<sup>®</sup>) was introduced in 1998 as the first effective oral medication for ED. It causes increased relaxation of the muscle tissue in arterial walls, which permits improved blood flow into the corpus cavernosum. Arteries in the rest of the body are affected as well, which can drop blood pressure as the medication takes effect.

Sildenafil does not itself produce erections – sexual excitation must be present for it to have an effect. The use of sildenafil, or similar ED medication, may not necessarily indicate the presence of an underlying disorder; these have become socially accepted as recreational medications. Other medications commonly utilized for ED include tadalafil (Cialis®) and vardenafil (Levitra®).

Contraindications for taking any ED medication include a history of arrhythmia or other unstable cardiac disorder treated with nitrates such as nitroglycerin.<sup>28</sup> Males with stable ischemia, hypertension, and/or severe coronary artery disease treated with other medications, such as antihypertensives, show no additional safety risks when taking sildenafil.<sup>29,30,31</sup>

## **Female Reproductive System Disorders**

### Diseases of the Breast

#### *Fibrocystic Disease*

Fibrocystic disease is a general term that encompasses a variety of conditions of the breast that involve lumpiness, cysts, or inflammation. Fibrocystic disease can be accompanied by mastalgia, which is pain that can be chronic or cyclic (i.e., apparent only during specific times during the menstrual cycle). Underlying causes can be hormonal changes that cause swelling, infections, or cysts.

Swelling can be treated with anti-inflammatory medications or with medications that interfere with the effects of estrogen. Infection (i.e., mastitis), is treated with antibiotics.

Benign breast lumps are usually detected during routine breast examination, either on self-examination or during physical examination by a physician. Breast cysts can be diagnosed with a mammogram, confirmed by ultrasound, and treated with aspiration. Follow-up involves detection of any reappearance of the cyst; if it reappears quickly, the cyst can be surgically removed.

#### *Fibroadenomas*

Fibroadenomas are benign tumors that usually develop in young females, often in teenagers. They are diagnosed by ultrasound and can be excised or treated by cryoablation, but they often recur. After an individual has had several fibroadenomas established as benign, a decision may be made not to excise any others unless considered suspicious. Other benign solid breast masses include fat necrosis and sclerosing adenosis, which can be diagnosed only with biopsy.

#### *Ductal Papilloma*

A papilloma is a benign tumor derived from epithelial cells. In the breast, papillomas arise from the epithelial cells lining the milk ducts (ductal or intraductal papilloma). These tumors can bleed, causing a bloody discharge from the nipple. Papillomas are diagnosed by a galactogram, also known as a ductogram. Treatment of benign tumors involves surgical removal, with routine follow-up to determine if there is recurrence. Occasionally these tumors can become malignant (papillocarcinomas).<sup>32</sup>

## *Paget's Disease of the Breast*

Paget's disease is a form of ductal carcinoma in situ.<sup>33</sup> Symptoms can consist of a crusting, scaling erosion of the nipple, and a discharge that can be milky (i.e., galactorrhea) or bloody. Sometimes the patient perceives this condition as benign and ignores it; this inaction can delay diagnosis of the underlying malignancy. Cancer is present in less than 10% of females who have any kind of nipple discharge; most bloody discharges are due to an underlying ductal papilloma.

## Disorders of the Female Reproductive Organs

### *Endometriosis*

Endometriosis is the occurrence of endometrial tissue outside of the uterine cavity.<sup>34,35</sup> These lesions consist of implants of endometrial tissue on the peritoneum, ovaries, bowel, bladder, lymph nodes, or other abdominal/pelvic sites. Though rare, endometrial implants can be found outside the abdominal and pelvic areas. Bleeding from endometrial tissue outside the uterus causes a localized inflammation, formation of scar tissue, and/or cystic structures (i.e., endometriomas) that contain blood, fluid, and menstrual debris. Depending on the location of the implants, complications such as adhesion formation, obstruction, infertility, and chronic abdominal pain can occur.

Endometriosis can have an underlying genetic component, can arise because of uterine surgery, or can arise from retrograde menstruation that releases endometrial cells into the abdominal cavity through the open ends of the fallopian tubes.

Symptoms suggesting endometriosis include unexplained infertility, worsening dysmenorrhea (i.e., painful menstruation), and/or dyspareunia (i.e., painful sexual intercourse), but a definitive diagnosis of endometriosis can only be confirmed by visualization of the lesion at the time of surgery or by biopsy. Laparoscopy is the preferred mode for diagnosis.

Treatment can consist of medications that affect the female hormonal cycle, such as progestins, androgens, medications that induce a menopause-like state (danocrine - Danazol<sup>®</sup>), and gonadotropin releasing hormone antagonists (leuprolide - Lupron<sup>®</sup>). Surgical removal of the uterus and ovaries is also an option for females with endometriosis who do not wish to remain fertile. Those who wish to remain fertile can opt for surgery or laser ablation that removes individual endometrial lesions.

### *Abnormal Uterine Bleeding*

Abnormal uterine bleeding is usually associated with inflammation, tumor, or pregnancy. There are various types of abnormal uterine bleeding.<sup>36,37</sup>

1. amenorrhea – absence of menstrual periods
2. dysmenorrhea – painful menstrual periods
3. oligomenorrhea – infrequent menstrual periods

4. polymenorrhea – menstrual periods occurring in cycles 21 days or less
5. menorrhagia – abnormally long menstrual periods or excessive bleeding during menstruation but occurring cyclically
6. metrorrhagia – bleeding between regular menstrual periods
7. postmenopausal bleeding – any bleeding occurring more than six months after menopause
8. dysfunctional uterine bleeding – bleeding associated with hormonal abnormalities.

Age and ovulatory status are the principal factors in making a diagnosis of abnormal uterine bleeding. Bleeding in infancy or childhood is always abnormal and must be investigated. For females of reproductive age, complications of pregnancy are the most common causes of abnormal uterine bleeding. Adenomyosis (benign endometrial invasion of the myometrium), leiomyoma (fibroids), and malignancy are other uterine causes of abnormal bleeding. Since abnormal uterine bleeding is a diagnosis of exclusion, anovulation, hormonal dysfunction, clotting disorders such as von Willebrand's disease, ovarian cysts or tumors, thyroid dysfunction, and infection must be ruled out. Trauma, granulomatous tissue (usually post-surgical inflammation), cervical polyps, and condyloma acuminata can cause cervical bleeding.

In postmenopausal females, abnormal uterine bleeding can indicate malignancy, particularly endometrial carcinoma. Benign causes of post-menopausal bleeding include atrophic vaginitis, atrophic endometrium, endometrial polyps, and endometrial hyperplasia.

Dysfunctional uterine bleeding (DUB) is usually seen in adolescents or in females older than 45 years of age. DUB usually refers to bleeding associated with hormonal imbalance, as seen in the use of unopposed estrogen, endometrial hyperplasia, and polycystic ovarian syndrome. Endometriosis and endometrial hyperplasia can also cause DUB. Endometrial hyperplasia is diagnosed by measuring endometrial thickness (i.e., the endometrial stripe) with transvaginal ultrasonography. In anovulatory females, a thickness >4 mm can be normal or can be indicative of hyperplasia or cancer; biopsy is usually indicated for DUB and endometrial thickening.<sup>38</sup>

Diagnosis of abnormal uterine bleeding can involve:

1. physical examination, including pelvic exam, reproductive history, and medication history
2. evaluation for pregnancy
3. evaluation of ovarian, thyroid, and coagulation functions
4. Pap smear (evaluation of a sample of cervical and uterine cells for abnormality)
5. ultrasound or CT scan.

Treatment of abnormal uterine bleeding depends on the diagnosis and age. Hormonal treatment (estrogen and progestin in combination, or progestin alone), dilation and curettage (D & C) of the endocervix and uterine cavity, induction of ovulation with clomiphene (Clomid®), or hysterectomy for refractory bleeding or atypical hyperplasia are the usual treatments.

### *Polycystic Ovarian Syndrome*

Polycystic ovarian syndrome (PCOS), also known as Stein-Leventhal syndrome, is a common ovarian disorder associated with oligomenorrhea or amenorrhea.<sup>39</sup> Elevated serum levels of male hormones (androgens), ovulatory dysfunction (oligo- or anovulation), abnormal menstrual cycles, obesity, and hirsutism (abnormal facial hair) are the main features. Infertility is common. Symptoms of PCOS can appear during adolescence and continue thereafter.

There are many underlying causes of PCOS including primary hyperandrogenism, adrenal hyperplasia, and hypothalamic-pituitary dysfunction. Another frequent finding is increased insulin resistance that is associated strongly with metabolic syndrome. Diagnosis is made by symptom presentation, hormonal testing, and ultrasonography.

Treatment of PCOS involves treating the underlying cause when possible. Since insulin resistance is so often found with PCOS, treatment can include insulin sensitizers such as metformin (Glucophage®). Oral contraceptives can be used to regulate the menstrual cycle.

### *Pelvic Inflammatory Disease*

Pelvic inflammatory disease (PID) is an acute infection of the female genital tract that can be caused by a number of pathogens—Chlamydia trachomatis and Neisseria gonorrhoeae being the most common.<sup>40,41</sup> PID is a general term that encompasses infections of the fallopian tubes (salpingitis) and uterine lining (endometritis), with the possibility of spreading to other tissues and organs. PID can lead to peritonitis and can result in infertility, increase the risk of ectopic pregnancy, or produce chronic pelvic pain.

Diagnosis consists of ruling out other possible underlying causes of chronic pelvic pain. The most common symptoms are abdominal pain, fever, vaginal or cervical discharge, and abnormal uterine bleeding. On examination, adnexal or cervical tenderness, abdominal discomfort, elevated white blood cell count of vaginal secretions, and elevated C-reactive protein are usually present. Treatment consists of antibiotics and anti-inflammatory medications. Surgery can be necessary to drain abscesses or remove tissue that is too damaged to heal.

### *Fibroids*

Uterine fibroids (i.e., leiomyomas) are benign tumors of smooth muscle tissue in the uterine wall and adjoining structures.<sup>42,43</sup> They can grow very large, causing bleeding, pelvic pain, and reproductive dysfunction. Causes of fibroids include genetic predisposition, response to injury, and the presence of growth factors important to fibrotic processes and angiogenesis (growth of new blood vessels from pre-existing vessels). It is important to follow up on fibroids because they can progress to malignancy (i.e., leiomyosarcoma).

Diagnosis typically involves physical examination and ultrasound. Treatment may first involve administration of medications that block the action of estrogen, inducing menopause-like side effects. An alternative to medical treatment is surgery that removes only the fibroid (myomectomy) or completely removes the uterus (hysterectomy). Other treatments include

localized destruction of the fibroid by myolysis (i.e., done by laser or electrical device during laparoscopy) or cutting off the blood supply with uterine artery embolization.

### Malignancies of the Female Reproductive Tract

With most malignancies, primary tumors that are treated when they are small and have not metastasized have much better prognoses than tumors that are large and have spread cells to other parts of the body. The presence of metastasis indicates a tumor that is more difficult to treat and is often associated with a higher mortality. Different histology types have different prognostic implications as well.

There is evidence that some families have a higher incidence of certain types of gynecologic tumors. A family history of these tumors increases the individual's risk of also developing cancer. Families with the following syndromes have increased risk for gynecologic tumors:

1. hereditary nonpolyposis colorectal cancer (HNPCC)
2. breast and ovarian cancer syndrome (linked to BRCA1 and BRCA2 genetic mutations).

Symptoms of female reproductive tract malignancies include abdominal pain, unusual bleeding, or vaginal discharge, and/or gastrointestinal symptoms. Diagnosis requires a pelvic examination and Pap test, and possibly an ultrasound or CT scan, analysis of serum tumor markers, or biopsy of the suspected lesion.

The pathology report of biopsied lesions should give the size, histological type, depth of invasion, stage and grade of any tumor tissue, and the presence of malignant cells at sites other than in the tissue of origin (e.g., cells found on peritoneal washings for ovarian cancer). Further information on staging and metastatic work-up is found in the attending physician's report or second pathology report. Treatment is based on the histological type, grade, and stage of the tumor, which include combinations of surgical, radiologic, and medication therapies. As with all malignancies, periodic follow-ups for possible recurrence are necessary, which should include a physical exam, serum tumor markers, and MRI or CT scans.

#### *Breast Cancer*

Breast cancer is covered in detail in the “Four Cancers” chapter of this text.

#### *Other Malignancies of the Female Genital Tract*

The following malignancies of the female reproductive tract are listed from most common to least common.

#### *Endometrial Cancer*

There are two types of endometrial cancer. Type 1 is related to increased levels of estrogen and is the most common, while type 2 tumors are not associated with increased levels of estrogen and tend to metastasize readily.<sup>44,45,46</sup> Both tumor types are typically treated with surgical removal

of the uterus (hysterectomy), the fallopian tubes, and ovaries (salpingo-oophorectomy). Surgical treatment is usually followed up with radiation and/or chemotherapy if indicated. The degree of tumor differentiation (e.g., well-differentiated/low grade), depth of invasion, cervical invasion, extrauterine metastasis, and presence or absence of progesterone receptors are the most significant prognostic indicators.

Females who are at most risk for type 1 endometrial cancer include those who:

1. have had unopposed estrogen treatment (estrogen not combined with progestins) that increases the risk of endometrial hyperplasia
2. have used tamoxifen
3. are morbidly obese
4. are diabetic and hypertensive
5. have had a history of ovulatory dysfunction
6. have a genetic predisposition.

Type 1 cancers tend to be low grade, endometrioid type tumors that have progesterone receptor levels that are high; clinical studies have shown these to be good prognostic factors.

Females who are at most risk for type 2 endometrial cancer are older, often over 70 years of age. These tumors have different histological types, such as papillary serous or clear cell. Type 2 tumors are higher-grade tumors and have lower progesterone receptor levels; clinical studies have shown these to be poor prognostic factors. Although these tumors account for around 10-20% of all endometrial cancers, they account for most of the mortality associated with endometrial cancer.<sup>47,48</sup>

Diagnosis is made for asymptomatic endometrial carcinoma by incidental discovery of abnormal endometrial cells on Pap testing. Since abnormal uterine bleeding is often the presenting symptom, a work-up with transvaginal ultrasonography, endometrial biopsy, hysteroscopy with dilation and curettage, or sonohysterography (hysteroscopy with instillation of fluid) is indicated.

## Ovarian Cancer

Half of all ovarian cancers arise among females over age 65.<sup>49,50,51,52,53,54</sup> About 5-10% of ovarian cancers are familial, with the highest risk among those with two or more first-degree relatives (e.g., mother or sister) affected. Risk is generally lower for females with only second-degree relatives (e.g., aunt or grandmother) affected, yet is still higher than for those with no familial occurrence.

Because ovarian cancer is often asymptomatic in its early stages, most patients have widespread disease at the time of diagnosis. CA 125, human chorionic gonadotropin (hCG), LDH, and transvaginal ultrasonography are performed for diagnosis. Treatment involves surgery that includes bilateral salpingo-oophorectomy, hysterectomy, pelvic washings, and a sampling of lymph nodes. Further treatment with radiation and/or extensive chemotherapy is indicated for advanced disease.

Good prognostic factors for ovarian cancer include:

1. younger age
2. good response to treatment
3. lower stage, well-differentiated histology (i.e., grade)
4. cell type other than mucinous and clear cell
5. smaller disease volume before surgery
6. absence of ascites before treatment.

## Cervical Cancer

The most frequent histological type of cervical cancer is squamous cell (80-85%), followed by adenocarcinomas (10-15%).<sup>55,56</sup> Over 90% of squamous cell carcinomas of the cervix are associated with infection with human papillomavirus (HPV). Risk of HPV infection increases with a history of multiple sexual partners. Risk is also increased for the sexual partners of males whose previous partners had cervical cancer. Cigarette smoking is associated with an increased risk of cervical intraepithelial neoplasia (CIN) and cancer.

In countries where there is routine screening with Pap smears, mortality from cervical cancer has decreased steadily over the last few decades. Pap smears often detect the presence of cervical intraepithelial neoplasia (CIN) or cervical dysplasia early during the malignancy, enabling treatment of cervical cancer in its earliest stages. For cervical cancer, stage is the most significant prognostic factor.

Symptoms of cervical cancer include vaginal discharge, abnormal bleeding, and pelvic pain. Diagnosis is made by Pap testing and biopsy. Treatment typically is surgical removal of the uterus (hysterectomy). For patients with carcinoma in situ (CIN III) who wish to remain fertile, conical removal of the cervical lining (conization) can be done. Those treated with conization require close follow-up for recurrence of cancer. For advanced disease, radiation and chemotherapy typically follow surgical treatment.

## Cancer of the Vulva

Vulvar intraepithelial neoplasia (VIN) is becoming a more commonly identified condition in young females, although the average age at diagnosis is age 70.<sup>57</sup> VIN is associated with human papillomavirus (HPV) infection; females with a history of squamous cell cervical or vaginal cancer are at higher risk. Treatment is typically local excision, but for extensive lesions, laser ablation is preferred.

Most cancers of the vulva (90%) are squamous cell tumors. The most significant prognostic factor for these tumors is stage at diagnosis. Symptoms, if present, include a palpable or open lesion and pruritus (itching). About 5% of vulvar cancers are melanomas with prognosis being related to tumor size and depth of invasion. The risk of metastasis is high for melanomas. Partial or total vulvectomy with lymph node dissection is indicated for invasive vulvar malignancies.

## Cancer of the Vagina

Although the average age of diagnosis for vaginal cancer is 60 to 65 years, some histological types of cancer occur at much earlier ages.<sup>58</sup> Most (95%) of vaginal cancers are squamous cell carcinomas. Individuals with a history of human papillomavirus (HPV) infections, and/or cervical or vulvar cancers are at increased risk.

Symptoms are vaginal discharge, bleeding, fistulas, and dyspareunia. Diagnosis can be made during pelvic exam, by findings on Pap testing, and by biopsy. The best prognosis is for very small and well-differentiated tumors. Most vaginal tumors are treated with radiation therapy, although more radical surgery is used for tumors located in the upper third of the vagina.

## Complications Associated with Pregnancy

Maternal death occurs in six out of 100,000 U.S. births.<sup>59</sup> The leading cause is motor vehicle accidents, followed by thromboembolic disease, anesthesia complications, hemorrhage, infection, and hypertension.

During normal pregnancy, the mother develops certain physiologic changes that the underwriter must consider, particularly when reviewing blood test results. Some of these changes include:

1. increased blood and plasma volume, red blood cell mass, and decreased hematocrit (not <30%)
2. increased iron utilization, iron deficiency anemia, decreased hemoglobin (not <10 g/dl) – exogenous iron supplementation is recommended
3. increased total cholesterol in late pregnancy
4. increased alkaline phosphatase in late pregnancy
5. decreased albumin in late pregnancy, globulin is not affected, but albumin/globulin ratio decreases
6. decreased BUN and creatinine secondary to increased glomerular filtration
7. decreased calcium in late pregnancy if insufficient calcium is ingested
8. decreased immune system reactivity, which protects the fetus from being attacked by the maternal immune system
9. increased coagulability and a decrease in natural inhibitors of coagulation
10. increased insulin release, but decreased tissue sensitivity to insulin, particularly as pregnancy progresses—If maternal insulin reserve is insufficient, gestational diabetes develops.
11. increased white blood cell count as pregnancy progresses (can be as high as 12-15,000 in third trimester).

These changes protect mother and fetus during gestation and delivery and usually revert to normal within 20 days of delivery.<sup>60,61</sup>

### *Pre-eclampsia and Eclampsia*

Pre-eclampsia is a syndrome that can arise suddenly during pregnancy and, if untreated, can progress to eclampsia, which can be fatal to both mother and fetus.<sup>62,63</sup> Pre-eclampsia includes the appearance of hypertension, proteinuria, and edema. Eclampsia includes these features, as well as seizures or coma for no other apparent reason. There is no known underlying cause for pre-eclampsia or eclampsia, although pregnant females with prior pre-eclampsia or pre-existing hypertension or vascular disease, and primigravidae (first pregnancy) are at higher risk.

In the absence of proteinuria, other indications of high risk associated with hypertension during pregnancy is the combined appearance of red cell hemolysis, elevated liver enzymes, and low platelet count, called the HELLP syndrome. Females with pre-eclampsia or the HELLP syndrome are treated with close medical observation (often in a hospital), antihypertensive medication that is safe for the fetus, bed rest, normal salt intake, and increased water intake. Females with eclampsia have anticonvulsant medication added to this treatment.

A severe case of pre-eclampsia, eclampsia, or HELLP syndrome can require immediate delivery of the fetus. Spontaneous rupture of the liver is a rare but life-threatening occurrence in such cases. Once the fetus is delivered, recovery is usually rapid.

Females with a history of chronic hypertension with associated organ damage (e.g., left ventricular hypertrophy, retinopathy, renal disease) can have progressive findings during pregnancy. Consequences for these individuals include encephalopathy, heart failure, pulmonary edema, and renal failure. Consequences for the fetus include miscarriage (i.e., spontaneous abortion), preterm delivery, or developmental abnormalities.

### *Hyperemesis Gravidarum*

Hyperemesis gravidarum (HG) is excessive nausea and vomiting during the first trimester of pregnancy.<sup>64</sup> These symptoms usually disappear by the beginning of the second trimester. HG is distinguished from typical morning sickness if the female develops symptoms of dehydration, acidosis, and abnormal weight loss. Persistent HG can cause serious liver disease. Treatment for HG includes rehydration with intravenous fluids, electrolytes, and vitamins. A bland diet is recommended. No medications have been approved in the U.S. as safe treatment for HG.

### *Liver Disorders*

The appearance of jaundice during pregnancy can be due to a pre-existing condition (such as viral hepatitis) or a condition that is specific to pregnancy.<sup>65</sup> Spontaneous rupture of the liver is a rare but life-threatening occurrence during pre-eclampsia, eclampsia, or HELLP syndrome.

### *Intrahepatic Cholestasis of Pregnancy*

Cholestasis of pregnancy is relatively common and involves the influence of elevated hormones on bile transport. Intense itching (pruritus) develops in the second or third trimester, associated with jaundice and dark urine. If no other impairments arise, the condition resolves

after delivery. However, those who experience cholestasis of pregnancy tend to experience it during each pregnancy. Treatment typically consists of cholestyramine and vitamin K.

### *Acute Fatty Liver of Pregnancy*

Fatty liver of pregnancy (obstetric yellow atrophy) is a rare disorder of unknown underlying cause. Onset is near delivery, with symptoms of nausea, vomiting, abdominal discomfort, and jaundice. Liver function tests are elevated. Liver biopsy shows small fat droplets in the hepatocytes. The risk of mortality for the mother and fetus is high; treatment involves the immediate termination of the pregnancy.

### *Peripartum and Postpartum Cardiomyopathy*

For females with pre-existing heart disease, maternal mortality is about one percent.<sup>66,67</sup> For most females with known heart disease, pregnancy progresses normally with no significant sequelae. However, some will deteriorate despite special precautions. Fetal mortality and premature birth are associated with maternal complications. Arrhythmia or evidence of pulmonary edema requires hospitalization and bed rest. During delivery, special attention by the obstetrician and anesthesiologist is required to monitor cardiac hemodynamics.

Peripartum cardiomyopathy is a rare disorder that is diagnosed within the last month of pregnancy (peripartum), or within five months after delivery (postpartum). Symptoms include dyspnea, fatigue, ankle edema, nocturia, and palpitations. The heart is dilated on echocardiogram. There is an increased risk of congestive heart failure, arrhythmia, and pulmonary emboli. Risk factors include obesity, history of other cardiac disorders, smoking, alcoholism, poor nutrition, and multiple pregnancies.

Good prognostic factors for peripartum cardiomyopathy include a heart that returns to normal size after delivery. Sustained dilation and rapid deterioration may require a heart transplant, in which case it is associated with a mortality rate as high as 25-50%.

### *Ectopic Pregnancy*

Ectopic pregnancy occurs when the zygote implants itself outside the uterine cavity. Tubal implantation is the most common, but implantation can take place in the cervix, ovary, or abdominal cavity.<sup>68</sup> The risk of mortality is high due to tissue rupture caused by the growing zygote, causing massive internal bleeding, hypotension, and shock.

Risk factors for ectopic pregnancy include pelvic inflammatory disease, history of induced abortion, or previous ectopic pregnancy. Symptoms include sudden abdominal pain and syncope. Diagnosis is made with ultrasound, monitoring of serum levels of hCG, and laparoscopy. Treatment involves surgical removal of the zygote and associated embryonic tissues.

### *Gestational Trophoblastic Tumors*

Gestational trophoblastic tumors (GTTs) are rare but highly curable tumors that arise from the

products of conception in the uterus.<sup>69,70</sup> The most common form of GTT is hydatidiform mole (molar pregnancy), a genetic disorder of pregnancy in which only placental tissue is present.

A less common form of GTT is invasive mole (chorioadenoma destruens), which is a locally invasive but rarely metastatic lesion. Choriocarcinoma is a malignant tumor that commonly follows a molar pregnancy, but can follow a normal pregnancy, ectopic pregnancy, or abortion.

A sign of GTT is abnormal bleeding, rapidly enlarging uterus, and passage of grape-like molar tissue. Diagnosis is made by ultrasound, and serum levels of beta human chorionic gonadotropin ( $\beta$ -hCG) are tested to determine if they are abnormally elevated. The mole can regress spontaneously. If it does not regress, evacuation by suction curettage is necessary. Beta-hCG levels are followed to determine if levels decrease to normal or remain elevated. Persistent elevations of  $\beta$ -hCG require further evaluation and treatment. Overall, even in metastatic disease, cure rate is 60–80%.

### **Sexually Transmitted Diseases**

Sexually transmitted diseases (STDs) are among the most common communicable diseases in the world.<sup>71</sup> They are transmitted when an infected partner, using no STD protection (such as a condom), has intercourse with an uninfected partner. The likelihood of catching an STD increases greatly for an uninfected person if there is unprotected sex with multiple partners.

Any STD that creates open sores improves the ease of transmitting human immunodeficiency virus (HIV). The presence of an STD increases the risk that HIV is also present. Since the risk of cross-contamination is high, anyone with a known STD should be tested for HIV. More information about HIV can be found in Chapter 4 of the ALU 301 text, Advanced Life Underwriting.

Although many STD pathogens have been successfully treated with antimicrobial medications, some strains of these pathogens are now demonstrating medication resistance. Untreated or resistant STD infections can lead to systemic infections and secondary impairments such as reactive arthritis, peritonitis, tumors, abscesses, pelvic inflammatory disease, and infertility.

The diseases discussed below are primarily transmitted via sexual contact. Other conditions associated with sexual transmission include hepatitis, cytomegalovirus, salmonellosis, giardiasis, amebiasis, shigellosis, and campylobacteriosis.

A STD may be indicated in a medical history as a nonspecific infection of the urethra (urethritis) or cervix (cervicitis). Infection of the rectum (proctitis) and pharynx (pharyngitis) can develop after anal- or oral-genital contact. Treatment can involve a broad-spectrum antibiotic; if the infection responds well, the attending physician may not pursue the precise identification of the pathogen.

### Human Papillomavirus

There are over 30 types of human papillomavirus (HPV) that are transmitted by sexual contact.<sup>72</sup> Several types can cause genital warts (i.e., condylomata acuminata, venereal warts) that are soft, polyp-like lesions often found in cauliflower-like clumps; certain types of HPV can cause squamous cell carcinoma of the external genitalia. Warts associated with HPV can usually be identified by visual inspection. HPV, particularly of the cervix, can also occur without genital warts and is diagnosed by the presence of squamous intraepithelial lesions (SIL) on Pap testing. Biopsy and detection of HPV-DNA in cervical cells may be necessary. Close follow-up of HPV-infected females with routine Pap smears is very important in detecting and treating premalignant dysplasia of the cervix.

Risk of HPV infection increases with history of multiple sexual partners. Risk is also increased for sexual partners of males whose previous partners had cervical cancer. Smoking and HPV infection increase the risk of cervical cancer. Removal of genital warts and dysplastic tissue can prevent further development into malignancy. It is not certain if removing this tissue also removes the HPV infection in its entirety. No treatment is completely satisfactory; relapse is frequent and requires re-treatment.

Electrocauterization, laser, cryotherapy, or surgical excision is often necessary to remove genital warts. Topical treatments using antimitotics (e.g., podophyllin, podofilox, 5-fluorouracil), caustic agents (e.g., trichloroacetic acid, bichloroacetic acid), or interferon inducers (e.g., imiquimod - Aldara<sup>®</sup>) are widely used, but are not always effective.

### Gonorrhea

Gonorrhea is caused by the bacterium *Neisseria gonorrhoeae* which is also called gonococcus (GC).<sup>73</sup> Signs of infection arise within two days to three weeks after contact. Burning with urination and penile or vaginal discharge are common symptoms but infection can occur elsewhere. Asymptomatic infection can also occur; the infected individual is able to spread the disease. Infection with gonorrhea is often associated with infection with chlamydia or HIV.

A swab of the infected area or discharge can be Gram-stained and looked at under the microscope. Serologic tests for gonorrhea, using genetic probes for gonococcal RNA, are reliable and rapid. Complications of gonorrhea include urethritis and epididymitis in males, and salpingitis and pelvic inflammatory disease (PID) in females.

Systemic infection with gonorrhea can lead to bacteremia, arthritis or joint infection, pericarditis, endocarditis, meningitis, and perihepatitis. Infection during pregnancy can lead to premature rupture of the membranes and preterm delivery. Infection of the newborn can lead to pneumonia and eye infections.

Treatment of gonorrhea is with broad-spectrum antibiotics. All the individual's sexual contacts must be treated as well. Many patients with gonorrhea are at risk of re-infection and should be retested within several months of treatment.

### Syphilis

Syphilis is a systemic disease caused by the spirochete *Treponema pallidum*.<sup>74</sup> After it enters the body, it rapidly disseminates, infiltrating lymphocytes. The incubation period for syphilis is typically three to four weeks after infection. The primary lesion is a painless ulcer called a chancre; if left untreated, it will heal within four to eight weeks.

The secondary stage of syphilis involves skin rashes 6 to 12 weeks after infection. Other symptoms can arise, including lymphadenopathy, enlarged liver and spleen, fever, headache, anemia, jaundice, and albuminuria. Acute meningitis can also develop. In untreated disease, syphilis can cause swelling and proliferation of the lining of small blood vessels, leading to endarteritis obliterans. Mucous membranes can erode, forming patches called condyloma lata. Hair can fall out in patches (alopecia areata).

In late disease (tertiary syphilis), the condition elicits an immune reaction to infected tissues, causing masses, ulcerations, and necrosis (gummata). The cardiovascular and nervous systems and the liver are especially at risk. Within 5 to 10 years after infection, the blood vessels and tissues supporting the brain and spinal cord are damaged, causing meningitis-like symptoms (neurosyphilis). Cerebrospinal fluid should be tested if neurosyphilis, tertiary syphilis, or HIV is suspected, or if there is a poor response to treatment.

Diagnosis of syphilis involves a clinical history, physical examination, serologic tests (such as RPR and VDRL), and confirmatory tests—fluorescent treponema antibody absorbed (FTA-AB) and *T. pallidum* agglutination (TP-PA). Attending physicians are advised to consider all genital ulcers to be syphilitic until proven otherwise. Exudates can be scraped from visible chancres and examined microscopically by darkfield exam for *T. pallidum*.

Penicillin is the antibiotic of choice for all stages of syphilis unless contraindicated. Individuals should be closely followed up to confirm cure, to detect reinfection, and to detect any impairment due to infection. RPR and VDRL titers should fall significantly after treatment; most become nonreactive over time.

### Herpes

Genital herpes is caused by the herpes simplex virus.<sup>75,76</sup> There are at least two serotypes of herpes simplex virus (HSV): type 1 (HSV-1) and type 2 (HSV-2). These are part of the larger human herpes virus family, which contributes to many conditions that impair immunity and cause malignancies.

HSV-1 is responsible for the appearance of cold sores and fever blisters; when symptoms arise in the oral region, it is called herpes labialis. HSV-2 is primarily responsible for sores and lesions

in the genital region, although cross-contamination with HSV-1 does occur. When symptoms arise in the genital region, it is called herpes genitalis.

Although HSV infections can lie dormant or remain asymptomatic in many individuals, others present with painful, ulcerated mucocutaneous lesions of the genitalia, fever, and enlarged lymph nodes. Symptoms often recur but the number of outbreaks decreases over time. Systemic complications of HSV infection include aseptic meningitis. HSV episodes can be severe in those who are immunocompromised by HIV. A pregnant female with new onset or active HSV infection can transmit the virus to the baby during birth; caesarean section decreases this risk. A newborn who contracts HSV from the mother is at risk for severe meningitis and fatal generalized infection. Administration of antiviral medication before, during, and after delivery can help prevent neonatal HSV infection.

Diagnosis is made by commercially available assays of blood, cell culture of lesions, or polymerase chain reaction (PCR) for HSV DNA. Treatment of genital HSV infection includes topical and oral medication such as acyclovir (Zovirax®), valacyclovir (Valtrex®), or famciclovir (Famvir®).

### Chlamydia

Genital chlamydia infections are caused by the bacterium *Chlamydia trachomatis*.<sup>77</sup> Signs of infection can arise within two to three weeks after contact. Asymptomatic infection is common, and the infected individual can spread the disease through sexual contact. Co-infection with gonorrhea is often seen in those with chlamydia infection.

Among males, symptoms can begin with urethritis. If left untreated, it can progress to epididymitis, infertility, and Reiter syndrome (a combination of urethritis, conjunctivitis, and arthritis).

Among females, symptoms may begin with cervicitis (infection of cervix), which, if left untreated, can progress to pelvic inflammatory disease, infertility, or ectopic pregnancy. Infection during pregnancy can lead to pneumonia and eye infections in the newborn.

Diagnosis of chlamydia is made with tests for Gram stain and nucleic acid amplification. Treatment is with broad-spectrum antibiotics of the infected individual and all sexual partners. Lymphogranuloma venereum is a manifestation of chlamydia infection in which a minor skin lesion progresses to inguinal or femoral lymphadenopathy (lymph nodes become swollen and firm). Testing is by complement fixation. Treatment is with doxycycline or another antibiotic.

### Chancroid

Chancroid is caused by the bacillus *Haemophilus ducreyi*.<sup>78</sup> It is considered a highly contagious, sexually transmitted disease that is often associated with the transmission of HIV. Symptoms include painful, irregularly shaped ulcers (soft chancres) in the genital area. Untreated infections can progress to lymphadenopathy, lymph node abscesses (buboës), and severe tissue

destruction. Diagnosis can be made with tests that identify the bacillus DNA. Antibiotic treatment usually cures the infection.

## **Review Questions – ALU 201, Chapter 4**

1. Which laboratory test is commonly elevated with a normal pregnancy?
    1. globulin
    2. glucose
    3. alkaline phosphatase
    4. serum creatinine
  2. All the following statements regarding prostate specific antigen (PSA) are correct EXCEPT:
    1. Finasteride (Proscar<sup>®</sup>) may decrease serum PSA by 50%.
    2. The normal range for PSA in a 50-year-old male is 0-5.0 ng/ml.
    3. A normal PSA does not rule out prostate cancer.
    4. Males with prostate cancer tend to have a lower percentage of free PSA than those without prostate cancer.
  3. Which of the following statements regarding testicular cancer is/are correct?
    - A. Treatment commonly consists of orchectomy.
    - B. Seminomas are more difficult to treat than non-seminomas.
    - C. Individuals with metastasis seldom achieve remission.
- Answer Options:
1. A only is correct.
  2. A and C only are correct.
  3. B and C only are correct.
  4. A, B, and C are correct.
4. There are two types of endometrial cancer. Compare and contrast type 1 and type 2.
  5. Review the different types of sexually transmitted diseases (STDs).

6. Which of the following statements regarding human papillomavirus (HPV) infection is/are correct?
- A. It can increase the risk of cervical cancer.
  - B. Relapse is frequent and requires re-treatment.
  - C. Its risk increases with a history of multiple sexual partners.

Answer Options:

1. A only is correct.
2. A and B only are correct.
3. B and C only are correct.
4. A, B, and C are correct.

7. All the following statements regarding cervical cancer are correct EXCEPT:
1. Clear cell carcinoma is the most common histological type.
  2. Routine Pap testing often detects early cervical dysplasia.
  3. It is often associated with certain strains of human papillomavirus (HPV).
  4. Cigarette smoking increases the risk of cervical intraepithelial neoplasia (CIN).
8. Review the four different types of breast diseases.
9. Review the types of abnormal uterine bleeding.
10. Identify three benign disorders of the prostate and briefly discuss each.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 3: alkaline phosphatase – page 18.

### *Review Question 2*

Answer 2: The normal range for PSA in a 40-year-old male is 0-5.0 ng/ml – page 6.

### *Review Question 3*

Answer 1: A only is correct – page 8.

### *Review Question 4*

Refer to pages 15-16.

### *Review Question 5*

Refer to pages 21-25.

### *Review Question 6*

Answer 4: A, B, and C are correct – page 22.

### *Review Question 7*

Answer 1: Clear cell carcinoma is the most common histological type – page 16.

### *Review Question 8*

Refer to pages 11-12.

### *Review Question 9*

Refer to pages 12-13.

### *Review Question 10*

Refer to pages 5-8.

## **CHAPTER 5**

### **DISORDERS OF THE NERVOUS SYSTEM**

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## DISORDERS OF THE NERVOUS SYSTEM

### Introduction

Neurological symptoms and nervous system disorders can be among the most complex problems that an underwriter encounters. These disorders can be notoriously difficult to diagnose, and it is important that the underwriter be equipped with the proper knowledge in order to reach a judgment about the relevance of certain symptoms and the prognosis of the most common disorders.

To this end, this chapter will explain:

1. the anatomy and basic physiology of the nervous system
2. the investigations and tests that can be used to aid in reaching a diagnosis
3. some of the more common nervous system disorders.

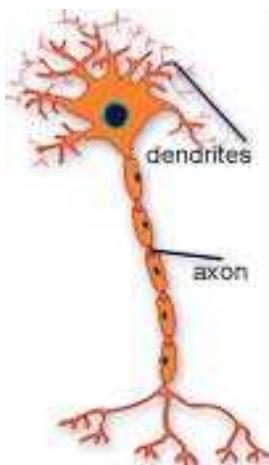
### Anatomy, Physiology, and Structure of the Nervous System

This section of the chapter will contain an abbreviated explanation of the human nervous system. For a more complete description, the reader is referred to the appropriate section in the *Essentials of Anatomy and Physiology* textbook.

The nervous system is comprised of two basic systems: the central nervous system (CNS), consisting of the brain and spinal cord, and the peripheral nervous system, consisting of all the nerves that connect the central nervous system with sensory receptors and muscles in the periphery of the body.

The nervous system is made up of specialized cells called *neurons*. There are approximately 200 billion neurons in the human body, about half of which are in the brain. A typical neuron consists of a cell body, from which dendrites spread, resembling the branches of a tree. A longer projection called an axon stretches out from the cell body, like the trunk of a tree. (Figure 1)

**Figure 1. Typical Neuron.**



*Source:*  
[www.brainexplorer.org/brain\\_atlas/Brainatlas\\_index.shtml#image](http://www.brainexplorer.org/brain_atlas/Brainatlas_index.shtml#image)

The axons are responsible for conducting impulses away from the cell body and dendrites conduct them towards it. Neurons connect with other neurons at specialized junctions called *synapses*, and the impulses themselves are passed from one neuron to another by way of chemicals called neurotransmitters.

Neurons are supported by a variety of other cells, to insulate them in much the same way as an electrical cable is insulated. Myelin, a white fatty substance, is wrapped around the axon of the nerve cell to protect it and to help with the conduction of nerve impulses. Axons that have this appearance are collectively known as “white matter;” the nerve cell bodies that are not covered in myelin are known as “gray matter.”

## The Central Nervous System

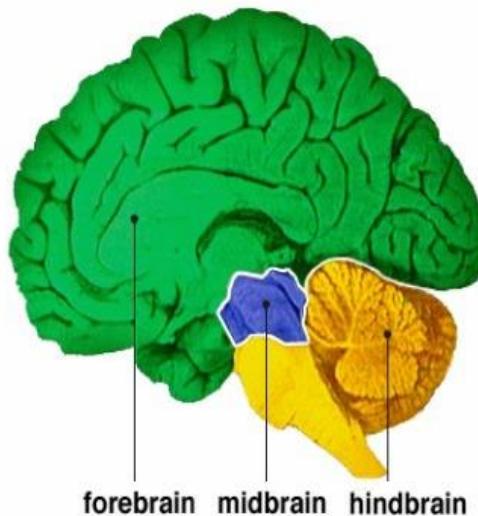
### *The Brain*

The brain is the control center not only of the nervous system, but the whole body. It contains the sum of an individual’s lifelong experience in the form of memories, as well as inherited information in the form of instincts and the genetic predisposition towards certain behaviors that underlie an individual’s personality. In evolutionary terms, all brains are an extension of the spinal cord. In the fetus, the brain develops at the head end of a hollow tube of cells, which later becomes the spinal cord.

Brains require a huge supply of oxygen. Approximately 18% of the entire blood supply is directed towards the brain via the carotid arteries, and around 20% of the oxygen absorbed by the lungs is used by the brain. The maintenance of a constant supply of oxygen is vital, as even a brief interruption in supply can result in symptoms, and a stoppage over a period of several minutes can cause permanent damage or even death.

The brain can be divided into three regions: the forebrain, the midbrain and the hindbrain.

**Figure 2. Regions of the Brain.**



*Source:* The Open University, Milton Keynes, United Kingdom.

Each area of the brain contains specific structures:

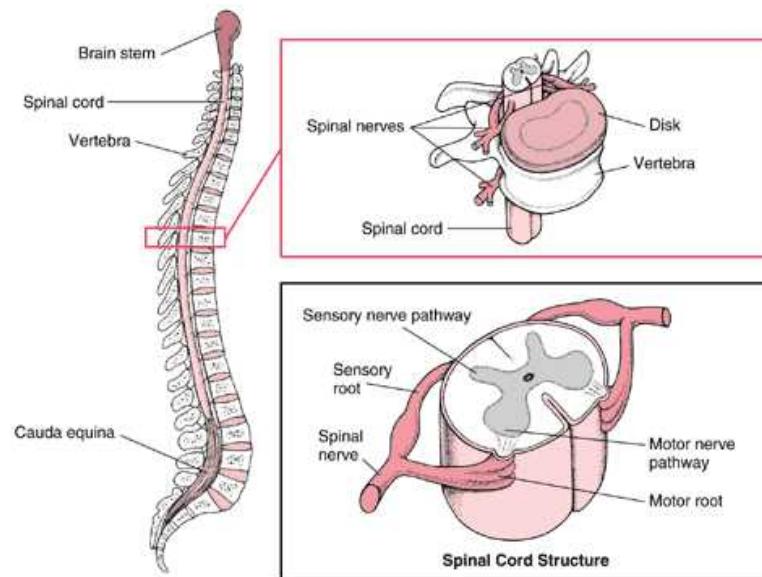
1. The forebrain consists largely of the cerebral cortex, which is the most highly developed part of the brain, making up about 70% of the total brain cells. It is here that nerve impulses are received and analyzed. Memories are also stored here, and processes such as conscious thought, reasoning, deliberation, and judgment are all said to take place within the cerebral cortex.
2. The midbrain is so called because of its physical position, between the forebrain and hindbrain. The midbrain connects the spinal cord with the forebrain and forms a major part of the brainstem, which is the connection between the brain and the spinal cord.
3. The hindbrain includes the medulla oblongata, which is joined to the spinal cord and is responsible for the control of vital functions such as breathing, blood circulation, and swallowing. Also included in the hindbrain is the cerebellum that coordinates movement and is partially responsible for learning motor actions, such as riding a bicycle.

### *The Spinal Cord*

The spinal cord runs from the end of the brain stem to the bottom of the spinal column. It is the pathway that carries both incoming and outgoing messages to and from the brain and the rest of the body.

Thirty-one pairs of spinal nerves come from the spinal cord, with a pair of spinal nerves emerging from behind each vertebral body (plus a pair above the C1 vertebra). Each spinal nerve has two short branches or roots, the front one being the motor root and the rear one, the sensory root (Figure 3). The sensory roots convey messages from the body to the brain, and the motor roots convey messages from the brain to the rest of the body, especially the skeletal muscles.

**Figure 3. The Spinal Column.**



**Source:** [www.merck.com](http://www.merck.com)

The ‘true’ spinal cord ends about three-quarters of the way down the spinal column, but its extension, the cauda equina, supplies the nerves to the legs. The spinal cord is also made up of

gray and white matter, although, in this case, it is the outside area that consists of white matter and the inner area that consists of gray matter. The white matter carries columns of sensory fibers (i.e., ascending tracts) and motor fibers (i.e., descending tracts).

### The Peripheral Nervous System

The peripheral nervous system consists of nerves that are outside the brain or spinal cord. It is comprised of the 12 cranial nerves, all of which originate from the brain, and 31 pairs of spinal nerves, which arise from the spinal cord.

The peripheral nervous system is split into two main separate systems, the somatic and autonomic nervous systems:

1. The somatic nervous system is made up of the nerves that connect the brain and spinal cord with skeletal muscles that are under voluntary control, such as the muscles of the arms and legs. The somatic nervous system also connects sensory organs with the brain, including receptors in the skin that convey information about touch and pain.
2. The autonomic nervous system connects the brain and spinal cord with the internal organs and all the processes within the body that are not under voluntary control, such as heart rate, respiration, and the digestive processes, the latter of which is sometimes known as the enteric autonomic nervous system. There are two parts to the autonomic nervous system that work in conjunction with one another: the sympathetic nervous system and the parasympathetic nervous system. The sympathetic nervous system prepares the body for flight or fight and deals with emergency situations. The parasympathetic nervous system maintains the internal status quo in everyday scenarios and will reduce heart rate and blood pressure after the response to an emergency.

### **Diagnostic Investigations**

This section of the chapter will look at the commonly used investigative techniques for diagnosing neurological disorders. The most important diagnostic techniques are the history taking and the physical examination. Observation of the patient is a very important part of the physical exam.

#### Observation

Observation of the individual is of vital importance and can be a primary tool in diagnosis and treatment. Is the person conscious? Is he having any form of seizure? Is there any overt sign of injury, especially a head injury? Is there any indication that psychoactive substances have been used? Does the person smell of alcohol? Is he confused? Is there any numbness? Is there any paralysis? All of these important observations are helpful in reaching a final diagnosis.

#### History

After the initial observation of the individual, it is usual for a history to be taken. This will involve the physician questioning the individual about the history of his illness, what his symptoms

are, how often they occur, how severe they are and how long they last. It is also likely that the person will be questioned about his past health, his lifestyle, including occupation, and whether there is any relevant family history. In addition to questions about the person's physical health, the physician will ask about mental health; for example, if there is any history of depression, or any problem related to work or family environment.

### Physical Examination

If a disorder is suspected, a physical examination will be conducted with emphasis on the nervous system. This will include tests for reflexes, sensation, motor movement, coordination, gait, and stance as well as for the internal body systems regulated by the autonomic nervous system. The mental status exam of the patient is also important.

Neurological symptoms and signs can be numerous and varied, but the more common ones include:<sup>1</sup>

1. pain – headache, neck pain, back pain
2. muscle problems – paralysis, weakness, abnormality in gait, clumsiness and/or poor coordination, muscle spasms, tremor, rigidity
3. sensory problems – loss of sensation of touch, heat, cold, or pain; loss of positional sense, tingling/paresthesia, vertigo, double/blurred vision, partial or complete loss of vision, deafness, altered smell or taste
4. altered consciousness – seizures, fainting, dizziness, confusion or delirium, dementia, coma, vegetative state.

Depending on which particular symptoms the individual is exhibiting, further investigation can be considered necessary to confirm the suspected diagnosis.

In addition to physical symptoms, the physician can also test the person's mental status by asking certain questions, for example:<sup>1</sup>

1. naming the day of week and the date
2. naming specific people (e.g., the President)
3. repeating a list of objects
4. recalling the same list after a period of time has elapsed
5. following simple commands
6. describing an event in the recent past and one in the distant past
7. describing his feelings and thoughts about his illness.

Following completion of the initial examination and history taking, the attending physician can request further tests, the most common of which are described below.

### Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can create highly detailed images of the internal structures of the body by using magnetic fields and very high frequency radio waves.<sup>1</sup> As MRI scanning is

able to provide detailed images of areas of the body that are surrounded by bone, it is ideal for examining the brain and spinal cord, and is, therefore, the best technique for diagnosing multiple sclerosis, brain tumors, or stroke.

Because MRI scanners use magnetic fields rather than x-rays, the procedure is generally considered to be safe, although it is not suitable for those with pacemakers or surgical clips, nor for those who suffer from severe claustrophobia since the individual must lie still within a cylindrical chamber for periods between 10-90 minutes. Although open-sided scanners can be used in the latter circumstance, the results will not be as detailed as those produced by the closed version.<sup>1,2,3</sup>

Functional MRI (fMRI) scanning is a relatively new procedure that is used to measure metabolic changes in the brain. It helps identify precisely which areas of the brain are used to process functions such as speech, movement, and sensation and it is of particular use following strokes to identify which areas of the brain have been damaged. Functional MRI is also useful in planning surgery on the brain. In surgeries involving a tumor, for example, the surgeon will be able to ascertain what functions are likely to be affected when the tumor is removed.<sup>4</sup>

### Computerized Tomography Scanning

Computerized tomography (CT) scanning, otherwise known as computerized axial tomography (CAT) scanning, uses x-rays taken from many different perspectives which are then processed on a computer to produce two-dimensional images.<sup>1,2</sup> CT scanning can be used to detect a wide range of neurological disorders, from hydrocephalus to brain tumors. It provides clearer images of the skull and spine than MRI scanning and is better at detecting bleeding within the brain in the first 24 hours after a hemorrhagic stroke.<sup>1</sup>

### Magnetic Resonance Angiography

A magnetic resonance angiography (MRA) uses much the same technology as MRI scanning, i.e., powerful magnetic fields and high frequency radio waves. It can be performed with or without the use of contrast material. An MRA looks specifically at blood vessels within the body, usually within key areas such as the brain, general head and neck circulation, heart, and lungs.<sup>5</sup>

It can be used to identify atherosclerosis within the carotid arteries, small aneurysms and arteriovenous malformations within the brain, and many other vascular problems. Like MRI scanning, because no radiation is involved, it is considered to be a safe procedure with the same caveats regarding unsuitable patients as for MRI.<sup>5</sup>

### Computerized Tomography Angiography

Like a standard CT scan, a CT angiography (CTA) uses x-rays to produce an image of the area under examination. In this case, a contrast material is injected into the individual before the scan takes place so that the blood vessels in the area under examination will be highlighted.<sup>6</sup>

A CT angiography is also used to examine blood vessels within specific areas of the body and for much the same purposes, although a CTA is better at capturing images of calcium deposits in blood vessels.<sup>6</sup> There are advantages and disadvantages associated with both MRA and CTA. High quality images are harder to obtain with MRAs; however, they do not expose the patient to radiation as does a CTA.

### Cerebral Angiography

Cerebral angiography provides an image of the blood vessels and circulation in the brain. A contrast is injected into the carotid arteries and then regular x-rays are taken which highlight the passage of the contrast medium through the cerebral circulation.<sup>7,8</sup>

This provides an extremely detailed and accurate picture of the blood vessels. If a catheter is used, it can enable treatment to take place at the same time as the diagnostic investigations.<sup>7,8</sup>

### Positron Emission Tomography

Positron emission tomography (PET) produces three-dimensional images. It is a metabolic imaging procedure in which a small amount of a radioactive substance, known as a tracer, is introduced into a person's body, usually by way of intravenous injection. This tracer is absorbed at differing rates by different tissues, and this is detected by the scanner, with active "hot spots," such as tumors, appearing brighter than normal tissues.<sup>9</sup>

PET is commonly used to detect tumors throughout the body, but it can also be used to evaluate individuals who have memory disorders or intractable seizure disorders.<sup>4,9</sup> It is very helpful in differentiating scar tissue from recurrent tumor.

### Lumbar Puncture

In a lumbar puncture, or spinal tap, a needle is inserted into the spinal canal to extract cerebrospinal fluid (CSF) from the subarachnoid space. It is used to detect tumors, infection, injury, and bleeding within the brain or spinal cord. White blood cells are indicative of infection. Culture of the fluid can be used to identify the type of infection. Examination of any abnormal-appearing cells can be used to identify tumors. High protein levels indicate brain or spinal cord damage but do not diagnose the cause of the damage. Elevated antibody levels are suggestive of multiple sclerosis, and low sugar levels relate to a diagnosis of meningitis or tumor.<sup>1,4</sup> The spinal fluid pressure can be measured. Elevated CSF pressure can be seen with tumors, bleeding, and venous thrombosis.

### Evoked Response Tests

Evoked response tests measure electrical activity in the brain in response to stimulation by sound, sight, or touch. The electrical activity in the relevant area of the brain is measured by electroencephalography (EEG) and provides information about how that area of the brain is functioning.<sup>1,10</sup>

Evoked response tests include:

1. The brainstem auditory evoked response (BAER) test is used to measure hearing ability. Abnormal results can be indicative of multiple sclerosis or brain stem tumors.<sup>10</sup>
2. The visual evoked response (VER) test is used to diagnose optic nerve problems. Abnormal results can be indicative of multiple sclerosis.<sup>10</sup>
3. The somatosensory evoked response (SSER) test is used to detect problems with the spinal cord as well as numbness or weakness of the extremities.<sup>10</sup>

### Electroencephalogram

An electroencephalogram (EEG) detects abnormalities in activity within the brain. It is mainly used to diagnose seizure disorders but can also be useful in evaluating brain damage caused by stroke or head injury.<sup>1,11</sup>

### Electromyography

Electromyography (EMG) is used to assess and record the electrical activity of muscles, both at rest and during contraction. In a normal muscle, there is no electrical activity at rest. Minor muscle contractions produce a small amount of activity that increases as the size of the contraction increases.<sup>1</sup> An EMG test is usually used in conjunction with nerve conduction studies to diagnose disorders of the muscles, peripheral nerves, or the neuromuscular junction.<sup>1,11</sup>

### Nerve Conduction Studies

Nerve conduction studies measure the speed of conduction of nerve impulses in both sensory and motor nerves. They are used in conjunction with an EMG test to determine whether symptoms such as muscle weakness are a result of a nerve disorder. For example, in carpal tunnel syndrome, the nerve is pinched by ligaments and the nerve conduction speed is usually slowed. However, if the weakness is the result of a muscle, brain, or spinal cord disorder, then conduction speeds are unaltered and the EMG is normal. Weakness can also occur where there is dysfunction at the neuromuscular *junction*, although both nerve and muscle are normal, as happens in myasthenia gravis.<sup>1</sup>

## **Neurological Disorders**

### Carotid Artery Stenosis

Carotid artery stenosis usually arises as a result of generalized atherosclerotic disease and is a significant cause of both transient ischemic attack (TIA) and stroke, accounting for up to 7% of strokes in previously asymptomatic individuals or in those with a stenosis of less than 60%. A much higher percentage of TIAs and strokes occur in those who are either symptomatic or who have a greater degree of carotid artery stenosis. It is more prevalent in females than in males and increases with age and the presence of other cardiovascular risk factors such as hypertension, dyslipidemia, obesity, diabetes, and smoking.<sup>12,13,14,15</sup>

In individuals who are asymptomatic, where there has been no history of TIA or stroke, carotid artery stenosis can be diagnosed by the detection of a carotid bruit (i.e., an audible sound due to turbulent blood flow in the affected artery) on physical examination. The diagnosis can be confirmed by non-invasive techniques such as carotid duplex ultrasonography, MRA, or computed tomographic angiography (CTA).<sup>12</sup>

In some cases, treatment can entail only reducing co-existing cardiovascular risk factors. Or it can involve the use of anti-platelet drugs (e.g., low dose aspirin) or, in some cases (usually when the stenosis is >70%), by having a carotid endarterectomy, although the benefit of all these forms of treatment is uncertain. High grade carotid stenosis associated with TIA is most successfully treated by endarterectomy.

The presence of carotid artery disease is usually associated with atherosclerosis in other organs such as the heart. When underwriting cases of carotid artery stenosis, it is important to ascertain:

1. results of all investigations, including the degree of stenosis
2. whether there is a previous history of TIA or stroke
3. the presence or absence of co-existing cardiovascular risk factors
4. treatment given, if any.

### Cerebrovascular Accident and Transient Ischemic Attack

The brain requires about 20% of the blood circulation. The primary blood supply to the brain is through the two carotid arteries in the neck, which then branch within the brain into multiple arteries, each supplying a specific part of the brain. Even a brief interruption to the blood flow can cause a decrease in brain function. The symptoms will vary depending on which part of the brain is affected, but they will commonly include changes in vision and/or speech, decreased movement or sensation, or changes in the level of consciousness. If the blood flow is interrupted for longer than a few minutes, then oxygen starvation sets off a chain of events that can result in destruction of brain cells, causing permanent damage. However, if blood flow is restored quickly, the effects can be reversible, as in a TIA.<sup>16</sup>

#### *Stroke*

A stroke is defined by the World Health Organization as “the clinical syndrome of rapid onset of focal (or global, as in subarachnoid hemorrhage) cerebral deficit, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one.”<sup>17</sup> A stroke, if survived, results in a loss of brain function or a neurological deficit caused by a lack of blood flow to a specific area of the brain, resulting in death of tissues in that area (i.e., infarction). The neurological deficit will vary depending on the location and the extent of damage and is typically exhibited on one side of the body, but can be isolated to specific functions.

Stroke affects about 700,000 Americans each year. It is the third leading cause of death in most developed countries and kills approximately 163,000 people in the U.S. annually. The incidence of stroke rises with age and is more common in females than in males.<sup>18,19</sup>

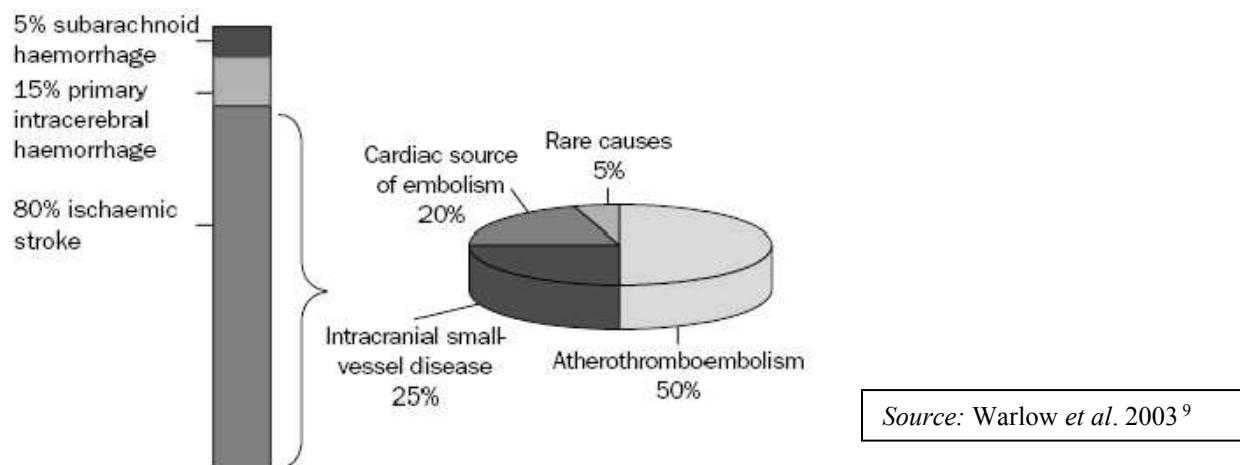
There are two main pathological types of stroke:

1. primary ischemic stroke
2. primary intracerebral hemorrhage.

Subarachnoid hemorrhage can be classified as a stroke, but it is more usually treated as a separate entity and is covered in further detail later on.

### Ischemic Stroke

By far, the most common cause of stroke is ischemia. (Figure 4)



**Figure 4. Approximate frequency of the main types of stroke (in a Caucasian population) as shown by population studies.**

Causes of ischemic stroke include:

1. atherosclerosis
2. blood clot that forms in the brain (thrombus)
3. blood clot or piece of atheromatous plaque or other material that travels to the brain from another location.

Ischemic stroke most commonly results from atherosclerotic disease. Occlusion of the artery develops slowly. However, since the brain is so well supplied with blood vessels, it tends to compensate for the blockage of one artery by increasing flow through others in the same area. Therefore, it is possible to observe totally blocked arteries within the brain without any sign of neurological deficit. Additionally, the arteries within the brain are sufficiently large that they can be blocked up to 75% of their diameter and still provide an adequate blood supply to that area of the brain.<sup>18,19,20</sup>

Ischemic strokes usually develop in the presence of atherosclerosis when a small thrombus, often from disease in the carotid arteries, develops and becomes lodged in one of the smaller cerebral vessels. This is similar to what occurs in the coronary arteries during a heart attack. Thrombotic stroke is most common in older people, and often there is an underlying disease process, such as ischemic heart disease or diabetes.

### Embolic Strokes

Strokes caused by embolism are most commonly due to cardiogenic emboli, that is, clots that develop secondary to heart disorders such as valve defects or arrhythmia. In those less than 45 years of age, or in those who have a history of clotting dysfunction, disorders such as sickle cell anemia, polycythemia vera, protein S or C deficiency, or antiphospholipid syndrome should be considered.

The embolism travels through the arteries and becomes lodged in the small vessels of the brain. Onset will be sudden with severe neurological deficit. The outcome is worsened if the blood vessel ruptures and blood escapes into the brain. For underwriting purposes, embolic strokes should be treated in the same way as ischemic strokes.

### Vertebrobasilar Strokes

The arterial vertebral systems circulate blood within areas of the brain such as the medulla, the cerebellum, and the midbrain.<sup>21</sup> The blockage of large arteries in this area almost always results in severe disability or death, although those that arise from smaller vessels are survivable.<sup>21</sup>

In common with other forms of stroke, clinical symptoms are dependent on the site of the lesion but commonly include:<sup>21</sup>

1. cerebellar signs (e.g., ataxia)
2. dysarthria and dysphagia
3. vertigo, nausea, and vomiting.

Approximately 20% of all ischemic strokes occur in the vertebral system.<sup>21</sup>

### Lacunar Strokes

A lacunar infarct commonly occurs as a result of an occlusion to a large cerebral artery; most occur in the subcortical white matter, the basal ganglia or the pons.

The following have been identified as highly predictive for the presence of lacunes on radiological examination:

1. pure motor hemiparesis (45-57% of lacunar strokes)
2. pure sensory stroke (7-18% of lacunar strokes)
3. ataxic hemiparesis (3-18% of lacunar strokes)

4. sensorimotor stroke (15-20% of lacunar strokes)
5. dysarthria-clumsy hand stroke (2-6% of lacunar strokes)

They account for around 15% of first ischemic strokes, and can have a better short-term prognosis when compared with other forms of stroke, but the longer-term outlook is not significantly different.

### Intracerebral Hemorrhage

The risk factors for stroke are similar to those for cardiovascular disease. About 70% of stroke sufferers have a known history of high blood pressure or heart disease. Especially vulnerable are individuals whose history includes atrial fibrillation or flutter, smoking, a history of transient ischemic attacks, generalized atherosclerotic disease, hyperlipidemia, diabetes, or the use of the oral contraceptive pill (especially when combined with any of the above risk factors, especially smoking).

### Primary Intracerebral Hemorrhage

A primary intracerebral hemorrhage can occur for a number of reasons:<sup>22</sup>

1. as a result of hypertension, accounting for about 50% of all cases
2. when a blood vessel affected by disease bursts
3. when a blood vessel blocked by an embolism burst
4. when an arteriovenous malformation (AVM) or aneurysm ruptures.

A hematoma then develops, with a subsequent increase in pressure inside the skull and a loss of blood supply to areas beyond the site of the hemorrhage. Continued bleeding and re-bleeding are not uncommon.<sup>22,23</sup> A hematoma of greater than 30 mm is associated with a poor prognosis, as is an increased pulse pressure or reduced Glasgow Coma Score.<sup>22,23</sup>

### *Neurological Deficits from Stroke*

As mentioned above, the specific neurological deficit that arises as a result of stroke depends on the location and the amount of injury to the brain.

#### Right-Sided Stroke

The right hemisphere of the brain controls the movement of the left side of the body. It also controls analytical and perceptual tasks, such as judging distance, size, speed, or position.<sup>18,19</sup>

A stroke in the right hemisphere often causes paralysis in the left side of the body, known as left hemiplegia. Survivors of strokes affecting this part of the brain can also have problems with spatial and perceptual abilities. They can also have judgment difficulties, and their behavioral style can change, with them often becoming impulsive. Memory can be impaired, but they may be unaware of their impairments and believe they have the ability to perform the same tasks as before the stroke.<sup>18,19</sup>

## Left-Sided Stroke

The left hemisphere of the brain controls the movement of the right side of the body. It also controls speech and language abilities for most people. A stroke in the left hemisphere often causes paralysis of the right side of the body, known as right hemiplegia. These stroke victims can also develop aphasia, which is a broad term used to describe a wide range of speech and language problems. However, these problems can be highly specific, perhaps affecting only the patient's ability to communicate, such as the ability to move their speech-related muscles to speak properly. The same person can be completely unimpaired when it comes to writing, reading, or understanding speech.<sup>18,19</sup>

In contrast to survivors of a right-sided stroke, those who survive a left-sided stroke often develop a slow and cautious behavioral style, requiring frequent instructions and feedback to complete tasks. They can also develop memory problems similar to those experienced by sufferers of right-sided strokes, which can include shortened attention spans, difficulty in learning new information, and problems with conceptualizing.<sup>17,18</sup>

There is no known cure for a stroke; however, thrombolytic treatment with "clot busting" drugs such as tPA, if given early enough after the onset of an ischemic stroke, can have a significant effect on prognosis.<sup>20</sup> Following stabilization of an individual, treatment generally consists of rehabilitation based on the symptoms presented; however, surgery can be used to remove blood or blood clots from the brain and to repair the source of any hemorrhage, if those areas are accessible. About one quarter of stroke victims die as a result of stroke, half have long-term disabilities, and the remaining quarter recover most or all function.

## Transient Ischemic Attack (TIA)

The symptoms and presentation of a transient ischemic attack can be similar to that of stroke. TIAs usually occur when the blood supply to the brain is only briefly interrupted. The terms minor stroke and TIA are often used interchangeably, but in general the symptoms of TIA persist for a period of less than 24 hours.<sup>18,24</sup> A transient ischemic attack leaves no permanent deficits. TIAs are often seen as a warning sign that an individual may be at an increased risk of a more serious cerebrovascular event.<sup>24</sup>

### *Underwriting Considerations*

The underwriting considerations for TIA and all types of completed stroke are similar, and should include:

1. age at time of episode
2. time elapsed since episode occurred
3. any persisting neurological deficit
4. underlying cause, if known
5. if hypertensive, adequacy of control (i.e., BP < 140/90)
6. presence or absence of co-existing risk factors.

## *Subarachnoid Hemorrhage*

The term subarachnoid hemorrhage indicates the presence of blood within the subarachnoid space, usually as a result of the rupture of an intracranial aneurysm.<sup>16</sup> An intracranial aneurysm is usually caused by the weakening of a blood vessel wall, causing bulging and potential rupture.

Other causes of subarachnoid hemorrhage include:

1. arteriovenous malformations (AVMs) – congenital abnormalities in the development of the vasculature of the brain and/or spinal cord – They are characterized by a tangle of arteries and veins with abnormal connections between the two, commonly called fistulas.<sup>25</sup>
2. hematomas - areas of bruising of the brain causing bleeding – The bleeding is commonly a result of trauma rather than a disease process.

The incidence of subarachnoid hemorrhage in the United States is estimated to be between 6-25 per 100,000, with more than 27,000 Americans suffering ruptured aneurysms each year. This annual incidence increases with age, and it is more common in females than in males. Up to 15% of individuals die before reaching the hospital, and up to 50% die within six months following the event.<sup>26</sup>

Common symptoms include:<sup>26</sup>

1. sudden onset of severe headache (although there can have been less severe headaches previously from leaking aneurysms, so called prodromal headaches)
2. nausea and vomiting
3. photophobia
4. possible loss of consciousness or convulsions
5. possible neurological symptoms - These are likely to vary depending on the site of the bleed.

If a diagnosis of a subarachnoid hemorrhage is suspected, a CT scan is usually performed, although in up to 20% of patients, the scan results are negative.<sup>26</sup> Once the diagnosis is confirmed, it is likely that a cerebral angiogram will be performed to identify the cause and precise location of the bleed and, if aneurysmal, whether there are other aneurysms present.

Treatment will depend on the site and size of the aneurysm(s). Clipping is still the most common therapy in the United States. The aneurysm is “shut-off” using a clip applied to the neck of the aneurysm, which stops blood flow to the aneurysm and separates the aneurysm from the rest of the blood vessel.<sup>27</sup> However, a newer procedure that is replacing clipping in many instances is endovascular coiling. In this procedure, a coil, usually consisting of platinum wire, is inserted through a catheter into the aneurysmal area of the affected blood vessel, effectively sealing it off from the general circulation and preventing further rupture.<sup>28</sup> Recent studies have shown that the use of endovascular coiling as a treatment for intracerebral aneurysms gives a much better prognosis than clipping, with those who have been treated with coiling having a much lower risk

of death or disability one year after the event, when compared with those treated by clipping.<sup>28</sup> The technique used will depend on the location and severity of the aneurysm.

In general, the prognosis of an individual who has suffered a subarachnoid hemorrhage is related to the severity of the initial episode. Even for those who have received appropriate treatment, more than a third of survivors will have cognitive and/or significant neurological deficits.<sup>28</sup>

Factors to consider when underwriting include:

1. severity of initial episode
2. results of all investigations and details of treatment given
3. presence or absence of continuing neurological symptoms, including epilepsy
4. control of any co-existing risk factors, particularly hypertension.

### Multiple Sclerosis

Multiple sclerosis (MS) is the most common disabling neurological disorder affecting young adults. It affects around two million people worldwide, of which approximately 450,000 are European and 400,000 are North American.<sup>29</sup> This disease is most common in Caucasians. The lifetime risk of developing multiple sclerosis in northern Europe is about one in 1,000, and females are twice as likely to be affected as males.<sup>29</sup>

MS is a multifactorial disease, with both genetic and environmental factors being associated with an increased risk of developing it. A genetic study conducted in 2001 was able to identify a complex trait related to multiple sclerosis that is not strictly dominant, recessive, or sex-linked, and appears to involve the interaction of two or more genes.<sup>30</sup>

The chance of developing multiple sclerosis among the United States population in general is roughly 0.1%. However, among first-degree relatives (i.e., parents, siblings, and children) the risk rises to approximately 3%. Studies suggest an incidence as high as 4% among siblings, due to simultaneous viral exposure while growing up. Also suspect is the possibility that members of the same family can have a genetic predisposition to the disease.<sup>30</sup>

#### *Subtypes of MS*

Multiple sclerosis can be classified into a variety of subtypes:

1. Most individuals (50-80%) present with a relapsing-remitting form of the disease, which is characterized by exacerbations followed by periods of remission.
2. The majority of these will develop a secondary progressive form of the disease that is characterized by insidious neurological deterioration, with or without superimposed relapses. It is this form of multiple sclerosis that most commonly leads to disability.<sup>30</sup> It is not possible at onset to judge when and at what stage the disease process will convert from a relapsing-remitting form of the disease to a secondary progressive form (see Table 1).<sup>31</sup>

- Primary-progressive multiple sclerosis accounts for only about 10% of those with MS and is characterized by progression from onset, usually without any superimposed relapses. This type is as common in males as in females and usually occurs at ages over 40 years.<sup>29,32</sup>

**Table 1. Conversion from relapsing-remitting to secondary progressive multiple sclerosis over time.**

*Source: [www.hta.ac.uk/fullmono/mon610.htm](http://www.hta.ac.uk/fullmono/mon610.htm)*

Duration of MS (years)	% Converted from RR to SP
1–5	12
6–10	41
11–15	58
16–25	66
26+	89

Most individuals will experience a “clinically isolated syndrome” (CIS); this must last at least 24 hours, and is likely to be caused by inflammation of the myelin sheath of the nerve in one or more sites in the central nervous system.<sup>33</sup> The most common initial symptoms of multiple sclerosis are likely to be a loss of sensation in the arms or legs, or a sensation often described as tingling or pins and needles in the affected areas. Alternatively, the disease can affect the optic nerve or the area of the brain controlling eye movement, with the individual suffering reduced, blurred, or double vision. However, as demyelination can affect any area within the central nervous system, the symptoms and signs are likely to vary from person to person, both at onset, and throughout the disease course.<sup>31,34,35</sup>

**Table 2. Multiple sclerosis related symptoms.**Source: [www.hta.ac.uk/fullmono/mon610.htm](http://www.hta.ac.uk/fullmono/mon610.htm)

Symptom	Symptom at any time (%)	Symptom at onset (%)	Symptom at prevalence (%)	Persistent symptom (%)	Mean time with symptom (years)	Maximum time with symptom (years)
Weakness	89	22	80	62	14.4	52.5
Sensory	87	34	73	52	13.1	44.5
Axiois	82	11	72	58	12.5	52.5
Bladder	71	1	62	45	8.1	35.5
Fatigue	57	2	48	31	10.9	42.5
Cramps	52	0.6	44	26	8.3	42.5
Diplopia	51	8	26	18	14	44.5
Visual	49	13	33	23	12	40.5
Bowel	42	0	37	19	6	22.5
Dysarthria	37	0.6	25	16	8	38.5
Vertigo	36	4.3	19	13	7.4	28.5
Facial pain	35	2	14	9	8.9	28.5
Poor memory	32	0.3	27	0	6.2	28.5
Headache	30	2	17	7	14	37.5
Neuro-psychiatric	23	0.3	16	7	8.4	26.5
Deafness	17	0.6	13	8	7.6	24.5
Facial weakness	16	1	5	3	11.8	35.5
Dysphagia	13	0.3	10	5	6.4	19.5
Skin sores	12	0	7	4	6.4	40.5
Blackouts	11	0.6	4	2	19.7	35.5
Ageusia	6	0.3	2	0.3	10.1	42.5
Other	10	1	8	5	8.8	38.5

Optic neuritis has a close relationship with multiple sclerosis and is characterized by loss of vision, dyschromatopsia (i.e., abnormal color vision), and eye pain. Loss of vision is usually most profound in the central visual field and can deteriorate with exercise or after taking a hot bath; this is known as Uthoff's phenomenon.<sup>36,37,38</sup>

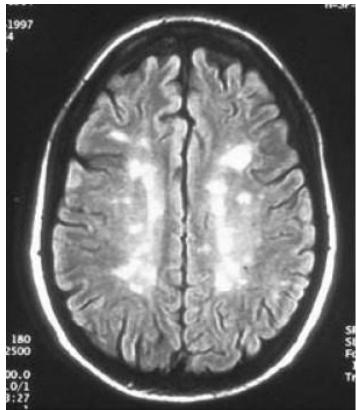
The close relationship of optic neuritis and multiple sclerosis is such that up to 85% of individuals who have suffered from optic neuritis will go on to develop clinically definite multiple sclerosis. Factors that seem to increase the risk include younger age at onset, female gender, and a history of non-specific sensory symptoms.<sup>39</sup> There are many other manifestations of multiple sclerosis including fatigue, weakness, increased muscle stiffness, poor coordination and balance, and problems with bladder and bowel control.<sup>34,35</sup>

### *Diagnosis of Multiple Sclerosis*

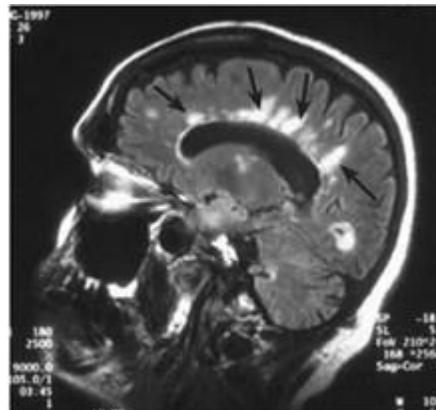
There is no single test that can confirm the diagnosis of multiple sclerosis; therefore, it is commonly diagnosed as a result of a combination of clinical symptoms and the results of certain investigations, most usually an MRI scan. Typically the MRI scan will show areas of high signal, predominantly in the cerebral white matter, especially in the peri-ventricular region or spinal cord (see Figures 5-7 and 8).<sup>40,42</sup>

## **Figures 5-6. MRI Brain Images.**

*Source:* Calabrese PA. *Am Fam Physician* 2004.



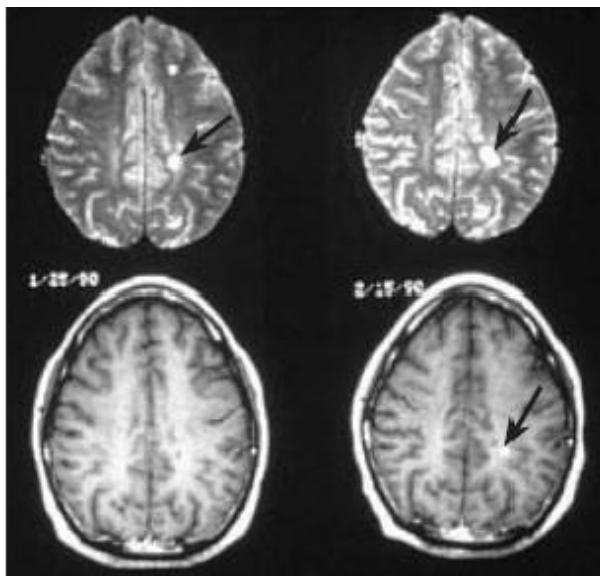
Multiple high signal peri-ventricular and white matter lesions.



Multiple high-signal white lesions (arrows) radiating from the surface of the lateral ventricles

## **Figure 7. MRI Brain Images.**

*Source:* Calabrese PA. *Am Fam Physician* 2004.



Top Left: T<sub>2</sub>-weighted slices showing characteristic high signal white matter lesions (arrows) and revealing the burden of disease over time.

Bottom Left: T<sub>1</sub>-weighted slices, with gadolinium contrast enhancement of one of the lesions (arrow) indicating permeability of the blood-brain barrier.

**Figure 8. MRI scans of spinal cord in a patient with multiple sclerosis.**

Source: Calabrese PA. *Am Fam Physician* 2004.



Left: Sagittal images reveal multiple high-signal lesions (arrows) within the spinal cord consistent with demyelination.

Right: These lesions that can also be seen on the transverse cuts, are often situated dorso-laterally and are usually less than one vertebral body in length. The lesions rarely cause cord swelling.

The diagnosis of clinically definite multiple sclerosis requires that there have been two attacks that are disseminated in time and space (i.e., they are two distinct attacks, affecting two different areas of the body). The McDonald criteria are those most commonly used in diagnosis, they were originally published in 2001, revised in 2005 and 2010, and reviewed again in 2017.<sup>41,42</sup>

	Number of lesions with objective clinical evidence	Additional data for a diagnosis of MS
<u>&gt;2 clinical attacks</u>	<u>≥2</u>	None*
<u>&gt;2 clinical attacks</u>	1(as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location <sup>†</sup> )	None*
<u>≥2 clinical attacks</u>	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI <sup>‡</sup>
<u>1 clinical attack</u>	<u>≥2</u>	Dissemination in space demonstrated by an additional

		clinical attack or by MRI* OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	<u>1</u>	Dissemination in time demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack OR by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonyms.		
*No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typically clinically isolated syndrome, or with atypical features. If imaging and other tests (e.g. CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternate diagnoses should be considered.		
† Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed.		
‡ The MRI criteria for dissemination in space are:		
<ul style="list-style-type: none"> <li>• One or more T2-hyperintense lesions that are characteristic of multiple sclerosis in two or more of four areas of the CNS: periventricular, cortical or juxtacortical, and infratentorial brain regions, and the spinal cord.</li> </ul>		
§ The MRI criteria for dissemination in time are:		
<ul style="list-style-type: none"> <li>• The simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI.</li> </ul>		
¶ The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.		

The diagnoses given are likely to be:

1. multiple sclerosis – There is evidence of dissemination of time and space, as well as clinical and paraclinical evidence to support a diagnosis of multiple sclerosis.
2. probable multiple sclerosis – Clinical and paraclinical evidence is strongly suggestive of multiple sclerosis, but perhaps the MRI is clear, or only shows one lesion, i.e., there is no evidence of dissemination in time and/or space.
3. possible multiple sclerosis – Symptoms are similar to those seen in multiple sclerosis, but the paraclinical evidence does not yet support this diagnosis. Additionally, alternate diagnoses cannot be held responsible for the symptoms.
4. not multiple sclerosis – Symptoms are able to be attributed to a cause other than multiple sclerosis.

In the relapsing-remitting form of the disease, relapses can occur one or more times a year, or even monthly. Recovery from an exacerbation can take days or weeks, but symptoms occasionally continue for several months. Upon resolution, the neurological symptoms can disappear completely, although meticulous examination often detects some residual deficit. Later exacerbations can be difficult to recognize, as the deficit can be superimposed on previous neurological impairment. In general, multiple sclerosis takes on a ‘waxing and waning’ character, although deficits tend to accumulate, with many individuals exhibiting progressively increasing disability.<sup>43,44</sup>

### *Treatment of Multiple Sclerosis*

Although there is no cure for multiple sclerosis, recent advances in treatment mean that some disease-modifying drugs can reduce the number and severity of relapses or slow the rate of progression.

Treatment for multiple sclerosis usually takes one of two forms:

1. symptomatic relief—Since symptoms are widespread, there are a wide variety of treatments available, from pain relief to antidepressants. Intravenous corticosteroid therapy can be used during acute attacks, and, while this therapy is likely to shorten the attack and facilitate recovery, there is no evidence to suggest that corticosteroids have a positive effect on long-term prognosis.
2. disease-modifying—The disease-modifying treatments are commonly split into 3 types as follows:
  - a. injectable therapies—These treatments are commonly used in relapsing-remitting (RRMS) disease and include beta-interferons such as (Avonex®, Rebif® and Betaseron®) and glatiramer acetate (Copaxone®))
  - b. infusion therapies—These treatments are usually monoclonal antibodies such as Lemtrada®, Campath® or Tysabri® which are used to treat RRMS, but other treatments also exist, such as Novantrone®. Because of cardiac toxicity, these treatments should only be used where the benefit to the patient will likely outweigh the risk, and is therefore more commonly seen in the treatment of progressive rather than relapsing disease.

- c. oral therapies—The use of oral treatments, such as Gilenta®, Tecfidera® and, Aubagio® is becoming more wide spread. These treatments are easier to administer and early results indicate that these treatments are appearing to be as successful as infusible drugs when measured by reduction in relapse rate.

These treatments are still relatively new, but it is hoped that they will reduce the severity and number of relapses in those with relapsing-remitting MS and will slow progression. However, treatment with beta-interferons can produce side effects such as influenza-type symptoms and fatigue.<sup>40, 45</sup>

Side effects also occur with monoclonal antibodies, as well as with oral treatments. Examples are infusion-related reactions, headache, nausea, and diarrhea. Serious side effects include bradycardia, elevated liver enzymes, and idiopathic thrombocytopenia.<sup>45</sup> The use of Tysabri, while effective at decreasing the rate of relapse and disability progression, has been complicated by the development of progressive multifocal leukoencephalopathy in some patients, which usually leads to severe disability or death.

Complementary treatments such as physiotherapy and reflexology can be helpful in alleviating symptoms, particularly muscle spasms and spasticity.

Products based on marijuana, including medical marijuana and Sativex, a sublingual spray derived from cannabis, appear to improve or alleviate some of the symptoms of multiple sclerosis in some patients, but these products do not work for everyone and are not considered disease-modifying treatments.

### *Financial and Emotional Impact*

The varied physical and mental impairments of multiple sclerosis, including loss of stamina, paresthesias, and reduced cognitive abilities, can impact one's employment status. Progression of the illness results in the steady decline in the ability to work. Presently, only 25-40% of Americans with multiple sclerosis remain employed. Most individuals with multiple sclerosis are diagnosed with the disease as young adults, during the time period when they would ordinarily be marrying and starting a family. The emotional impact of MS can include diminished self-esteem, and depression is a natural side effect of multiple sclerosis as health declines.

### *EDSS Disability Scale*

Disability in multiple sclerosis is measured using the Expanded Disability Status Scale, which was developed by Kurtze in 1983. The scale ranges from 0-10 in increments that each represent a higher level of disability. Scoring is based on examination by a neurologist.

Grade	Status
0	Normal neurological examination
1.0	No disability, minimal signs in one FS*
2.0	Minimal disability in one FS*
3.0	Moderate disability in one FS*, or mild disability in 3 or 4 FS*. Patient is fully ambulatory.

4.0	Patient still fully ambulatory, self-sufficient and up 12 hours a day despite relatively severe disability in one FS*. Able to walk some 500 meters without aid or rest.
5.0	Ambulatory without aid or rest for about 200 meters. Disability severe enough to impair full daily activities.
6.0	Intermittent and unilateral assistance (cane, crutch, or brace) required to walk about 100 meters.
7.0	Unable to walk more than 5 meters even with aid; essentially restricted to wheelchair.
8.0	Essentially restricted to bed or chair. Unable to use wheelchair alone.
9.0	Helpless bed patient; can still communicate and eat.
10.0	Death due to MS.

\*FS – Functional System: Pyramidal functions; cerebellar functions; brainstem functions; sensory function; bowel and bladder function; visual function; cerebral (mental) function.

### *Underwriting Considerations*

The prognosis with MS can be difficult to ascertain; however, there are certain features that can help to identify those cases that can have a better outlook.

Favorable Features	Unfavorable Features
Female	Male
Relapsing-remitting onset	Progressive
Complete resolution of symptoms	Incomplete resolution of symptoms
Sensory symptoms only at onset	Bowel or bladder involvement
Long time period between attacks	Frequent attacks
Younger age at onset	Older age at onset
Long time to EDSS score of 4	Short time to EDSS score of 4

In line with these features, information that should be collected during underwriting includes:

1. whether there is a definite diagnosis
2. age at onset
3. which subtype of MS
4. date of last attack
5. frequency of attacks
6. current level of disability.

### Epilepsy

Epilepsy is a group of chronic disorders in which there is a tendency towards recurrent unprovoked and unpredictable seizures.<sup>46</sup> A seizure is an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex. Seizures can occur as a consequence of a wide range of genetic disorders, structural and functional abnormalities, and metabolic and other insults. Many non-epileptic events can be mistaken for seizures, depending on the individual's age, nature of the symptoms, and the circumstances of the attack; however, *epilepsy* is generally diagnosed after two or more unprovoked seizures.

Approximately 50 million people are affected with epilepsy worldwide. An incidence of around 50-70 cases per 100,000 per year and a prevalence of 5-10 cases per 1,000 population emphasize the frequency of this condition.<sup>46,47</sup>

Most causes of epilepsy are idiopathic, but about 1% of all epilepsies are caused by the inheritance of a single gene, while other forms can arise as a result of the interaction of many genes. The major known causes of epilepsy include:<sup>47,48</sup>

1. brain tumors
2. arteriovenous malformations
3. stroke.

The following can increase the relative risk of epilepsy by up to ten times:

1. head injury with concussion and one or more of the following:
  - a. loss of consciousness in excess of 30 minutes
  - b. some loss of memory after the injury
  - c. neurological abnormalities (e.g., weakness/poor coordination)
  - d. skull fracture
2. central nervous system (CNS) infections, e.g. meningitis
3. cerebral palsy with mental handicap
4. febrile seizures that are unusually long or frequent or that involve only one side of the body
5. alcohol abuse.

### *Types of Seizures*

Seizures are either focal or generalized at onset. Seizures can also begin focally and then evolve into generalized seizures.

#### Focal or Partial Seizures

This implies that the seizure is confined to a localized area of the brain. Such seizures are usually idiopathic in children but can be a result of a tumor or other underlying brain disorder in adults and rarely in children. Focal seizures include:

1. simple seizures (including temporal lobe, psychomotor, and Jacksonian seizures), in which there is no loss of consciousness
2. complex partial seizures, including focal seizures that become generalized; there can be a change in or loss of consciousness; automatisms can occur (e.g., lip smacking or repetitive complicated movements).

#### Generalized Seizures

In generalized seizures, there is abnormal electrical activity that is spread throughout the brain. Generalized seizures are usually developmental in origin; that is, during the development of the

brain, an anomaly arises that predisposes the individual to seizures. Types of generalized seizures include:<sup>48</sup>

1. grand mal – Often before an attack, the individual can experience an “aura,” or warning symptom, of an impending seizure. These symptoms vary widely among individuals and can consist of emotional sensations such as anxiety or sensory disturbances such as unusual tastes, odors, or visual changes. The aura is typically followed by loss of consciousness with rhythmical jerky contractions of the limbs, incontinence, and tongue biting, usually followed by a period of drowsiness. Grand mal seizures can occur at any age, but onset is often in adolescence or early adulthood.
2. absence seizures (includes petit mal) – These are an idiopathic form of epilepsy, with attacks that always commence in childhood. Typical absence seizures or petit mal attacks are characterized by altered consciousness (absence). They can occur up to 100 times a day and can pass unnoticed (i.e., atypical absence seizures).
3. other generalized seizures (e.g., myoclonic seizures) – Myoclonic seizures consist of a single or multiple, brief, irregular muscular contractions of the trunk and/or extremities. Short periods of unconsciousness sometimes occur.

Epilepsy is a chronic cerebral disorder with many medical and social implications. There are clear connections to be made between the diagnosis of epilepsy and a risk of reduced life expectancy. This risk is highest at the time of the initial seizure and reduces over time, particularly if the epilepsy is idiopathic and effectively treated. There is also an increased risk of accident, injury, and social isolation as a result of reduced levels of education.<sup>48</sup>

Epilepsy is usually treated with drug therapy. Some of the most common and effective drugs include:<sup>49</sup>

1. carbamazepine
2. phenobarbitol
3. valproic acid
4. phenytoin.

Despite the use of modern anti-epileptic drugs (AEDs), such as those listed above, approximately 50% of patients continue to experience seizures. Some of them have progressive features, such as increasing seizure frequency and cognitive decline.

#### *Underwriting Considerations*

<b>Favorable Features</b>	<b>Unfavorable Features</b>
Well controlled	Uncontrolled
Infrequent seizures	Frequent seizures
Maximum of 2 types of anti-epileptic treatment	More than 2 types of anti-epileptic treatment
Compliant with treatment	Non-compliant with treatment
Consistent employment record	Inconsistent employment record

In line with these features, information that should be obtained for underwriting evaluation includes:

1. type of epilepsy
2. results of investigations, where applicable
3. frequency of attacks
4. date of last attack
5. type and level of treatment
6. compliance with treatment
7. occupational history.

### Intracranial Tumors

Tumors that arise within the brain are generally considered to be malignant because of invasion of local tissue. However, since they rarely metastasize to sites outside the brain itself, they do not fit the usual definition of cancer. These tumors are rare, accounting for less than 2% of all primary cancers, but they are statistically more common in those under age 15 and in older adults, with approximately 3,140 children under age 20 in the U.S. being diagnosed with a primary brain tumor each year.<sup>50</sup>

Benign tumors do occur. They are usually slow growing, have distinct borders and rarely spread to invade local tissue. Surgery can usually be an effective cure unless the tumor is located in a vital area, in which case it can be regarded as life-threatening despite its benign status.<sup>50</sup>

There are many different forms of brain tumor. Since the majority arise from cells called glial cells, they are commonly known as gliomas. This broad category includes astrocytomas, which are categorized into four types, reflecting their increasing malignancy:

1. grade I – pilocytic astrocytoma
2. grade II – low-grade astrocytoma
3. grade III – anaplastic astrocytoma
4. grade IV – glioblastoma multiforme.

Prognosis in intracranial tumors is extremely variable and depends principally upon histological type. Glioblastoma multiforme is usually fatal within a year, while low-grade gliomas (grades I & II) can be compatible with several years of survival. In children, about two-thirds of medulloblastomas are cured by radiotherapy. Germ cell tumors (usually pinealomas) can often be cured by radiotherapy and/or chemotherapy, while survival in primary central nervous system lymphoma can be prolonged with chemotherapy. High cure rates are achieved by surgery alone for meningiomas and acoustic neuromas.<sup>50</sup> The table below groups these tumors by typical prognosis:

<b>More Favorable Prognosis</b>	<b>Less Favorable Prognosis</b>
Meningioma	Astrocytoma
Acoustic neuroma	Glioma
Pinealoma	Medulloblastoma
	Neuroblastoma
	Sarcoma

Information that should be obtained for underwriting includes:

1. precise histology
2. results of all investigations
3. treatment given
4. time since diagnosis and completion of treatment
5. any residual neurological or psychological impairment.

### Headache

Headache is extremely common, and, from an underwriting perspective, it is important to distinguish between those forms that are significant and those that are of no importance. Primary headache syndromes such as migraine, cluster, and tension types are rarely associated with any underlying organic disorder and, therefore, can largely be disregarded. However, occasionally those who suffer with migraine will experience sudden onset unilateral weakness, or even loss of speech or consciousness. The symptoms usually resolve within 24 hours. This form is known as hemiplegic migraine. It is rare but can be familial in nature and, in some cases, can be linked to an increased risk of stroke.<sup>52,53,54</sup>

Serious causes of headache can include bleeding from an arteriovenous malformation (AVM) or from a ruptured cerebral artery aneurysm (previously described). Most AVMs are asymptomatic, but headache can be a presenting feature. The type of headache is variable, depending on the individual, but it can indicate leaking of blood from the AVM into surrounding tissue. Hemorrhages from AVMs vary from microscopic to a massive blood loss resulting in a catastrophic stroke. It is estimated that 2% of all hemorrhagic strokes occur as a result of an AVM.<sup>55</sup>

Other causes of headaches include tumors and temporal arteritis, an inflammation of the arteries supplying the scalp. Cervical disc disease can produce neck pain radiating up to the head, causing pain and headache symptoms.

Over 90% of headaches are of the primary variety and are unlikely to have an adverse effect on life expectancy; however, it is important that any episodes of recurrent headaches or those with sudden onset have been fully investigated to rule out possible underlying causes of concern, such as vascular causes or tumors.<sup>52,53,54</sup>

Information that should be obtained during underwriting evaluation includes:

1. type of headache
2. results of any investigations
3. treatment
4. any history of neurological symptoms.

## Encephalitis, Meningitis, Hydrocephalus

### *Encephalitis*

Encephalitis literally means inflammation of the brain; in many cases, it is due to a viral infection, but it can also be due to bacterial, parasitic, or fungal organisms. Encephalitis usually arises as a result of a primary infection (i.e., one that arises in the brain and/or spinal cord) or as a result of a secondary infection (i.e., one that arises elsewhere within the body and subsequently affects the brain and/or spinal cord).

Symptoms of encephalitis include:<sup>56</sup>

1. severe headache
2. sudden onset of fever
3. photophobia
4. stiff neck
5. nausea and vomiting
6. drowsiness and confusion
7. seizures.

Common causes include:<sup>56</sup>

1. herpes virus infections
2. common childhood illnesses (e.g., measles, mumps, rubella)
3. insect-borne viruses (e.g., West Nile, Japanese encephalitis, eastern and western equine encephalitis).

Treatment generally involves rest and pain relief, including anti-inflammatories to reduce any swelling within the brain. Although viral encephalitis can be difficult to treat because some viral causes do not respond to treatment, occasionally anti-viral drugs such as acyclovir (Zovirax®) will be administered.<sup>56</sup>

### *Meningitis*

Meningitis is inflammation of the meninges, the membranes that surround the brain and the spinal cord. The condition can be caused by a virus or by bacteria. Viral meningitis, while a severe illness, has a much better prognosis than the bacterial form of the disease. The most common forms of bacterial meningitis are streptococcal and meningococcal meningitis. These are highly infectious, serious illnesses that can result in septicemia in addition to meningitis.<sup>57,58</sup>

The symptoms of meningitis often manifest over a period of one to two days and can easily be mistaken for those of influenza. These symptoms commonly include:<sup>58</sup>

1. severe headache
2. high fever
3. photophobia
4. stiff neck
5. nausea and vomiting
6. drowsiness and confusion
7. rash - in some cases
8. seizures.

The bacterial form of the disease requires immediate treatment with intravenous antibiotics, with the type and/or combination of antibiotics depending on the nature of the disease-causing organism.<sup>58</sup> Treatment for viral meningitis is likely to involve rest and pain relief, with most people recovering within a short period of time without intervention.

The prognosis in bacterial meningitis can be extremely poor if early medical intervention does not occur, with death occurring from septicemia or other complication. Many individuals can have permanent neurological deficits, such as deafness or speech difficulties; limbs may need to be amputated as a result of septicemia. Renal and adrenal problems are common.<sup>58</sup>

The poor prognosis of this disease led to the development of vaccines for some strains of bacterial meningitis. These are safe and highly effective, and in most developed countries there is a program of vaccination for all children.<sup>59</sup>

When reviewing cases of encephalitis and meningitis, the underwriter will need to know:

1. cause of the infection, if known
2. results of all investigations
3. details of treatment given
4. details of any ongoing complications, particularly neurological complications.

### *Hydrocephalus*

The term hydrocephalus literally means “water in the head.” In medical terminology, this refers to an accumulation of cerebrospinal fluid within the skull. Normally, cerebrospinal fluid travels between the four ventricles, around the surface of the brain, and down the spinal cord. It is then reabsorbed into the blood stream. If this process is slowed or blocked, the fluid accumulates and the ventricles swell, compressing normal brain tissue.<sup>60</sup>

There are many causes of hydrocephalus. It can be due to a congenital malformation, such as occurs in spina bifida, the result of an infection, such as meningitis or encephalitis, or as a result of injury to the brain.<sup>60</sup>

Treatment is usually necessary to relieve the increased intracranial pressure. If this cannot be done by removing the cause, then it is usually necessary to insert a shunt to remove excess fluid. The shunt consists of a plastic tube with a one-way valve. One end of the tube is placed into one of the cerebral ventricles. The other end is inserted either into the jugular vein and threaded down toward the right atrium, or into the peritoneal cavity (ventriculo-atrial or ventriculo-peritoneal shunt). Shunt complications include blockage and infection; revisions and/or replacements are common.<sup>60</sup>

The prognosis of those with treated hydrocephalus is usually closely linked to the underlying cause, although further complications can arise as a result of problems with shunts as outlined above. When underwriting cases of hydrocephalus, it is important to ascertain the following:

1. the underlying cause, if known
2. type of treatment and the response to treatment
3. if a shunt is in place, whether there is any history of complications, blockages, or infections
4. whether there are any residual problems as a result of the hydrocephalus.

### **Morbidity Considerations**

All neurological conditions have the potential to have a significant impact on morbidity, not only as a result of the disease process, but also as psychological and other problems. Cerebrovascular diseases such as carotid artery stenosis and transient ischemic attacks (TIAs), may not themselves lead to an increase in morbidity, but there is an increased risk of stroke, and treatment for carotid artery stenosis by way of endarterectomy carries some risk of sequelae.

Individuals who suffer a stroke are at risk of a number of conditions which may affect their morbidity. One study of stroke sufferers aged >65 years showed that six months after the stroke, the following neurological deficits were present:<sup>61</sup>

1. hemiparesis (50%)
2. cognitive deficits (46%)
3. hemianopsia (20%)
4. aphasia (19%)
5. sensory deficits (15%).

Disabilities at six months after stroke included:<sup>61</sup>

1. depressive symptoms (35%)
2. inability to walk unassisted (31%)
3. social disability (30%)
4. institutionalization (26%)
5. bladder incontinence (22%).

Just over half of individuals returned to paid work within a year of their stroke.<sup>61</sup> It is possible to assess the outcome following stroke by using two separate scales of assessment. The modified

Rankin Scale (below) is widely used to measure functional independence and is considered a “core metric” in stroke centers in the United States:<sup>61,62</sup>

<b>Score</b>	<b>Description</b>
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

The Barthel Index (BI) (below) measures self-care and physical dependency. A score of 100 is considered normal, with lower scores indicating increasing levels of disability. A BI score of <40 would indicate severe dependency:<sup>61,62</sup>

<b>Activity&amp; Score</b>	
<i>Feeding</i>	
0	Unable.
5	Needs help cutting, spreading butter etc., or requires modified diet.
10	Independent.
<i>Bathing</i>	
0	Dependent.
5	Independent (or in shower).
<i>Grooming</i>	
0	Needs help with personal care.
5	Independent face/hair/teeth/shaving (implement provided).
<i>Dressing</i>	
0	Dependent.
5	Needs help but can do about half unaided.
10	Independent (including buttons, zips, laces, etc.).
<i>Bowels</i>	
0	Incontinent.
5	Occasional accident.
10	Continent.
<i>Bladder</i>	
0	Incontinent, or catheterized and unable to manage alone.
5	Occasional accident.
10	Continent.
<i>Toilet use</i>	

0	Dependent.
5	Needs some help, but can do some alone.
10	Independent (on and off, dressing, wiping).
<i>Transfers (bed to chair and back)</i>	
0	Unable, no sitting balance.
5	Major help (one or two people, physical), can sit.
10	Minor help (verbal or physical).
15	Independent.
<i>Mobility (on level surfaces)</i>	
0	Immobile or <50 yards
5	Wheelchair independent, including corners, >50 yards.
10	Walks with help of one person (verbal or physical), >50 yards.
15	Independent (but may use aid, e.g., a stick or cane), >50 yards.
<i>Stairs</i>	
0	Unable.
5	Needs help (verbal, physical, carrying aid).
10	Independent.

Survivors of subarachnoid hemorrhage can have symptoms of memory impairment, depression, anxiety, and disturbed sleep, and there is an ongoing risk, even following treatment, of a recurrent bleed.<sup>63</sup>

Since multiple sclerosis generally affects younger people, it is important for the underwriter to consider the morbidity implications. In addition to any disability caused by the disease process itself, it is important to consider symptoms such as fatigue, depression, and bowel and bladder impairment, all of which are prevalent in individuals with MS. In the later stages of the disease there can also be symptoms of cognitive dysfunction and seizures.<sup>64</sup>

The more obvious morbidity risks associated with epilepsy are well documented, such as the increased risk of accident, but it has a significant effect on employment, with around 40% of those who are well educated with well-controlled seizures being unemployed.<sup>65</sup> There is also evidence to suggest that those with epilepsy have poor health-related behaviors, such as increased levels of tobacco and alcohol consumption and reduced amounts of physical activity, which in turn lead to hypertension, obesity, and atherosclerosis.<sup>64,63</sup>

Intracranial tumors are usually associated with significant mortality and morbidity. The most common disabling symptoms are those of neurological deficits, such as motor and language problems, and psychological problems such as depression. In children, there can be endocrinological complications.<sup>65,66</sup>

Infectious diseases of the nervous system such as encephalitis and meningitis are usually associated with a complete recovery and few long-term complications, but when severe, there can be issues such as impaired mental status, seizures, or, in meningitis, amputation of limbs as a result

of septicemia. About 25% of those who were previously employed do not return to full time work.<sup>67,68</sup>

### **Conclusion**

It is important to remember that disorders affecting the nervous system are complex, may not always present in the same way, and that the disease process can be as individual as the person who is suffering from that particular disorder. Therefore, it is vitally important that underwriters understand the signs and symptoms that could be a first manifestation of a disorder, as well as understand what the likely effect on mortality a disorder will present. The information presented in this chapter should help underwriters have a better understanding of the disease processes for the more common nervous system disorders, thus making a more informed decision possible.

## **Review Questions – ALU 201, Chapter 5**

1. The major known causes of epilepsy include all of the following EXCEPT:
    1. thyroiditis
    2. arteriovenous malformation (AVM)
    3. stroke
    4. brain tumor
  2. The intracranial tumor that has a high cure rate with surgery alone is:
    1. sarcoma
    2. medulloblastoma
    3. astrocytoma
    4. meningioma
  3. All of the following can cause epilepsy EXCEPT:
    1. migraine headache
    2. brain tumor
    3. head injury
    4. stroke
  4. A stroke, as defined by the World Health Organization, includes which of the following?
    - A. gradual onset of cerebral deficit
    - B. symptoms lasting more than 24 hours
    - C. no apparent cause other than vascular
- Answer Options:
1. A only is correct.
  2. A and B only are correct.
  3. B and C only are correct.
  4. A, B, and C are correct.
5. Describe the subtypes of multiple sclerosis.

6. Multiple sclerosis would have an unfavorable prognosis with the presence of which of the following?

- A. older age at onset
- B. bowel or bladder involvement
- C. relapsing-remitting form

Answer Options:

- 1. A only is correct.
- 2. A and B only are correct.
- 3. B and C only are correct.
- 4. A, B, and C are correct.

7. Compare and contrast the favorable and unfavorable features associated with epilepsy.

8. What are some of the symptoms survivors of subarachnoid hemorrhage experience?

9. Describe the types of generalized seizures.

10. Describe the neurological deficits and disabilities that can be present six months after a stroke.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 1: thyroiditis – page 24.

### *Review Question 2*

Answer 4: meningioma – page 26.

### *Review Question 3*

Answer 1: migraine headache – page 24.

### *Review Question 4*

Answer 3: B and C only are correct – page 9.

### *Review Question 5*

Refer to pages 15-16.

### *Review Question 6*

Answer 2: A and B only are correct – page 23.

### *Review Question 7*

Refer to page 26.

### *Review Question 8*

Refer to page 32.

### *Review Question 9*

Refer to pages 24-25.

### *Review Question 10*

Refer to page 30.

## **CHAPTER 6**

### **UNDERWRITING MENTAL ILLNESS AND PSYCHIATRIC DISORDERS**

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## **UNDERWRITING MENTAL ILLNESS AND PSYCHIATRIC DISORDERS**

### **Introduction**

The COVID-19 pandemic that began in 2020 has caused a heightened awareness of mental illness with noted increases in stress, anxiety, depression, and domestic violence. Accidental deaths in the United States related to substance use were greater than 100,000 lives lost in 2020, the most ever. Underwriting mental illness and psychiatric disorders accurately becomes more crucial. The principles of underwriting those disorders have not changed, but their underwriting requires more scrutiny and diligence.

Psychiatric disorders are common human problems. But in many ways, they are baffling illnesses to understand and to underwrite. The exact causes of all mental illnesses and psychiatric disorders are unknown and the pathogenesis of how they develop is also unknown. Many psychiatric illnesses, in addition, have an undefined genetic component, the details of which remain to be identified.

The diagnosis of all psychiatric disorders is based on the presence or absence of subjective symptoms. There are no specific laboratory tests or markers to separate psychiatric disorders from the normal state. The Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition (DSM-5) contains the diagnostic criteria and classification for all psychiatric disorders. These criteria are used uniformly in the United States.

Prior to the DSM-5, and using DSM-IV methodology, a psychiatric attending physician's statement (APS) contained five axes, noting the presence or absence of diagnoses plus social issues and a general scale of how well the person was functioning:

1. Axis I lists major psychiatric illnesses (e.g., depression, bipolar disorder, schizophrenia).
2. Axis II is for personality disorders (e.g., schizoid, narcissistic, anti-social).
3. Axis III is for general medical conditions (e.g., diabetes, ulcer, high blood pressure).
4. Axis IV is for psychosocial and environmental problems (e.g., unemployment, marital separation, loss of spouse).
5. Axis V is a global assessment of function, called the GAF score.

**The DSM-5 no longer uses the DSM-IV axes listed above.** The multiaxial system was intended to help make distinctions between diagnoses, but instead created confusion. DSM-5 has created a nonaxial system by combining the first three axes into one to eliminate the distinctions between diagnoses and includes separate notations for the type of information that was previously documented in Axes IV and V.

The GAF score sheet ranges from 1 to 100, divided into 10s, e.g., 1-10, 11-20, 21-30. A GAF score in the 91-100 range is near normal functioning with the psychiatric impairment. A GAF score of 51-60 indicates significant difficulty functioning with the psychiatric impairment. The GAF score given to an individual is based on the subjective determination of a trained clinician.

When looking at medical records, it is usually not known whether the doctor or care provider used the actual DSM-5 criteria in establishing a psychiatric diagnosis. Thus, when underwriting psychiatric disorders, it is not always clear if the criteria for diagnosis are present and whether the diagnosis given is indeed the correct diagnosis.

There are several reasons that mental disorders are difficult to understand and to underwrite:

1. The diagnoses of all mental illnesses and psychiatric disorders are based on the presence or absence of subjective symptoms.
2. Specific objective biochemical or physiological laboratory tests for psychiatric disorders and brain imaging studies specific for psychiatric diagnoses remain to be identified for all psychiatric disorders.
3. There are no gross anatomical abnormalities noted in the brains of people who die from non-psychiatric illnesses, but who have a definite psychiatric diagnosis.
4. There are no biological markers of psychiatric disorders. Therefore, individuals with psychiatric impairments cannot be separated from those without psychiatric disorders using biological markers.
5. Brain biopsies of patients with psychiatric illness are difficult to obtain in a living person (*in vivo*). Understandably, most individuals are hesitant to have one or multiple brain biopsies performed on themselves.
6. There are no good animal models of psychiatric disorders that can be studied.
7. The interactions of psychosocial stressors and biological predispositions are very complex, making specific focused studies of psychiatric disorders very difficult.

Psychiatric disorders often occur together. Examples are depression occurring with alcoholism or with eating disorders, depression occurring with schizophrenia, and anxiety occurring with mood disorders. The term used to describe the occurrence of impairments together is comorbidity and the impairments themselves are termed comorbidities. Comorbidity can also occur when a psychiatric disorder and a medical disorder, such as diabetes and depression, are found together. A key point to remember in reviewing medical records is to look for possible comorbidities with all psychiatric disorders.

## **Mood Disorders**

A mood is a conscious state of mind or prevailing emotion or feeling. The mood disorders include:

1. depression
2. dysthymia
3. bipolar disorders I and II
4. cyclothymia.

Mood disorders have been known for a long time. Melancholia is mentioned in Egyptian and Sumerian writings from 2600 BC, while psychiatric terms are mentioned in medical writings from India dating back to 1400 BC. Hippocrates developed a theory of temperaments in 400 BC

and the connection between melancholia and mania (i.e., bipolar disorder) was made by Aretaeus of Cappadocia in 150 AD. The first textbook devoted to mood disorders was published in the seventeenth century.

For all mood disorders, the causes are unknown, no specific diagnostic tests are available, and there are no absolute therapies. Therapy is, however, very effective in most cases. There are undefined genetic components to the mood disorders, with bipolar disorder having the strongest genetic component. Comorbidities, such as obsessive-compulsive disorder, panic disorder, eating disorders, schizophrenia, alcohol abuse, and substance abuse, are common with all mood disorders. The underwriter must look for comorbidities in all cases.

### Depression

Depression can be a normal feeling, a symptom associated with another problem, a reaction to another problem, or a mental disorder. The DSM-5 contains the criteria used to diagnose a major depressive disorder (MDD), as well as the criteria for the other mood disorders. Diseases commonly seen in association with depression include heart disease, cancer, central nervous system (CNS) diseases, endocrine diseases, and connective tissue diseases. Almost all medications have been reported to cause depression in a variable percentage of individuals taking the medication. Over forty different symptoms can be related to depression. The difficult task for clinicians is to sort out the symptoms to arrive at the correct diagnosis.

Depression is the most common mood disorder. It is estimated that 6-8% of all primary care outpatients satisfy diagnostic criteria for a major depressive disorder (MDD). The median age of onset is 34, with 20% developing depression during the teenage years. Two females are affected for every male. It is felt that genetic predisposition is the main cause of the increased incidence in females.

Depression is characterized by three main symptoms:

1. loss of energy (anergia)
2. loss of ability to experience pleasure (anhedonia)
3. loss of sexual desire or libido.

According to the DSM-5 criteria to make a diagnosis of depression, an individual must experience five or more of the following symptoms during the same 2-week period and at least one of the symptoms should be depressed mood or loss of interest or pleasure:

1. Depressed mood most of the day, nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down)
5. Fatigue or loss of energy nearly every day

6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
7. Diminished ability to think or concentrate, or indecisiveness, nearly every day
8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

It is estimated that 17% of people experience a major depressive disorder at some time during their lifetime. Over 50% of individuals who have a MDD are at risk to have a recurrence of depression. (A recurrence is an episode of depression more than six months after the initial episode, while a relapse is depression returning less than six months after the initial episode.) Without treatment, the average duration of a MDD is 8 months; 50% recover within one year, 70% recover in five years and 85% recover in fifteen years. With treatment, 63% of those with MDD recover in four months and 80% recover in three years. Unfortunately, 15% of individuals with untreated MDD commit suicide, while 10-15% develop or progress to a bipolar disorder. In addition, it is estimated that close to one-third of those with MDD develop panic attacks.

Depression is common after a major life event, such as the diagnosis of a chronic medical condition, loss of a loved one, divorce, loss of employment, bankruptcy and, in these circumstances, is sometimes called reactive or situational depression. This depression can range from mild to severe and suicide can occur. Treatment of reactive or situational depression is the same as for all other types of depression. The hope is that the episode of depression will resolve with treatment and not recur.

### Dysthymia

Dysthymia is the presence of chronic depressive symptoms for two years that are not severe enough to be diagnosed as a MDD. It is estimated that 5% of outpatients satisfy the diagnostic criteria for dysthymia.

### Treatment of Depression

It is stated that 70% of people with depression do not receive treatment. There are three types of treatment available to treat depression:

1. psychotherapy
2. electroconvulsive therapy (ECT)
3. medications.

### *Psychotherapy*

Psychotherapy is the use, by health professionals, of verbal and non-verbal communication to deal with depression and other psychiatric disorders. Psychotherapy is usually used in combination with medications. There are two general types: individual psychotherapy (IPT) and cognitive behavior therapy (CBT).

1. Individual psychotherapy (IPT) uses the skills of empathy, emotional sensitivity, and listening accurately to intervene, giving helpful and corrective information during patient

encounter sessions. The goal of IPT is to enhance the patient's social functioning by improving abilities to deal with life stressors and the consequences of the depressive episode.

2. Cognitive behavior therapy (CBT) uses the principle of focusing on thoughts, emotions, and behavior present at a specific time to appropriately intervene during patient encounter sessions. The goal of cognitive behavior therapy (CBT) is to guide the patient to develop more positive and constructive tools to assess his capabilities and circumstances.

### *Electroconvulsive Therapy*

Electroconvulsive therapy (ECT) uses a small electric current to produce a generalized cerebral seizure under general anesthesia. Its exact therapeutic mechanism of action is unknown. The primary indication for ECT is severe major depression that is life-threatening or that significantly impairs functioning, but ECT can also be used for patients with other conditions, including bipolar disorder, schizophrenia, and schizoaffective disorder.

It is estimated that remission occurs in 70 to 90% of patients who receive ECT. There are no biologic predictors to identify which patients are most likely to respond to ECT. A typical course of ECT consists of 6 to 12 treatments, individualized for each patient-2-3x per week.

The adverse effects of ECT include medical and cognitive effects. Medical adverse effects include cardiopulmonary events, aspiration pneumonia, dental and tongue injuries, and headache. Cognitive adverse effects include acute confusion, anterograde amnesia, and retrograde amnesia. The mortality rate of ECT is about 2 to 4 deaths per 100,000 treatments. It is considered one of the safest procedures performed under general anesthesia. Mortality is mostly related to cardiopulmonary events.

### *Medications*

Antidepressant medication is the mainstay of treatment for depression, with approximately 65% of people responding to medication. About 15% of patients are refractory or resistant to treatment. There is currently no way to predict who will respond to treatment, which medication will be the most effective, or, if a medication is ineffective, which medication is the next best option. All the antidepressant medications have been reported to have beneficial effects in a certain percentage of individuals.

Antidepressant medications can be divided into various groups depending upon:

1. chemical structure
2. physiological effects
3. (presumed) method of action.

All antidepressant medications are felt to exert beneficial effects by affecting various neurotransmitters (i.e., norepinephrine, dopamine, and serotonin) levels, though exactly how antidepressant medications work remains uncertain. The suspected mechanisms of action of the various medications on the neurotransmitters and neuroreceptors are beyond the scope of the

text. It should also be noted that antidepressant medications can be used for a wide variety of purposes including situational problems, such as for premenstrual syndrome and smoking cessation (e.g., Wellbutrin®). Be aware that the use of antidepressants does not necessarily mean that an individual has a MDD. An underwriting task is to determine the correct diagnosis for which the antidepressant medication is used.

There are six main groups of antidepressant medications (see Appendix 2 for a list of the functional classes of antidepressant medications with some examples and Appendix 3 for a list of the common antidepressant medications, typical daily dosage ranges and functional class).

The duration of treatment will vary from case to case. For a MDD, at least six to nine months of medication treatment is recommended. If there is a MDD recurrence, long-term medication treatment is usually recommended.

### Mortality Risk of Depression

Depression and all mood disorders are associated with an increased mortality risk, primarily due to accidents, suicides, and adverse effects on other illnesses. Depression has been shown to increase the mortality risk of heart disease, cancer, stroke, diabetes, and other illnesses. The more chronic and severe the depression, the greater the increase in mortality risk is.

A test used to measure the severity of depression is the Beck Depression Inventory (BDI). The test is self-administered. It contains 21 items that are rated 0-4, depending how severe the symptoms of the item are. The scores from the items are added together for a total score. The BDI is quite effective for measuring severity of depression (see Appendix 1 for the BDI scoring guidelines). Medical studies have shown that higher BDI scores at the time of a hospital admission are associated with a worse prognosis for unstable angina and acute heart attacks. There are many other tests developed to assess the severity of depression; however, the BDI remains one of the best. It is easy to perform and commonly used.

### Bipolar Disorder

Bipolar disorder is characterized by depression and periods of mania. Mania is characterized by distractibility, rapid flight of ideas, excessive involvement in pleasurable activities, loss of economic and social judgment, and impaired social function. It is estimated that bipolar disease is present in approximately 2% of the population, with bipolar I present in about 0.8%, bipolar II in 0.5%, and cyclothymia present in 0.5%. There may be more subsets of bipolar disorder, but currently bipolar I and bipolar II are the only accepted bipolar diagnoses.

1. Bipolar I manifests with episodes of major depression and mania. It occurs equally in males and females. The lifetime prevalence of bipolar disorder is 1-3% of the population with the mean age of onset of 19 years old.
2. Bipolar II will have at least two major depression episodes and hypomanic episodes. It is more common in females. Symptoms of hypomanic episodes are less intense than those of the full-blown manic episode of bipolar I. (The DSM-5 contains all the criteria of manic and hypomanic episodes.)

3. Cyclothymia is characterized by fluctuating periods of depressive and hypomanic symptoms for at least two years with the symptoms not meeting the criteria for a major depressive episode or manic episode.

Ten to fifteen percent of people with bipolar disorder have four or more episodes of mania per year, called rapid cycling. This is more common in females and carries a worse prognosis.

As with all mood disorders, the cause of bipolar disorder is unknown. Studies of families and twins have shown that bipolar disorder has the strongest genetic predisposition of the mood disorders. Suicide risk is increased during the depression phase of bipolar disorder, and accidents and injuries are more common during the manic phase of bipolar disorder.

### *Treatment and Comorbidities*

Medications are the treatment of choice for bipolar disorder. Treatment recommendations for bipolar disorder have changed within recent years. The recommended first line medications for a manic episode are now quetiapine (Seroquel®) or lurasidone (Latuda®). If those drugs fail, the second line recommended medications are olanzapine plus fluoxetine (Symbyax®) or valproate or a first line drug plus lithium. Lithium was the most used medication in the past and many bipolar patients may still be treated with lithium. Lithium is useful in both the manic and depressive phases of bipolar disorder, and it also reduces recurrences. Mild side effects (e.g., weight gain, increased thirst) from lithium are common. Hypothyroidism is a potentially serious side effect that is well known. Other medications used for bipolar disorder include oxcarbazepine (Trileptal®), and carbamazepine (Tegretol®). The duration of treatment is usually lifelong. If an individual is taking lithium, it is almost certain that bipolar disorder has been diagnosed (see Appendix 4 for a list of medications used to treat bipolar disease). ECT can also be used to treat bipolar disorder for refractory patients and with maintenance medications being strongly recommended after ECT. Alternative treatments are not recommended as substitutes for medications in the treatment of bipolar disorders, though alternative treatments can be used as adjunctive therapies.

## **Anxiety Disorders**

Anxiety and depression are the two most prevalent psychiatric disorders. Anxiety is a feeling of fear and apprehension and a sense of dread, unease, and foreboding. These feelings, often intense, can lead to a wide variety of physical symptoms. Anxiety can be a normal feeling, an acute problem, or a chronic illness. As an illness, anxiety is associated with five disorders:

1. panic disorder
2. phobias
3. generalized anxiety disorder (GAD).

The anxiety disorders are chronic illnesses, occurring two to three times more often in females. Anxiety disorders also occur more frequently in lower socioeconomic groups. Their onset is typically in adolescence or early adulthood. There is approximately a 15% prevalence of anxiety in the U.S. population: approximately 8% with GAD, 2% with phobias, 2% with panic

disorder, 2-3% with OCD and 1% with PTSD. Anxiety disorders are not curable. Mood disorders and substance abuse have an increased incidence in individuals with anxiety disorders. Like most psychiatric illnesses, the anxiety disorders are diagnosed after excluding other medical conditions that could possibly cause the exhibited symptoms.

### Panic Disorder

The cause of panic disorder is unknown. There is thought to be an undefined genetic component. It is twice as common in females as in males. Onset is usually in young adulthood, and onset after age 50 is unusual. The hallmark of panic disorder is panic attacks associated with some social dysfunction. Panic attacks are episodes of severe acute anxiety, characterized by various combinations of palpitations, chest pain, shortness of breath, sweating, lightheadedness, choking, flushing, gastrointestinal symptoms, and fear of dying. Attacks typically resolve after 10 minutes. In addition to the attacks themselves, persistent concern or worry about their recurrence can lead to behavior changes.

Treatment of panic disorder consists of psychotherapy and medications. Psychotherapy is psychoeducation aimed at symptom control. It sometimes includes education in breathing techniques aimed at controlling the symptoms. About 30% have significant improvement, 50% have some improvement, and 20% have a static or worse course.

Two groups of medications are used to treat panic disorder. Antidepressants, usually in the SSRI group, are used for maintenance therapy, and the benzodiazepines (listed in Appendix 5) are used for immediate symptom relief. TCAs and MAOIs are as effective as the SSRIs, but have more unpleasant side effects or, in the case of MAOI drugs, have a risk of causing a hypertensive crisis. The main risk with benzodiazepines is the development of addiction with chronic use. It is recommended that benzodiazepines not be used as to treat depression associated with anxiety. Rather, the depression should be treated specifically with antidepressants.

Comorbidities associated with panic disorder are depression in 50%-60% of cases, substance abuse in 33%, and agoraphobia in about 33%. Suicide attempts occur in about 20% of people with panic disorder.

### Phobias

Phobias are excessive fear surrounding a specific event or object. Exposure to the event or object provokes anxiety, and impairment of social function occurs. The cause of phobias is unknown. Onset is usually by young adulthood. An example of a phobia is agoraphobia, which is a fear of leaving a familiar home setting or venturing into the open.

The mainstay of treatment is psychotherapy. Cognitive behavior therapy and desensitization therapy are the common types of psychotherapy used. Medications are also used, but without psychotherapy, they are not as effective as in some other psychiatric disorders. Beta blockers, antidepressants (often SSRIs), benzodiazepines, and newer anticonvulsants, gabapentin

(Neurontin®) and pregabalin (Lyrica®), are medications used to treat social phobias and anxiety. Beta blockers are used for performance anxiety.

Comorbidities are common with phobias. About one-third develop a mood disorder, and one-fourth develop substance abuse. Eating disorders are also common.

### Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is a state of chronic, continuous low-grade excessive worry leading to various symptoms such as tension, irritability, fatigue, sleep disturbance, and mild impairment of social function. The cause of the anxiety is unknown. Males equal females in incidence with the onset of symptoms occurring usually before age 20. It is estimated that over 80% of those with GAD also develop a mood disorder or social phobia.

Treatment consists of psychotherapy and medications. The medications used are benzodiazepines, antidepressants, and bupropion.

### **Obsessive-Compulsive Disorder**

In the DSM-5 there is a new grouping of obsessive-compulsive related disorders which include obsessive compulsive disorder (OCD), body dysmorphic disorder, hoarding disorder, trichotillomania (e.g., hair-pulling disorder), and (skin) excoriation disorder.

Obsessive-compulsive disorder (OCD) affects up to 3% of the population. OCD is slightly more common in the U.S. than worldwide. Obsessions are intrusive thoughts or ideas, while compulsions are repetitive behaviors performed to reduce the anxiety associated with obsessive thoughts. In OCD, the obsessions and compulsions that are present cause marked distress, interfere with normal functioning, and are present for more than one hour per day. An example of a compulsion is frequent hand washing (sometimes more than 100 times per day) because of the fear of germs. These behaviors can significantly interfere with daily living and cause considerable anxiety. However, insight is preserved, and the obsessions and compulsions are viewed as unwanted.

The cause of OCD is unknown, though there is a definite genetic component, and stress plays a role. OCD is more common in males and firstborn children. Onset is usually in young adulthood and its course is one of waxing and waning symptoms. About 10% of cases develop significant chronicity. The common areas of obsessions are:

1. contamination due to germs - 38%
2. fear of harming oneself or others - 24%
3. symmetry - obsessions regarding real or imagined defects in appearance - 10%
4. somatic - obsessions regarding the body - 7%.

Treatment includes medications and psychotherapy. The medications used are SSRIs, typically fluvoxamine (Luvox®), and TCAs, such as clomipramine (Anafranil®). Medications alone are seldom sufficient in treating OCD. Psychotherapy is an important adjunct.

Comorbidity is very common. Two-thirds to three-fourths of OCD patients have anxiety and/or depression. Eating disorders is another common comorbidity.

### **Post-Traumatic Stress Disorder**

In the DSM-5 post-traumatic stress disorder (PTSD) is the co-occurrence of re-experiencing, avoidance, negative beliefs, and hyperarousal symptoms in survivors of extreme adversity (i.e., a traumatic event). As with OCD, PTSD is slightly more common in the U.S. than worldwide.

The traumatic events are sexual relationship violence in about 33% (e.g., rape), interpersonal network trauma in about 30% (e.g., death or illness of a loved one), interpersonal violence in about 12% (e.g., physical abuse), life-threatening trauma in about 12% (e.g., natural disaster, MVA), and participation in organized violence in about 11% (e.g., combat). The traumatic event causes intense fear or horror. The symptoms can be acute or delayed. Risk factors for PTSD include a past psychiatric diagnosis and an undefined genetic component. Symptoms occur in three domains following the trauma:

1. intrusion symptoms—flashbacks, distressing recollections, or dreams
2. avoiding stimuli associated with the trauma
3. increased automatic arousal—i.e., enhanced startle.

The National Comorbidity Study found 60% of males and 50% of females had experienced significant trauma. The incidence of PTSD is 9% to 15% with the lifetime prevalence estimated to be 8% to 10% in females and 4% in males. Exactly why an individual develops PTSD while other individuals who have had similar experiences do not is unknown.

Comorbidities are common with PTSD with 66% of patients with PTSD having two other disorders, such as mood disorders, anxiety disorders, and alcohol and substance abuse disorders. In general, the very young and the very old have more difficulty with PTSD.

It is estimated that without treatment 30% recover completely, 40% have mild symptoms, 20% have moderate symptoms, and 10% will have severe symptoms.

PTSD requires complex and chronic treatment consisting of psychotherapy and medications. Psychotherapy consists of avoidance behavior and learning to not feel guilty or responsible for the traumatic event. Medications commonly used are the antidepressants—SSRIs, trazodone, benzodiazepines, carbamazepine, and valproate. Alcohol and substance abuse are common comorbidities with PTSD. When underwriting an individual with PTSD, evaluate for comorbid conditions and the level at which the person is functioning.

### **Personality Disorders**

Personality disorders are common problems that manifest as maladaptive behavior patterns. These patterns develop during the teenage years and are inflexible, pervasive, stable, and enduring. They cause distress and lead to impaired work and social relationships. The behavior patterns are associated with low self-directedness and low cooperativeness (i.e., the inability to

work with others), and tend to elicit strong emotional reactions from others. Personality disorders are said to affect 10%-25% of the population and are a suicide risk factor. There is an undefined genetic component to personality disorders. They occur more often in young adults and have a decreasing incidence in older ages. Personality disorders are difficult to define and have multiple sub-types.

Generally, there are three groups of personality disorders:

1. odd/eccentric group – This group is made up of the schizoid (socially indifferent), paranoid (suspicious), and schizotypal (eccentric) patterns. Antidepressant and low-dose antipsychotic medications are often used for treating this group.
2. dramatic/impulsive group – This group is made up of anti-social (disagreeable), borderline (unstable), histrionic (attention-seeking), and narcissistic (self-centered) patterns. Anti-social personality disorder, also called sociopathic personality, is four times more common in males than in females. Carbamazepine, valproate, and MAOIs are often used for treating this group.
3. anxious/fearful group – This group is made up of the dependent (submissive), avoidant (inhibited), obsessive (perfectionistic), passive-aggressive (negativistic), and depressive (pessimistic). Antidepressants, benzodiazepines, and bupropion are often used for treating this group. Psychotherapy is also used as a treatment modality.

The main underwriting concerns of personality disorders are impulsive behavior, suicide attempt, and, especially, comorbidities. The comorbidities often seen are depression, alcoholism, eating disorders, panic attacks, phobias, and tobacco addiction. Criminal and aggressive behaviors are often associated with the anti-social personality.

## Somatoform Disorders

Somatoform disorders are symptoms and complaints that cannot be explained by a known medical condition, medication, or mood-altering substance. The DSM-5 contains definitions and criteria to diagnose these disorders, which are characterized by many unexplained symptoms in at least four organ areas. Ninety-five percent of cases occur in females, with onset of symptoms in adolescence. The symptoms are chronic and lead to problems functioning in relationships and socially. Common symptoms are pain, gastrointestinal, sexual, and neurological symptoms.

Three recognized types of somatoform disorders are:

1. somatic symptom disorder
2. conversion disorder - the transformation of an emotion into a physical manifestation
3. hypochondriasis - an individual believes he has an illness or chronic pain when he does not; sometimes called factitious disorder - feigning illness and assuming the role of a sick person.

Treatment of these disorders is difficult. The main treatment modality is cognitive behavioral therapy. Antidepressant medications are also used. The key to underwriting this group of psychiatric disorders is to look for comorbidities, especially substance abuse and depression.

## **Thought Disorders**

Thought disorders are a group of psychiatric disorders characterized by delusions. The two main types of thought disorders are delusional disorders and schizophrenia. Schizophrenia is no longer considered a single disease but now is considered a heterogeneous group of illnesses.

### Delusional Disorders

Delusional disorders are characterized by delusions for at least one month but without bizarre behavior or marked impairment of function. Delusions are an abnormal mental state of false beliefs regarding self or individuals, or objects outside of oneself. The false beliefs persist despite known facts to the contrary.

### Schizophrenia

Schizophrenia is the most common thought disorder, affecting 1-1.5% of the population. The exact cause is unknown. Known risk factors are an undefined genetic component, winter birth, and undefined early developmental injuries or insults. Onset is typically in late teenage years or young adulthood. It is estimated that individuals with a diagnosis of schizophrenia use 25% of U.S. hospital beds per year.

For a diagnosis of schizophrenia to be made, symptoms must have been present for at least six months. Classic symptoms of schizophrenia are disorganized behavior with delusions, hallucinations, and disorganized speech or negative symptoms. Hallucinations are sensory perceptions of objects with no basis. The hallucinations can be auditory, visual, olfactory, or gustatory. Unfavorable symptoms include loss of function, pleasure, emotional expression, and concentration, and decreased social engagement. The negative symptoms occur in about one-third of schizophrenics; those individuals have a worse prognosis.

Schizophrenia can be arbitrarily divided into four subtypes depending on symptoms.

1. Catatonic subtype has profound changes of motor activity.
2. Paranoid subtype has a prominent preoccupation with a delusional system.
3. Disorganized subtype has disorganized speech and behavior and a superficial, sometimes silly affect.
4. Residual subtype is characterized by negative symptoms without delusions, hallucinations, or decreased motor activity.

Anti-psychotic medication is the treatment of choice. The use of an anti-psychotic medication indicated in a medical record implies that a thought disorder can be present (see Appendix 6 for a list of anti-psychotic medications). (Be aware that some of these anti-psychotic medications are also used for bipolar disorder.)

Schizophrenia is associated with an increased mortality rate, up to eight times normal in some studies. There is a high risk of suicide attempt. Schizophrenia is said to have a 10% suicide rate, usually in males within the first year of diagnosis.

The keys to underwriting are to determine the severity of the schizophrenia and to look for comorbidities, especially depression. Evidence of frequent hospitalizations, poor support system, and past suicidal attempts are poor prognostic indicators.

## **Eating Disorders**

The eating disorders are anorexia nervosa, bulimia nervosa and binge eating, and obesity. Anorexia and bulimia are much more common in younger females, while obesity affects both genders.

Anorexia nervosa is characterized by a refusal to maintain minimal body weight and denial of the seriousness of the low body weight. There is a disturbance in the individual's own perception of weight and body shape. Preoccupation with food and weight occurs and amenorrhea is common. There is often an over-indulgence in exercise. The 20-year mortality is 10%-20%.

Bulimia nervosa is characterized by a preoccupation with food, binges of excessive eating, and inappropriate compensatory behaviors, such as self-induced vomiting/purgung, fasting, and excessive exercise. (These same inappropriate compensatory mechanisms can also be seen with anorexia nervosa.) The loss of eating control leads to significant psychological discomfort. Usually, the body weight is normal. Two percent of young females are affected by bulimia. Problems related to induced vomiting are common, such as dental enamel erosion, esophagitis, reflux, and aspiration.

Obesity can be defined as excessive eating without appropriate or inappropriate compensatory mechanisms and leading to an increased body mass index (BMI).

The key to underwriting a history of an eating disorder is to look for several years of stability in body weight and symptoms and to look for comorbidities, especially depression, obsessive-compulsive disorder (OCD), and substance abuse.

## **Suicide**

Suicide is the intentional ending of one's life by violent means, such as gunshot, hanging, carbon monoxide poisoning, or drug overdose. Suicide is the number ten cause of death overall in the U.S., accounting for about 41,000 deaths each year, and the number three cause of death in young adults aged 10-24 years. The actual numbers of suicide deaths are probably higher since it is quite likely that suicides are under-reported on death certificates as the cause of death.

There are about 12 suicide attempts for every completed suicide. Suicide is four times more common in males than in females. Females do attempt suicide more, but males are more

successful at completing suicides. Incidence of suicide is increased in certain ethnic groups, notably those from South Korea, Russia, Hungary, and the Baltic States.

Suicide rates increase with age. In the U.S., males over age 65 have the highest suicide rate - 40/100,000 people. For males under age 30, depression, substance abuse, and antisocial personality are common comorbidities. For males over age 30, depression, cognitive disorders, grief/death of spouse, and ill health are common comorbidities.

There is no way to predict who will commit suicide. However, suicide is strongly associated with depression, alcohol and substance abuse, or other mental disorder in 95% of cases. In fact, comorbidity of some type is present in 75% of cases. Major depressive disorder is present in 80% of suicides, while substance abuse and alcohol abuse are present in over 30%. More than 30% of those who commit suicide have a personality disorder and 10% have schizophrenia. (Note: because of comorbidity, the percentage numbers do not add up to 100%).

Given that there is no way to predict who will commit suicide, it is important for an underwriter to evaluate proposed insureds for suicide risk factors. Known suicide risk factors include: male gender, divorce, unemployment, family history of suicide, prior suicide attempt, recent discharge from a psychiatric unit, serious spousal argument, having a psychiatric diagnosis (especially depression, alcohol/substance abuse, eating disorders), having a history of being abused as a child, having a central nervous system (CNS) disease (such as seizures, multiple sclerosis, Parkinson's disease, Huntington's chorea, and schizophrenia), and finally, having a serious medical illness, such as renal failure with dialysis, heart disease, various cancers, cirrhosis, and many other chronic diseases.

## **ADHD/ADD**

Attention deficit hyperactivity disorder (ADHD) and attention deficit disorder (ADD) are relatively newly described mental disorders. Originally seen and diagnosed in children, it is now realized that many individuals carry these illnesses into adulthood. The American Academy of Childhood and Adolescent Psychiatry has published guidelines for the assessment of ADHD. There are no adult guidelines. The DSM-5 has diagnostic criteria for ADHD.

The classic symptoms of ADHD include:

1. inattention/attention deficit (e.g., failure to pay attention to details, making careless mistakes, having difficulty sustaining tasks, seeming not to listen, not following through with chores or duties, having difficulty organizing, often losing things, being easily distracted, often forgetting things)
2. hyperactivity/impulsivity (e.g., fidgeting or squirming, leaving seat in classroom inappropriately, running or climbing excessively, having difficulty playing quietly, talking excessively, having difficulty awaiting one's turn, often blurting out answers before question is completed, interrupting, or intruding).

In adults, the inattention symptoms are more common and tend to predominate.

ADHD affects every cultural and ethnic group. The worldwide prevalence is estimated to be between 3-5%. ADHD is felt to be the second most common psychiatric disorder in the U.S. In children, the incidence of ADHD is about 3 males to 1 female, while in adults, the incidence is 3 males to 2 females. It is estimated that 33-60% of children with ADHD will exhibit the disease in adulthood, yet 90% of adult cases of ADHD are undiagnosed.

The exact cause of ADHD is unknown. There are genetic risk factors associated with mutations in the dopamine receptors and the serotonin transporters genes. Some non-genetic postulated causes include lead contamination, complications during pregnancy, low birth weight, traumatic brain injury, maternal smoking during pregnancy, and severe or extreme maltreatment during childhood. It is not known whether the disease plateaus in adulthood or progresses with age.

Untreated adult ADHD is associated with increased unemployment, divorces, arrests, sexually transmitted diseases (STDs), unplanned pregnancies, and underachievement in school. Seventy percent of ADHD patients have one other psychiatric comorbidity and 22% have two psychiatric comorbidities. Depression and bipolar mood disorders, alcohol and drug abuse, and anxiety are the more common, more serious comorbidities that can be associated with ADD/ADHD. The main task in underwriting is to look for serious comorbidities.

There is no cure for ADHD/ADD. Treatment of symptoms is successful in up to 90% of cases with neuro-stimulating medications such as methylphenidate (Ritalin®) and amphetamines and with psychotherapy and behavior modification. The key is diagnosing the problem so that proper treatment can be instituted.

The exact mortality risk associated with ADD/ADHD is unclear and there is no helpful data at this point in time. It is known that adults with ADD/ADHD remain impulsive and prone to accidents. As adult diagnostic criteria are developed and pediatric groups are followed in adulthood, then studies can be performed, looking to answer questions regarding clinical course, effective treatments, prognosis, and mortality risk.

### **Autism Spectrum Disorders**

Autism is a spectrum of disorders previously known as the pervasive developmental disorders. The two core diagnostic impairments are deficits in social communication and restricted and repetitive behaviors. The DSM-5 criteria changed considerably from the DSM-IV criteria.

Autism is usually diagnosed in early childhood, with the average age of diagnosis for autistic disorder being 3.1 years and for Asperger's disorder 7.2 years. About 30% of children with autism have intellectual disability. Autism spectrum disorder is four times more common in males than females. There is a genetic component to autism spectrum disorders, with 15% of cases having a known genetic mutation. Those with autism spectrum disorders have elevated serotonin in their blood, almost exclusively in platelets and 90% have larger brain volumes than normal. Seizures and EEG abnormalities are not common, while insomnia is. Precocious skills can be present.

Children with IQs >70, who develop language communication by age seven and have reasonable social skills have the best prognosis. The degree of independence and level of social functioning are important factors to consider in underwriting.

## **Psychiatric Illnesses and Morbidity**

A key point to remember is that there is no cure for any of the psychiatric illnesses. Thus, there is always a possibility of relapse with the inability to function, increased treatment needs, development of another psychiatric illness, and short- or long-term disability. There is currently no way to determine which individuals are likely to become disabled from their mental illness. In general, if a psychiatric illness is present, the individual is not a good candidate to receive disability insurance, long term care insurance, or waiver of premium.

### **Summary and Key Points**

Psychiatric disorders are common illnesses worldwide in every race, ethnic group, and gender. Psychiatric disorders are diagnosed by the presence or absence of subjective symptoms. There are no diagnostic laboratory tests. The exact causes and pathogenesis of all psychiatric disorders are unknown. When the exact cause of a disease is unknown, there is no exact or curative treatment. Fortunately, there are many medications and other treatment modalities that are effective in treating the various psychiatric disorders.

The main impairments of concern are depression, bipolar disorder, schizophrenia, and eating disorders. All those impairments are associated with increased mortality and suicide risks. Alcohol/substance abuse is a serious adverse factor. Depression has also been shown to adversely affect other illnesses, such as heart disease and cancer, and depression increases the risk of accidents. An important underwriting task is to look for comorbidities and known suicidal risk factors with all psychiatric disorders.

In the end when underwriting psychiatric disorders, six important questions need to be answered:

1. What is the exact psychiatric diagnosis?
2. How pervasive or frequent is the psychiatric disorder? That is, is it episodic, intermittent, or chronic?
3. How severe is the disorder?
4. Is the individual well-followed for the psychiatric disorder?
5. Is the individual compliant with treatment of the disorder?
6. Is more than one psychiatric disorder present?

The answers to these questions, along with the insurance company's guidelines, will enable the underwriter to assess the risk in these situations.

**Note to the student: Material in the Appendices will not be tested on the examination.**

**Appendix 1. Beck Depression Inventory (BDI) Score Interpretation.**

- |          |  |
|----------|--|
| <4       | possible denial of depression, faking  |
| 5 to 9   | no or minimal depression   |
| 10 to 18 | mild to moderate depression  |
| 19 to 29 | moderate to severe depression  |
| >40      | significantly above even severely depressed persons, possible exaggeration of depression; possible borderline or histrionic personality disorder |

**Appendix 2. Functional Classes of Antidepressant Medications – Some Examples with Generic (Trade) Names.**

- Selective Serotonin Reuptake Inhibitors (SSRIs):** citalopram (Celexa®), fluoxetine (Prozac®), escitalopram (Effexor®), paroxetine (Paxil®), sertraline (Zoloft®),
- Serotonin (5-HT) Receptor Blocker/mixed action:** Mirtazapine (Remeron®), Nefazodone (Serzone®), Trazodone (Desyrel®), Amoxapine (Asendin), Clomipramine (Anafranil)
- Dopamine Reuptake Inhibitor:** bupropion (Wellbutrin®)
- Norepinephrine (NE) Reuptake Inhibitor:** maprotiline (Ludiomil), desipramine (Norpramin), nortriptyline (Aventyl, Pamelor), protriptyline (Vivactyl®)
- NE and 5-HT Reuptake Inhibitors:** amitriptyline (Elavil), doxepin (Sinequan), imipramine (Tofranil), trimipramine (Surmontil), venlafaxine (Effexor), duloxetine (Cymbalta)
- Monoamine Oxidase Inhibitor:** phenelzine (Nardil®), tranylcypromine (Parnate®)

**Appendix 3. Antidepressant Medications - Generic (Trade) Names, Usual Dosage, Functional Class Mechanism of Action.**

Medication	Dosage range	Functional Class of Medication
amitriptyline (Elavil, Endep)	50-300 mg	NE and 5-HT Reuptake Inhibitors
amoxapine (Asendin)	150-450 mg	Serotonin (5-HT) Receptor Blocker/mixed action
bupropion (Wellbutrin)	250-450 mg	Dopamine Reuptake Inhibitor
citalopram (Celexa)	20-40 mg	Selective Serotonin Reuptake Inhibitors (SSRIs)
clomipramine (Anafranil)	100-250 mg	Serotonin (5-HT) Receptor Blocker/mixed action
desipramine (Norpramin)	150-300 mg	Norepinephrine (NE) Reuptake Inhibitor
doxepin (Sinequan)	150-300 mg	NE and 5-HT Reuptake Inhibitors
duloxetine (Cymbalta)	40-60 mg	NE and 5-HT Reuptake Inhibitors
escitalopram (Lexapro)	10-20 mg	Selective Serotonin Reuptake Inhibitors (SSRIs)
fluoxetine (Prozac)	20-60 mg	Selective Serotonin Reuptake Inhibitors (SSRIs)
fluvoxamine (Luvox)	100-300 mg	Selective Serotonin Reuptake Inhibitors (SSRIs)
Imipramine (Tofranil)	150-300 mg	NE and 5-HT Reuptake Inhibitors
maprotiline (Ludiomil)	150-200 mg	Norepinephrine (NE) Reuptake Inhibitor
mirtazapine (Remeron)	15-45 mg	Serotonin (5-HT) Receptor Blocker/mixed action
nefazadone (Serzone)	300-500 mg	Serotonin (5-HT) Receptor Blocker/mixed action
nortriptyline (Aventyl, Pamelor)	50-150 mg	Norepinephrine (NE) Reuptake Inhibitor

paroxetine (Paxil)	20-60 mg	Selective Serotonin Reuptake Inhibitors (SSRIs)
phenelzine (Nardil)	45-90 mg	Monoamine Oxidase Inhibitor
protriptyline (Vivactyl)	15-60 mg	Norepinephrine (NE) Reuptake Inhibitor
sertraline (Zoloft)	50-200 mg	Selective Serotonin Reuptake Inhibitors (SSRIs)
trazodone (Desyrel)	150-300 mg	Serotonin (5-HT) Receptor Blocker/mixed action
trimipramine (Surmontil)	150-300 mg	NE and 5-HT Reuptake Inhibitors
venlafaxine (Effexor)	125-375 mg	NE and 5-HT Reuptake Inhibitors

#### **Appendix 4. Bipolar Medications - Generic (Trade) Names.**

carbamazepine (Esquetro®, Tegretol®)  
 divalproex (Depakote®)  
 lamotrigine (Lamictal®)  
 lithium (Eskalith®, Lithobid®)  
 olanzapine + Fluoxetine (Symbyax®)  
 olanzapine (Zyprexa®) used for schizophrenia and bipolar disorder  
 quetiapine (Seroquel®) used for schizophrenia and bipolar disorder  
 risperidone (Risperdal®) used for schizophrenia and bipolar disorder

#### **Appendix 5. Benzodiazepines - Generic (Trade) Names.**

alprazolam (Xanax®, Niravam®)  
 chlordiazepoxide (Librium®)  
 clonazepam (Klonopin®)  
 clorazepate (Tranxene®)  
 diazepam (Valium®)  
 lorazepam (Ativan®)

#### **Appendix 6. Antipsychotic Medications - Generic (Trade) Names.**

aripiprazole (Abilify®)  
 clozapine (Clozapine®, Clozaril®, FazaClo®)  
 molindone (Maban®)  
 olanzapine (Zyprexa®) used for schizophrenia and bipolar disorder  
 pimozide (Orap®) used for Tourette's syndrome  
 quetiapine (Seroquel®) used for schizophrenia and bipolar disorder  
 risperidone (Risperdal®) used for schizophrenia and bipolar disorder  
 thioridazine  
 thiothixene (Navane®)  
 ziprasidone (Geodon®)

## **Review Questions – ALU 201, Chapter 6**

1. Maladaptive behavior patterns to personal and social stress are characteristic of:
  1. thought disorders
  2. personality disorders
  3. anxiety disorders
  4. panic disorders
2. All the following are considered mood disorders EXCEPT:
  1. depression
  2. cyclothymia
  3. bipolar disorder
  4. panic disorder
3. Which of the following can be used to diagnose psychiatric disorders?
  - A. subjective symptoms
  - B. brain imaging scans
  - C. biological markers

Answer Options:

1. A only is correct.
2. A and B only are correct.
3. B and C only are correct.
4. A, B, and C are correct.

4. Name the four common areas of obsession in obsessive-compulsive disorder.
5. List the six main groups of antidepressant medications.

6. Which of the following are considered anxiety disorders?
- panic disorder
  - obsessive-compulsive disorder (OCD)
  - body dysmorphic disorder
- Answer options:
1. A and B only are correct.
  2. A and C only are correct.
  3. B and C only are correct.
  4. A, B, and C are correct.
7. All of the following statements regarding schizophrenia are correct EXCEPT:
1. It is associated with a high risk of suicide attempt.
  2. Onset prior to age 25 is uncommon.
  3. Symptoms often include delusions.
  4. Anti-psychotic medications are the treatment of choice.
8. Name three primary characteristics of depression.
9. Describe at least three characteristics exhibited by the anxious/fearful group of personality disorders, and how they are often treated.
10. Name at least four common characteristics of attention-deficit hyperactivity disorder (ADHD).

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 2: personality disorders – page 10.

### *Review Question 2*

Answer 4: panic disorder – page 2.

### *Review Question 3*

Answer 1: A only is correct – page 1.

### *Review Question 4*

Refer to page 9.

### *Review Question 5*

Refer to page 17.

### *Review Question 6*

Answer 1: A and B only are correct – page 7.

### *Review Question 7*

Answer 2: Onset prior to age 25 is uncommon. – pages 12-13.

### *Review Question 8*

Refer to page 3.

### *Review Question 9*

Refer to page 11.

### *Review Question 10*

Refer to pages 14-15.



## **CHAPTER 7**

### **THE RESPIRATORY SYSTEM**

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## THE RESPIRATORY SYSTEM

### Introduction

The purpose of this chapter is to expand the intermediate underwriter's knowledge of the respiratory system, basic testing, and some of the more commonly seen disease entities. The respiratory system, like the skin, is in constant contact with the environment. Its function is to allow oxygen in the air to be absorbed into blood and, just as important, for carbon dioxide to be expelled into the exhaled breath.

### Anatomy

The lungs are entirely within the chest cavity. They are covered by the pleura, which are thin continuous tissue layers that also line the inner surface of the chest wall. The parietal pleura lines the chest wall and the visceral pleura covers the lungs. Normally there is 5-15 mL of very slippery fluid between these two plural surfaces, allowing for smooth movement of one surface over the other. In disease states, abnormal collections of fluid occurs between these two layers (i.e., a pleural effusion). Anatomically the lungs are divided into lobes, with the right lung having three lobes and the left lung having two. The lobes, in turn, are divided into two to five segments each.

Air reaches the lungs via the nose, mouth, trachea, and then through a branching system of tubes, collectively called the bronchial tree. The upper nasal airway hydrates and warms the air and filters out large particles keeping them from reaching the lungs. The trachea in the neck and upper chest bifurcates to the right and left lung and then successively divides to the lobes and segments, finally ending in terminal air sacs called alveoli. The alveoli are tiny air sacs surrounded by capillary where the blood exchanges carbon dioxide for oxygen. (The walls of both the alveoli and the capillaries are only one cell thick.) The bronchial tree divides about 27 times before reaching the alveoli. Respiration is the gas exchange that takes place in the alveoli by which oxygen ( $O_2$ ) is taken up by the capillary red blood cells and carbon dioxide ( $CO_2$ ) is expelled into the alveolus and removed by exhalation.

Deoxygenated blood reaches the lungs through the pulmonary arteries from the right side of the heart (right ventricle), which has received deoxygenated blood from the rest of the body. Once the blood has reached the alveoli and carbon dioxide has been exchanged for oxygen, oxygenated blood is then returned by the pulmonary veins to the left atrium. As in the circulation to other areas, the pulmonary circulation is a branching system in which the arteries taking blood to the lungs finally end in tiny capillaries. The capillaries then merge to form the veins that return blood to the heart. The pulmonary veins carry oxygenated blood from the lung to the left atrium and then left ventricle, to be distributed to the rest of the body.

The terminology may be confusing as we normally think of *veins* as carrying deoxygenated blood and *arteries* as carrying oxygenated blood. In the lung it is the opposite – deoxygenated blood arrives into the lung via pulmonary *arteries*, and oxygenated blood leaves to alveolar bed and organizes into pulmonary *veins* returning the oxygenated blood to the left side of the heart.

The pressure in the pulmonary arterial system is much lower than that in the circulation to the rest of the body. In the pulmonary arteries the average pressure is in the range of 10-20 mmHg.

The circulation in the lungs is affected by any disease process that alters respiratory function, whether circulatory or pulmonary. For example, pulmonary emboli (i.e., blood clots from the distal body passing through the right ventricle into the pulmonary circulation) primarily affect circulation, with respiration being secondarily compromised.

The hundreds of millions (300,000,000) of alveoli are only one cell thick and are in intimate contact with the capillaries, which are also one cell in thickness. It is here, at this very thin interface, that O<sub>2</sub> and CO<sub>2</sub> exchange takes place. It has been estimated that if the entire alveolar-capillary membrane were stretched out, the surface area would cover two tennis courts.

## Physiology

The lungs are inflated primarily by the diaphragm. With inspiration (inhalation), chest muscles move the ribs up and out. At the same time the diaphragm, an upwardly-domed muscle separating the lungs from the abdomen, moves downward. The net result of these actions causes a negative airway pressure that draws air in through the nose and mouth, inflating the lungs. In expiration (exhalation), the chest wall muscles relax, the diaphragm passively moves upward, and air is thereby released from the lungs.

Air is delivered to the alveoli, and the pulmonary circulation carries blood to the alveolar capillaries. The alveoli exchange the oxygen contained in the inhaled air for carbon dioxide from the red blood cells, while the red blood cells exchange carbon dioxide for oxygen from the alveoli.

Oxygen (O<sub>2</sub>) is required by all cells for metabolism and for the healthy function of all body tissues. The by-product of metabolism is carbon dioxide (CO<sub>2</sub>), but CO<sub>2</sub> is more than a waste product. Carbon dioxide combines with water in the tissues to form a weak acid, carbonic acid. The level of CO<sub>2</sub> or carbonic acid can be adjusted rapidly by the body to maintain the critical balance of acid and alkali in the body. A measure of this level of alkalinity or acidity is known as pH. The body pH must remain within a very small range to maintain life. An example of how a tiny change in pH can alter body function is the hyperventilation syndrome. Rapid breathing causes excess CO<sub>2</sub> (and consequently carbonic acid) to be lost, and body fluids become less acidic (i.e., respiratory alkalosis). With this comes dizziness, numbness, lightheadedness and, if allowed to continue, tetany (i.e., muscle contractions) and convulsions.

In the reverse situation with respiratory failure due to severe lung disease, there is decreased air exchange resulting in low oxygen and high CO<sub>2</sub>, resulting in body fluids become too acidic (i.e., respiratory acidosis). Over long periods of time, the kidneys can partially compensate for this acid load by creating sodium bicarbonate, a weak alkali.

Oxygen toxicity (too much oxygen) can occur while breathing high concentrations of O<sub>2</sub> during artificial ventilation. While hemoglobin's characteristics prevent it from taking on too much O<sub>2</sub> in the blood, exposure to high levels of oxygen can result in excessive oxygen unbound to hemoglobin and dissolved in blood and that can damage the eyes, central nervous system, and lungs. Premature

infants requiring very high oxygen levels and individuals with severe lung disease requiring oxygen concentrations well above 60% are examples of eye (in the case of the infant) and lung (in the case of the adult) damage resulting from excessive levels of inhaled oxygen dissolved in blood.

## Pulmonary Function Testing

The fundamental and most frequently performed of the lung function tests is basic spirometry, in which an individual takes as deep a breath as possible and then exhales as forcefully as possible for (ideally) a minimum of six seconds. In an optimal setting, several spirometric measurements are done, with at least two of these results achieving 10% or better concordance. Spirometry gives measurements for forced vital capacity (FVC), which is the maximum volume of air exhaled; forced expiratory volume in one second (FEV<sub>1</sub>), which is the amount of air exhaled in the first second; and the ratio of the two – the FEV<sub>1</sub>/FVC ratio. The results are usually recorded along with percentages of normal based on sex, age, and height. For underwriting purposes, any FEV<sub>1</sub>/FVC ratio that is > 80% can be considered normal. If the spirometry is done with bronchodilators and the post-bronchodilator FEV<sub>1</sub>/FVC is < 70%, this individual meets global obstructive lung disease (GOLD) criteria for having chronic obstructive pulmonary disease (COPD).

Spirometry can reveal any of the following:

1. airway **obstruction** (in which the reduction in FEV<sub>1</sub> is larger than the reduction in FVC resulting in an FEV<sub>1</sub>/FVC < 80%)
2. chest wall or lung **restriction** (in which the FVC and FEV<sub>1</sub> are both proportionally reduced with the FEV<sub>1</sub>/FVC > 80%)
3. **normal** lung function (with all results being > 89% of predicted).

In addition, there can also be cases of mixed airway obstruction and chest/lung restriction.

Spirometry that reveals airway obstruction can be all that is needed for an underwriting decision, but if possible, the underwriter should confirm that the spirometry was done when the individual was well, not during an exacerbation of asthma or COPD. Any spirometry testing that reveals restriction requires need for further testing, since a suboptimal or poor effort on spirometry can be interpreted as restrictive lung disease. Whether disease is present can be confirmed only by actual measurement of lung volume.

FVC is a volume measurement and can be decreased with severe airway obstruction in diseases such as lung fibrosis or bronchiectasis, in which lung tissue is scarred, or in conditions of the chest wall that interfere with breathing. Two examples of chest wall problems are 1) paralysis of the chest muscles in traumatic quadriplegia and 2) chest deformities (e.g., kyphoscoliosis), which restricts chest wall motion. These conditions would cause spirometry to show reduced FVC but normal FEV<sub>1</sub>/FVC ratio, indicating restriction. In such cases, the reduced lung volumes would need to be confirmed by actual measurement of lung volumes and lung diffusion for this spirometric diagnosis to be confirmed and for this finding to be relevant to any underwriting decision.

Other tests of lung function are occasionally seen in underwriting. Most measure airflow. Maximum voluntary ventilation (MVV) is the volume of air expired in a specific period during which the subject is breathing as hard and as fast as possible. Very low percentages of predicted on this measure can be an indicator of poor effort. Any value below  $FEV_1 \times 40$  should also suggest suboptimal effort. Forced expiratory flow during the middle half of the FVC ( $FEF_{25-75\%}$ ) of < 70% predicted can be particularly helpful because it is measuring only the middle portion of the spirometric effort, when patient effort has least effect.

Other volumes measured with more complete pulmonary function testing include the functional residual capacity (FRC) or amount of air in the chest cavity after normal exhalation in tidal breathing and inspiratory capacity (IC), which is the volume of air measured from normal exhalation to as much as can be taken in on a maximal inspiration effort. The IC is not routinely reported on spirometry results but probably should be, since it is the only measurement in spirometry that indirectly reflects air-trapping and hyperinflation. A reduced IC can be the result of an increased functional residual capacity (FRC) when other indices of good patient effort are present. All lung volume measurements on pulmonary function testing begin at end-exhalation and measure FRC. The total lung capacity (TLC) is then the addition of the measured FRC + IC. An accurate measurement of hyperinflation would be to look at the measured FRC rather than the calculated TLC.

Pulmonary diffusing capacity can be measured by carbon monoxide diffusion capacity (DLCO). It measures the total alveolar-capillary volume available for gas exchange. It is decreased by inflammatory diseases, by fibrosis of the lung or capillaries, and by pathology causing lung destruction such as emphysema. The DLCO is usually reported as a percentage of predicted, and that is the value that is to be used in underwriting. There is frequently an additional measurement labeled DLCO/Va, which for underwriting purposes, can be ignored. For insurance underwriting purposes any  $DLCO > 70\%$  of predicted may be considered normal.

### Clinical History

In lung disease, as in many medical conditions, clinical history is the most valuable segment of information. In general, ratable lung conditions are progressive, so the rate of progression is extremely important. Shortness of breath (i.e., dyspnea) is one of the most common symptoms of lung disease. If two years ago a proposed insured could climb two flights of stairs without stopping but now has to pause for breath before completing one flight, his disease is severe and progressing. Progressive worsening is a poor prognostic sign. Medications taken, especially daily corticosteroids or narcotics, and the need for continuous supplemental oxygen, help to define the severity of the disease process. The number and frequency of hospitalizations are also helpful guides, especially if frequent or prolonged.

Occupational history is important in those who have had exposure to hazardous environments. The list of occupational lung diseases is long, but coal workers and asbestos workers are the largest affected groups. Duration and intensity of exposure, as well as the impact on health, are necessary pieces of information.

## **Physical Exam**

Physical findings in lung disease are significant if abnormalities are found. Paramedical examiners rarely make observations regarding the respiratory status of the proposed insured. Most physician examiners will note marked deviations from normal, but subtle findings can escape detection. Rales, rhonchi, and crackles are terms used to describe the sounds heard with the stethoscope when there is fluid in the airways or the lung is fibrotic. They are not diagnostic of any specific disease but always indicate an abnormality. Wheezes are whistling sounds heard when the airways are partially obstructed by spasm of the bronchi (as in asthma) or by fluid (as in heart failure or pneumonia). Diminished or absent breath sounds can be a common finding in emphysema but can also be described in the very obese or those muscular individuals with thick chest walls.

Physical findings of lung disease are not confined to the chest. Clubbing (i.e., bulbous enlargement of the tips of the fingers and toes) is associated with pulmonary disorders, cardiac problems, and other conditions. Cyanosis (i.e., blue discoloration of the nails and lips) indicates poor oxygen levels. The heart may be enlarged and abnormal heart sounds heard, especially if there is associated elevation of pressure in the pulmonary artery. Individuals who have severe airways disease may purse their lips on exhalation – usually a sign of advanced disease.

In the absence of a history of respiratory disease, abnormalities on physical examination of the lungs should be investigated further. With a positive history, the underwriter must decide if the abnormalities are consistent with the proposed insured's known condition.

## **Chest X-Ray**

Chest x-ray reports may or may not be helpful to the underwriter evaluating a proposed insured with lung disease, as a normal chest x-ray can be seen with even significant asthma or COPD. A chest x-ray report of "hyperinflation" without other comments can be misleading. A chest x-ray report specifically describing loss of lung markings in the lung apices (i.e., centrilobular emphysema) or lung bases (i.e., panlobular emphysema) or description of lung bullae can be helpful in confirming a suspicion of emphysema, as is a description of flattening of the diaphragm and the presence of an "increased airspace" on lateral chest x-ray views. However, an otherwise healthy individual who really takes as deep a breath as possible on chest x-ray can appear to be "hyperinflated."

With occupational lung disease, there can be a marked disparity between the x-ray showing interstitial changes and the clinical condition. The proposed insured can have an abnormal x-ray but be nearly symptom-free and have good lung function. The clinical history and pulmonary function tests can be better than chest x-ray at identifying the severity of lung function abnormalities.

## **Ventilation and Perfusion Lung Scans (V/Q Lung Scans)**

These studies use radionucleotide-tagged elements injected into the bloodstream or inhaled. They are used primarily to evaluate for pulmonary emboli (i.e., blood clots in the lungs). The perfusion scans are read as either “low or no probability” for blood clots, “intermediate probability” (read that as a 50-50 chance), and “high probability.” The risk of false positives with perfusion scans is lessened by the inhalation (ventilation) portion of the scan. Pulmonary emboli should cause “perfusion defects” (usually wedge-shaped lack of filling of the periphery of the lung) with corresponding areas showing normal ventilation. Emphysema and lung infiltrates of any cause greatly lessen the reliability of V/Q imaging.

## **CT Angiograms**

Computed tomography (CT) angiograms are now considered the best way to evaluate for pulmonary emboli because there can be many causes for false-positive perfusion scans. CT angiography, however, requires injection of dye that can be harmful to kidney function, and there is a relative contraindication to doing CT angiography whenever the serum creatinine is at the upper limits of normal. There is also a relative contraindication to the use of CT angiograms in younger persons with chest pain because of the risk of accumulated radiation over the person’s lifetime. Excellent radiographic reports now record the exact dose of radiation given.

## **Computed Tomography (CT) Lung Imaging**

CT lung imaging is now the best way to define the anatomy of the lung and mediastinum (and chest wall, for that matter). Magnetic resonance imaging (MRI) is rarely used for this part of the body because of motion artifact with respiration. Of particular use is CT angiography for detection of pulmonary emboli, arterial wall dissection, or abnormal aneurysms of major blood vessels. High-resolution computed tomography (HRCT) is relatively low-resolution (fewer cuts, wider apart) except for a single area in the lower part of the lung, where the cuts are super-dense at 1 mm each for several centimeters, giving much-needed definition to airways and lung parenchyma in interstitial lung disease.

## **Positron Emission Tomography Imaging**

Positron emission tomography (PET) attaches radionucleotides to molecules of glucose and injects them into the body. This is imaging function, not anatomy (as seen with CT), with metabolically active nodules or masses taking up these radioactive molecules. Such uptake is measured as standardized uptake value (SUV), with the higher the SUV, the higher the uptake. One caveat is that study reports should now also include the patient’s blood glucose at the time of the study. Blood glucose levels greater than 200 mg/dL can seriously decrease the amount of radionucleotide-tagged glucose molecules entering the infiltrate or nodule of interest. A high SUV does not automatically translate to cancer since any infection or inflammation can actively take up the glucose molecules. Most cancer patients undergoing therapy are followed with a combination of CT and PET imaging superimposed on each other – the so-called PET/CT – to best judge improvement or progression of disease.

## **Fiberoptic Bronchoscopy**

The most common way of obtaining visual assessment of the tracheobronchial tree and to acquire sampling from the lung is using a fiberoptic bronchoscope. A thin lighted tube is passed down the throat and into the airways. During this procedure, the lung can be lavaged with saline and the fluid collected, areas of concern can be brushed - with the material obtained transferred to a slide or solution for subsequent cytology evaluation, and/or biopsies of bronchial masses and peripheral transbronchial lung biopsies of the lung parenchyma can be obtained. Because lung cancer remains the number one cause of cancer death in both males and females, creative algorithms have been developed that allow the CT lung imaging to "guide" the bronchoscope to the lesion, and there are now creative ways to assess cellular return from bronchoscopy for detection of malignancy.

## **Underwriting Approach**

Underwriting respiratory disease is somewhat more straightforward than diseases of other systems. In most individuals, symptoms are persistent (asthma being an exception) and some abnormality can be demonstrated that is in proportion to the severity of the disease. This abnormality can be a symptom, the results of pulmonary function testing, physical findings, or findings on a chest x-ray. There is a moderate degree of predictability in chronic lung diseases. If progression has been slow, then it may continue to be so; if rapid, then disability and/or early demise can be anticipated.

## **Selected Lung Diseases**

### Lung Abscess

A lung abscess is an infection resulting in a localized destruction of and accumulation of pus in lung tissue. The infections can be due to bacteria, tuberculosis, or fungi and are treated with antibiotics. Rarely is surgery needed. In an otherwise healthy person, a lung abscess can usually be cured without sequela. The incidence of serious underlying disease is usually uncommon with lung abscesses that are caused by bacteria. Of greater cause for concern for the underwriter is the possibility of alcoholism with aspiration, seizure disorder, cancer, or chronic debilitating disease of any type that can be the underlying cause of a lung abscess.

### Alpha-1-Antitrypsin Deficiency

Alpha-1-antitrypsin (AAT) is a protein that protects tissues from destruction from naturally occurring proteolytic enzymes of the pancreas that normally digest protein in the duodenum but that can gain access to the general bloodstream and may need to be neutralized. A deficiency of this protein is a genetically-determined condition, which in its homozygous (complete) form predisposes an individual to severe destructive emphysema and liver disease. Emphysema is more common in adults, while liver disease is the most common manifestation in children. A strong family history of emphysema, especially at early ages (30s and 40s), suggests this condition which can readily be diagnosed by a simple finger-stick blood sample.

In normal individuals (genetically designated PiMM), the serum levels of AAT are 150-350 mg/dL. Those with the severe homozygous form (designated PiZZ) have AAT levels of 18-52 mg/dL. There are milder forms (designated PiSS, PiSZ, PiMZ) that usually do not carry the same grave prognosis. Most of these individuals do not develop emphysema if their serum AAT level is above 80 mg/dL. Those with low levels and who smoke have increased risk of developing emphysema. Replacement therapy involving IV infusions of antitrypsin can mitigate ongoing lung and/or liver damage.

### Sleep Apnea-Hypopnea Syndromes

It is estimated that several million Americans suffer from some form of chronic sleep disorders, many of which are undiagnosed and untreated. It is estimated that two percent of females and four percent of males 30 to 60 years old have sleep apnea, defined as having an average of at least 5-10 events per hour causing a reduction in oxygen saturation. Such individuals will often have daytime complaints of chronic fatigue, difficulty with concentration and task persistence, irritability, and depression. Eighty percent are obese (but, importantly, 20% are not) and they often have hypertension, and this condition may confer additional cardiovascular mortality.

Sleep apnea is defined as the absence of airflow, through the nose or mouth, for at least 10 seconds during sleep. Apnea can occur due to failure of the respiratory drive (i.e., central apnea), obstruction of the upper airway (i.e., obstructive apnea), or in a mixed pattern. In obstructive sleep apnea, negative pressure in the pharynx during inspiration causes the posterior pharyngeal wall to collapse onto the back of the tongue. Definitions associated with sleep apnea are:

1. apnea – absence of airflow > 10 seconds
2. apnea index (AI) – number of apnea episodes in one hour
3. hypopnea – partial apnea with physical evidence such as a drop in the partial pressure of oxygen ( $pO_2$ )
4. apnea-hypopnea index (AHI) – the number of apneas and hypopneas per hour of sleep—This is the major finding of note that diagnoses sleep apnea and its severity, with an AHI >10/hr being a concern.
5. respiratory disturbance index (RDI) – apneas plus hypopneas plus number of respiratory-effort related arousals per hour
6. central apnea – apneic episode without any diaphragmatic effort to breath (i.e., NOT due to airway obstruction).

There are many risk factors for obstructive sleep apnea. They include:

1. male gender
2. older age
3. snoring
4. obesity
5. nasal obstruction
6. tonsillar or uvular hypertrophy
7. jaw abnormalities
8. alcohol abuse

9. hypothyroidism
10. COPD
11. acromegaly
12. use of tranquilizers
13. post-menopause.

Central sleep apnea can be associated with severe cardiomyopathy, with Cheyne-Stokes respiratory pattern of breathing, myasthenia gravis, muscular dystrophy, brainstem lesions, Shy-Drager syndrome (after cervical cordotomy), and central alveolar hypoventilation (Ondine's curse). It calls for more underwriting caution than a similar level of obstructive apneas. Central apneas are of much greater concern when found on the initial polysomnogram (PSG) testing. The more central apneas there are, the greater the concern is. Central apneas can also be seen with continuous positive airway pressure (CPAP) titration and, in this setting, are of less concern but still can reflect more serious underlying pathology. Central apneas elicited by CPAP often necessitate use of bilevel positive airway pressure (BiPAP), rather than CPAP.

The most common complaint of obstructive apnea is a history of snoring or witnessed apneas provided by a bed partner or roommate. Quiet snoring is common and benign. Loud, irregular snoring is a frequent precursor or component of sleep apnea. Snoring as a part of sleep apnea is often accompanied by gasping and thrashing movements. Other symptoms include daytime sleepiness, fatigue, cognitive impairment, personality change, and morning headache.

When sleep apnea syndrome is strongly suspected by history, a full polysomnography (PSG) study should be done in a sleep laboratory. Monitoring includes:

1. electroencephalogram (EEG)
2. electrooculogram to record rapid eye movement (EOG)
3. electrocardiogram (EKG)
4. oximetry
5. measurement of airflow at the nose and mouth
6. measurement of inspiratory effort
7. monitoring of limb movement.

Normal sleep consists of two phases:

1. rapid eye movement (REM) sleep
2. non-REM sleep.

Non-REM sleep is divided into three stages on the basis of EEG patterns ranging from light sleep (Stage 1) to deep sleep (Stage 3). A normal adult sleep cycle begins with a brief Stage 1, then non-REM sleep, and progresses through the deeper stages until REM occurs in one to four hours. Then the cycle of alternating non-REM and REM phases of sleep continue fairly regularly throughout the night. Towards morning, the REM periods become longer, and the deeper stages of non-REM sleep disappear. REM sleep constitutes about 25% of total sleep, and it is during this phase that dreams occur. Stage 3 sleep is the deep, restorative sleep that often confers a sense of

“a good night’s sleep” the following morning. It is often this stage of sleep that is interrupted by obstructive apneas or hypopneas causing a sleep arousal to improve breathing.

There are two major consequences of sleep apnea:

1. sleep fragmentation
2. episodic hypoxia.

The typical frequency of sleep disruption in symptomatic sleep apnea is more than 5-10 times an hour or 40-100 arousals/night. Oxygen desaturation (decreased pO<sub>2</sub>) and hypercapnia (increased pCO<sub>2</sub>) occur with similar frequency as the arousals, and when severe, can be associated with arrhythmias, changes in blood pressure, left ventricular dysfunction, increased pulmonary artery pressure, right ventricular overload, depression, and cognitive impairment.

Weight loss is strongly encouraged if obesity is present but is rarely achievable until the sleep apnea is diagnosed and adequately treated, and even then requires combined changes in dietary habits and some form of exercise.

The treatment of choice for obstructive sleep apnea (OSA) is nasal CPAP. Pressurized room air is applied by mask and acts as a pneumatic splint to keep the upper airway open. Compliance with CPAP use usually varies directly with severity of the sleep apnea. Persons with severe sleep apnea usually perceive an immediate improvement in their sleep and functioning the next day, and they are the most compliant of the patients receiving this therapy. The least compliant are individuals with mild sleep apnea who usually do not perceive that they have a problem in the first place (commonly it was their bed partner who insisted upon their evaluation and testing), and with no perceived benefit to wearing the device at night, they often abandon it (unless their bed partner convinces them otherwise). Compliance with CPAP use is now measurable, with third-party medical insurers requiring that small computer chips implanted in the CPAP machine be downloaded and reviewed by a physician at least once yearly. Studies have shown that wearing CPAP four or more hours nightly substantially removes the mortality implications of untreated sleep apnea.

Possible surgical treatments include correction of a deviated nasal septum, tonsillectomy, and uvulopalatopharyngoplasty (UPPP). Success rates with UPPP have been about 50%. Mandibular/maxillary surgery is showing some success. A tracheostomy is usually done as a last resort but is a definitive cure. A follow-up sleep study is the best way to confirm that surgical treatment has been successful in improving or eliminating the sleep-disordered breathing.

Causes of death with sleep apnea include accidents (two- to seven-fold increase in motor vehicle accidents), myocardial infarction, stroke, congestive heart failure, and sudden death from cardiac arrhythmias. In one study of 181 people with proven OSA, 13% had a history of a sleep-related accident. Severe apneics had twice as many of these accidents as mild or moderate apneics. Cardiac arrhythmias can be present only during sleep and not be identified during the waking hours. The most common arrhythmias are bradycardia, prolonged asystole, and second-degree AV block. In OSA, deaths due to arrhythmia usually occur between 5:00 and 9:00 a.m. Long-

term untreated sleep apnea can result in hypertensive left ventricular hypertrophy, pulmonary hypertension, and right heart failure.

When underwriting an individual with sleep apnea, the following factors should be considered: the severity of the condition, compliance with treatment, and secondary effects such as hypertension and pulmonary hypertension. Markers for severity include an apnea-hypopnea index (AHI) over 20, significant hypoxia, and arrhythmias. Significant hypoxia is considered to be present when the mean oxygen saturation of the blood is less than 85%. Many underwriting manuals would consider AHI < 20 as being very mild, with little increased mortality unless there is also history of severe O<sub>2</sub> desaturation and/or excessive daytime somnolence with accidents. Persons with persisting nocturnal hypoxemia (or with other co-morbidities such as COPD) can be given supplemental oxygen while wearing CPAP.

Unfortunately, even with ideal CPAP confirmed by repeat overnight polysomnography, many individuals with OSA continue to suffer with daytime sleepiness and even somnolence. There are now drugs on the market to address this puzzling problem.

A major evolving, and as yet unanswered, question is whether much simpler and less expensive home testing can be done for diagnosis of sleep apnea. As of this writing there has not been proven equivalency in-home testing, if for no other reason than electroencephalogram (EEG) recordings and EKG recordings are not done, nor is there direct observation by a trained technician to validate what is being recorded. There can be significant value in home nocturnal oximetry testing as a screening test to decide which persons need a full PSG.

### Asthma

Asthma is a clinical syndrome characterized by completely reversible airway obstruction at some point in the clinical history (i.e., when the individual is completely well and asymptomatic). The airway obstruction of asthma is secondary to spasm and excess mucus in the bronchial tree. Clinically, the individual has intermittent wheezing and shortness of breath. If asthma is mild and there is no underlying lung disease, normal lung function between episodes is expected. Asthma can be precipitated by allergens such as ragweed, cat dander, infections, cold air, or exercise. Occupational exposure can also cause attacks. The occupational exposure can occur in a wide variety of settings such as in heavy industry, clinical laboratories, or office settings. In most cases, there is no known cause.

Asthma with onset in childhood tends to diminish in severity with increasing age, but some individuals will continue to have severe asthma in adult life. The potential for asthma recurrence in adulthood after childhood asthma is lifelong but uncommon. Even less commonly seen is adult-onset asthma, which usually is much more severe and with more morbidity and mortality consequences than is seen in childhood asthma. Sensitive tests of lung function in those who have had childhood asthma will show increased bronchial reactivity in many.

An interesting observation of childhood asthma is that it seems to be much more common in children raised in “sterile” environments such as homes and high rises, than in children raised on “non-sterile” farms. It is thought that early exposures to “allergens” allows the farm children’s

immune system to develop a tolerance that the city children don't have. This is called the hygiene hypothesis.

Asthma has an inflammatory component that, if suboptimally treated or untreated, can evolve into COPD in a process called lung remodeling. For this reason, recurrent asthma is treated with daily inhaled steroids for inflammatory suppression, as well as inhaled bronchodilators as needed for symptoms. Bronchospasm and wheezing are often manifestations of COPD, and adults who are said to have asthma can indeed have COPD with wheezing. The two conditions are really different diseases, with childhood asthma incurring an inflammatory cascade with eosinophils, while COPD/asthma incurs inflammatory cascade with neutrophils, with no hope of individuals with COPD ever achieving complete reversal back to normal lung function.

Underwriting evaluation of asthma is by history. Important historical information is:

1. frequency and severity of attacks
2. hospitalizations
3. treatment
4. long-term therapy with systemic (oral or IV) corticosteroids.

For years pediatric pulmonologists, in particular, advocated children doing full-exhalation maneuvers through a peak-flow meter several times a day and adjusting therapy as needed by deviation of their expiratory airflow from normal. The experience of doing peak-flow measurements actually induces coughing and some degree of bronchospasm in children, and this practice is no longer as commonly advocated to be done on a regular daily basis.

Asthmatics wheeze intermittently, so wheezing noted at the time of exam in a known asthmatic adds little information. Pulmonary function testing in an asthmatic can change markedly within a day. While normal pulmonary function studies are helpful, abnormal ones are usually only useful when the person is as stable and free of symptoms for as long as possible (preferably a minimum of 90 days from exacerbation). Measuring spirometry during an exacerbation only documents severe airway obstruction and rarely is of clinical usefulness. A chest x-ray is usually not helpful for evaluation of asthma for insurance purposes.

Asthma is not a benign disease. An attack can quickly become severe, causing death before the individual can reach a medical facility. Special caution is warranted in those who:

1. are not on appropriate inhaled corticosteroid daily therapy
2. take oral corticosteroids daily
3. do not have medical facilities or physicians readily available
4. have attacks that are severe and/or frequent requiring either hospitalization or frequent ER or unscheduled physician office visits
5. have **ever** required intubation with mechanical ventilation.

Status asthmaticus is a severe attack that does not respond to the usual measures. It usually requires hospitalization and suggests a poor prognosis, if recurrent. Poorer prognosis has also been noted in those whose first attack of asthma occurred after the age of 40.

The importance of the appropriate use of corticosteroids in asthma must be stressed. In acute episodes, the early use of systemic (oral or IV) corticosteroids is associated with improved outcome and lower mortality. Use of high-dose oral corticosteroids for 5-10 days several times a year for viral upper respiratory infections (URIs) is not associated with increased morbidity or mortality risk. However, those individuals who require long-term, daily systemic use of this class of drugs usually have more severe disease and a poorer prognosis. The use of inhaled corticosteroids does not have the same significance as the use of systemic steroid drugs. There is no significant adverse effect from the use of inhaled corticosteroids, and, in fact, failure of patients to be on inhaled corticosteroids when they have significant asthma can be a cause for concern in underwriting.

Concern about increased mortality in childhood asthma is rarely justified, as most of these children do not meet the above concerns, and the vast majority of children “grow out of their asthma” with no further sequela. Increased mortality has been seen in adolescents who refuse to use their medicines as expressions of rebellion against their parents and in children who live in impoverished communities. Obviously, any child who exhibits poor control of his disease as reflected in a history of intubation, hospitalization, or frequent ER or unscheduled physician office visits would be an underwriting concern.

### Atelectasis

Atelectasis is the collapse of a portion of lung tissue. This is a radiological observation. Signs and symptoms are often absent. The cause is usually obstruction of an airway, as seen in pneumonia when airways become plugged with mucus. However, atelectasis can also be caused by aspiration of foreign bodies or, most importantly, tumors (e.g., cancer) growing into and obstructing an airway. If the atelectasis was transient and associated with a condition that has been cured, there is no problem.

Unexplained atelectasis, even without symptoms, requires evaluation that usually means postponement of underwriting. An exception to this approach is *plate-like atelectasis (discoid atelectasis)* noted on chest x-ray. The significance of these small patches of lung collapse is not completely known, but they are invariably associated with diminished excursions of the diaphragm. Obesity is the major contributor. Most cases are seen to be resolved upon repeat x-ray. It can be expected that plate-like atelectasis will be transient and not seen on a subsequent film.

### Blebs, Bullae and Cysts

Blebs and bullae are air-containing cavities within the lungs. They have no symptoms and are usually found incidentally on x-ray. Blebs are small air sacs on the surface of the lung. Other than the occasional rupture with resultant spontaneous pneumothorax, they have little significance.

Bullae are large collections of air that have a tendency to increase in size and may rarely severely compress the normal surrounding lung. These can become infected or rupture, causing pneumothorax. In most cases, bullae without associated lung disease cause little problem. If

associated with chronic obstructive pulmonary disease (COPD), the risk is that of the underlying disease.

Cysts contain fluid and are often congenital. Some lung cysts can be the residua of previous infection such as lung abscess. Lung cysts have little significance in the absence of underlying lung disease.

### Bronchiectasis

Bronchiectasis is defined as abnormal dilation of a distal bronchus. Clinically, it is manifested by chronic cough, sputum production, hemoptysis (expectoration of blood or blood-stained sputum), and, if it is extensive, shortness of breath. It is caused by a prior lung infection that has destroyed the normal muscular and elastic tissues of the bronchial wall and the cilia lining that helps clear secretions. There can be an underlying problem that has impaired the defenses against infection such as cystic fibrosis, deficiencies in antibodies, or immotile cilia syndromes (Kartagener's).

In the presence of diffuse significant underlying disease, the long-term prognosis is usually poor, as these individuals invariably have recurring infectious exacerbations. However, localized bronchiectasis in an otherwise healthy person can have a good prognosis. The major hazards are recurrent and severe hemoptysis and ongoing and ever-worsening lung infection. Administration of chronic antibiotic therapy is done only in significant, severe disease in which the mortality risk is high.

### Chest Deformities

Funnel chest (i.e., pectus excavatum) is depression of the sternum (breastbone) toward the spine, and pigeon breast (i.e., pectus carinatum) is a protrusion of the sternum. They are rarely associated with any serious problem and, unless there is evidence of cardiopulmonary compromise, can be ignored with regard to underwriting. Pectus excavatum is often associated with systolic murmurs and can be a physical finding in Marfan's syndrome, but generally it is a benign finding carrying no excess morbidity or mortality.

Kyphosis is an abnormal forward bending of the spine, and scoliosis is a lateral curvature of the spine. Together, they are kyphoscoliosis. This spinal deformity, and its attendant deformity of the ribs, can compromise the bellows function of the rib cage. When the angle of the scoliosis exceeds 100 degrees and the kyphosis exceeds 20 degrees, respiratory compromise can occur. In very severe cases, respiratory failure requiring treatment with external respiratory assistance can occur.

### COPD: Chronic Bronchitis, Emphysema, Chronic Asthma, and Bronchiectasis

Chronic obstructive pulmonary disease (COPD) is now internationally defined by the Global Obstructive Lung Disease (GOLD) initiative as being present when a post-bronchodilator FEV<sub>1</sub>/FVC ratio is less than 70%. The severity of the COPD is then measured by the FEV<sub>1</sub> percent predicted, with FEV<sub>1</sub> percent predicted > 80% being "mild," FEV<sub>1</sub> percent predicted 50-80% being

“moderate,” FEV<sub>1</sub> percent predicted 30-49% being “severe,” and FEV<sub>1</sub> percent predicted <30% being “very severe.”

COPD is an encompassing term including chronic bronchitis, emphysema, chronic asthma (with remodeling), and bronchiectasis. Although some individuals can have just one of these entities, far more commonly, affected persons have combinations of these disorders and now the preferred terminology is COPD, sometimes with a “/” after the term with listing of the predominant disease present (e.g., COPD/emphysema). COPD is now recognized as the third leading cause of death worldwide and the fourth leading cause of death in the U.S.

COPD has historically been seen as a gradual progressive loss of lung function and, in the case of emphysema, air-trapping and hyperinflation. Exacerbations of COPD, usually caused by viral or bacterial acute bronchitis, are now recognized to portend more significant loss of lung function, with the individual rarely returning to full former lung function. COPD with exacerbations is now viewed with much greater concern for morbidity and mortality than COPD without exacerbations.

Bronchitis is an inflammation of the inner lining of the bronchial tree and is manifested by cough and sputum production. Acute isolated bronchitis can be seen in otherwise healthy individuals with a bacterial or viral upper respiratory infection (URI) and in this setting causes no future adverse consequences. Chronic bronchitis is a serious disease that can lead to progressive disability and death due to respiratory failure. Chronic bronchitis is defined as chronic cough and sputum production for at least three months a year for two consecutive years.

Although emphysema, which is the destruction of alveoli, is distinct from chronic bronchitis, these two disorders are often seen in combination, generally in individuals with a smoking history. Increasingly COPD/emphysema is being seen in rural areas in Africa, China, and India, due to inhaled smoke from indoor fires for cooking and industrial pollutants. However, since cigarette smoking is rising in these areas of the world, it can be a contributing factor as well.

COPD is the most common chronic pulmonary problem in adults. Its course is often one of progressive deterioration of lung function marked by acute bouts of exacerbations, with shortness of breath and cough with sputum production being the chief symptoms. History is important for estimating prognosis. Its association with cigarette smoking is well known and, after the diagnosis is established, continued smoking contributes to mortality. A history of repeated respiratory infections and family history of chronic bronchitis are additional risk factors. A particular form of emphysema, panlobular or panacinar emphysema, which is associated with predominant loss of alveoli in the lung bases, is associated with alpha-1-antitrypsin deficiency (discussed previously). Emphysema associated with cigarette smoking preferentially destroys alveoli in the lung apices and is called centrilobular emphysema.

The rate at which the disease has progressed since the time of diagnosis is a good indicator of prognosis. An individual who was able to walk two flights of stairs without stopping two years ago and who now must stop before completing one flight has progressive disease. If there had been minimal change in exercise tolerance, the prognosis would be better. A more accurate way to assess progression is by serial pulmonary function tests. If these have been done, it is essential

to request the results. A current FEV<sub>1</sub> and inspiratory capacity (IC) are the best prognosticators and provide additional refinement when done after treatment with bronchodilators.

If the FEV<sub>1</sub> is over 80% of predicted and has been stable, the prognosis is good. With an FEV<sub>1</sub> of 60-80%, the mortality is increased significantly, and below 60% the individual requires careful underwriting. If the FEV<sub>1</sub> is one liter or less, the risk of respiratory failure is high.

Chest x-rays are of limited value in assessing the extent of COPD, especially in the early stages. Some people with severely impaired lung function will have relatively normal films. More potential value of the chest x-ray can be in the finding of occult lung cancer.

The underwriter must be cautious of the diagnoses of "chronic bronchitis," "emphysema," or "COPD" on an attending physician's statement. Strict definitions are not adhered to in all instances, and the diagnosis of chronic bronchitis can be given when the individual merely had an acute bronchitis that lasted somewhat longer than is usual. A statement of emphysema, when some minimal hyperinflation was seen on x-ray, is insignificant in an asymptomatic person. Emphysema is a pathological, not radiological, diagnosis, but it can be inferred from clinical assessment. There are x-ray findings that are typical of emphysema (as noted earlier), but these are only of help in the advanced stages.

When an underwriting decision is to be made on the basis of one of these diagnoses, it is imperative that documentation of the diagnosis and its severity be sought through accurate historical data and lung function testing.

### Cystic Fibrosis

Cystic fibrosis (CF) is a genetically-determined disease of the lungs and pancreas with initial manifestations at an early age. The incidence is said to be 1 in 2000 live births. Production of thick mucus and progressively deteriorating lung function are characteristic of the course of cystic fibrosis. Pancreatic insufficiency with digestive problems also occurs in many.

The disease is suspected in children with recurrent respiratory infections and/or intestinal malabsorption who have a family history of CF. Diagnosis is confirmed by determination of the chloride concentration in the sweat. As with most laboratory tests, there are ranges of normal and abnormal with no precise cutoff between the two. Sweat chloride of 80 meq/L or more is generally considered diagnostic for adults over age 20 and 60 meq/L or more for those ages 20 and under.

Increased understanding of CF has led to improved treatments. This has resulted in an increase in average life expectancy to mid- to late-30s, with some individuals now living into their 40s. The genetic abnormality that causes cystic fibrosis has been identified, and there is hope that introduction of the normal gene into persons with CF will be helpful in arresting or preventing the disease.

### Honeycomb Lung

Honeycomb lung is a term occasionally seen on chest x-ray reports and invariably indicates serious disease. It is indicative of end-stage chronic lung fibrosis of any cause – most commonly end-stage idiopathic pulmonary fibrosis. It also may be caused by any chronic inflammatory/infectious disease such as sarcoidosis, chronic tuberculosis, or fungal disease.

### Hypersensitivity Lung Disease

Hypersensitivity lung disease is a pulmonary reaction to organic dust, such as fungal spores and aerosolized particles of vegetable and animal materials. Symptoms begin several hours after exposure and consist of fever, chills, dyspnea, dry cough, and malaise. Recovery is spontaneous if there is no further exposure, but symptoms recur if one is again exposed to the offending agent. Chronic and repeated exposures often result in irreversible lung disease.

These disorders are known by the occupation or agent involved. Some of the more common are farmers' lung, pigeon breeders' disease, humidifier lung, bagassosis (in sugar cane workers), maple bark strippers' disease, and mushroom workers' lung. This group of disorders is relatively benign unless there are repeated exposures leading to permanent fibrosis.

### Interstitial Lung Disease

This pathologic entity causes inflammation and eventual fibrosis in the interstitial space – that anatomical space in between and surrounding all alveoli. There are some 200 known occupational causes of interstitial lung disease (ILD), but most are exceedingly rare. The most serious consequence of ILD is seen when it occurs along with a collagen vascular disease such as rheumatoid arthritis, systemic lupus erythematosus (SLE), or scleroderma. When ILD is part of these collagen vascular disease entities, it is invariably the cause of death in the individuals.

Another emerging disease problem is idiopathic interstitial lung diseases, with "idiopathic" meaning that they occur with no identifiable cause. Desquamative interstitial pneumonitis (DIP) can stabilize if the individual quits smoking, and inflammatory cryptogenic organizing pneumonitis (COP) can respond to high-dose corticosteroids, giving both of these diseases a more favorable outcome. Otherwise, most cases of ILD are relentlessly progressive and associated with very high mortality. The most common of the ILDs is usual interstitial pneumonitis (UIP) leading to idiopathic pulmonary fibrosis (IPF) with a median survival of 2.4 years.

### Pleural Disease

The most common symptom with pleural disease is chest pain, which can be aggravated by deep inspiration and is called pleurisy. Most pleural diseases are either infectious (pleuritis) or malignant. *Pleural effusion* is fluid collection in the pleural space (the space between parietal and visceral pleura) and is common in both pleurisy and malignancy. Diagnosis is made by analysis of this fluid. With infectious pleurisy, complete recovery is the rule.

*Empyema* (not to be confused with emphysema) is pleurisy with a collection of pus in the pleural space. It is usually secondary to pneumonia. Since the advent of antibiotics, it is seen infrequently. As with pus in any body cavity, surgical drainage is necessary. After resolution, residual scarring of the pleural surfaces is usually seen on x-ray. This is rarely severe enough to compromise lung function. The vast majority of those with a history of empyema present no extra mortality.

In the rare case of lung entrapment by a dense pleural scar, surgical removal (decortication) to free the lung can be necessary. Caution should be exercised in these cases, for there can be residual lung disease.

Malignant disease of the pleura is more often metastatic than primary. However, mesothelioma, seen in asbestos workers, is a primary pleural cancer. Any malignant pleural disease carries a grave prognosis. Occasionally the pleura will be involved in collagen vascular disease, such as systemic lupus erythematosus. Unexplained pleurisy with effusion, especially if recurrent, points to this group of diseases. Pleural disease in collagen vascular diseases is much rarer and is of much less mortality and morbidity concern than is interstitial lung involvement. ILD in collagen vascular diseases usually defines the cause of death in these disorders and carries high morbidity and mortality prediction.

Hemothorax is blood in the pleural space. It is most often secondary to injury, but malignant pleural tumors must be considered. Failure to remove a bloody pleural effusion by thoracentesis or chest tube can result in some degree of pleural fibrosis.

### Pneumoconioses

Pneumoconioses are a group of diseases produced by prolonged inhalation of inorganic dust. As in hypersensitivity pneumonitis, there is a growing list of offending agents, the major ones being asbestos, silica dust, and coal dust.

*Asbestosis* is a lung disease caused by inhalation of asbestos fibers in enough quantity to cause pulmonary fibrosis. Worsening shortness of breath indicates a high likelihood of progression to respiratory failure. Asbestosis is found in asbestos workers as well as in those with "stand by" exposure, such as those living or working near asbestos processing facilities and families of workers exposed to the dust brought home on clothing. The majority of deaths in asbestos workers are from cancer, either lung cancer (the most common) or mesothelioma. If cigarette smoking is added, the risk is much greater. The risk of lung cancer is 7-10 times higher than expected and in smokers it is 100 times higher. Evidence of disease secondary to asbestos exposure may not appear until 7-10 years after the exposure.

*Silicosis*, caused by prolonged inhalation of silica dust, is associated with shortness of breath. The typical x-ray picture can precede the onset of symptoms by as many as 20 to 40 years. Hard coal miners and those digging tunnels through rock are at serious risk. It is also seen in sandblasters and those who work with grinding wheels.

Underwriting assessment requires evaluation of severity in this group of diseases, as measured by symptoms, pulmonary function studies, and rate of progression. Prognosis in those with stable disease is more favorable, while continued progression of the disease has a poor prognosis.

*Coal workers' pneumoconiosis (black lung)* is a complex spectrum of conditions that has as its common denominator the history of prolonged exposure to coal dust. Evaluation consists of assessment of extent and rate of progression of the disease. Better cases are characterized by pulmonary function test results that are only mildly abnormal and stable. Chest x-ray is of lesser importance for it can show extensive abnormalities with few symptoms, or the reverse can be true (i.e., severe symptoms with few x-ray findings).

### Pneumonia

Pneumonia is inflammation of the lungs and is commonly caused by infection. Infectious agents include bacteria, virus, and fungi. It is important to determine if there is an underlying condition that would predispose the individual to infection. Immunocompromise, such as HIV, or alcohol abuse with vomiting and aspiration, must be considered when infections have been severe or recurrent.

### Pneumothorax

Pneumothorax is collapse of the lung, or part of the lung, caused by the leakage of air into the pleural space. The most common cause is rupture of a small bleb on the lung surface. Chest pain and shortness of breath are presenting complaints. Rarely, there is severe distress. All but very small pneumothoraces are treated by insertion of a tube into the pleural space and maintenance of suction for several days to keep the lung expanded. However, there is now a trend to allow small to moderate pneumothoraces to resolve on their own.

Normal lung function usually returns, although recurrence of pneumothoraces is not uncommon. Procedures that cause the lung to adhere to the chest wall are occasionally necessary in these recurrent cases. In general, mortality is normal in those with history of pneumothorax if there is no serious underlying lung disease.

### Pulmonary Emboli

Blood clots that form in the peripheral veins (i.e., venous thromboses) and migrate to the lungs are known as pulmonary thromboemboli (PTE). The classic presentation is the sudden onset of chest pain, shortness of breath, and cough productive of bloody sputum. Diagnosis is difficult. About 75% of cases are misdiagnosed, and many tests are often employed in an effort to distinguish this from other conditions causing similar symptoms.

There are three overlapping factors that predispose to venous thrombosis:

1. local trauma to the vessel wall
2. hypercoagulability
3. stasis.

Many who have a pulmonary embolism have an inherited susceptibility that is activated when a stressor, such as surgery, occurs. Other predisposing factors are pregnancy, fractures, cancer, and obesity. The most common inherited predisposition to hypercoagulability is factor V Leiden which is normally not a major concern. Other genetic diseases (protein C deficiency, protein S deficiency, and antiphospholipid syndrome) are much more serious.

Most emboli originate in the leg veins where deep vein thrombosis (DVT) and thrombophlebitis are found. Unless pulmonary emboli are massive or recurrent, the lungs are able to recover from the insult, and normal function can be anticipated. However, large emboli can cause immediate death. Multiple small emboli over a period of time eventually lead to compromise of pulmonary circulation, pulmonary hypertension, and its consequences. Large or recurrent DVT can lead to chronic changes in the veins that will predispose to further recurrent disease.

A single episode of pulmonary emboli in an otherwise healthy person usually does not result in any permanent impairment. If, after careful evaluation, the cause has been found and has been eliminated, the peripheral veins are normal on exam, there is no edema, and recovery is complete, there should be little extra mortality. A typical example would be a pulmonary embolus following knee surgery (referred to as a “provoked” embolus). The recurrence rate is higher in those in whom no cause is found (“unprovoked” embolus), and more caution should be exercised in these cases.

The standard treatment includes anticoagulation with intravenous heparin followed by warfarin (Coumadin®), which is usually continued for several months after the acute event. This treatment can have complications, so careful monitoring is required. Because warfarin requires frequent blood monitoring and dietary restriction and can be difficult to manage, newer oral anticoagulant medications—apixaban (Eliquis®), rivaroxaban (Xarelto®), dabigatran (Pradaxa®)—have been introduced. These medications are useful for prevention of DVT and pulmonary embolism following surgery (particularly orthopedic operations), as well as providing treatment of these disorders.

The risk of false positives with perfusion scans is lessened by the inhalation (ventilation) portion of the scan. Pulmonary emboli should cause “perfusion defects” (usually wedge-shaped lack of filling of the periphery of the lung) with corresponding areas showing normal ventilation. Emphysema and lung infiltrates of any cause greatly lessen the reliability of V/Q imaging.

### Pulmonary Hypertension

Pulmonary hypertension (PH) occurs when the pressures in the outgoing pulmonary tree rise to pathologic degrees. The most serious of the groups of pulmonary hypertension is Group I PH – idiopathic or hereditary etiology, or secondary to connective tissue diseases, HIV, portal

hypertension, and veno-occlusive disease in sickle cell patients. Group II PH is due to left-sided heart disease—both systolic and diastolic disease and valvular heart disease. Group III PH is caused by chronic hypoxemia, usually COPD but can also be seen by persons living at very high altitudes. Group IV PH is due to chronic thromboembolic disease. Group IV is everything else that may elevate pulmonary pressures, including hematologic/myeloproliferative disorders, sarcoidosis, and glycogen storage diseases.

The best screening test for pulmonary hypertension is echocardiography. Pulmonary hypertension is likely if PASP (pulmonary artery systolic pressure) is >50 mmHg, TRV (tricuspid regurgitant velocity) > 3.4, and if there is mention of enlargement of RA and/or RV on the echo report. Confirmation of pulmonary hypertension requires right heart catheterization.

### Pulmonary Nodules

A coin lesion or solitary pulmonary nodule is a finding on chest x-ray of a round shadow, 0.8 to 2.9 centimeters in diameter and surrounded by lung tissue (i.e., not a pleural-based nodule), with no other lung abnormality. **Note that any lung nodule that is 3+ cm in size is called a mass and is to be considered cancer until proven otherwise.**

A spectrum of disease processes can present as a solitary pulmonary nodule, so a diagnosis must be reasonably certain before an underwriting offer can be made. Overall, the incidence of cancer in these nodules is less than one percent. At the younger ages cancer is a rare cause, but the incidence rises with age. Non-cancerous nodules are most often granulomas, a form of scar tissue caused by a prior infection such as tuberculosis or histoplasmosis. Other causes include benign tumors, such as hamartomas and bronchial adenomas.

When a solitary pulmonary nodule is discovered during the course of an insurance evaluation and there is no record of a workup for it, previous x-rays should be sought. If it can be demonstrated that this nodule has been present and unchanged for three or more years, it is almost certainly benign. In the absence of previous x-rays, it can be possible to make an offer, especially if the proposed insured is a young nonsmoker and there are radiologic characteristics that make malignancy very unlikely (e.g., various forms of calcification). On the other hand, an older smoker needs follow-up and often no offer can be made until a thorough evaluation has been completed.

The increased use of CT scanning for diagnostic purposes has resulted in finding small pulmonary nodules in many individuals. Nodules that are less than 1 cm are difficult to see on regular chest x-rays. CT scanning can detect tiny nodules less than 4 mm. Most of the nodules under 1 cm will be benign but do require follow up to see if there is an increase in the size, which would be suspicious for malignancy. Clinically, nodules less than 4 mm are usually considered to be benign while those 4 mm or larger need follow up. The location of the nodule is also important, with upper lung zone solitary nodules being significantly more likely to be malignant than lower lung zone nodules. On the other hand, multiple nodules of varying sizes in the lower lung zones are more suspicious for neoplasm than if they occur in the upper lung zones. There are pulmonary nodule calculators that can be found on Google that can help with deciding the seriousness of a nodule.

**If any radiographic report (either chest x-ray or CT lung imaging) uses the terms “spiculated nodule” or “ground-glass-associated nodule,” the nodule should be considered to be malignant until proven otherwise.** Positron emission tomography (PET) imaging uses a radioactive isotope attached to a glucose (sugar) molecule to look at the metabolic activity of a nodule. A “positive” PET scan (high SUV numbers) shows the nodule to be metabolically active. This does not prove cancer, as any infectious cause (e.g., TB, fungi, bacterial pneumonia) will also be positive on testing, and the real value of PET imaging is when there is little (SUV <3) or no uptake. Even so, a very slow-growing malignancy like bronchoalveolar carcinoma (or adenocarcinoma in situ) can exhibit no uptake, and the two-year serial CT imaging will be needed. Additional caveats relating to PET imaging include documentation that the nodule being imaged is 1 cm or larger and that the person being tested does not have existing hyperglycemia (reports usually include the tester’s blood glucose at time of imaging), which would inhibit the uptake of the radioisotope-labeled glucose moiety.

The only absolute proof that a nodule is innocent is surgical removal, but even then the final histology report must be reviewed, and **there must be some pathology on the report accounting for the nodule**. Not infrequently, a video-assisted thoracoscopic (VATS) procedure will fail to remove a small nodule, and the report then will reflect only “normal lung tissue.”

It is now generally accepted that any nodule that is found to be unchanged in size or appearance after two years of serial imaging by CT can be considered to be benign.

### Pulmonary Fibrosis

Fibrosis of the lung is a general term meaning the presence of scar tissue in the lungs. It is seen on chest x-ray or CT scan and is caused by a variety of disease processes. Fibrosis, if localized, is usually insignificant and is most often a residual of old infection, such as tuberculosis. If diffuse, underlying serious disease must be considered. Diffuse pulmonary fibrosis or, more accurately, *diffuse interstitial lung disease* (also called diffuse infiltrative lung disease) has varied etiologies that share the findings of diffuse chronic inflammation and secondary fibrosis.

Onset of diffuse interstitial lung disease is usually between ages 40 and 70, and for many individuals the course is one of progressive deterioration of respiratory function. The duration from the time of onset of breathlessness (which is the presenting and major symptom in most cases) until death varies from a few months to as long as 20 years. In some cases, the fibrotic process can cease spontaneously.

Among the many causes for diffuse interstitial lung disease are:

1. infections, including viral pneumonia and fungal disease (e.g., histoplasmosis)
2. occupational exposure, most commonly in asbestos and coal workers with pneumoconiosis
3. heart disease with chronic pulmonary congestion
4. collagen vascular diseases such as SLE, rheumatoid arthritis, and progressive systemic sclerosis
5. sarcoidosis
6. cancer.

Diffuse pulmonary fibrosis can be considered the end-stage of a variety of inflammatory diseases and disorders. When end-stage fibrosis is present, the original cause of the damage is usually not discernable. The most common of the end-stage fibrotic lung diseases is idiopathic pulmonary fibrosis (IPF), the end-stage of most of the idiopathic interstitial pneumonias. The most common precursor of IPF is usual interstitial pneumonitis (UIP) which in turn is the most common of the idiopathic pneumonias. It is thought that UIP is the inflammatory stage and IPF is the final fibrotic stage of the same disease continuum. The etiology of pulmonary fibrosis may, therefore, never be known, but as end-stage disease carries a very high risk for mortality.

### Respiratory Distress Syndrome

The early newborn form of respiratory distress syndrome is hyaline-membrane disease and occurs chiefly in premature infants. It is characterized by difficulty breathing. The majority with mild disease recover completely. Those who are severely affected and who have required intensive respiratory care are quite likely to be left with permanent lung damage in the form of bronchopulmonary dysplasia. In very small infants who develop bronchopulmonary dysplasia, the mortality during the first year of life can be as high as 30-60%. Mortality is less during the ensuing years, but it is reasonable to assume that there is added risk throughout life.

The adult form of respiratory distress syndrome (ARDS) is associated with severe acute disease or trauma and requires intensive care treatment, frequently including prolonged periods of artificial ventilation. Acute interstitial pneumonitis (AIP) is the most deadly of the idiopathic interstitial pneumonias and is essentially ARDS of unknown etiology. Those who survive can be left with significant residual abnormalities of lung function and require careful evaluation before any decision is made as to insurability.

Of course, the most common cause of ARDS today is COVID-19 pneumonia.

### Sarcoidosis

Sarcoidosis is a disease of unknown cause characterized by microscopic inflammatory nodules called non-caseating granulomas that can be present in various tissues. Almost any organ can be involved, but the intrathoracic structures, especially the lungs and mediastinal and hilar lymph nodes, are affected in over 95% of cases. Lung nodules or reticulonodular infiltrates of sarcoidosis are much more prominent in the upper lung zones (compared with other causes for interstitial lung disease and/or fibrosis which are more common in the lower lung zones). Other areas that are involved less frequently are skin, eyes, heart, nervous system, bones, joints, and endocrine system. Young adults between the ages of 20 and 40 are most commonly affected, but it can occur in children and the elderly.

The most important diagnostic finding is a lung biopsy that shows non-caseating granulomas. Although two-thirds of individuals can have an elevated angiotensin-converting enzyme (ACE) level, the more usual use of this blood test is to help identify persons with recurrent or relapsed disease. About 10-20% of individuals with sarcoidosis go on to develop progressive fibrosis with severe damage to the lungs. Some can have damage to the heart, eyes, or nervous system.

Sarcoidosis is staged based on the amount of lung and mediastinal/hilar lymph node involvement on a regular chest x-ray (note: *not* lung CT). Stage 1 is bilateral enlargement of the lymph nodes at the root of the lungs (hilar nodes) and no lung involvement on chest x-ray. Stage 2 shows both lung reticulonodular interstitial changes and prominent mediastinal/hilar lymph node enlargement. Stage 3 has persisting lung involvement with gradual resolution of the mediastinal/hilar lymph node enlargement. Stage 4 is end-stage fibrotic lung disease often indistinguishable from any other cause of end-stage lung fibrosis.

Stage 1 is the most common presentation, generally is without symptoms, resolves spontaneously over time, and has an excellent prognosis with no extra mortality. The usual initial concern with stage 1 sarcoidosis is excluding the possibility of early, asymptomatic lymphoma.

Stage 2 sarcoidosis is much more likely to be found with symptoms of cough, shortness-of-breath, or other systemic symptoms. Symptoms and all radiographic changes of sarcoidosis can be rather quickly resolved with administration of oral corticosteroids, and such treatment has been the standard-of-care in the U.S. for years. However, studies from the United Kingdom have shown that if stage 2 sarcoidosis and any attending symptoms can be tolerated without pharmacologic intervention, then much more often than not—as in stage 1—the disease will ultimately remit and not recur. However, when remission is induced by steroids, then remission is often short-lived, and ultimate remission can require months and even years of tapering steroids.

Stage 3 sarcoidosis is characterized by more interstitial fibrotic change as the mediastinal and hilar lymph nodes melt away, and these changes are much more likely to be permanent. Stage 3 disease carries a much greater likelihood of not improving with steroid therapy and of progressing to end-stage lung disease. Sarcoidosis can be suspected by its propensity for upper lung zone distribution, as opposed to other interstitial lung processes that more typically have a mid-to-lower lung zone distribution.

Sarcoidosis can present acutely with erythema nodosum, a skin eruption. A self-limited course and spontaneous resolution can usually be anticipated. Skin involvement of the face and around the nasolabial folds, on the other hand, portends a much more serious course. Cardiac involvement is a major cause of sudden death in Japan. Liver involvement is common but may not be of major significance unless the elevation of liver enzymes far exceed three times normal. Peripheral neurological involvement with sarcoidosis rarely calls for major underwriting concern, but central nervous system involvement is associated with very high mortality.

If there is progressive fibrosis of the lungs, there will be decreased respiratory function. A few individuals will go on to respiratory failure and death. Corticosteroids are used to suppress the fibrotic stage of the disease, so evaluation of prognosis while on treatment is difficult. Once corticosteroids have been stopped and there is clinical and x-ray evidence of no further progression over many months, then some optimism is warranted. If the disease has spontaneous remission without corticosteroids, it will not recur.

Progression and/or regression of symptoms, x-ray findings, and pulmonary function tests are important in assessment. The vital capacity is reduced because fibrosis of the lungs will cause restriction of lung expansion. Airflow, as measured by FEV<sub>1</sub>, will be normal in many cases, but airway obstruction with asthma-like symptoms can occur because of endobronchial sarcoid infiltration causing narrowing of airways. DLCO will be decreased if there is significant interstitial lung involvement. Serial measurements showing stability or improvement in vital capacity are more valuable than a single measurement. Even when the process in the lungs has been stabilized, some permanent lung damage can remain.

### Tobacco Use

Smoking as a health hazard is well known and is reflected in smoker ratings. The association of smoking with COPD and vascular disease, especially coronary artery disease, is equally well known. Lung cancer is 5-10 times more frequent in smokers and has a prognosis of 10% five-year survival. Lung cancer is currently the number one cause of cancer death in males *and* the number one cause of cancer deaths in females, with the number of males and females in the U.S. dying of lung cancer exceeding the combined cancer deaths of breast cancer in females, prostate cancer in males, and colon cancer in both sexes. Increased risk of lung cancer can decline with increasing years of smoking abstinence but never reverts to that of a never-smoker.

Smoking is also associated with cancers of the esophagus, pancreas, kidney, and bladder. Asbestos exposure on top of smoking multiplies the cancer risk. Similar relationships exist for smoking in conjunction with exposure to chromate, nickel, coal, or uranium.

A very large female smoking study in Great Britain has found that smoking reduced average life expectancy in that country's female population by 12 years. Ex-smokers are at less risk than those who continue to smoke, and there always appears to be some mortality advantage to quitting smoking even in advanced COPD. Some of the anatomical and physiologic abnormalities that are caused by tobacco smoke will revert towards normal after exposure is eliminated, but many changes will persist. The decrease in incidence of chronic obstructive lung disease in ex-smokers is not as impressive, but there is some lessening of risk, especially in those who stopped smoking before age 45.

Although childhood educational efforts towards avoidance of smoking have helped, the single most effective anti-smoking initiative has been gradually increasing taxation of cigarette smoking. Other initiatives, such as banning smoking in public establishments, have also helped. Less than 20% of the U.S. population now smokes.

Although “vaping” nicotine through a battery-powered heating device would seem to be preferable to smoking tobacco (since the smoker is avoiding inhaling many of the other toxic chemicals and tars in cigarette smoke), there is mounting evidence of harmful effects of “electronic cigarettes,” and the safety of this substitution has not been proven.

## Tuberculosis

Tuberculosis (TB) is an infectious disease affecting the lungs primarily, but any tissue or organ can be infected. Initial lung infection with *Mycobacterium tuberculosis* (M.tb) is called primary infection, with almost all persons so infected being unaware of infection and the only sequelae being positive TB tests (see below) and emergence of granuloma, the body's defense against this bacteria that it cannot kill. Clinical disease with TB is called secondary infection (a recurrence of the primary infection) and most commonly recurrence is seen in the lung apices. Before the advent of effective therapy in the 1940s and 1950s, it was a disease with high mortality. With specific treatment, the incidence of TB decreased dramatically. Since the mid-1980s, there has been an increase in the number of TB cases. Individuals with acquired immune deficiency syndrome (AIDS) have been the primary group contributing to this increase. Other groups at risk are the elderly, minorities, immigrants (especially from Asia and Latin America), and prisoners. It is worth noting that until the advent of the COVID pandemic, M.Tb has been the #1 cause of infectious death in the world.

There is a new wave of TB that is resistant to the usual drugs—multiple drug-resistant TB. Those with AIDS, or those who are immunocompromised for any reason, are especially vulnerable. In those who are not immunocompromised, who have minimal disease, and whose TB organisms are sensitive to the usual drugs, the extra risk is small.

Those with a newly positive skin test for TB (e.g., PPD, Mantoux) should have a chest x-ray to exclude the presence of active TB, as a positive TB skin test (and, more recently, blood work such as Quantiferon TB Gold) should be accepted as evidence that the affected individual has actually had an initial TB infection (called primary infection and usually with no symptoms). False positives on testing are rare but can include prior immunization with BCG; however, changes in reading a skin test as positive have largely eliminated false positives. Newer rapid genetic tests are becoming more commonly used, both for diagnosis and to predict susceptibility to drugs used to treat TB.

Primary infection with the TB bacillus is extraordinarily common, with it being estimated that between 25% and 33% of the entire world's population has been primarily infected. TB disease—usually called secondary infection—can occur in 1 to 10% of people with primary infection and is the reason that in the U.S. at least, (the only country in the world to do TB skin testing) actual TB therapy with INH for 6-12 months is advocated in persons under age 35. The British have long been at the forefront of developing other short courses of multi-drug therapy for treating primary infection or mild disease. In an otherwise healthy person with no symptoms, there should be no extra risk associated with primary infection.

Less common are infections by *mycobacterium avian complex* (MAC), a group of related mycobacterium that cause infections in immunocompromised individuals, such as those with AIDS and end-stage COPD and/or bronchiectasis. It can rarely cause infection in older individuals without underlying lung pathology. The infection is treated with antibiotics, which generally results in remission, but rarely, if ever, a true cure. These cases need to be reviewed to be sure that the infection is cured and not just suppressed. Because MAC infections usually occur in already sick people, additional mortality concern reflects that of the underlying cause.

## **Review Questions – ALU 201, Chapter 7**

1. Pulmonary diffusing capacity measures the:
    1. capacity of the lungs during rapid breathing
    2. total alveolar-capillary volume available for gas exchange
    3. amount of air expired in the first second of forced expiration
    4. total amount of air that can be exhaled after deep inspiration
  2. Lung diseases attributable to asbestos exposure include all of the following EXCEPT:
    1. mesothelioma
    2. asbestosis
    3. black lung
    4. lung cancer
  3. Respiratory sounds caused by fluid in the airways include which of the following?
    - A. rales
    - B. rhonchi
    - C. crackles
- Answer Options:
1. A only is correct.
  2. A and B only are correct.
  3. B and C only are correct.
  4. A, B, and C are correct.
4. What physical evidence of lung disease might be found during an examination that is not confined to the chest?
  5. What are the risk factors for, major consequences of, and treatment options for obstructive sleep apnea?

6. Which of the following is the most likely to be malignant?

1. bronchial adenoma
2. spiculated nodule
3. granuloma
4. hamartoma

7. A family history of early onset emphysema is suggestive of:

1. cystic fibrosis
2. myasthenia gravis
3. alpha-1-antitrypsin deficiency
4. muscular dystrophy

8. Describe the staging criteria for sarcoidosis.

9. List the various causes of diffuse interstitial lung disease.

10. List the three predisposing factors for venous thrombosis.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 2: total alveolar-capillary volume available for gas exchange — page 4.

### *Review Question 2*

Answer 3: black lung — page 19.

### *Review Question 3*

Answer 4: A, B, and C are correct – page 5.

### *Review Question 4*

Refer to page 5.

### *Review Question 5*

Refer to pages 8-11.

### *Review Question 6*

Answer 2: spiculated nodule — page 22.

### *Review Question 7*

Answer 3: alpha-1-antitrypsin deficiency — page 7.

### *Review Question 8*

Refer to page 24.

### *Review Question 9*

Refer to pages 22-23.

### *Review Question 10*

Refer to page 20.



## **CHAPTER 8**

### **DISORDERS OF THE KIDNEY AND URINARY TRACT**

**MARTY MEYER, FALU, CLU, ChFC, FLMI**

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## **DISORDERS OF THE KIDNEY AND URINARY TRACT**

### **Introduction**

Isak Dinesen, the 20<sup>th</sup> century Danish author, wrote in Seven Gothic Tales, “what is man... but a(n)... ingenious machine for turning, with infinite artfulness, the red wine of Shiraz into urine?” While that statement may satisfy poets and philosophers, the anatomy and function of the human urinary system is much more complex. Malfunction of the urinary system can cause disorders that range from mild and benign to life threatening. Modern medicine has access to a variety of tests to evaluate kidney function and to diagnose urinary tract and kidney disease. Treatment of these disorders can be with a variety of medications and surgical procedures, including actual replacement of the kidney itself.

### **Anatomy and Physiology**

Normally, the two kidneys are located at the back of the abdomen in the retroperitoneal space, one on each side of the spinal column. Each kidney is about five inches (13 cm) long and weighs about four ounces (110 gr).

The kidney's primary purpose is:

1. to filter the nitrogenous products of metabolism (e.g., urea and creatinine) from the blood
2. to maintain water and electrolyte homeostasis.

The kidney also produces two hormones that have nothing to do with its excretory function:

1. erythropoietin, which stimulates the bone marrow to produce red blood cells
2. an active form of vitamin D that the kidney makes from the inactive form consumed in the diet or formed in the skin on exposure to sunlight.

There are two distinct zones in a kidney:

1. an outer layer, the cortex
2. an inner layer, the medulla.

The cortex is composed of about one million nephrons. Filtration takes place in the nephron of the kidney, which has two parts:

1. the glomerulus
2. the tubule.

The kidneys receive about 20% of the cardiac output through the renal arteries. Each renal artery divides into smaller and smaller arteries after it enters the kidney until the smallest arteries terminate in a looped coil of capillaries – the glomerulus (also called the glomerular tuft). Each glomerulus is a tiny, delicate structure. The walls of glomerular capillaries are composed of only three layers of cells, which can be seen with an electron microscope. Moving from inside the capillary to outside, these layers are the:

1. endothelial layer
2. basement membrane
3. epithelial layer.

Each of these layers is one cell in thickness and acts as a kind of sieve, allowing certain size molecules through and keeping others in the circulating blood.

1. The endothelial layer allows the passage of proteins but not of blood cells through openings called fenestrae.
2. The basement membrane traps the larger protein molecules and does not allow them into the filtrate.
3. The epithelial layer is composed of modified epithelial cell called podocytes. These podocytes have several radiating foot-like processes and slit diaphragms that form narrow channels that further restrict the molecules that pass into the filtrate.

The capsule that surrounds a glomerulus is the Bowman's capsule. Bowman's space is the space within the capsule surrounding the glomerulus. The tubule is the other structure in the nephron. The tubule is contiguous with the capsule and follows a circuitous route through the kidney cortex into the medulla where it joins with other tubules to form a collecting duct. The collecting ducts empty through structures called papilla into the pelvis of the kidney.

It is in the nephrons of the kidney that the two-step filtration process of waste products takes place.

1. First, the capillaries of the glomeruli filter 120 to 180 liters of fluid per day. This glomerular filtrate, composed of water, glucose, minerals, some protein, and the waste products of metabolism, flows into the capsule (i.e., Bowman's capsule) that surrounds the glomerulus.
2. Second, the filtrate flows into the tubule where the other step of filtration occurs – involving the reabsorption of over 99% of the filtrate (i.e., most of the water and proteins plus glucose and minerals).

The concentrated fluid that remains is urine. On average, urine forms at about one cc per minute. At this rate, the concentration of waste products of metabolism is about 100 times that in blood. Urine flowing through the tubules passes into the cortex of the kidney to the medulla where it joins up with other tubes (i.e., collecting ducts) that empty via the papillae into the pelvis of the kidney.

Each kidney has a ureter – a long, hollow, muscular tube – that conducts the urine from the kidney pelvis to the urinary bladder. Peristaltic contractions of the muscles in the ureter walls forces urine downward. Small quantities of urine empty into the bladder about every 15 seconds. There are sphincter muscles at the ureterovesical junction (where the ureters enter the bladder) that prevent urine from flowing backward into the kidneys when the bladder contracts during urination. A normal bladder can hold up to 16 ounces (approximately half a liter) of urine for up to four hours comfortably. There is a sphincter that prevents the leakage of urine from the bladder into the urethra. Contraction of the bladder for urination is not really a voluntary action. What is done voluntarily is the relaxation of the sphincter at the bladder outlet and the contraction of the abdominal wall. The contraction of the bladder itself is completely involuntary. In males, the

urethra is longer than it is in females since it passes through the prostate gland and the penis after it leaves the bladder.

Though a primary purpose of the kidneys is to excrete waste products of metabolism, another related purpose is to maintain water and electrolyte balance in the body. Since the kidneys also excrete water and salts that are in excess of the body's needs, they regulate the amount of fluid the body contains and, therefore, the volume of blood in the blood vessels and, in turn, the blood pressure. For example, if the kidneys retain more salt and water than they should, the volume of fluid in the blood vessels increases and the blood pressure rises.

Several hormones, including antidiuretic hormone (ADH), which is controlled by the hypothalamus and produced by the pituitary, and aldosterone from the adrenal gland, work together to control the amount of salt and water that are reabsorbed by the kidneys during the filtration process.

1. ADH is produced when the concentration of sodium rises. It acts on the kidney to retain water until the concentration of sodium falls to normal.
2. Aldosterone causes the kidneys to retain sodium.

Under the influence of the two hormones, both blood volume and sodium level are controlled.

In addition, renin, which is produced by the kidneys, triggers the formation of angiotensin in the bloodstream when the blood volume or blood pressure falls. Angiotensin is a hormone that not only causes more salt to be retained but also directly constricts small blood vessels, causing an increase in blood pressure. This mechanism explains why so many kidney disorders are associated with high blood pressure. Whenever the kidneys fail to get as much blood as they need, they react as though the blood pressure were low (i.e., more renin is produced in an attempt to increase the blood pressure and thus their own blood supply).

### **Clinical Manifestations and Terminology**

#### Proteinuria

Normal kidneys do not filter much protein (e.g., albumin, globulin) from the blood. The normal amount of protein in a random urinalysis is up to 30 mg/dl. In a 24-hour urine collection, the normal amount is up to 150 mg/24 hours. The most common evidence of renal disease is an excessive amount of protein in the urine (>150 mg total protein – containing 50 mg albumin) in a 24-hour collection.

The acceptable concentration in a random sample depends on whether the urine is being formed rapidly, and is therefore dilute, or being formed slowly, and so is concentrated. A fairly good rule is that the concentration of protein in mg/dl should be less than the last two figures in the specific gravity. For example, with a specific gravity of 1.015 mg/dl, 15 mg/dl of protein would be about the upper limit of normal.

Common benign causes of proteinuria are:

1. exercise, fever, stress, excessive cold, vaginal contamination
2. orthostatic proteinuria – a condition in which an individual has proteinuria when upright

but does not when supine. It can be intermittent. Some of those with orthostatic proteinuria have mild renal lesions, but overall excess mortality is very low.

### Microalbuminuria

Microalbuminuria refers to small amounts of albumin in the urine, not to smaller albumin molecules. Microalbumin of 30 mg/dl in a 24-hour specimen is considered elevated. In addition to diabetes, microalbuminuria can also be associated with hypertension, lipid abnormalities, and some immune disorders. It is also considered a risk factor for coronary artery disease.

### Hematuria

Hematuria is the finding of red blood cells or frank blood in urine.

1. Gross hematuria indicates that the blood can be seen with the naked eye.
2. Microscopic hematuria indicates that there is not enough blood to color the urine, but that red blood cells can be seen on microscopic examination.

Hematuria can be due to bleeding anywhere in the urinary tract – from the urethra to the kidney. Red blood cells in the urine can originate from bleeding in the kidneys, ureters, bladder, urethra, or from the prostate in males. The most common causes are:

1. stones
2. nephritis – usually associated with proteinuria and casts
3. tumors – both benign and malignant
4. prostate disease
5. benign familial hematuria (i.e., thin basement membrane disease).

Menstrual contamination can also be a cause of isolated hematuria in a pre-menopausal female.

### Pyuria

Pyuria is the presence of white blood cells (i.e., pus) in the urine sediment. It is often associated with infection as well as with inflammation. It is most commonly due to cystitis, urethritis, or prostatitis.

### Casts

Casts in the urine are formed when a protein produced by the nephrons (i.e., Tamm-Horsfall protein) gels around whatever is in its vicinity. Casts are named for their contents – e.g., red blood cell casts, granular casts, fatty casts. Hyaline casts are empty casts – just the gelled protein.

A finding of hyaline casts in a urinalysis is considered benign. Other types of casts usually indicate renal disease:

1. red blood cell casts – glomerulonephritis
2. white blood cell casts – inflammatory conditions, glomerulonephritis, pyelonephritis, interstitial cystitis
3. epithelial casts – nephritic syndrome, tubular injury, glomerulonephritis
4. granular casts – glomerulonephritis

5. fatty casts – nephrotic syndrome
6. waxy casts – advanced renal failure.

### Dysuria

The word dysuria actually means discomfort on urination, but it usually is used to refer specifically to a burning sensation felt in the urethra on urination. It is caused by inflamed mucosa in the urethra and at the base of the bladder and is a usual symptom of urethritis and/or cystitis.

### Retention

If urine is being formed normally, but there is inability to void it from the bladder, urinary retention exists. It can be complete urinary retention, requiring catheterization. More often, it is incomplete or chronic, with the bladder being incompletely emptied at each voiding. Most cases of urinary retention are due to prostate enlargement, but other causes include neurological disease (e.g., spinal cord injury), diabetes mellitus, cystocele, and some medications (e.g., cold medications and antidepressants).

### Azotemia

Azotemia refers to an elevation of blood urea nitrogen (BUN) and creatinine levels. It can be caused by:

1. intrarenal causes (e.g., diseases affecting the glomeruli)
2. pre-renal causes due to failure of blood to reach the kidney for filtration (e.g., severe burns, hemorrhage, congestive heart failure, prolonged vomiting, renal artery embolism)
3. post-renal causes due to obstruction to urinary flow after it leaves the kidney (e.g., benign prostatic hypertrophy).

### Uremia

Uremia is the condition resulting from the advanced stages of kidney failure. In addition to azotemia, it is marked by a variety of signs and symptoms (e.g., anemia, weight loss, weakness, nausea and vomiting, excessive bleeding, edema, convulsions, and lethargy progressing to coma) that are secondary to renal damage.

### Oliguria

Oliguria is decreased urine output (less than 500 ml in 24 hours). Common causes are:

1. dehydration
2. total urinary tract obstruction ((e.g., stones, enlarged prostate))
3. severe infection leading to shock
4. medications (e.g., anticholinergics, methotrexate, diuretics).

### Anuria

Anuria is defined clinically as less than 100 ml of urine in 24 hours. Urgent assessment is required to differentiate the cause of lack of urine production. It can occur in a variety of conditions that produce a sustained drop in blood pressure, such as shock or hemorrhage. It can also be caused

by obstruction to the flow of urine from the kidneys (e.g., with kidney stones or benign prostatic hypertrophy).

### Renal Colic

Renal colic is a sharp, often excruciating pain felt in the back, groin, or urethra that is caused by spasm of the ureter as a stone is being forced from the kidney to the bladder.

### Nephrotic Syndrome

Nephrotic syndrome is characterized by heavy proteinuria ( $>3.5$  gr/24 hr), often accompanied by edema, hyperlipidemia, hypercoagulability, and hypoalbuminuria. The massive proteinuria is triggered by damage to the glomeruli, which causes them to become more permeable to protein molecules.

## **Laboratory Testing**

### Urinalysis

A complete urinalysis involves testing a random sample of urine for protein, sugar, blood, ketones and pH (acidity). A microscopic examination of urine sediment is also done. For the microscopic test, a small quantity of urine is spun in a centrifuge and the extracted solids are examined under a microscope for red blood cells, white blood cells, and casts. A specific gravity measurement is done to determine if the specimen is dilute or concentrated. The more dilute the specimen is, the less reliable a negative test becomes. In fact, in specimens with specific gravities below 1.005, cells and casts are likely to dissolve and disappear.

### Blood Testing

#### *Blood Urea Nitrogen (BUN)*

Urea is a waste product of protein metabolism and the amount formed depends on the amount of protein ingested. The BUN level, in turn, depends both on kidney efficiency and the amount of protein consumed. Kidney efficiency for excreting urea is further influenced by the volume of urine being formed. If smaller volumes are being formed, urea is reabsorbed in the kidney tubules, causing BUN levels to rise with renal insufficiency or if dehydration and high protein intake are present. Since BUN levels can be influenced by all the above factors, some judgment in interpreting moderate elevations is needed. In addition, acute gastrointestinal bleeding can increase BUN significantly due to all the protein (i.e., blood) in the gut. The creatinine will, however, be normal in this situation.

#### *Serum Creatinine*

Creatinine is a waste product of muscle metabolism. Serum levels are not dependent on diet or urine volume and need not be taken fasting. It is, therefore, much more accurate as a measure of kidney function. The normal serum level is up to 1.3 mg/dl in females and 1.6 mg/dl in males. Although the amount of creatinine formed each day does not depend on activity, it does depend on the amount of muscle in the body. Large muscular males can have normal levels of serum creatinine above 1.6 mg/dl.

### *Creatinine Clearance*

Creatinine clearance represents the volume of plasma cleared of creatinine per minute. Normal volumes for creatinine clearance are 100-120 ml per minute. The normal value does not depend on the individual's muscle mass or diet, but does depend on his size (or, more accurately, his surface area). The main disadvantage of a creatinine clearance is that it requires a timed collection of urine, usually over 24 hours, which is neither easy to do nor reliable. For this reason, creatinine clearance is not more useful than a simple serum creatinine in most circumstances. Creatinine clearance is a commonly used clinical measurement that closely estimates the glomerular filtration rate. Renal insufficiency must usually progress to the point at which creatinine clearance levels are less than 50% of normal before the serum creatinine will rise to abnormal levels.

"Normal" creatinine clearance ranges may be given on a report, but the "expected" creatinine clearance levels can also be calculated using the formula below for males (for females subtract 15%).

$$\text{Creatinine Clearance (expected)} = \frac{(140 - \text{age}) \times \text{weight in kilograms}}{72 \times (\text{serum creatinine in mg/dl})}$$

### *Cystatin C*

Cystatin C can be used as a sensitive early marker for chronic kidney disease. It is especially useful in cases in which the creatinine measurement is not reliable (e.g., in individuals who are very obese, malnourished, or who have a reduced muscle mass). Cystatin C is a protein that inhibits the action of substances that break down proteins in the body. Produced at a constant rate by all body cells that have nuclei, it is found in virtually all body tissues and fluids. The one exception is urine since cystatin C is filtered from the blood in the glomeruli and is then reabsorbed from the filtrate and metabolized by the kidneys. Thus, if the kidneys are not functioning properly, cystatin C levels in the blood will increase. This increase is often detectable before there is a measurable decrease in the glomerular filtration rate. Cystatin C can be used to detect suspected kidney disease and to monitor known kidney disease. There is also evidence that increased levels can be associated with an increased risk of cardiovascular disease and heart failure in older individuals.

### Diagnostic Testing

1. *Cystoscopy* allows a direct look at the inside of the bladder and urethra and is also used to inspect the prostate. A cystoscope is inserted through the urethra into the bladder and allows viewing of the surface either through lenses or via optical fibers that carry the image from the tip of the instrument to a viewing piece at the other end. Cystoscopy can be used to delineate many bladder conditions such as infections, hematuria, abnormal cells in a urine sample, or painful urination.
2. *Intravenous pyelogram (IVP)* is a procedure in which an iodine-containing substance is injected intravenously. An x-ray is taken as it passes through the kidneys. Much more detail can be seen than with a kidney, ureter, bladder (KUB) scan. The calyces, pelves, and ureters can be seen. The rapidity with which the substance is excreted allows some crude measure of kidney function, and allows one kidney to be compared to the other.

3. *Retrograde pyelogram* provides the same information as an IVP. A small catheter is placed in a ureter, dye is injected through the catheter, and x-rays are taken. The retrograde pyelogram is done when an individual is allergic to the intravenous contrast used for an IVP or when an IVP cannot be done due to poor kidney function or obstruction.
4. *Renal scans* are similar to an IVP but the substance that the kidney is excreting is labeled with a radioactive isotope (i.e., iodine or technetium), and the scan is done with a gamma camera, which forms a picture from the radiation given out by the isotope. These scans are excellent at showing blood flow and organ function.
5. *Ultrasonography* of the kidneys is a painless, noninvasive procedure that uses sound waves to delineate structures in the urinary system. It can be used to detect hydronephrosis, kidney stones, diffuse renal disease, and other abnormalities. It is also used to differentiate solid from cystic lesions. Doppler ultrasound is used to examine the blood flow in the renal arteries and veins.
6. *CT scanning* is done using a computer-controlled scanner that produces a series of x-ray images of a selected portion of the body. The computer then combines the information to create views (called slices) of the body part with ten to twenty times the detail of regular x-ray pictures. A CT scan can help diagnose kidney and ureteral stones, pyelonephritis, urinary obstruction, and malignancies.
7. *Magnetic resonance imaging (MRI)* is useful for staging renal cancers, evaluating other renal masses seen on CT scan or ultrasound, and for evaluating renal vascular disease. MRI cannot detect calcifications so it is not useful for detecting urinary tract stones.
8. *Renal angiography* (renal arteriography) is a specialized x-ray of the blood vessels of the kidneys. Contrast medium, introduced into the blood stream by catheter, is used to allow the renal arteries to be better seen than they can be on x-ray. Renal angiography can show the presence of tumors, blood clots, stenosis, or aneurysms of the renal artery.

Other tests that can be done to evaluate urinary tract disease include:

1. flow studies that measure the actual flow of urine
2. urethral pressure recordings that help diagnose outflow obstruction
3. cystometry to delineate total bladder capacity, the ability of the bladder to contract, initiation and/or inhibition of voiding, and the presence and/or absence of residual urine after voiding.

### **General Mortality and Morbidity Considerations**

Disorders of the kidney and urinary tract can impact both mortality and morbidity. Whether a mortality-based product like life insurance or a morbidity-based product like long term care is being underwritten, these disorders need to be carefully evaluated. In the simplest terms, both adverse mortality and morbidity are dependent on the decrease in renal function caused by the disorder (i.e., if the disorder is negatively impacting kidney function), and on the probability of renal failure and the need for dialysis or kidney transplant in the future. If the renal disorder is secondary to another disease such as diabetes or lupus erythematosus, the mortality/morbidity associated with that disorder should also be considered.

## **Disorders of the Lower Urinary Tract**

### Infections

Infections in the urinary tract are very common, especially in females. Infections of the lower urinary tract in females are usually cystitis or urethritis. They occur commonly in normal females during the years of sexual activity. Their symptoms are frequency, dysuria, and sometimes hematuria. Both are easily treated and very rarely have serious consequences. The causative bacteria are those that normally live in the intestine (e.g., E. coli) and enter the urethra from the skin around it and are not transmitted from a sexual partner.

In males, infection of the lower tract is most commonly urethritis or prostatitis. Urethritis can be caused by a specific infection (e.g., gonorrhea) or can be categorized as non-specific. Both types are nearly always contracted during sexual exposure.

Prostatitis is not caused by sexual exposure but by ordinary intestinal bacteria. It can be either:

1. acute, with symptoms similar to acute cystitis
2. chronic, with milder, more prolonged symptoms.

Most urinary tract infections respond well to treatment with antibiotics.

### Interstitial Cystitis

Interstitial cystitis is a syndrome of urinary frequency and severe irritative voiding symptoms with no indication of infection. In fact, interstitial cystitis is probably not infectious in origin, though its cause is still unknown. Suggested causes include collagen diseases or other autoimmune processes.

On cystoscopy, the bladder wall is ulcerated and inflamed. Since carcinoma in situ can have the same findings, repeated biopsies and urine cytologies are needed to eliminate that as a cause. The inflammation and ulceration cause scarring and contracture of the bladder, leading to:

1. diminished capacity
2. hematuria
3. painful urination.

Interstitial cystitis occurs most often in middle-aged females. It is often associated with incontinence.

Various medications (e.g., antibiotics, anti-inflammatories, anticholinergics, antispasmodics such as oxybutynin [Ditropan®]), and procedures (e.g., instillations of medications such as DMSO directly into the bladder, bladder dilatation, fulguration of bladder ulcers) are used to treat interstitial cystitis, with varying degrees of success. In a small percentage of individuals, all treatments fail to provide relief. For these individuals, removal or denervation of their urinary bladder can be performed.

## Vesicoureteral Reflux

Vesicoureteral reflux is a congenital disorder that allows the backward flow of urine from the bladder to the kidney.

The most common cause of reflux is an abnormality of the ureterovesical sphincter, located between the ureter and the bladder. Urine flows back up the ureter, especially with the increased pressure of voiding. When this occurs, any bacteria in the bladder will be transmitted to the kidneys causing persistent infection. Uncorrected reflux eventually causes the loss of renal function.

Reflux can be intermittent, unilateral, or bilateral. Reflux is graded from mild to massive, depending upon the degree of ureteral dilatation.

Surgical correction of severe cases usually results in improved renal growth and function. Mild cases often self-correct without any specific treatment being necessary.

## Bladder Cancer

Bladder cancer is no different than other types of cancer in that most deaths are the result of the malignancy spreading beyond the organ in which it first occurs. It is, however, different from other cancers since it is often viewed as a chronic disease necessitating lifelong surveillance, making it one of the most expensive cancers to treat. Since the survival rate for the most common type of bladder cancer is quite high, it is important for underwriters to understand that all bladder cancers are not created equal and that some are almost guaranteed to progress to serious, life-threatening disease. While males get bladder cancer more often than females, females have a slightly worse 5-year survival rate – 80% for males versus 73% for females.

The most important risk factor for the development of bladder cancer is cigarette smoking. It is believed to be a contributing factor in 50% of the bladder cancers in males and 33% in females. Those who smoke have a risk of developing bladder cancer two to three times that of non-smokers. With cessation of smoking, it takes up to ten years for the bladder cancer risk to revert to that of a non-smoker.

Other risk factors include:

1. age – incidence increases with age—Bladder cancer is an uncommon diagnosis before age 40; 90% of cases occur after age 55.
2. race – Hispanics, African Americans, and those of Asian descent have a lower risk than Caucasians.
3. gender – more common in males; male to female ratio 2.7:1
4. family history of bladder cancer – Research is ongoing to determine if certain genes and genetic variations increase the risk.
5. personal history – Bladder cancer has an up to 80% recurrence rate.
6. chemotherapy for other types of cancer – e.g., high doses of cyclophosphamide (Cytoxan®) are thought to cause a nine-fold increase in the risk of bladder cancer
7. occupation – if there is exposure to carcinogens—aniline dyes are a major one. Workers

in rubber, chemical, and leather industries, plus printers, painters, textile workers, and hairdressers have a higher risk. Probably 25% of bladder cancers are due to occupational exposure.

Ninety-five percent of all bladder cancers are transitional cell carcinoma (TCC). Up to 80% of these tumors are termed superficial (its significance is discussed below). These cancers arise in the normal cells lining the bladder. The other, much rarer types which are considered more aggressive than TCC are:

1. squamous cell – 3%
2. adenocarcinoma – 2%
3. small cell and others (e.g., lymphoma, sarcoma) - <1%.

TCCs can be easily treatable superficial tumors growing on the bladder lining or they can be aggressive tumors prone to invade through the bladder wall and spread to lymph nodes and distant organs. In addition, superficial tumors have a tendency to recur, necessitating lengthy follow up surveillance. Treatments for bladder cancer include removal of the superficial tumors by curettage or laser ablation, instillation of therapeutic agents into the bladder, and removal of the bladder (i.e., cystectomy) in more serious cases.

### *Superficial Bladder Cancer*

Superficial bladder cancer is, by definition, cancer that is confined to the transitional cell lining of the bladder. (Strictly speaking, this definition also includes carcinoma in situ [CIS], but since CIS tends to behave in a much different manner than the more common noninvasive bladder tumor, it will be discussed separately).

These superficial transitional cell cancers (which are stage Ta and grade G1) are usually papillary tumors that grow outward into the bladder (“are exophytic”). Papillary tumors have slender finger-like projections growing from a small stalk. They are very friable and bleed easily. Their natural history is recurrence, not invasion. They tend to recur in different sites in the urinary tract over the course of time.

### *Carcinoma in Situ (CIS) of the Bladder*

The term “in situ” with its connotation of “not very serious” is somewhat misleading with carcinoma in situ of the bladder. Bladder carcinoma in situ is, by definition, always a high grade tumor, making it aggressive in its growth patterns. If left untreated, bladder CIS is a precursor to a lethal muscle-infiltrating tumor in more than 50% of cases.

CIS is seldom the only tumor found in a bladder and since it is a flat tumor, it is often difficult to find among multiple papillary tumors. In fact, it is a solitary tumor in only 1-2% of new cases of bladder cancer. It is, however, found in over 50% of the bladders that have multiple papillary tumors.

### *Invasive Bladder Cancer*

Bladder cancer is considered invasive when it is found beyond the urothelium (i.e., transitional cell membrane) in the lamina propria or muscle. Almost all such tumors are high grade and tend

to show a higher level of genetic abnormalities than noninvasive tumors. Once invasion occurs, the risk of lymph node involvement and metastasis increases. For all invasive bladder cancer, stage is the most important independent prognostic indicator.

### *Treatment of Bladder Cancer*

Treatment of bladder cancer begins during the diagnostic cystoscopy. During that procedure, all of the visible tumors are removed along with a snippet of the underlying muscle to determine if there is any invasion. Normal-appearing areas of the bladder are also biopsied so those cells can be assessed for any cancer-promoting genetic defects.

After that, close follow-up is vital since about half of bladder tumors will recur. If the original tumors are large, multiple, poorly differentiated and/or have certain genetic alterations, there is a greater risk of recurrence and progression. The risk is also increased if the original tumor is carcinoma in situ or if dysplasia is found in the grossly uninvolved bladder.

Cystoscopy is advised every three months for the first five years after diagnosis. Newer testing modalities, which are done on urine samples, are gaining acceptance for doing surveillance post bladder cancer, though they have not replaced cystoscopy yet. These tests look for the DNA abnormalities that indicate that a new cancer is present.

If the cancer is superficial ( $T_a$ ), the first recurrence is usually treated with cystoscopic removal or laser fulguration of the new tumors, followed by intravesical therapy. If the original tumor is carcinoma in situ ( $T_{is}$ ) or a  $T_a$  tumor of other-than-well-differentiated grade, the intravesical therapy is done as part of the original treatment.

Intravesical therapy is done once a week for several weeks and involves filling the bladder with a solution containing the treating agent. *Bacillus Calmette-Guerin* (BCG), a bacterial organism that was originally produced as a tuberculosis vaccine in the first decade of the 20<sup>th</sup> century, is the standard agent. Though the mechanism is still unclear, instillation of BCG appears to trigger a local immune reaction that prevents recurrence of bladder tumors in approximately 75% of individuals. Other agents that can be used for intravesical therapy include thiotepa, mitoycin-C, and doxorubicin.

### Neurogenic Bladder

Normal bladder function requires a coordinated interaction of sensory and motor components of both the somatic and autonomic nervous systems. Recent studies have shown that regulation of voiding function is quite complex, involving multiple neurotransmitters and various neural pathways.

Normal voiding requires the coordination of a contraction of the muscle in the bladder wall at the same time the muscles in the opening of the bladder relax. This so-called “micturition” reflex is mediated by the spinal cord and is required for normal voiding. Areas of the brain are also required for coordination of these muscular events.

Neurogenic bladder is the term used to describe any dysfunction of the urinary bladder resulting from congenital abnormality, injury, or lesions of the central or peripheral nervous systems. It can be caused by a variety of conditions, such as:

1. multiple sclerosis
2. spinal injury or surgery
3. cerebral vascular disease
4. Parkinson's disease
5. diabetes mellitus
6. meningocele
7. amyotrophic lateral sclerosis (ALS)
8. disc herniation
9. pelvic surgery (e.g., hysterectomy).

Bladder dysfunction can also be the result of long-term poor voiding habits and/or aging. Disruption of the normal reflex coordination between the bladder muscle and the external sphincter can lead to symptomatic voiding difficulties as well.

The clinical picture of neurogenic bladder is totally dependent upon the level of the neurologic disease and/or deficit. In simple terms, the higher in the spinal cord the causative lesion is, the more spastic the bladder is. Conversely, the lower the spinal cord lesion is, the more flaccid the bladder is.

Neurogenic bladder can lead to progressive renal damage, stone formation, and/or recurrent infections, but most cases can be managed in a manner consistent with long-term survival.

### **Disorders of the Upper Urinary Tract**

#### Acute Pyelonephritis

Acute pyelonephritis is caused by an infection, often bilateral, of the pelvis and parenchyma of the kidney. The most common causative organisms, accounting for 85% of the cases, are the bacteria that are normally found in the intestinal tract (e.g., E. coli, Klebsiella, Enterobacter).

Ascending pyelonephritis begins with a bacterial infection in the bladder. Ordinarily bacteria in the bladder are flushed out by the constant flow of urine. However, if there is any obstruction to voiding (e.g., benign prostatic hypertrophy) or incomplete emptying of the bladder (e.g., cystocele), bacteria can multiply unabated. The infection will stay in the bladder unless the vesicoureteral valve allows backward flow up the ureters. An incompetent valve allows the infected urine to reflux into the kidney. Pyuria, bacteria, and leukocyte casts appear in the urine and a CBC will show an elevated white blood cell count. A urine culture will show the causative bacterium.

While the rare severe case can require hospital admission for treatment, most occurrences of acute pyelonephritis are treated with antibiotics appropriate for the causative bacterium with prompt resolution of the infection.

#### Hydronephrosis

Hydronephrosis is a dilatation of the renal pelvis and calyces due to obstruction to the outflow of urine. There are many causes of urinary tract obstruction, such as:

1. urinary stones
2. benign prostatic hypertrophy
3. congenital anomalies of the urinary tract (e.g., strictures, meatal stenosis, bladder neck obstruction, ureteropelvic junction narrowing)
4. tumors.

A complete obstruction will cause acute renal failure. A long-standing partial or intermittent obstruction will produce a variety of alterations in kidney function, affecting first the concentrating ability of the tubules and, eventually, the filtering ability of the glomeruli.

If hydronephrosis is unilateral, it often is unnoticed since the unaffected kidney maintains the renal function.

Relief of the obstruction will reverse hydronephrosis. If residual hypertension or diminished renal function still exists after treatment, permanent renal damage can have occurred. However, considerable improvement in renal function often occurs, even after prolonged obstruction.

### **Disorders of the Kidney**

#### Congenital Urinary Tract Anomalies

Congenital anomalies of the urogenital tract are abnormalities of the urinary tract that arise as the result of a developmental defect that occurs during gestation.

These abnormalities can affect the size, shape, and/or position of kidneys and can cause duplication of a kidney or ureter or the absence of a kidney. These abnormalities are usually found incidentally during an investigation of an unrelated condition. Unless there is obstruction to urine outflow, none of these conditions affect mortality. If there is obstruction, surgical correction often is necessary.

Urinary tract obstruction is more common with abnormalities of ureters, but can happen when the two kidneys are joined at their lower poles (i.e., horseshoe kidney).

#### Medullary Sponge Kidney

Medullary sponge kidney is a disorder in which the terminal collecting ducts that drain urine into the renal pelvis are dilated, which slows the passage of urine from the kidneys.

The cause of medullary sponge kidney is unknown. On an IVP, ectatic areas in the collecting tubules with a typical ‘flower-spray’ appearance can be seen. Often, calcifications can be seen on x-ray.

Though usually asymptomatic, medullary sponge kidney can cause hematuria or pyuria. In addition, over half of the individuals with this disorder will have kidney stones. Asymptomatic individuals require no treatment other than to avoid dehydration to reduce the risk of stone formation.

## Nephrocalcinosis

Nephrocalcinosis is a condition marked by calcium deposits in kidney tubules, parenchyma, and, sometimes, even in the glomeruli. It is characterized by an insidious onset and progression. Kidney stones often occur. The renal tubules eventually become obstructed and no longer drain urine, which causes atrophy in areas of the kidney cortex drained by these tubules.

Diseases that induce hypercalcemia, such as hypertension, sarcoidosis, multiple myeloma, excessive intake of vitamin D, or medullary sponge kidney can cause nephrocalcinosis. The inability to produce concentrated urine is the earliest functional defect in this condition. If uncorrected, renal insufficiency will slowly develop.

Treatment of the causative disorder treats nephrocalcinosis. If hypercalcemia is reversed, the disease process stops. Kidney transplantation is the only option if severe renal insufficiency develops.

## Nephrosclerosis

Nephrosclerosis results from prolonged existence of hypertension, which causes atherosclerosis in the arteries within the kidneys. Nephrosclerosis can be classified as benign, senile, or malignant.

*Benign nephrosclerosis* is associated with many years of no-more-than-moderate hypertension, which causes thickening of the walls of the small arteries in the kidney. Ischemia occurs in the areas of the kidneys supplied by these vessels. If it is not complicated by uncontrolled hypertension or diabetes, benign nephrosclerosis seldom causes renal insufficiency. However, individuals with a moderate degree of benign nephrosclerosis can have lost some renal reserve so that under stressful conditions (e.g., surgery, volume depletion, GI hemorrhage), some renal insufficiency can occur. Appropriate treatment of hypertension stabilizes and can reverse renal damage.

*Senile nephrosclerosis* also produces arteriolar wall thickening, similar to benign nephrosclerosis, but does not appear to be related to hypertension. It is characterized by insidious onset and progress and is often marked by mild proteinuria and slow elevation of serum creatinine. If an elderly individual with senile nephrosclerosis has normal renal function, there should be no additional mortality associated with this disorder.

*Malignant nephrosclerosis* occurs in the setting of accelerated hypertension that most often develops in an individual with pre-existing hypertension. The blood pressure rises rapidly to over 130 mmHg diastolic, most likely due to intense vasoconstriction of the renal arteries. The marked increase in blood pressure causes extensive damage to the renal vessels, triggering profound ischemia and renal insufficiency. The kidneys can actually show surface hemorrhages. Headache, visual impairment, retinal papilledema, and even convulsions and loss of consciousness can occur. Lab tests will often reveal hematuria, proteinuria, and blood cell casts in a setting of rapidly rising serum creatinine. Irreversible renal damage will occur if the blood pressure is not quickly controlled.

## Diabetic Kidney Disease

The kidneys can be damaged or involved in diseases that are not primarily kidney diseases. Individuals with diabetes, particularly the insulin-dependent type, are prone to develop diabetic nephropathy. In the early stages, this causes only mild proteinuria, but over a period of several years, it often progresses to chronic renal failure. Approximately one-half of insulin-dependent diabetics ultimately develop renal failure. Almost one-third of individuals entering dialysis programs are diabetic. Early treatment of diabetic nephropathy with an angiotensin-converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril) can retard its progression.

## Polycystic Kidney Disease and Other Inherited Kidney Disorders

There are two forms of polycystic kidney disease:

1. autosomal dominant
2. autosomal recessive.

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. It is estimated to affect 600,000 individuals in the United States, over 66,000 in Canada, and more than 12 million worldwide. It is characterized by numerous cysts in both kidneys. The cysts, which arise from the nephrons, gradually increase in size until they replace all functioning tissue.

ADPKD exhibits some variability of expression. Some individuals will develop symptomatic disease when they are quite young while others never develop it. In fact, only about half of the individuals with the genetic defect will develop renal insufficiency by age 70.

Kidneys affected by polycystic kidney disease have “grape-like” clusters of cysts. These cysts can contain clear watery fluid, blood, or pus. In between the cysts, the once normal renal tissue is obliterated, leaving only atrophic, sclerotic tissue. Individuals with the disorder sometimes also have cysts in the liver, pancreas, and spleen.

Hypertension is often present and tends to develop in the third decade. Other conditions associated with polycystic kidney disease include:

1. mitral valve prolapse
2. berry aneurysm of the circle of Willis
3. diverticula of the colon
4. hiatal hernia.

Since cyst development begins in utero, the finding of at least three cysts in each kidney in an individual with a family history of polycystic kidney disease makes the diagnosis certain. Alternatively, if an individual with a family history of the disorder has no evidence of renal cysts by age 30, there is almost no chance it will manifest later.

Diagnosis of ADPKD can also be made with a genetic test that detects the mutations that cause the disease. Its usefulness is somewhat limited since the knowledge of the existence of the mutated genes cannot alter the course of the disease, given that there is no curative treatment nor can it predict the ultimate severity of the disease.

Certain factors are associated with more rapidly progressive disease, such as:

1. diagnosis at a younger age
2. male gender
3. gross hematuria
4. large kidney size
5. hypertension.

There is no treatment that will prevent progressive destruction of functioning renal tissue. Dialysis or kidney transplantation will eventually be needed.

*Autosomal recessive polycystic kidney disease (ARPKD)* is a rare disease that almost always manifests in early childhood. With this disorder, the kidney cysts arise from the collecting ducts and are smaller than those seen with ADPKD. Kidney failure usually develops before reaching adulthood. Congenital liver fibrosis occurs in all individuals with this disorder and becomes more of a problem with increasing age. As with ADPKD, dialysis or kidney transplantation will be needed if kidney failure occurs. If serious liver disease develops, a combined liver and kidney transplantation can be done.

Besides polycystic kidney disease, there are other rare genetic kidney disorders.

*Alport syndrome*, which can be inherited in either an X-linked or an autosomal dominant manner, manifests in early childhood with hematuria. It is marked by sensorineural hearing loss and a progressive nephropathy, usually leading to renal insufficiency in the third or fourth decade of life.

*Benign familial hematuria*, or thin basement membrane disease, is usually inherited in an autosomal dominant manner. It is probably the most common cause of microscopic hematuria in asymptomatic individuals who have normal findings on urologic evaluation. Most individuals with this disorder have an excellent prognosis, but a few will develop progressive renal insufficiency.

*Nephrogenic diabetes insipidus* can be either an acquired or inherited disorder. The acquired disorder can be caused by:

1. blockage in the urinary tract
2. high calcium levels
3. low potassium levels
4. certain drugs (e.g., lithium, amphotericin B).

The inherited disorder is acquired in either an X-linked recessive or an autosomal recessive manner. Both the acquired and inherited forms are characterized by kidney tubules that do not respond to the antidiuretic hormone vasopressin. As a result, the kidneys produce a large amount of very dilute urine, which causes dehydration. If the condition is not well managed, it can damage the bladder and kidneys and eventually lead to kidney failure. With appropriate treatment, affected individuals usually have few complications and a normal lifespan.

## Chronic Pyelonephritis

Chronic pyelonephritis is the cause of end-stage renal failure in 3% of those undergoing dialysis or kidney transplantation.

It is a chronic interstitial nephritis (i.e., inflammation of the spaces between the kidney tubules) caused by recurrent or persistent infection of the kidney(s). These infections almost always occur due to an anatomic anomaly in an individual's urinary tract. The anomaly can be one that causes obstruction to the flow of urine from the kidney or can be one that allows reflux of urine into the kidney from the bladder.

The course of the disease is extremely variable, but it usually progresses quite slowly, with most individuals having adequate renal function for more than twenty years.

The most obvious change in a kidney damaged by chronic pyelonephritis is the scarring and contraction of the parenchyma over the damaged calyces. Usually, the calyces in the upper and lower poles of the kidney are the most severely damaged.

Other causes of chronic pyelonephritis-type disorders include:

1. exposure to lead or cadmium
2. radiation
3. metabolic abnormalities (e.g., hyperoxaluria, hyperuricemia, hypercalcemia, hypokalemia)
4. systemic diseases (e.g., multiple myeloma, amyloidosis, sarcoidosis, systemic lupus erythematosus, systemic infections, hypertension, sickle cell anemia).

## Glomerulonephritis

Glomerulonephritis refers to a group of diseases that affect the structure or function of the glomeruli. It can be acute or chronic. Glomerulonephritis can be a primary disorder of glomeruli or can be secondary to a systemic disease.

The causative factor in most of the cases of primary glomerulonephritis is an inappropriate immune response in the glomeruli. It can be due to:

1. antigen/antibody complexes becoming trapped in one or more layers of the glomerular capillary membrane (90%)
2. antibodies that are specifically directed against or are deposited on the basement membrane of the glomeruli (10%).

All of the following can cause a secondary glomerulonephritis:

1. diabetes mellitus
2. immune-mediated disorders (e.g., system lupus erythematosus, Wegener's granulomatosis, systemic vasculitis, cryoglobulinemia)
3. infection (e.g., streptococcal, staphylococcal, bacterial endocarditis, hepatitis B and C, AIDS, syphilis)
4. cancer

5. congenital defects (e.g. Alport's syndrome)
6. medications (e.g., fenoprofen [Nalfon®])
7. drug abuse (e.g., heroin).

Definitive diagnosis of glomerulonephritis can be made only by kidney biopsy. Light microscopy will show the amount and the type of glomerular involvement as follows:

1. focal lesions involve less than half the glomeruli
2. diffuse lesions involve half or more than half of the glomeruli
3. global lesions involve all parts of the glomerulus
4. segmental lesions involve only part of the glomerulus.

Immunofluorescence shows immune deposits, while electron microscopy allows intracellular and basement membrane abnormalities to be seen. Membranous lesions indicate that the glomerular basement membrane is infiltrated and expanded by immune deposits (i.e., "protein-leaking" lesions). Proliferative lesions indicate an increase in glomerular cell numbers (i.e., capillary lumen-obstructing lesions).

Two other terms – crescent and sclerosis – are used to describe specific abnormalities seen with some of the chronic glomerulonephropathies. A crescent is a half moon-shaped collection of cells and extracellular matrix material that accumulates in Bowman's space when severe glomerular injury causes breaks in the capillary wall. Crescents will compress and distort the glomerular capillaries and can even cause capillary collapse. Sclerosis refers to the replacement of the delicate structures of the glomeruli by collagen, mesangial matrix, and fibrous materials. This is the end-stage, irreversible finish for damaged glomeruli.

#### *Types of Glomerulonephritis*

1. Post-infectious glomerulonephritis occurs after an infection. Hepatitis C and HIV are now the most common infectious causes of glomerulonephritis in developed countries. The classic post-streptococcal glomerulonephritis still occurs frequently in other parts of the world. It is a self-limiting disease usually seen in children after streptococcal pharyngitis or impetigo and occurs about 10 days after the infection. Fewer than 5% develop end-stage renal failure, with complete recovery within two weeks being the rule in most cases.
2. IgA nephropathy (Berger's disease) is caused by deposition of immunoglobulin A in the kidney, which produces an inflammatory reaction in the glomeruli. It is a slowly progressive, indolent disease in the majority of cases. Treatment of IgA nephropathy has been disappointing, although ACE inhibitors can slow progress of the disease and use of prednisone and azathioprine has benefitted some individuals.
3. Minimal change disease (nil disease) is marked by very little inflammation, but by damage to the foot processes on the basement membrane. It is the most common cause of nephrotic syndrome in children. The cause is probably secondary to an immune reaction involving specific antibodies directed against the foot processes.
4. Focal segmental glomerulosclerosis is a leading cause of nephrotic syndrome in adults. It is thought to be part of the spectrum of glomerulonephropathies that includes minimal change disease. Like minimal change disease, it presents with nephrotic syndrome, shows effacement of the foot processes on microscopic examination and is steroid responsive. It is different than minimal change disease in that nephritic-type urinary sediment (i.e., red

blood cells, white blood cells) is present in addition to proteinuria in up to 80% of individuals. Another difference is that some, but not all, glomeruli show sclerosis (i.e., a focal lesion) and, in the glomeruli affected, only a portion of the tuft is involved (i.e., segmental lesion). The affected glomeruli tend to be found in the area closest to the medulla of the kidney. A biopsy can miss the lesions because disease begins at the corticomedullary junction and spreads outwards through the cortex. About half of those affected have hypertension and hematuria and 30% exhibit renal insufficiency.

5. Anti-glomerular basement membrane disease/Goodpasture's syndrome is caused by circulating antibodies that attack the glomerular basement membrane. It is called anti-glomerular basement membrane disease when only kidneys are involved and Goodpasture's syndrome when both the lungs and the kidneys are involved. Intensive therapy with prednisone and cyclophosphamide is necessary. Plasma exchanges are given until circulating anti-glomerular basement membrane antibodies are no longer detectable. Though treatment can have to be continued for up to a year, more than 70% of individuals recover renal function.
6. Renal vasculitis is a severe disease with necrotizing glomerular damage caused by circulation of antibodies that damage small blood vessels. It can affect primarily the kidneys (i.e., idiopathic necrotizing glomerulonephritis) or it can be secondary to Wegener's granulomatosis or to a microscopic polyarteritis. In most cases, it is a rapidly progressive glomerulonephritis requiring urgent treatment with corticosteroids and immunosuppressive therapy.
7. Membranous nephropathy is an immune disease that causes thickening of the glomerular basement membrane. In 80% of cases it is a primary disorder. In the other 20%, it is secondary to diseases such as systemic lupus erythematosus, hepatitis B, or malignant tumors. Severe nephrotic syndrome is present in the majority of individuals with this disorder, although some can actually be asymptomatic. Prognosis is extremely variable with about a third of cases having complete remission, another third left with mild non-nephrotic proteinuria, and the final third progressing to end-stage renal failure.
8. Membranoproliferative glomerulonephritis (mesangiocapillary glomerulonephritis) is idiopathic in most cases, although it can be secondary to viral infections, collagen diseases, and malignancies. It has several distinct types, each being triggered by a different immunological complement pathway. Type I is notable for its association with hepatitis C. Prognosis is poor for idiopathic disease with almost half progressing to end-stage renal failure in 10 years. Unfortunately, there is a high recurrence of the disease in transplanted kidneys.
9. Rapidly progressive glomerulonephritis is an acute glomerulonephritis of any cause that has at least the doubling of serum creatinine levels within three months. Renal function deteriorates rapidly over days or weeks. It is a medical emergency requiring management of renal failure.

### Kidney Stone Disease and Lithotripsy

Kidney stones are abnormal concretions, usually composed of mineral salts, which form in the urinary tract. Stones can form anywhere in the urinary tract (e.g., bladder, ureter), but most often occur in the kidney. Stones usually form at the ends of the collecting ducts where they enter the calyces of the kidney. If they are passed when very small, they cause no symptoms but can be recognized in the urine as "gravel." If they remain attached to the calyceal tissue, they will become

larger. Most will eventually break off and flow with the urine into the ureter, where they cause pain and bleeding as they pass from the body.

There are four major types of renal stones:

1. calcium oxalate and/or phosphate (75%) – Disorders that derange calcium levels in the body, such as hyperparathyroidism, sarcoidosis, or bone diseases, cause calcium stones.
2. magnesium ammonium phosphate, i.e., struvite (15%)
3. uric acid (6%) – Though uric acid stones are common in individuals with gout, over half of those with such stones do not have elevated levels of uric acid.
4. cystine (2%) – cystine stones are caused by a genetic defect in renal transport of the amino acid, cystine.

Though there are many underlying causes for stone formation, there is one factor that is constant – the increased urinary concentration of the offending mineral. The urine becomes supersaturated with the substance, which then precipitates out of the urine and begins the stone formation process.

Many individuals have one or two episodes and have no further trouble. Some individuals pass stones repeatedly and are called stone formers. Many stone formers have an underlying condition responsible for the problem.

### *Lithotripsy*

Urinary tract stones that do not pass and that cause obstruction, infection, serious bleeding, or intractable pain can be removed by either open surgery or by cystoscopic basket extraction. In addition to these procedures, there are three types of lithotripsy that can be used:

1. Extracorporeal shock-wave lithotripsy (ESWL) uses shock waves to shatter the stone. The high-intensity waves reduce most stones to a powder that passes through the ureter into the bladder.
2. Percutaneous ultrasonic lithotripsy requires a small incision in the flank through which a cystoscope-like instrument is inserted into the kidney pelvis. The stones are shattered by a small ultrasound transducer and the fragments can be removed directly.
3. Laser lithotripsy uses pulses of intense laser light to shatter the stone. It is used for the removal of ureteral stones. An endoscope is used to position the laser close to the stone.

Preventive therapy with diet modification, increased fluid intake, and treatment with medications to reduce a particular type of stone formation (e.g., allopurinol for elevated uric acid levels) is usually advised.

Apart from the pain of renal colic, the health implications associated with kidney stones are their tendency to cause both obstruction and/or infection in the urinary tract. In the absence of underlying disease or chronic infection, there does not seem to be any additional mortality associated with kidney stones.

### Renal Failure

Renal failure occurs when renal function has deteriorated to the point that the nitrogenous waste products of metabolism, serum creatinine, and BUN are found at elevated levels in the blood.

Renal failure can be acute or chronic.

### *Acute Renal Failure (ARF)*

Acute renal failure is characterized by:

1. rapid reduction of the glomerular filtration rate
2. rapid rise of serum creatinine and BUN
3. usually reduced urine volume.

The cause can be pre-renal, post-renal, or intra-renal.

Many cases of acute renal failure are caused by a disorder outside the kidneys. Disorders that interfere with blood flow before it gets to the kidneys (i.e., pre-renal disorders) can trigger acute renal failure. The most common pre-renal causes are:

1. volume depletion (e.g., hemorrhage, intractable vomiting)
2. congestive heart failure
3. advanced liver disease.

If the cause is post-renal, it occurs after the kidneys have done an appropriate job of filtration. For example, urinary tract obstruction in combination with vesicoureteral valve incompetence can cause acute kidney failure because the increased pressure in the kidneys caused by the refluxing urine interferes with the filtering function across the glomerular membrane.

The intra-renal causes of acute failure are disorders that affect the integrity of the glomeruli or tubules, such as acute tubular necrosis or glomerulonephritis. Acute tubular necrosis causes acute renal failure through damage and blockage of the renal tubules. Injury to the tubules can occur from:

1. ischemia – hypovolemia, major surgery
2. endogenous toxins – heme from myoglobin resulting from a large amount of muscle damage (i.e., rhabdomyolysis) or intravascular hemolysis, uric acid
3. exogenous toxins – radiocontrast media, platinum, amphotericin B, aminoglycosides, and other drugs.

If acute renal failure lasts more than a few days, dialysis is the treatment. In many cases, renal function does not begin to return for two to three weeks, but complete recovery with no significant permanent renal damage is the usual outcome.

### *Chronic Kidney Disease*

Chronic kidney disease (previously called either chronic renal insufficiency or chronic renal failure) occurs when there is permanent impairment of kidney function. The classification of severity is based on the glomerular filtration rate (GFR) and is divided into stages, with stage 1 being the least serious and stage 5 indicating end-stage kidney failure.

Stage	GFR	Description
1	90+	normal GFR with other signs of kidney damage such as proteinuria

2	60-89	kidney damage with mildly decreased GFR
3	30-59	moderately decreased GFR
4	15-29	severely decreased GFR
5	<15	end-stage kidney failure

Chronic kidney disease usually develops over months or even years. If uninterrupted, it can progress to end-stage renal disease (ESRD), leaving dialysis or kidney transplantation as the only means of survival.

Diabetic nephropathy and glomerulonephritis are the two most frequent causes of chronic kidney disease. Vascular renal disease, chronic pyelonephritis, and polycystic kidney disease account for most of the remainder.

Until renal function has dropped by at least 50%, there are few symptoms of chronic kidney disease. When symptoms appear, the first is usually nocturia, resulting from the kidneys' inability to properly concentrate urine.

When kidney function drops to less than 30% of normal, serum creatinine and BUN levels will necessitate dialysis. The time it takes to reach renal failure varies with the disease causing kidney damage. For example, progression tends to be faster with diabetic nephropathy and slower with polycystic kidney disease. In addition, diastolic hypertension greater than 95 mmHg or proteinuria greater than 5 g/day indicates a more rapid decline in kidney function.

The rate of progression to inevitable ESRD can be greatly slowed with effective treatment, such as:

1. control of blood sugar and use of ACE inhibitors in diabetics
2. control of blood pressure – preferably to 120/80 mmHg or better
3. specific therapy for the renal disease causing chronic renal failure (e.g., immunosuppressive therapy for membranous nephropathy).

### Dialysis

There are two types of dialysis: hemodialysis and peritoneal dialysis. Both types involve using diffusion across a semi-permeable membrane to remove waste products from the blood. With hemodialysis, the membrane is in the dialysis machine, while with peritoneal dialysis, the individual's peritoneum is used as the membrane. The impurities that need to be filtered from the blood are, in effect, pulled through the membrane by dialysate fluid on the other side of the membrane.

Survival rates are similar whether individuals are treated with hemodialysis or peritoneal dialysis. There is a mortality rate of about 20% per year. Cardiovascular disease and infections are the main causes of death.

### Kidney Transplantation

Kidney transplantation involves the surgical replacement of a diseased kidney with a donated kidney. For over 30 years, renal transplantation has provided the best therapy for end-stage renal disease. The other alternative, chronic renal dialysis, has higher mortality and morbidity.

After transplantation, lifelong immunosuppressive therapy is required to prevent rejection of the transplanted kidney. Though these therapies are absolutely necessary to preserve the grafted kidney, they do reduce resistance to all types of infection. The closer the tissue match is between donor and recipient, the lower the required dosage of immunosuppressant medications is. Compatibility is likely to be best with family member donors. Incidence of rejection reflects this, as both short-term and long-term survival are better when the donor is a family member.

Donor and recipient must have the same ABO blood group. Tissue compatibility is further assessed using the human lymphocytic antigen (HLA) phenotype found on lymphocytes in peripheral blood.

Careful selection and management of individuals for kidney transplantation is required, especially when systemic disease, such as Goodpasture's syndrome or systemic lupus erythematosus (SLE), is the cause of kidney failure. In general, kidney transplantations performed due to polycystic disease do well. Those done for diabetic nephropathy are less successful.

Probability of transplant rejection and mortality are highest during the first year after surgery. At the end of the first year, 95% of transplant recipients have survived when there was a good tissue match with a living, related donor. A survival rate of nearly 85% has been reached with cadaver grafts. After the first year, mortality is:

1. less than 5% a year for individuals with a transplant from a living, related donor
2. less than 10% a year for those with a kidney from a cadaver.

Unfortunately, some individuals will experience chronic graft rejection, with progressive hypertension and deteriorating renal function. Retransplantation or renal dialysis often becomes necessary. The most frequent cause of death in kidney transplant recipients is bacterial, viral, fungal, or other infections. Immunosuppressive drugs are also associated with a higher incidence of cancer after a few years of therapy, particularly squamous cell carcinoma and lymphoma.

### Nephrectomy

Nephrectomy, the surgical removal of a kidney, can be done for a variety of reasons:

1. chronic infections (e.g., abscess, pyelonephritis)
2. trauma to the kidney
3. renal cancer
4. tuberculosis.

Nephrectomy is fully compatible with good health and a normal life span, provided the remaining kidney is free of disease and the underlying disease process does not carry its own mortality implications (e.g., renal cancer, tuberculosis).

Occasionally, a severely diseased kidney is removed from an individual with bilateral disease. In these cases, prognosis is directly related to the function of the remaining kidney.

### Cystectomy

Cystectomy is the surgical removal of the urinary bladder. The most common reason for cystectomy is advanced bladder malignancy. Other less common reasons are:

1. intractable interstitial cystitis
2. incurable urinary tract infection in a dysfunctional bladder.

Once an individual's bladder is removed, another form of urinary diversion must be constructed. Several methods are available:

1. urostomy/ileal conduit – the most common method—The ureters are anastomized to a segment of small bowel that is then brought through the abdominal wall. The opening, called a stoma or urostomy, allows the drainage of urine into a flat, watertight bag that is attached to the abdomen.
2. continent pouch – a reservoir for urine is created from a section of bowel that is connected to the abdominal wall and is drained by using a small catheter inserted through the small periumbilical stoma.
3. orthotopic neobladder – which can be employed if the urethra is not removed. As with the continent pouch, a section of bowel is used to create a pouch for urine that is then connected to the urethra. Urine may be able to be passed by contraction of the abdominal muscles but, more often, requires the use of a catheter inserted through the urethra.

There appears to be no increased mortality if the original disease is treated in time.

### Cysts and Tumors

Renal cysts are fairly common and do little harm. They can be multiple and/or bilateral. A solitary renal cyst usually has no functional significance. Occasionally a large, simple cyst will cause severe pain or constant hematuria and will have to be drained or surgically removed.

Most solitary cysts are found incidentally on ultrasonography or CT scan and/or as part of a workup for hematuria. It is always necessary to distinguish the benign cyst from renal carcinoma with a cystic component.

Multiple renal cysts usually have no mortality significance if it can be verified that they do not represent polycystic kidney disease.

An IVP with an ultrasound of kidneys can diagnose a benign cyst versus a renal carcinoma almost every time. Sometimes a cyst puncture, under ultrasound guidance, is needed to retrieve cyst fluid to examine for malignant cells. Benign cyst fluid is straw-colored, while malignant fluid is dark-colored or bloody.

Benign tumors of the kidney are rare. Most solid tumors of the kidney are malignant and, unfortunately, tend to metastasize early. Wilms' tumor is a malignant tumor of the kidney that occurs in children under the age of 10. With modern cancer therapy, many cases of Wilms' tumor can be cured.

## **Review Questions – ALU 201, Chapter 8**

1. Decreased urine output is:
  1. dysuria
  2. pyuria
  3. azotemia
  4. oliguria
2. Urinary retention can be caused by all of the following EXCEPT:
  1. prostate enlargement
  2. mucous colitis
  3. diabetes mellitus
  4. neurological disease
3. Benign causes of proteinuria include which of the following?
  - A. fever
  - B. stress
  - C. exercise

Answer Options: 1. A only is correct.  
2. C only is correct.  
3. A and B only are correct.  
4. A, B, and C are correct.

4. What is the function of the glomeruli?
5. Explain what is meant by the terms pre-renal, intra-renal, and post-renal and give an example of each.

6. All of the following statements regarding polycystic kidney disease are correct EXCEPT:
  1. Multiple cysts are present in both kidneys.
  2. It rarely progresses to end-stage renal disease.
  3. Hypertension is often present.
  4. Cysts can occur in the liver.
7. A measurement that closely estimates the glomerular filtration rate (GFR) is:
  1. serum creatinine
  2. BUN/creatinine ratio
  3. creatinine clearance
  4. microalbumin/creatinine ratio
8. What are the characteristics of nephrotic syndrome?
9. What are the probable causes and the symptoms of interstitial cystitis?
10. Describe some of the conditions that could cause neurogenic bladder?

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 4: oliguria – page 5.

### *Review Question 2*

Answer 2: mucous colitis – page 5.

### *Review Question 3*

Answer 4: A, B, and C are correct – page 3.

### *Review Question 4*

Refer to pages 1-2.

### *Review Question 5*

Refer to page 22.

### *Review Question 6*

Answer 2: it rarely progresses to end-stage renal disease – pages 16-17.

### *Review Question 7*

Answer 3: creatinine clearance - page 7.

### *Review Question 8*

Refer to page 6.

### *Review Question 9*

Refer to page 9.

### *Review Question 10*

Refer to pages 13-14.

## **CHAPTER 9**

# **AN OVERVIEW OF ENDOCRINOLOGY**

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## **AN OVERVIEW OF ENDOCRINOLOGY**

### **Introduction**

This chapter will build on the basic anatomy of the endocrine system and focus on the relationship between specific hormone excess and hormone insufficiency states and the clinical syndromes that result. In addition, it will introduce background principles for underwriting of diabetes mellitus.

### **Hormones**

Hormones are peptides that are secreted into the bloodstream and act on target tissues. Target tissues have specific receptors for hormones. Hormones can act systemically on a site distant from the gland (classic endocrine pathway), locally on adjacent tissue (paracrine pathway), or reciprocally on the gland from which they originated (autocrine pathway). Hormone secretion is controlled by a feedback loop. A feedback loop is a circuit of signaling that operates to turn off the release of hormone from a gland once the action of the hormone has had its effect. Understanding this integrated system is the basis for understanding clinical syndromes in endocrinology and metabolism. Most disorders of endocrinology and metabolism are caused by diseases that result in either hormone excess or hormone deficiency.

### **Pituitary Gland**

The pituitary gland is found in the sella turcica above the sphenoid sinus. It is attached to the brain via the pituitary stalk, which is a vital link of communication between the pituitary and the hypothalamus. Colloquially, the pituitary is referred to as the master gland, since it produces peptides that regulate the adrenal glands, thyroid glands, ovaries, and testes, thereby affecting linear growth, fuel metabolism, water balance, pregnancy, and lactation. However, the pituitary is only partially the master gland as it is regulated by neuronal and chemical input from the hypothalamus. Fortunately, compared to the pituitary, hypothalamic dysfunction is rare.

#### Prolactinoma

A common pituitary abnormality is the prolactinoma, a benign tumor of lactotroph cells. Normally, prolactin secretion is under chronic inhibition by dopamine, except in pregnancy when prolactin secretion increases to stimulate the production of breast milk. In prolactinomas, there is clonal proliferation of lactotrophs and unregulated secretion of prolactin. This can also be seen in multiple other conditions that affect the dopamine inhibitory feedback. A partial list of examples includes drugs (especially dopamine antagonists), pituitary stalk disease, untreated hypothyroidism, chest wall diseases, renal failure, and seizures.

The clinical presentation of prolactinoma differs for males and females. It also depends on the size of the tumor. In females, the tumors are usually small (microadenoma – less than 10 mm), and the excess prolactin causes menstrual irregularities and galactorrhea. In males, the tumors are usually large (macroadenoma – greater than 10 mm), and the excess prolactin causes impotence

and loss of libido. In addition, large tumors can cause headache or visual disturbance if the tumor is compressing the optic chiasm. For small tumors, treatment is aimed at restoring normal menstrual cycles in females and potency in males. Because dopamine inhibits prolactin secretion, dopamine agonist drugs such as bromocriptine (Parlodel®), pergolide (Permax®), and cabergoline (Dostinex®) are used as primary therapy. Large tumors can be removed surgically or treated with external beam radiation. The risks associated with surgery and radiation are destruction of the remaining gland and hypopituitarism. Life expectancy is normal for those individuals with treated microadenomas. Mortality is increased for those with macroadenomas if hypopituitarism developing after surgery or after radiation is not detected or is not treated appropriately. Annual testing should be performed to rule out the development of hypothyroidism from loss of thyroid stimulating hormone (TSH), hypoadrenalinism from loss of adrenocorticotrophic hormone (ACTH), hypogonadism from loss of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and hyposomatotrophism from loss of growth hormone (GH).

### Hypopituitarism

Not only can hypopituitarism result from surgical removal of a prolactinoma, it often develops after surgery for other pituitary tumors (e.g., craniopharyngioma) or any destructive process of the pituitary (e.g., metastatic cancer). Hypopituitarism is of clinical and underwriting significance. Individuals with hypopituitarism need replacement with cortisol (because of lack of ACTH), thyroid hormone (because of lack of TSH), estrogen for females (because of lack of LH and FSH), and testosterone for males (because of lack of LH and FSH). Growing evidence suggests that there can be a state of growth hormone (GH) deficiency in those with hypopituitarism. In the past, GH was felt to only be necessary until the end of puberty when linear growth ceased. However, multiple studies have shown that GH secretion persists into adulthood and contributes to maintenance of muscle mass, lean body mass, and sense of well-being. Studies conducted by Bengtsson, et al., suggest that individuals with hypopituitarism have a two-fold greater mortality compared to case controls. Thus, for underwriting, there is some excess mortality in those who have documented hypopituitarism and incomplete replacement of hormones.

### Diabetes Insipidus

Diabetes insipidus is another pituitary abnormality that can result from surgery for pituitary lesions. It is the result of lack of antidiuretic hormone (vasopressin) that is produced in the hypothalamus and stored in and released from the posterior pituitary. Antidiuretic hormone acts on the distal convoluted tubule and collecting duct of the kidney to increase water absorption. When antidiuretic hormone is missing, free water is not absorbed and is lost into the urine causing hypernatremia (high serum sodium). Antidiuretic hormone can be replaced by using intranasal, intravenous, or oral desmopressin (DDAVP®), which thus restores normal water balance. Individuals with loss of antidiuretic hormone that is adequately replaced with desmopressin have normal life expectancy. However, the underwriting focus should be the primary etiology of the loss of antidiuretic hormone (i.e., the pituitary tumor or destructive process).

## Acromegaly

Acromegaly is a rare pituitary disorder that one can see in underwriting. The most common cause of acromegaly is a benign tumor of somatotroph cells that produce growth hormone (GH). The tumor causes excessive and unregulated secretion of GH. GH exerts most of its effects by stimulating the production of insulin-like growth factor-1 (IGF-1), formerly known as somatomedin C. Excess GH and IGF-1 cause enlargement of the feet, hands, and mandible, soft tissue swelling, carpal tunnel syndrome, hypertension, left ventricular enlargement, cardiomyopathy, colon polyps, sleep apnea, and glucose intolerance. Acromegaly occurs equally in males and females with an incidence of one in 250,000. However, the diagnosis is often missed, and an acromegalic can have the disease seven to ten years before it is detected. The mainstay of treatment is surgical removal of the tumor. Surgical success depends on the size of the tumor and experience of the neurosurgeon. The goal is suppression of GH with normalization of IGF-1 levels. If surgery does not accomplish this, adjunctive treatment with somatostatin (Octreotide<sup>®</sup>), GH receptor antagonist (pegvisomant), or radiation is used. The importance for underwriting is that untreated acromegalics have twice the mortality of age- and sex-matched controls. In addition, failure to achieve an average 24-hour GH level of less than 2.5 ug/L results in a mortality risk slightly higher than that of the general population.

## **Thyroid Gland**

### T<sub>4</sub> and T<sub>3</sub>

The hypothalamic-pituitary axis regulates the production and release of thyroxine (T<sub>4</sub>) and tri-iodothyronine (T<sub>3</sub>) from the thyroid gland. In addition, T<sub>4</sub> and T<sub>3</sub> exert feedback to the hypothalamus and pituitary to inhibit thyroid releasing hormone (TRH) and thyroid stimulating hormone (TSH). T<sub>4</sub> and T<sub>3</sub> are derived by the iodination of tyrosine within the thyroid gland, making iodide a vital dietary nutrient. One needs to ingest 150 micrograms of iodide daily to supply substrate to the thyroid gland for T<sub>4</sub> and T<sub>3</sub> synthesis. In the United States, iodide is plentiful in the average diet and more than meets the daily requirement. However, in certain areas of the world (e.g., the Swiss Alps, parts of Germany, the Andes) that are not near the sea and that have been covered by glaciers, there is often a relative deficiency of iodide in the diet. These populations are prone to goiter formation (excessive growth of thyroid) in an attempt to overcome lack of iodide in the diet. Thus, salt iodination is vital in many of these areas to prevent goiter and hypothyroidism.

T<sub>4</sub> is the primary secretory product of the thyroid; however, it is also converted to T<sub>3</sub> in peripheral tissues. Both T<sub>4</sub> and T<sub>3</sub> are carried in the bloodstream on thyroid-binding globulin, albumin, and pre-albumin. Only the free forms of T<sub>4</sub> and T<sub>3</sub> are metabolically active. T<sub>4</sub> is more abundant than T<sub>3</sub>, but T<sub>3</sub> is more potent. Both act on specific T<sub>4</sub> and T<sub>3</sub> receptors that result in the activation of many different cellular processes. These include:

1. increased oxygen consumption
2. stimulation of protein synthesis
3. enhanced lipolysis
4. enhanced response to epinephrine and norepinephrine

5. increased heart rate and contractility
6. increased growth and development.

When evaluating the possibility of thyroid hormone excess or insufficiency, several blood tests can be performed, depending on the physician's diagnostic suspicion. Common blood tests are total T<sub>4</sub>, thyroid-binding globulin, free thyroxine index, and TSH. In some situations, free T<sub>4</sub> and free T<sub>3</sub> are necessary. Antithyroglobulin, antimicrosomal, and thyroid stimulating antibodies help the physician diagnose autoimmune thyroid disease. In addition, there are several radiologic methods for looking at thyroid size and function. These include thyroid ultrasound, CT or MRI scanning, radioiodine uptake scans, and technetium scans. Radiologic tests are often helpful when evaluating a thyroid nodule or glandular enlargement. For underwriting, the two major etiologies of thyroid dysfunction are hyperthyroidism and hypothyroidism.

### Hyperthyroidism

Hyperthyroidism is a constellation of clinical symptoms and signs that result from excess T<sub>4</sub> and/or T<sub>3</sub>. All the symptoms and signs reflect heightened sympathetic nervous system and metabolic activity. Symptoms include heat intolerance, weakness, diarrhea, palpitations, nervousness, anxiety, weight loss, and excessive sweating. Clinical signs of hyperthyroidism are tachycardia, widened pulse pressure, moist skin, thin hair, hair loss, brittle nails, muscle weakness, muscle atrophy, eyelid lag, stare, bulging eyes, tremor, and hyperactive reflexes. In older individuals, hyperthyroidism can trigger atrial fibrillation. In addition, older people with atrial fibrillation and hyperthyroidism have a higher likelihood of an embolic event compared to those with atrial fibrillation alone. Thus, untreated hyperthyroidism in the older ages is most likely associated with extra risk.

Untreated hyperthyroidism also increases the risk for thyroid storm in any age group. Thyroid storm is a life-threatening condition of thyroid excess that results in end organ damage and even death. It occurs when hyperthyroidism is not treated and a concomitant "crisis," such as infection or myocardial infarction, triggers a cascade of hyperadrenergic stimulation. Signs of thyroid storm include hyperthermia, cardiac arrhythmias, malignant hypertension, coma, seizures, and hepatic failure. Fortunately, thyroid storm is rare.

A common cause of hyperthyroidism is Graves' disease. Graves' disease occurs at younger ages (ages 20 to 40) and more frequently in females than in males. Graves' disease is caused by autoimmune stimulation to the thyroid gland. Antimicrosomal, antithyroglobulin, and thyroid stimulating antibodies are frequently positive. At the time of diagnosis, total T<sub>4</sub> is usually elevated with suppression of TSH. A radioiodine uptake scan shows increased uptake, which reflects the increased production and secretion of T<sub>4</sub> and T<sub>3</sub>. There are several ways to treat Graves' disease including medications, ablative doses of radioiodine, or occasionally surgery. In most cases of treatment with ablative radioiodine or surgery, replacement doses of thyroxine are necessary since the gland is rendered inactive or removed, respectively. Graves' disease can also be complicated by ophthalmologic involvement, in which the autoimmune attack is on the orbital soft tissue and muscle. Graves' ophthalmopathy can worsen, improve, or remain unchanged after treatment. It can lead to severe disability. In terms of mortality, treated Graves' or Graves' disease in remission presents no extra risk.

## Hypothyroidism

Hypothyroidism represents the opposite end of thyroid dysfunction from hyperthyroidism. Hypothyroidism is insufficient T<sub>4</sub>/T<sub>3</sub> with symptoms and signs of decreased sympathetic nervous system and metabolic activity. Clinically, individuals have weakness, fatigue, cold intolerance, hair loss, weight gain, hoarse voice, dry skin, loss of lateral eyebrow, slowed reflex relaxation and impaired growth. Hypothyroidism develops gradually, often taking years before symptomatology becomes noticed.

Untreated hypothyroidism increases the risk for a rare syndrome, myxedema coma. Myxedema coma is a life-threatening condition of severe hypothyroidism superimposed on another illness, such as sepsis, hypothermia, or myocardial infarction. It involves multi-organ collapse with impaired respiration, cardiac failure, coma, intestinal ileus (i.e., loss of peristalsis), and even death. Like thyroid storm, myxedema coma is rare.

A common cause of hypothyroidism is Hashimoto's thyroiditis. It occurs in all age groups and is associated with an autoimmune attack on the thyroid gland. In this case, however, the autoantibodies cause a destructive process that leads to impaired synthesis and release of thyroid hormone. Antimicrosomal and antithyroglobulin antibodies are usually present. Total T<sub>4</sub> levels are low and TSH is elevated. Radiouptake scans are usually not performed or necessary. Treatment involves replacement of thyroid hormone with any number of oral preparations (e.g., levothyroxine [Synthroid®, Levoxyl®, Levothyroid®], Armour Thyroid®). Life expectancy is normal for individuals with Hashimoto's who are on adequate replacement.

## Thyroid Nodules and Goiter

Thyroid nodules are common and often discovered incidentally. Single, solid nodules that are greater than or equal to 1.0 cm in any dimension raise a concern for thyroid cancer. Most thyroid cancers will appear hypofunctioning or "cold" on a radioiodine uptake scan; however, a fine needle aspiration (FNA) is the best procedure to help with the differential diagnosis. If fine needle aspiration is not suspicious for cancer, some physicians will place a patient on suppressive doses of thyroid hormone in an attempt to prevent further growth of the nodule. If the fine needle aspiration is suspicious or positive for thyroid cancer, surgery is performed. Purely cystic nodules with no solid component require no FNA, although they are often aspirated if causing problems. The American Thyroid Association has revised guidelines for when FNA is needed, now allowing for no FNA for very low suspicious nodules – those without any microcalcifications, irregular margins, extrathyroidal extensions, or taller than wide shape - until greater than or equal to 2.0 cm. They do still recommend FNA for all solid nodules at 1.0 cm or those 1.5 cm with partially cystic with highly eccentric solid areas. Multiple nodules can be of concern if any are solid and 1.0 cm or greater in size. Same guidelines for which ones require FNA are same depending on level of suspicion. There are instances of thyroid cancer found in multinodular glands; however, this usually does not lead to early mortality if the cancer is in an early stage and is not anaplastic (i.e., an aggressive form of cancer with a poor prognosis).

As noted earlier, goiter is enlargement of the thyroid gland. Goiter that is diffuse and homogeneous is usually seen in Graves' disease. Goiter can develop in areas of the world with

iodide deficiency. Goiter can also be the result of multiple nodules. Treatment of a goiter depends on symptoms, size, and underlying disease.

### **Adrenal Gland**

The adrenal gland is located in the retroperitoneal space on top of each kidney. The adrenal gland is composed of several distinct cell types that each have a specific function. The outer portion is called the cortex. It is divided into three zones:

1. the glomerulosa that produces aldosterone
2. the fasciculata that produces cortisol
3. the reticularis that produces androgens.

The center of the adrenal gland is called the medulla and produces epinephrine and norepinephrine.

ACTH from the pituitary affects the production of cortisol and androgens. Aldosterone secretion is governed by renin, potassium, and intravascular volume status. Secretion of epinephrine and norepinephrine is partially controlled by ACTH, but the main stimulus for secretion is nervous system input that regulates the “fight or flight” response. For underwriting, there are several different syndromes related to hormone excess or insufficiency of the adrenal gland. In each of these impairments, the etiology is related to the specific part of the gland affected.

#### Primary Hyperaldosteronism

Overproduction of aldosterone by the glomerulosa cells of the adrenal gland leads to the development of hypertension. Of all hypertensives, primary hyperaldosteronism accounts for less than 2% of the hypertensive population. Primary hyperaldosteronism is often associated with low to low normal potassium levels because aldosterone acts on the kidney to increase sodium reabsorption and potassium excretion. Clinical symptoms are often related to low potassium levels and include muscle weakness, fatigue, increased urination, and increased thirst. The two most common etiologies of primary hyperaldosteronism are aldosterone-producing adenoma and bilateral adrenal hyperplasia. There are several blood tests that are used to differentiate the two. Imaging of the adrenal is performed only after the diagnosis of aldosterone excess is made because incidental adrenal masses are common and do not need treatment. Treatment of an aldosterone-producing adenoma by surgical removal usually “cures” the hypertension. However, some individuals will still have, or will develop essential hypertension. The treatment for bilateral adrenal hyperplasia causing primary hyperaldosteronism is the use of antihypertensive medication that blocks the effect of aldosterone on the kidney. The most commonly used medication is spironolactone. Overall, the prognosis is excellent for both etiologies, and life expectancy is normal with normalization of blood pressure.

## Hypercortisolism

The symptoms and signs of hypercortisolism are truncal obesity, moon facies, buffalo hump, hypertension, striae, hyperglycemia, proximal muscle weakness, amenorrhea, hirsuitism, acne, easy bruising, osteoporosis, depression and/or psychosis. When the excess cortisol production is the result of hypersecretion of ACTH from a pituitary microadenoma, it is Cushing's disease. Cushing's disease accounts for 60% of cases of hypercortisolism. Two other etiologies of hypercortisolism are a primary adrenal tumor that is secreting excessive cortisol (25% of cases) or ectopic production of ACTH, usually from a small cell carcinoma of the lung (15% of cases). In addition, individuals who are treated with high doses of steroids, such as prednisone, can develop many of the features of Cushing's syndrome. Overall, treatment is aimed at the underlying disease.

If the diagnosis is Cushing's disease from an ACTH-secreting pituitary microadenoma, surgery is the usual treatment. In the hands of an experienced neurosurgeon, cure rates are 80%. However, hypopituitarism is probable after surgery, so individuals must be followed closely to detect it early and begin replacement of thyroid hormone, cortisol, estrogen or testosterone, and growth hormone when they are found to be deficient. If the first operation is not curative, additional surgical treatment, bilateral adrenalectomy, medication to stop steroid production, or external beam radiation can be necessary.

For adrenal tumors, surgical removal of the involved adrenal gland is curative if the final pathology is not carcinoma. Adrenal carcinoma requires adjuvant chemotherapy. For small cell lung carcinomas that produce ACTH, removal of the lung tumor often "cures" the Cushing's syndrome; however, overall prognosis is usually poor.

## Adrenal Insufficiency

The other spectrum of adrenal disease is adrenal insufficiency. Adrenal insufficiency can be caused by (1) primary destruction of the adrenal glands (i.e., Addison's disease) or (2) secondary insufficiency (i.e., lack of ACTH, or exogenous steroid use which suppresses ACTH). In Addison's disease, the adrenal glands can be destroyed by:

1. autoimmune attack
2. infections with HIV, tuberculosis, or histoplasmosis
3. metastatic spread of cancer
4. hemorrhage.

Secondary adrenal insufficiency is more common and usually due to exogenous use of supraphysiologic amounts of steroids that are given for other diseases such as systemic lupus erythematosus. An individual can develop secondary adrenal insufficiency if high-dose steroids are used for more than two weeks, which would cause production of ACTH to be suppressed. ACTH is necessary to keep the adrenal gland "primed." If ACTH is suppressed for long periods of time, the adrenal glands can atrophy and not respond readily to a pulse of ACTH.

Regardless of whether the adrenal insufficiency is primary or secondary, the clinical symptoms that an individual will experience are similar. They include weakness, fatigue, nausea, vomiting,

abdominal pain, joint pain, muscle tenderness, and dizziness. If not recognized, adrenal insufficiency can be life-threatening in situations of acute stress. For example, if an individual had unrecognized adrenal insufficiency and had a motor vehicle accident, he would not mount an acute stress response with production of such hormones as cortisol and epinephrine. As a result, he can go into shock with cardiovascular collapse. Thus, for underwriting, adrenal insufficiency that is untreated has a mortality risk for sudden death. In addition, when evaluating an individual with adrenal insufficiency, an underwriter must also consider the underlying cause of the adrenal insufficiency and assess the risk of that impairment.

### Pheochromocytoma

Another adrenal disorder is pheochromocytoma. This is a tumor of chromaffin-containing cells that produce epinephrine and norepinephrine. Pheochromocytoma refers to tumors found specifically in the adrenal medulla. (A paraganglioma is a tumor located in chromaffin tissue outside the adrenal, mostly in the sympathetic/parasympathetic nervous system.) Of the broad category of pheochromocytomas, 10% are familial, 10% are bilateral, 10% are malignant, 10% are paragangliomas, 10% occur in children, and 10% are recurrent.

Pheochromocytomas produce excessive amounts of epinephrine and/or norepinephrine. They can be life-threatening. Individuals usually have symptoms of headache, perspiration, and palpitations. In addition, they have accelerated hypertension, cardiac arrhythmias, or high output congestive heart failure. Once catecholamine excess is documented (24-hour urinary levels are usually the best test), surgery to remove the pheochromocytoma is essential. Surgery must be carefully planned and executed by experienced physicians, as life-threatening complications can occur if pre-operative, operative, and post-operative care is not judiciously given. If the pheochromocytoma is not malignant, most individuals will have normal life expectancy once the tumor is removed. If malignant, long-term prognosis is not favorable in most cases.

## **The Parathyroid Glands**

The parathyroids are four pea-sized glands located near the thyroid. They produce parathyroid hormone (PTH), which is the most important hormone regulating serum calcium concentration. Parathyroid hormone act on multiple tissues but predominately on kidney, bone, and intestine to increase serum calcium concentrations when levels are low.

### Hyperparathyroidism

A common disorder of the parathyroids is hyperparathyroidism. Hyperparathyroidism is excessive production of PTH. It occurs in up to one in 1000 adults. The most common cause of hyperparathyroidism is a single parathyroid adenoma, accounting for 85% of cases. Four-gland hyperplasia accounts for 15% of cases. In less than 1% of cases, hyperparathyroidism is caused by a parathyroid carcinoma. (Parathyroid carcinoma is often incurable, even after surgery.)

All types cause hyperglycemia. Hypercalcemia causes polyuria, thirst, abdominal pain, constipation, kidney stones, mental confusion, and even coma. Longstanding hyperparathyroidism leads to osteoporosis. Treatment depends on degree of hypercalcemia, rate of onset, and an

individual's symptoms. Some with mild disease, mild elevations of calcium (less than 11.0 mg/dl), and no symptoms can be watched medically. Others with severe osteoporosis, kidney stones, renal damage from hypercalcemia, decreased mental acuity, or higher elevations of calcium require surgery to remove either the adenoma or the hyperplastic glands (usually only 3.5 glands are removed). After surgery, most individuals are cured and life expectancy is normal. For those who are followed medically, there can be some morbidity or even mortality if the individual is not closely followed (every six months to one year).

Another cause of hypercalcemia that is important to recognize is malignancy. Hypercalcemia of malignancy is caused by:

1. elaboration of parathyroid hormone-related peptide (PTH-rP) by a tumor
2. metastasis to bone, causing bone resorption and release of calcium from bone
3. both 1 and 2.

Hypercalcemia of malignancy is usually severe and acute in onset. Serum calcium concentrations are frequently 13 mg/dl or higher. This is often life-threatening because of cardiac arrhythmias and/or coma. Acute treatment is aimed at reducing serum calcium levels with saline hydration, furosemide calciuresis (Lasix®, used to promote increased calcium excretion by the kidneys), and bone antiresorptive therapy with medications such as pamidronate (Aredia®). Overall, hypercalcemia of malignancy is a poor prognostic sign. Mortality risk is extremely high.

Finally, hyperparathyroidism can be seen with the familial syndromes of multiple endocrine neoplasia (MEN). There are three endocrine neoplasia syndromes with different combinations of disorders. They are as follows:

1. MEN 1
  - a. primary hyperparathyroidism (present in 90%)
  - b. pituitary adenomas (present in 30%)
  - c. pancreatic tumors (present in 60%)
2. MEN 2A
  - a. medullary carcinoma of thyroid (present in 100%)
  - b. pheochromocytoma (present in 50%)
  - c. primary hyperparathyroidism (present in 30%)
3. MEN 2B
  - a. medullary carcinoma of thyroid (present in 100%)
  - b. pheochromocytoma (present in 50%)
  - c. Marfanoid body habitus, intestinal ganglioneuromas (present in 100%).

Increasing evidence demonstrates that the MEN syndromes are caused by inherited DNA mutations. In fact, a majority of MEN 2A and 2B cases have been demonstrated to contain a *RET* proto-oncogene mutation in the tyrosine kinase receptor. The important point is that physicians can now do a blood test on family members of those who have the *RET* proto-oncogene defect to see whether or not family members are affected. If a family member does not have the mutation, the likelihood of developing the MEN 2A or 2B syndrome is very low to zero. If he does have the

same mutation, the likelihood of developing the MEN 2A or 2B syndrome is very high (almost 100%). Thus, genetic screening is very important in MEN 2A or 2B families.

MEN 1 is a rare autosomal dominant disorder with a prevalence of two per 100,000. The gene, located on the long arm of chromosome 11 (11q13), produces a tumor suppressor protein, menin. There are multiple MEN 1 genotype mutations that disrupt menin function and result in the loss of tumor suppression and produce one of the clinical phenotypes of this syndrome. Genetic testing for it is available.

## **Diabetes Mellitus**

Maintaining normal glucose levels involves the interplay of several hormones:

1. insulin
2. glucagon
3. somatostatin
4. cortisol
5. epinephrine
6. growth hormone.

This system of having several hormones control glucose levels evolved for two reasons. First, there had to be a system of maintaining a constant level of glucose in the bloodstream, because glucose is the only fuel that the brain can utilize. Second, there had to be a way of storing glucose, so that food did not have to be ingested 24 hours a day.

Insulin and glucagon are the key hormones that regulate glucose levels. They have opposing effects. Insulin is made in and released from the beta cells of the pancreatic islets. Insulin acts to promote glucose utilization by increasing tissue uptake of glucose and stimulating glycogen synthesis. It also has anticatabolic properties by sparing protein catabolism, lipolysis, and ketogenesis. In other words, it is the hormone of the “fed” state, being utilized after food is ingested to promote its use and utilization. In contrast, glucagon is secreted from the alpha cells of the pancreatic islets. It acts to counterbalance insulin and can be viewed as the hormone of the fasting state. It acts to maintain glucose levels between meals by stimulating the formation of glucose from stored glycogen, free fatty acids, or amino acids.

Finally, somatostatin is a hormone that is secreted from delta cells in the pancreatic islets and acts to inhibit both insulin and glucagon. Thus, it acts in a paracrine manner on the alpha and beta cells. By inhibiting insulin and glucagon, it prevents rapid exhaustion of glucose when a meal is eaten. Cortisol, epinephrine, and growth hormone act in a manner similar to glucagon, maintaining blood glucose in times of stress.

Diabetes mellitus (DM) is a disorder of glucose metabolism. It is caused by either absolute or relative lack of insulin. Absolute insulin deficiency is evidenced by absent secretion of insulin from the beta cells of the pancreatic islets. Relative lack of insulin refers to a state of insulin resistance, whereby insulin is present, but there are problems involving insulin binding to the insulin receptor, a lack of insulin receptors, or lack of response once insulin is bound to to

receptors. In each situation, glucose is not utilized as fuel and is lost into the urine. Diabetes mellitus (a name that means sweet siphon) is the end result.

The diagnosis of DM is made by demonstrating any of the following:

1. fasting blood glucose measurements on two separate occasions of greater than or equal to 126 mg/dl
2. a glucose measurement of greater than or equal to 200 mg/dl at any time of day
3. a glucose measurement greater than or equal to 200 mg/dl at any time during an oral glucose tolerance test
4. a hemoglobin A1c (HgbA1c) value of 6.5% or greater and confirmed on another day (this is reserved for nonpregnant adults without evidence of hemoglobinopathy or other disease of red blood cell turnover)
5. evidence of acute diabetic ketoacidosis or diabetic hyperosmolar coma with extreme hyperglycemia.

Impaired fasting glucose and impaired glucose tolerance are considered at-risk states for the future development of type 2 diabetes. In addition, a HgbA1c of 5.7-6.4% is considered “prediabetes.” Impaired fasting glucose is defined as a fasting glucose measurement greater than 100 mg/dl but less than or equal to 125 mg/dl. Impaired glucose tolerance is a blood glucose measurement greater than or equal to 140 mg/dl but less than 200 mg/dl at any time during a glucose tolerance test. Both conditions are often seen in individuals who are overweight. About 25% of those with impaired fasting glucose or impaired glucose tolerance will develop frank type 2 DM in their lifetime.

DM is classified into four main categories. These are:

1. type 1
2. type 2
3. other
4. gestational.

This classification scheme is based on the underlying pathophysiology, not age of onset or type of treatment. In addition, there is debate about a type 1.5 diabetes or, as some researchers are calling this type, “double diabetes.” Those with this type are mostly children and adolescents, who are overweight or obese, and yet have antibodies to insulin, islet cells, and glutamic acid decarboxylase. In other words, they present like type 2 diabetics, however, have an autoimmune profile like a type 1. There will be more literature about this diabetic profile in the future.

### Type 1 Diabetes Mellitus

Type 1 is caused by autoimmune destruction of the pancreatic beta cells. Absolute insulin deficiency occurs, and insulin injections are necessary for survival. It is most commonly diagnosed in childhood to young adulthood, usually in individuals under 21 years of age. The development of type 1 diabetes involves multiple genes (i.e., polygenic inheritance) and likely some environmental exposure or trigger. In the U.S., there are over one million type 1 diabetics.

Caucasians, especially of Scandinavian heritage, account for the greatest population at risk. There is another form of insulin-requiring diabetes called latent autoimmune diabetes in adults (LADA). The presentation of LADA is usually in those age >35, initially treated as type 2 diabetic, and treated over a 6-month time frame. A LADA individual will absolutely need insulin for survival. Persons with LADA will have positive results on testing for at least 2 of 4 of the autoantibodies indicative of diabetes. (The antibodies are glutamine acid decarboxylase antibodies, islet cell antibodies, tyrosine phosphate-related islet antigen, or insulin antibodies.)

Insulin is necessary treatment for type 1 diabetics. Because insulin is a large molecule and is susceptible to degradation by stomach acid and enzymes, it can only be administered by injection. Insulin injections are commonly given in one of two ways: either by two or more subcutaneous injections daily or by a portable subcutaneous insulin pump. With both, the goal is to provide insulin replacement as close to normal physiologic secretion as possible.

The types of insulin vary in their formulation and duration of action. Some of the traditional insulins include lente, regular, NPH (i.e., neutral protamine Hagedorn), and ultralente. Newer insulins include aspart, lispro, glulisine, glargine, and detemir. Insulin can be given by subcutaneous injection, pen injection, or continuous pump infusion. Insulin pump therapy is increasing in acceptance due to improvements in pump technology and glucose monitoring systems. In the motivated individual, insulin pump therapy improves glucose control.

Type 1 diabetics must monitor their blood glucose levels several times a day. Continuous glucose sensors are now in high adoption, allowing a person to instantaneously look at glucose levels or glucose trends and set alarms for high glucose and low glucose values. Ideal goal is time in range glucose of 70-180 for 70% or more of the time in 24-hour period. With continuous monitoring, individuals can adjust the amount of insulin that they inject or adjust the infusion rate on their pump. In addition, many pumps today have reservoirs for glucagon, to be readily injected when severe hypoglycemia is detected.

### Type 2 Diabetes Mellitus

The pathophysiology of type 2 DM is distinctly different from that of type 1 DM. Type 2 is characterized by a relative lack of insulin or a state of insulin resistance. In other words, insulin is present, but the peripheral tissues do not respond appropriately. Over two to five years, even with excess insulin secretion, hyperglycemia will occur permanently, leading to the diagnosis of type 2 diabetes. In addition, there are some type 2 diabetics who, over many years (10 to 20), have complete exhaustion of the pancreatic beta cells, such that insulin replacement is necessary. In type 2 diabetics, obesity is the greatest culprit that causes insulin resistance.

In the United States, there are approximately 34 million type 2 diabetics. Type 2 DM has a higher genetic predisposition than type 1 DM. Certain ethnic groups are also at higher risk. For example, the prevalence of type 2 DM in Hispanic-Americans is 12% compared with 7% for African-Americans and 5% for Caucasian-Americans. Asian-Americans and Indian-Americans are at risk for type 2 diabetes at slimmer waist circumference and lower body mass indices than other Americans. This is believed to be from difference in distribution of visceral adipose tissue versus subcutaneous adipose tissue. Visceral adipose tissue is that which deposits around deep

organs and is more pro-inflammatory and insulin resistant. Like type 1 diabetes, type 2 risk inheritance involves multiple genes(polygenic). Finally, with increasing longevity of the population, it is estimated that type 2 DM will affect nearly 25% of the population over 65 years old. Favorably, with recognition that most diabetics are at high risk for cardiovascular disease (CVD) and with improved efforts to treat all related CVD risk factors, the number of people dying from diabetes is dropping dramatically in the U.S. over the last ten years and life expectancy for diabetics is likely to continue to improve.

The recommended first line therapy for type 2 diabetics is metformin therapy along with intensive lifestyle changes of proper diet and exercise. Today physicians will work with patients for individualized and personalized plans for control of glucose and will often utilize not only HgbA1c but continuous glucose sensor data, as they do in type 1 diabetics.

In diabetics not controlled with first line therapy, physicians add additional medications. There are numerous to choose from and physicians will often work with patient to address other needs like cost, wanting to avoid hypoglycemia, promote weight loss, or minimize weight gain. In addition, for those diabetics who are high risk for cardiovascular or kidney complications or already have a complication, such as heart failure, newer medications like glucagon-like peptide 1 analogs and sodium-glucose cotransporter 2 inhibitors are utilized sooner.

The important point is that not all the medications work 100% of the time in 100% of individuals. Close monitoring and follow-up with a physician are necessary to insure the blood glucose levels are controlled. It is often necessary to switch medications, combine two medications, or even use insulin. The desired goal is to achieve normal glucose homeostasis. Also, an astute underwriter must keep in mind that a physician can use some of the medications to “prevent” diabetes, treat insulin resistance syndrome, polycystic ovarian syndrome, or other at-risk diabetes states.

### Other Causes of DM

Other causes of DM include rare disorders of the insulin receptor, disorders of insulin binding, diabetes mellitus that is a result of other destructive diseases of the pancreas, and diabetes mellitus that occurs in the setting of other disorders like Cushing’s syndrome.

An interesting subgroup of the “Other” category that is important for underwriting is individuals with an autosomal dominant form called maturity-onset diabetes of youth or MODY—a monogenic form of diabetes, in contrast to type 1 and type 2 diabetes which have polygenic inheritance. This type of diabetes mellitus involves mutations in the sensing of a glucose load by the pancreatic beta cell. Three distinct defects have been described:

1. MODY 1, a defect in hepatic nuclear factor 4
2. MODY 2, a defect in glucokinase enzyme
3. MODY 3, a defect in hepatic nuclear factor 1.

The main characteristic is a defect in the secretion of insulin. In some cases, the MODY patient presents to the physician with an acute episode of diabetic ketoacidosis (DKA). However, once the DKA is controlled and the individual is started on insulin, recovery of the beta cell occurs. These individuals then stop insulin and manage glucose control with diet and oral medications. MODY is important for an underwriter to recognize because it can present like type 1 diabetes, but the clinical behavior is more representative of type 2 diabetes. MODY is rarer than type 2 or type 1 and only accounts for approximately 1% of diabetics. Most MODY diabetics can be adequately controlled with an ADA diet, exercise, and occasionally a sulfonylurea drug.

### Gestational DM

Gestational diabetes mellitus is, obviously, diabetes that occurs during pregnancy. It is detected first by screening during the 24-28<sup>th</sup> week of gestation with a 50-gram glucose load and measuring a one-hour glucose. A glucose greater than 140 mg/dl prompts further testing. The next test is a 100-gram glucose load given after a 12-hour fast. Measurements are made fasting, and at one hour, two hours, and three hours after the glucose load. If two measurements are elevated (fasting greater than 105mg/dl, one hour greater than 190mg/dl, two hours greater than 165 mg/dl, and three hours greater than 145mg/dl), the diagnosis of gestational diabetes mellitus is made.

Treatment is aimed at maintaining normal glucose levels. Insulin is the only medication safe to use in pregnancy. When a female has uncontrolled gestational diabetes mellitus, the risks to the fetus are hypoglycemia, hypocalcemia, macrosomia (large body habitus), and hyperbilirubinemia. Gestational diabetes mellitus affects roughly 3% of all pregnancies. A history of gestational diabetes mellitus increases a female's risk for possible type 2 DM in later life. In fact, up to 40%-60% of females who have gestational diabetes will develop type 2 diabetes over the next 5-10 years.

### Complications of DM

The complications that a diabetic can experience are multiple. Acute complications include:

1. diabetic ketoacidosis, which occurs in type 1 and MODY
2. diabetic hyperosmolar coma that occurs in type 2
3. acute hypoglycemia that can occur in all types.

All the acute complications have some mortality risk with the acute episode. For example, the mortality rate for an episode of diabetic ketoacidosis is 10%.

Chronic complications of diabetes mellitus are related to degree of glucose control and duration of disease. One way of monitoring glucose control is measurement of the hemoglobin A1c (HgbA1c). It is considered the gold standard for monitoring control. It reflects the average blood glucose over the preceding three months. It utilizes the fact that glucose binds to a portion of the hemoglobin chain. When glucose levels are high, more glucose binds to the hemoglobin. There are situations that can give falsely high or falsely low readings. For example, if a specimen is not processed quickly, a false elevation in HgbA1c can occur. Conversely, falsely low HgbA1c values occur in certain hemoglobinopathies. The International Federation of Clinical Chemists has

developed a pure assay for HgbA1c. This assay has been deployed worldwide and is used to certify all labs. As such, HgbA1c values should be comparable. In addition, a recent study proved a mathematical relationship between HgbA1c and average glucose. As such, lab reports usually show both the HgbA1c and average glucose. This is similar to the way laboratories translate a serum creatinine value to an estimated glomerular filtration rate (eGFR).

Fructosamine is another available blood test to monitor glucose control. It closely correlates with HgbA1c levels, but it is more prone to falsely high and falsely low readings because of changes in the albumin status of the individual. In addition, fructosamine only reflects the average blood glucose for the preceding 10 to 20 days.

A new lab marker, Glycomark®, which measures 1,5 anhydroglucitol, is useful for evaluating postprandial glucose levels. The role in underwriting for Glycomark® remains to be determined. Postprandial control is still more likely to be self-monitored by the individual with finger stick glucose measurements.

Diabetes-related morbidity is directly related to the development of acute and chronic complications associated with the disease and the individual's ability to function with the symptoms associated with end-organ damage. In most instances, longer duration of disease is associated with greater likelihood of a complication. If glucose control has been excellent (i.e., close to the normal non-diabetic range), the development or progression of chronic complications can be reduced significantly. Chronic complications are often divided into two groups:

1. related to microvascular disease—These include diabetic retinopathy, nephropathy, and neuropathy (both peripheral and autonomic).
2. related to macrovascular disease—Macrovascular complications involve larger arterial vessels such as the coronary arteries, carotid arteries, and arteries of the distal extremities.

Diabetic retinopathy develops in stages, starting as nonproliferative changes, evolving into proliferative changes, microaneurysms, retinal infarcts, macular edema, and eventual blindness. In fact, DM is the leading cause of adulthood blindness in the United States. The risk of a diabetic developing retinopathy is 5%-8% per year or 50%-90% cumulative risk over 20 years. Each year about 5,000 diabetics become blind, and the death rate is 10% per year when blind. With proliferative retinopathy only, the death rate is 5% per year. Most diabetics develop some degree of retinopathy over their lifetime of disease. Good glucose control can prevent the development and/or progression of retinopathy.

Diabetic nephropathy has similar devastating effects on the long-term survival of a diabetic. Nephropathy develops in stages. The earliest sign of nephropathy is the presence of microalbuminuria. Microalbuminuria is significant when the levels are 30-300 mg/24 hour urine collection, 20-200 micrograms/minute on a timed specimen, or 30-300 micrograms/mg of creatinine on a spot (random) specimen. Of all the methods, the 24-hour urine collection provides the most useful information because creatinine clearance can also be calculated from the collection. After microalbuminuria is present, more severe albuminuria/proteinuria develops, often reaching nephrotic levels (i.e., 1.5 grams per 24-hour urine collection). Unlike retinopathy, there are some diabetics who will never develop nephropathy. For example, if a diabetic has not

developed any evidence of nephropathy after 35 years of the disease, his chances of developing nephropathy approach zero. Nevertheless, nephropathy develops in 35-45% of type 1 diabetics by 20 years. In type 2 diabetics, nephropathy develops in 20% over 20 years. Once nephropathy develops, 25% will develop end-stage renal disease and require dialysis and/or transplantation. In addition, the risk of concomitant cardiovascular disease when nephropathy occurs in a diabetic is 30-40 times that of a non-diabetic individual. Thus, nephropathy is a significant marker for increased mortality risk in a diabetic.

Neuropathy in DM is common and is present in 12% of diabetics at the time of diagnosis. Peripheral neuropathy involves destruction of both small and large nerve fibers. When small fibers are damaged, the clinical presentation is pain, loss of thermal recognition, and loss of light touch sensation in the distribution of the nerve fiber affected. When large fibers are damaged, there is loss of vibratory and position sense, muscle weakness, and absent deep tendon reflexes in that nerve distribution. The cumulative effect is that a diabetic is prone to extremity injury and infection because of lack of sensation. Often infections are not recognized until osteomyelitis or gangrene occurs. In fact, half of all amputations in diabetics are the result of underlying peripheral neuropathy. Autonomic neuropathy interferes with multiple organ system functioning. The underlying defect involves the vagus nerve. This results in cardiac, gastrointestinal, and genitourinary difficulties. For example, autonomic neuropathy can cause orthostatic hypotension due to failure to increase cardiac output with standing. Diabetics with cardiac autonomic neuropathy have very high mortality—in some studies, a 35% death rate over eight years.

Macrovascular disease, in particular cardiovascular disease (CVD), in diabetics is the leading cause of mortality. Tobacco use, in particular smoking cigarettes, in diabetics increases risk for CVD events, as nicotine can contribute to vasospasm, platelet stickiness, plaque rupture, and inflammation. Males with DM have two times the rate of myocardial infarction (MI) compared to non-diabetics. For female diabetics, the risk of MI is five times that of non-diabetic females. Lastly, for teen-age diabetics, the risk of MI is ten times that of non-diabetic teenagers. The clinical presentation of MI is also different for the diabetic. Forty percent have no history of chest pain, previous angina, or shortness of breath. One-third of diabetics who suffer a MI die in the hospital. In addition, overweight female diabetics with an MI die at twice the rate of male diabetics. Even if a diabetic survives the first MI, the risk remains high (60%) for suffering a second MI within the first six months. The five-year death rate after MI is 75%. Thus, heart disease is the leading cause of mortality for the diabetic. Recent studies have shown improved MI and all cause mortality in intensively treated type 1 diabetics compared to conventionally treated type 1 diabetics (EDIC study). In addition, in the UKPDS study of early onset type 2 diabetics, there is improved mortality long term with control of HgbA1c either by sulfonylurea, insulin, or metformin. Newer drugs like empagliflozin and liraglutide have been shown in clinical studies to reduce the risk of CVD death in diabetics taking these medications. More medications in development are poised to work similarly and thus further help increase life expectancy of persons with diabetes.

Other macrovascular diseases affecting diabetics are cerebrovascular disease and peripheral vascular disease. Cerebrovascular infarcts are three times more likely to occur in a diabetic than in a non-diabetic. In addition, 45% of diabetics will have peripheral vascular disease after 20 years of disease. This is four times the rate of non-diabetics.

Finally, uncontrolled DM contributes to changes in cholesterol patterns, especially in overweight type 2 diabetics who are insulin resistant. This subgroup often has elevated triglycerides, low high-density lipoprotein (HDL) levels, and high low-density lipoprotein (LDL) levels. In addition, the LDL particles are often smaller and denser than in non-diabetics. As such, they are more easily oxidized and incorporated into atheromatous plaque.

For underwriting, it is very important to classify DM properly. Overall mortality is approximately 1.5 to 2.0 times (females slightly higher than males) that of the non-diabetic population. The goals of treatment are to normalize blood glucose and prevent complications. The Diabetes Care and Complications Trial studied 1,441 type 1 diabetics who demonstrated near normal glucose control and showed significant reductions in the development and progression of retinopathy, nephropathy, and neuropathy. Stringent control is not suitable for everyone, and practitioners try to individualize treatment. For example, a doctor can aim for a HgbA1c of 7.0 to 7.2 for an older person (> age 70) and aim for a HgbA1c < 7.0 for a 40-year-old. Thus, good risk classification of DM will consider multiple factors including duration of disease, degree of glucose control, frequency and severity of acute complications, and presence and severity of chronic complications.

### Hypoglycemia

Hypoglycemia is low blood glucose. Individuals are frequently evaluated for hypoglycemia, but it is rarely found. The diagnosis requires that all three components be present:

1. The individual must have symptoms of low blood glucose.
2. The symptoms must correspond to documented low blood glucose (less than 50 mg/dl in females, less than 55 mg/dl in males).
3. The symptoms must resolve with the administration of glucose.

The symptoms of hypoglycemia reflect activation of the sympathetic nervous system and lack of glucose to the brain. Thus, symptoms range from tachycardia, sweating, and palpitations to mental confusion, neurological deficits, and coma. Hypoglycemia can result in death.

Hypoglycemia is divided into two categories: reactive and fasting. Reactive is a fall in blood glucose that usually occurs several hours after eating. Some common causes include delayed gastric emptying, delayed onset of insulin action, and factitious disorders. The underlying impairment is usually non-life-threatening. Fasting hypoglycemia occurs in the absence of food and is usually indicative of a more serious disorder. The differential diagnosis of fasting hypoglycemia is broad but includes: a pancreatic insulin-producing tumor (insulinoma), liver failure, undiagnosed Addison's disease, undiagnosed hypopituitarism, alcohol intoxication, renal failure, sepsis, and neoplasms which secrete insulin-like growth factor-II. Correction of the underlying disorder usually resolves the hypoglycemia. Underwriting of hypoglycemia should focus on the underlying disorder.

## **Metabolic Syndrome**

The metabolic syndrome is a clinical syndrome characterized by the presence of impaired glucose metabolism, a proatherosclerotic lipid profile, hypertension, and abdominal obesity. It has undergone various name changes over the years, having previously been referred to as the deadly quartet, Reaven's syndrome, dysmetabolic syndrome, syndrome X, and insulin resistance syndrome. The common feature for all these terms is the recognition that the metabolic milieu is prothrombotic, proatherosclerotic, and "pre-diabetic." Some definitions do include those with an established diagnosis of diabetes mellitus. Metabolic syndrome is defined using different criteria by various organizations such as National Cholesterol Education Program/Adult Treatment Program III (NCEP/ATP III), World Health Organization (WHO), American Association of Clinical Endocrinologists (AACE), and International Diabetes Federation (IDF). The uniting principle of all the definitions is the recognition that the clustering of various risk factors in individuals with metabolic syndrome predisposes those individuals to increased cardiovascular disease and overall mortality.

Underwriters will recognize that many of the components of the metabolic syndrome are routine parameters evaluated in underwriting. Metabolic syndrome is coded as E88.81 by the International Classification of Diseases 9<sup>th</sup> Revision-Clinical Modification (ICD-10-CM).

Table 1 below shows the criteria as defined by NCEP/ATP III, which requires three or more criteria to be present for diagnosis and Table 2 shows the criteria as defined by WHO, which requires insulin resistance to be present, plus two additional criteria.

**Table 1. NCEP/ATP III definition of metabolic syndrome.**

The metabolic syndrome is defined by the presence of three or more of the following according to NCEP/ATP III.		
Abdominal obesity	Waist circumference	Men > 40 inches (102cm) Women >35 inches (88cm)
Triglycerides	$\geq$ 150 mg/dL (1.69mmol/L)	
HDL cholesterol	Men <40 mg/dL (1.03mmol/L) Women < 50mg/dL (1.29mmol/L)	
Blood pressure	$\geq$ 130/ $\geq$ 85 mmHg	
Fasting glucose	$\geq$ 110 mg/dL (6.1mmol/L)	

**Table 2. WHO definition of metabolic syndrome.**

<b>The metabolic syndrome is defined by the presence of insulin resistance* and any of two of the following according to WHO:</b>			
*Insulin resistance (hyperinsulinemia defined by upper quartile of the nondiabetic population) or fasting glucose $\geq 110\text{mg/dL}$ (6.1mmol/L) or a two hour glucose $\geq 140\text{ mg/dL}$ (7.78mmol/L) or taking medications for diabetes mellitus.			
Obesity	Body mass index $\geq 30\text{kg/m}^2$		
	Waist to hip ratio	Men $>0.9$	
		Women $>0.85$	
Triglycerides	$\geq 150\text{mg/dL}$ (1.69mmol/L)		
HDL cholesterol	Men $<35\text{ mg/dL}$ (0.91mmol/L)		
	Women $< 39\text{ mg/dL}$ (1.01mmol/L)		
Blood pressure	$\geq 140 / \geq 90$ or documented use of antihypertensive therapy		
Microalbuminuria	Urinary albumin excretion rate $\geq 20\text{mg/min}$ or urinary albumin/creatinine ratio $\geq 30\text{mg/g}$		

Using the NCEP/ATP III definition and results of the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of metabolic syndrome in the United States varies by age and gender. For example, 44% of males and females aged 60-69 had metabolic syndrome compared with 6% of males aged 20-29 and only 5% females aged 20-29. There is also ethnicity-specific prevalence, depending on the study population and the criteria used. The IDF has criteria that vary for European and Asian populations. For underwriting, the important point is the recognition that presence of metabolic syndrome increases risk of morbidity and mortality.

Treatment is aimed at therapeutic lifestyle changes, including diet, exercise, and modest weight loss. Targeted therapy is also used to treat hypertension, lipids, and abnormal glucose control. Again, many physicians will use medications approved for type 2 diabetes to treat the metabolic syndrome. Most commonly used are metformin, acarbose, and the thiazolidinediones, such as rosiglitazone and pioglitazone. The overall goal is to reduce the cardiovascular risk associated with the syndrome.

## Summary

This chapter introduced the principles behind disorders in endocrinology and metabolism. It is important to recognize that some disorders are very common, like treated Hashimoto's thyroiditis, and do not represent any excess mortality risk. Other disorders, such as acromegaly, although rare, do occur with some frequency and represent some excess risk. This chapter also introduced the principles behind underwriting diabetes mellitus. All of these topics are important for risk classification. Readers are encouraged to supplement their learning with other textbooks and journals that will give more specific details of these topics.

## **Review Questions – ALU 201, Chapter 9**

1. In diabetes, the leading cause of mortality is:
  1. renal failure
  2. diabetic coma
  3. macrovascular disease
  4. infectious disease
  
2. All of the following statements regarding thyroid nodules are correct EXCEPT:
  1. Goiters can be the result of multiple nodules.
  2. Purely cystic nodules are not usually an underwriting concern.
  3. Benign nodules generally appear cold on radioiodine uptake scans.
  4. American Thyroid Association has revised guidelines for when fine needle aspiration is recommended based not just on size but also overall degree suspicion for malignancy.
  
3. Hormones that regulate glucose levels include which of the following?
  - A. cortisol
  - B. glucagon
  - C. thyroxine
  

Answer Options:

  1. A only is correct.
  2. B only is correct.
  3. A and B only are correct.
  4. B and C only are correct.

  
4. Describe hyperparathyroidism, its primary cause, symptoms, treatment, and prognosis.
  
5. Describe two distinct disorders of the adrenal gland and their significance to mortality risk assessment.
  
6. A disease characterized by the destruction of the adrenal glands is:
  1. Addison's disease
  2. hyperparathyroidism
  3. diabetes mellitus
  4. Cushing's syndrome

7. Which of the following statements regarding type 1 diabetes mellitus is/are correct?

- A. It is caused by destruction of the pancreatic beta cells.
- B. It is characterized by insulin resistance.
- C. It is usually diagnosed before age 21.

Answer Options:

- 1. A only is correct.
- 2. A and C only are correct.
- 3. B and C only are correct.
- 4. A, B, and C are correct.

8. What do peptides produced by the pituitary gland regulate?

9. Describe how fructosamine and hemoglobin A1c are alike and how they differ.

10. What are the characteristics of metabolic syndrome?

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 3: macrovascular disease – page 16.

### *Review Question 2*

Answer 3: Benign nodules generally appear cold on radioiodine uptake scans – page 5.

### *Review Question 3*

Answer 3: A and B only are correct – page 10.

### *Review Question 4*

Refer to pages 8-10.

### *Review Question 5*

Refer to pages 6-8.

### *Review Question 6*

Answer 1: Addison's disease – page 7.

### *Review Question 7*

Answer 2: A and C only are correct – page 11.

### *Review Question 8*

Refer to page 1.

### *Review Question 9*

Refer to pages 14-15.

### *Review Question 10*

Refer to page 17.

## **CHAPTER 10**

### **MUSCULOSKELETAL SYSTEM DISORDERS**

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## MUSCULOSKELETAL SYSTEM DISORDERS

### Introduction

The older term “rheumatism” was originally used to describe all types of pain and stiffness associated with arthritis and other disorders of the musculoskeletal system. Currently, rheumatism is used to refer primarily to soft tissue and/or musculoskeletal disorders such as tendonitis, bursitis, and fibromyalgia. Arthritis means joint inflammation characterized by swelling, pain, and loss of motion. There are more than 100 diseases that cause arthritis and related disorders of the joints, muscles, and bones in children and adults of all ages. Some of these rheumatic diseases also cause inflammation in other organs. These systemic diseases are sometimes called connective tissue disorders or collagen vascular disorders. Examples of rheumatic diseases include:

1. rheumatoid arthritis (RA)
2. osteoarthritis (OA)
3. crystal-induced arthritis (gout and CPPD arthritis)
4. systemic lupus erythematosus (SLE).

The field of rheumatology is a confusing one to non-rheumatologists. The cause of many types of arthritis is unknown. Diagnosis is usually made by assessing the pattern of the arthritis, in conjunction with the age and gender of the individual. Symptoms outside of the joints can provide hints to the correct diagnosis.

Laboratory tests are not always useful. There is often no definitive diagnostic test. Many of the test abnormalities in rheumatic diseases are non-specific—examples include normochromic, normocytic anemia seen on CBC, an elevated erythrocyte sedimentation rate (ESR), or an elevated C-reactive protein (CRP)—all of which are non-specific markers of inflammation. A positive rheumatoid factor (RF) test is seen in only 75% of those with rheumatoid arthritis. A newer biomarker for RA is the antibody to cyclic citrullinated peptide (anti-CCP), the presence of which is a predictor of poor prognosis. However, it is also only present in 70-80% of RA patients. A positive anti-nuclear antibody (ANA) test is seen in 90% or more of individuals with systemic lupus, but it can also be present in other diseases, such as rheumatoid arthritis and scleroderma, as well as in non-rheumatologic conditions, such as autoimmune thyroid disorders. ANA is a very poor screening test, as it is positive in up to 13-15% of the general population. Antibodies to neutrophil cytoplasmic antigens (ANCA) are a newer marker for certain forms of vasculitis (i.e., granulomatosis with polyangiitis [GPA], and microscopic polyangiitis [MPA]).

The most common form of arthritis, osteoarthritis, is not associated with any abnormalities in routine laboratory tests. Many people, particularly healthy older individuals, and the relatives of those with rheumatic diseases, are incidentally found to have a positive serologic test for rheumatoid factor or antinuclear antibodies. Many individuals with a positive RF or ANA test will not have a diagnosable systemic rheumatic disease. X-rays and other imaging studies, such as CT and MRI scans and ultrasound, can be of help in making a diagnosis. However, early in the course of many rheumatic diseases, the x-rays can be normal. At other times, non-specific x-ray abnormalities can be present. For example, many individuals with low back pain have x-ray abnormalities in the lumbar spine that are unrelated to the cause of their pain. Therefore, diagnosis is based primarily on history

and physical examination. Criteria for diagnosis of various rheumatic diseases have been developed by the American College of Rheumatology (ACR) and are in widespread use, particularly for RA and SLE.

Treatment of the rheumatic diseases involves a multi-disciplinary approach. Numerous health professionals, such as physiotherapists, occupational therapists, social workers, and dietitians can assist in the care of these individuals. Non-traditional and alternative therapies are often sought by those with rheumatic disease. This reflects the incomplete efficacy of current medical therapies. Most rheumatic diseases are chronic lifelong conditions for which a cure is not possible. We speak instead of control of disease and remission of symptoms. Education of the patient, rest, exercise, and various aids can be of great benefit. Non-steroidal anti-inflammatory drugs (NSAIDs), as well as simple analgesics, are in widespread use as basic therapies. More powerful drugs, such as systemic corticosteroids (e.g., prednisone) and various disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate are also used, particularly for rheumatoid arthritis and systemic connective tissue diseases. These more powerful drugs can also include immunosuppressant drugs. The use of more potent medications is generally a marker of more severe disease, which is associated with an increased potential for morbidity and mortality. However, intensive, early, aggressive therapy using a “treat-to-target” approach is associated with better outcomes in general. In some cases, the late side effects of therapy, particularly steroids, can be quite debilitating. Newer, targeted “biologic” therapies are increasingly used to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, with results exceeding those previously seen with conventional therapies.

### **Patterns of Arthritis**

There are no definitive tests for the diagnosis of many forms of arthritis. Rather, the diagnosis of a specific type of arthritis depends on recognition of the pattern and distribution of affected joints. In the hand, the joints immediately next to the fingernails are the distal interphalangeal or DIP joints. They are commonly affected by osteoarthritis and by the arthritis associated with psoriasis. They are much less commonly involved in rheumatoid arthritis. The next row of finger joints is the proximal interphalangeal or PIP joints. These are commonly involved in both osteoarthritis and rheumatoid arthritis. The knuckle joints, where the fingers join the hand, are the metacarpal-phalangeal or MCP joints. These are commonly involved in rheumatoid arthritis. They are much less often involved in osteoarthritis, except in those who do heavy manual work. The thumb has an interphalangeal, or IP joint, as well as an MCP joint. These can be involved in both OA and RA. The thumb also has a joint with the wrist called the first carpal-metacarpal or CMC joint. This is most involved in osteoarthritis.

Involvement of the wrist, elbow, and shoulder joints is common in rheumatoid arthritis and much less so in osteoarthritis, though those who do heavy manual labor can have OA involving these joints. The shoulder is also the site of a variety of soft tissue problems, such as rotator cuff tendonitis and bursitis.

In the spine, the neck or cervical spine is frequently involved in both rheumatoid arthritis and osteoarthritis. It can also be affected by seronegative spondyloarthritides, such as ankylosing spondylitis. The thoracic and lumbar spines are never involved in rheumatoid arthritis, but the lumbar spine is a common site of OA and degenerative disc disease (DDD). The spondyloarthritides (SpA)

are a group of seronegative disorders that involve the spine, sacroiliac joints, and sometimes peripheral joints quite diffusely.

In the lower extremities, the hips can be involved in both OA and RA. The knees are the most involved joints in most systemic forms of arthritis, as well as OA, and are the largest joints in the body. The ankle joints can be involved in RA and generally are not affected by OA, except after ankle fractures or other injuries. The subtalar and midtarsal joints, which make up the hindfoot and midfoot, are commonly involved in RA.

The metatarsal-phalangeal (MTP) joints, where the toes join the foot, are commonly involved in RA. In OA, often only the first and fifth MTP joints are involved, giving characteristic bunion and bunionette deformities. The small joints of the toes can be involved in OA and RA as well as in psoriatic arthritis.

Thus, the pattern and distribution of involved joints can provide important clues to the diagnosis of a specific form of arthritis. Similarly, assessment of the extra-articular features associated with a particular arthritis can be helpful in diagnosis. For example, a careful search of the skin for psoriasis can reveal that an inflammatory arthritis is, in fact, psoriatic arthritis. Inflammatory eye (i.e., uveitis, iritis) or bowel involvement (e.g., ulcerative colitis) can point to a seronegative spondyloarthritis, rather than RA. The presence of nodules can indicate either rheumatoid arthritis or gout.

## Epidemiology

Arthritis and musculoskeletal disorders are among the most common chronic conditions. They are the second leading cause of visits to the doctor, ranking only behind colds and upper respiratory tract infections. More than one individual in ten has clinical features of osteoarthritis. Fibromyalgia has a prevalence of 3%, and RA affects 1% of the general population. The prevalence of gout is about 13 per 1,000. Ankylosing spondylitis and related spondyloarthropathies are found in at least one in 200 individuals. Systemic lupus is less common with a prevalence of one in 2,000.

Arthritis can begin at any age, affecting children as well as elderly individuals. However, the most common period of onset is in the third to sixth decades of life. Females are more commonly affected than males. Ninety percent of individuals with systemic lupus are female, as are two-thirds of those with RA. Only in the cases of gout and seronegative arthritis do males predominate. Arthritic disorders are the most common cause of long-term disability in the general population. Disability can be related directly to joint damage, as in osteoarthritis or uncontrolled RA. In systemic forms of arthritis, extra-articular manifestations can involve multiple organ systems, potentially leading to disability. Fatigue and mood disorders are common in individuals with arthritis and other chronic diseases and can be disabling. Cardiovascular disease risk is increased in most patients with inflammatory arthritis and is the leading cause of mortality in most.

## Osteoarthritis

Osteoarthritis is the most common form of arthritis. It is commonly referred to as “wear and tear” arthritis. It occurs radiologically in almost everyone over the age of 50 and, clinically in about 10-15% of the population. It is now clear that osteoarthritis is a group of joint disorders, in which the

normal balance between the synthesis and the repair of joint cartilage is disturbed. This eventually leads to destruction of the joint cartilage, often in a focal way, marked by typical changes that develop in the bone and around the joints. On x-rays, one sees joint space narrowing, and the formation of bony spurs (osteophytes), as well as thickening of the bone adjacent to the joint cartilage (sclerosis). Clinically, the result is pain, stiffness, loss of range of motion, and deformity.

Osteoarthritis can be asymmetric. It sometimes involves only one compartment of a joint, such as the medial compartment of the knee leading to a bow-legged (varus) appearance, or the lateral compartment of the knee leading to a knock-kneed (valgus) appearance. Typical joint distribution includes the DIP and PIP joints of the hands, the first CMC joints of the thumbs, as well as the hips, knees, and MTP joints of the feet.

The prevalence of osteoarthritis increases steadily with age, with females affected more often than males. There can be discordance between the degree of radiologic change and the severity of symptoms. Osteoarthritis can have a genetic component. The typical polyarticular (multiple joints), nodal osteoarthritis of the hands, with significant bony enlargement in the small finger joints, is rare in Afro-Americans, while osteoarthritis of the hip is more common in Caucasians than in the Afro-American or Asian populations.

Risk factors for OA include previous damage to a joint (such as a ligament or meniscus injury in the knee), developmental abnormalities of the joint, and obesity (particularly for OA of the hips and knees). Various rarer metabolic disorders, such as acromegaly and hemochromatosis, are associated with accelerated osteoarthritis as well.

Individuals with osteoarthritis tend to have pain after use of the involved joints. There is often short-lived morning stiffness. There can also be inactivity gelling—the joints will be stiff after immobility, such as after a long automobile trip. Inflammation in the joints tends to be low-grade and intermittent, rather than continuous and severe, as it is with rheumatoid arthritis.

Treatment includes simple measures such as weight loss and exercise, which can be extremely helpful and can reduce progression of OA. For weight bearing joints, the use of a cane on the opposite side can also be useful. Physiotherapy to strengthen muscles around damaged joints and occupational therapy to help in coping with activities of daily life are also useful. Emotional support can reduce pain. Regarding medications, simple analgesics such as acetaminophen (Tylenol®) are baseline therapy. Anti-inflammatory drugs can be useful as well, but there are concerns about their toxicity to various organ systems, which can result in GI ulceration and bleeding, renal dysfunction, hypertension, and increased risk of cardiovascular (CV) events. Gastroprotective drugs, such as proton-pump inhibitors (PPIs) are often required with NSAIDs. Opioids should be avoided if possible. An SNRI-type antidepressant, duloxetine (Cymbalta®), is approved for low back pain and chronic musculoskeletal pain, including OA. Local steroid injections are sometimes given; oral steroids are not used. Viscosupplementation injections with hyaluronic acid or similar agents can provide temporary relief of OA knee pain. Surgery has a major role in the treatment of end-stage osteoarthritic joints, with total hip and knee replacements having revolutionized the management of osteoarthritis. More conservative therapies such as osteotomy or hemiarthroplasty (i.e., Oxford knee) are sometimes used in younger individuals to delay the need for total joint replacement. Arthroscopic lavage and debridement have been shown to be no better than physiotherapy for knee OA in

randomized controlled trials. Multiple supplements and disease-modifying drugs have been proposed as OA therapies, generally with disappointing results.

### **Spinal Osteoarthritis**

The above discussion concerns osteoarthritis in the peripheral skeleton. The cervical, thoracic, and lumbar spine are frequently involved by osteoarthritis as well. The lower cervical and lower lumbar spine areas are under the greatest physiologic stresses and are the most common sites of spinal osteoarthritis. This is referred to as spondylosis or degenerative disc disease (DDD). The discs between the vertebrae change with aging, gradually lose their elasticity, and become compressed. The small facet joints, which link adjacent vertebrae, also develop the same osteoarthritic changes as do the joints in the extremities. Significant pain can arise from these sites. Often, there is a marked discrepancy between x-ray severity and clinical symptoms. Surgery is rarely required unless there is nerve root or spinal cord compression. Most individuals are treated with conservative measures including analgesics, anti-inflammatory drugs, physiotherapy, and attempts at weight loss and posture modification. Spinal exercises can be helpful. Osteoarthritis, whether of the peripheral or spinal variety, can have a small negative impact on life expectancy, mediated through reduction in activity level and an increase in cardiovascular disease risk. OA can increase the risk of falls, particularly at older ages.

### **Diffuse Idiopathic Skeletal Hyperostosis (DISH)**

DISH is a variant of osteoarthritis, characterized by the formation of large flowing osteophytes connecting vertebral bodies, usually anterolaterally. The ossification is seen radiologically. It typically involves the thoracic spine. In the peripheral skeleton, DISH is characterized by large, bony spurs at tendon or ligament insertions such as at the elbows, heels or around the pelvis.

DISH is most common in older individuals. It is associated with spinal stiffness and reduction in spinal range of motion, but little pain. Rarely, there can be difficulty swallowing due to involvement of the cervical spine with large anterior bony spurs.

The etiology of DISH is unknown. It is associated with diabetes. Some studies have shown a prevalence of diabetes of up to 40% in those with DISH. It is thought that insulin acts as a growth factor for bone, resulting in the exuberant osteophyte formation. Aside from the association with diabetes, DISH does not have any mortality implications.

### **Rheumatoid Arthritis**

Rheumatoid arthritis is the most common inflammatory polyarthritis. Its prevalence is about 1% of the general population. Two-thirds of affected individuals are females. The most common age of onset is in the middle decades, though it can occur in children and in the elderly as well. There is no single test for rheumatoid arthritis. Any individual who has at least one joint with definite clinical synovitis (swelling) not better explained by another disease should be assessed for rheumatoid arthritis. New criteria for the diagnosis of rheumatoid arthritis were established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010.

They are based on the pattern of joint involvement, serologic tests for RF and anti-CCP antibodies, tests for markers of inflammation such as ESR and CRP, and duration of symptoms.

RA is a heterogeneous illness. It encompasses some individuals with mild seronegative (RF-) arthritis and others with very severe, progressive, destructive, erosive seropositive (RF+) arthritis.

The disease frequently begins insidiously with fatigue, morning stiffness, swelling and pain in several joints, and disturbance of normal joint function. Over time, without effective treatment, irreversible joint damage develops. Factors associated with poor prognosis include:

1. male gender
2. early functional disability
3. high titer of rheumatoid factor or antibodies to CCP
4. early development of radiologic erosions
5. extra-articular manifestations
6. smoking (which is also a risk factor for the development of RA).

Extra-articular manifestations are much less common than in the past due to earlier and more effective RA treatments. These include the development of rheumatoid nodule, vasculitis (inflammation of blood vessels), and cardiac disease which can include pericarditis. Serious eye inflammation (scleritis), causing vision impairment, is rare. Another unusual manifestation is Felty's syndrome, which is a combination of splenomegaly, low white blood cell counts associated with serious infections, and arthritis. Other common extra-articular manifestations of RA are pulmonary disease including pleural effusions and fibrosis, and dry eyes and dry mouth, a combination known as sicca syndrome.

In addition to a positive rheumatoid factor, laboratory tests frequently show other features of inflammation, such as anemia, elevated platelet counts, and elevated ferritin. Lipid levels are suppressed with active inflammation and rise with therapy. X-rays are normal initially or show only soft tissue swelling, but with progressive disease, there will be development of osteoporosis, erosions, and joint deformities.

The goals of treatment in RA are to relieve symptoms, preserve function, and prevent structural damage. The treatment target is remission or low disease activity. Various indices of disease activity are used, including the disease activity score (DAS) and clinical disease activity index (CDAI). Early aggressive treatment of rheumatoid arthritis is important in preventing long-term damage and disability. Simple measures such as disease education as well as physiotherapy and occupational therapy are used. Drug treatments, however, are the mainstay of therapy. Baseline drugs include simple analgesics and non-steroidal anti-inflammatory drugs. These are useful only for symptomatic relief, and have no role in preventing disease progression.

The most important conventional disease-modifying anti-rheumatic drugs (DMARDs) include methotrexate (Rheumatrex®); hydroxychloroquine (Plaquenil®), sulfasalazine (Azulfidine®), and leflunomide (Arava®). Patients not controlled on these drugs progress to "biologic" therapies targeted at TNF- $\alpha$  (tumor necrosis factor alpha), IL(interleukin)-6 and other interleukins, or at affecting the function of T and B lymphocytes. Results from biologic therapies used for as long as 20 years are

very promising, including remission in many patients and arrest of radiological progression. Side effects of TNF antagonists include increased risk of infections, such as tuberculosis and other opportunistic infections, development of multiple sclerosis, exacerbation of congestive heart failure, and an increased risk of non-melanoma skin cancers. Biologic agents are generally combined with methotrexate or other DMARDs. These combinations provide better control of the disease. Biologic therapies are given by the subcutaneous or intravenous routes only. The frequency of administration ranges between once a week and once every 6-9 months. JAK inhibitors are newer oral drugs with similar efficacy to biologics. Therapies under development include many more JAK inhibitors and biosimilars of existing biologic therapies. Recent safety concerns have been raised about JAK inhibitors, including risks of venous thromboembolism, cardiovascular events, and malignancies.

Local steroid injections into inflamed joints are used adjunctively. Oral steroid therapy is controversial, as it is associated with an increased risk of long-term side effects. If used, oral steroids should be kept to the lowest dose possible, often as an initial bridging therapy in early active disease. Joint replacement surgery is becoming rare in RA due to more effective medical therapy.

Mortality studies indicate that rheumatoid arthritis, particularly when severe, is associated with increased mortality. Markers of reduced survival include:

1. poor functional capacity
2. multiple joint involvement
3. need for hospitalization.

In prospective studies, the standardized mortality ratio for rheumatoid arthritis is in the range of 150% and is higher in more severe disease. Median age at death in male RA patients can be up to four years younger than in the general male population. In females, the median age at death in RA can be up to 10 years younger than in the general female population. The most common cause of death in RA patients is cardiovascular disease. Inflammation in RA is an independent risk factor for cardiovascular disease. Aggressive treatment of cardiovascular risk factors is required in RA patients, as well as control of inflammation. The latter is associated with reduced morbidity and mortality (closer to that of the general population), although a mortality gap still persists.

### **Spondyloarthropathies (SpA)**

The spondyloarthropathy group of arthritic disorders is comprised of four related disorders that share some common features, including a negative rheumatoid factor test (RF), an increased frequency of the genetic marker HLA-B27, and a predilection for involvement of the spine as well as the peripheral joints. The spondyloarthropathies include:

1. ankylosing spondylitis (AS)
2. psoriatic arthritis (PsA)
3. arthritis of inflammatory bowel disease (enteropathic arthritis)
4. reactive arthritis.

## Ankylosing Spondylitis

Ankylosing spondylitis is an inflammatory disorder of the spine that can also involve peripheral joints. It is more common in males than in females, usually beginning in the twenties. Symptoms in females are often under-recognized, as the features are often atypical, with earlier involvement of the neck and thoracic areas and more limited involvement in the lumbar spine. The classic case begins with inflammatory-type back pain. There is morning stiffness and pain that improves with activity. The pain tends to be in the lumbar spine and sacroiliac joint regions and then works its way up the back, towards the neck. Over time, the spinal joints may actually fuse, and limitation of motion becomes permanent. Peripheral joints can be involved, particularly the shoulders and hips (i.e., root joints). Insertions of ligaments and tendons into bone (entheses) are also commonly involved.

The cause of ankylosing spondylitis is not known, but it is associated with a genetic marker, HLA-B27. Though it is not necessary for diagnosis, it is found to be positive in 90% of affected individuals. In the U.S., the prevalence is approximately 130 cases per 100,000 of the general population. Ankylosing spondylitis is frequently associated with extra-articular manifestations such as acute eye inflammation (iritis) and rarely with cardiac disorders such as heart block or aortic regurgitation. Pulmonary fibrosis can also occur, though it is quite rare.

Diagnosis is usually based on clinical features, including loss of spinal motion and decreased chest expansion, as well as inflammatory type back pain. Laboratory studies can show mild normocytic, normochromic anemia, the “anemia of chronic inflammation.” X-rays can be normal early on, but characteristic changes eventually develop symmetrically in the sacroiliac joints and then proceed up the spine with fusion of the vertebrae and ossification of the spinal ligaments. Diagnosis is now frequently made before typical x-ray changes develop (i.e., “non-radiographic axial SpA”), by using MRI scans of the sacroiliac (SI) joints and the spine. Even when spinal fusion is complete, pain can still persist. A rare late complication is fracture through the brittle, osteoporotic spine, which can occur with minor trauma. This can be devastating in the neck area, resulting in spinal cord compression.

Treatment consists of education, as well as exercise and physiotherapy to maintain proper spinal posture and range of motion. Anti-inflammatory drugs are used for symptomatic. The remittive drugs used for RA are occasionally used, such as sulfasalazine. Their efficacy is extremely limited for axial disease, but they can be helpful if associated peripheral arthritis is present. Multiple TNF- $\alpha$  inhibitors have been approved for use in the treatment of ankylosing spondylitis. Other effective agents are IL-17 inhibitors and JAK inhibitors. Biologics are helpful in reducing pain and stiffness, improving function, preventing radiographic progression, and treating extra-articular manifestations such as iritis. With current therapeutic modalities, there is generally no increased mortality associated with ankylosing spondylitis.

## Psoriatic Arthritis

Psoriasis is a very common skin condition characterized by scaly plaques developing on the skin at various sites. The nails can also be involved. The frequency of arthritis is increased in those with psoriasis. Various types of arthritis can occur. One of the more common is involvement of the DIP joints in the fingers and toes immediately adjacent to nails that are involved by psoriasis. Other

individuals have an asymmetric, oligoarthritis involving only a few joints scattered throughout the body. A symmetrical polyarthritis like rheumatoid arthritis can develop. Involvement of the spine and sacroiliac joints can mimic ankylosing spondylitis, though psoriatic spondylitis tends to be more asymmetric. Rarely, a destructive, mutilating arthritis known as arthritis mutilans can develop with severe erosion of bone and destruction of joints.

Forty percent of individuals with psoriatic arthritis have a history of psoriasis or arthritis in their family. About 10% of individuals with psoriasis suffer from psoriatic arthritis. In the U. S., this amounts to about 300,000 people. The ratio of males to females is one to one. The age of onset can be at any time, although it is usually between the ages of 30 and 50. Psoriatic-type arthritis develops before the onset of psoriatic skin lesions in about 15% of individuals.

Blood tests are often normal in limited disease. Rheumatoid factor is negative in 95% of patients. An elevated serum uric acid can be seen and reflects the increased cell turnover in the psoriatic skin plaques. With greater inflammation, anemia and high ESR and CRP will be noted.

The treatment of psoriatic arthritis can include non-steroidal anti-inflammatory drugs (NSAIDs), as well as the typical remittive drugs used for rheumatoid arthritis, including anti-TNF- $\alpha$  biologic therapies. Methotrexate can be particularly useful for treatment, as it has an impact on both the skin and joint lesions. Sulfasalazine and leflunomide are also used. Newer biologic agents used in psoriatic arthritis include IL-12/IL-23 inhibitors (ustekinumab, Stelara®), IL-17 inhibitors (secukinumab, Cosentyx® and ixekizumab, Taltz®), as well as an oral targeted PDE4 inhibitor (apremilast, Otezla®). IL-23 inhibitors are now approved as well, with the first agent in this class being guselkumab (Tremfya®). The mortality impact of psoriatic arthritis is due to an increased risk of cardiovascular disease, which can be like that seen in RA if the psoriatic arthritis is moderate to severe.

### Reactive Arthritis

This form of seronegative arthritis is more common in males. It typically begins after an acute diarrheal illness caused by various bacteria (e.g., salmonella, shigella, yersinia, or campylobacter). Alternatively, it can begin after a venereal infection, such as chlamydia. The classic triad of reactive arthritis is:

1. arthritis - tends to be an asymmetric oligoarthritis of lower extremity joints and can also involve the spine, like ankylosing spondylitis
2. urethritis
3. conjunctivitis.

Scaly skin lesions that resemble psoriasis can be seen over the penis or soles of the feet. Pain at tendon and ligament insertions into bones (i.e., enthesitis), such as at the Achilles tendon insertion into the heel is also common.

Reactive arthritis is associated with the presence of the HLA-B27 antigen. It was formerly felt to be a self-limiting disorder. However, more recent studies show that up to one-third of patients develop a chronic arthritis that can be disabling. Treatment of acute episodes is with anti-inflammatory drugs.

Chronic forms can benefit from antibiotic therapy, as well as DMARDs. There is usually no impact on mortality.

### Arthritis and Inflammatory Bowel Disease (IBD)

Both ulcerative colitis and Crohn's disease can be associated with arthritis. The peripheral arthritis tends to be a mild, non-destructive arthritis involving large joints, such as the knees. Generally, it can be treated with anti-inflammatory drugs, although these can exacerbate the underlying inflammatory bowel disease. In addition, those with inflammatory bowel disease can develop spondylitis identical to that seen with idiopathic ankylosing spondylitis. Anti-TNF agents are used in IBD and effectively treat the musculoskeletal features, if present.

The mortality impact of this combination is dependent entirely to the underlying inflammatory bowel disease, rather than to the associated arthritis or spondylitis.

### **Gout and Crystal-Induced Arthritis**

Gout was formerly called "the disease of kings," thought to be associated with a high standard of living and the over-consumption of rich foods and alcohol. Gout can occur in almost anyone. It is the most common inflammatory arthritis in males, and usually starts in the middle decades of life. Gout beginning before the age of 30 suggests an inherited metabolic abnormality of uric acid metabolism. Gout in premenopausal females is extremely rare.

Gout is characterized by recurrent attacks of acute joint inflammation. Typically, lower extremity joints are involved, such as the MTP joint of the big toe, the instep, ankle, or knee. Diagnosis is confirmed by detection of crystals of monosodium urate in joint fluid. The serum uric acid is elevated. Between attacks, individuals can be completely asymptomatic. Some individuals have only one attack of gout in their lifetime, whereas others will have recurrent attacks. Deposits of uric acid (tophi) can develop in the joints and over pressure points, such as the external ears or the elbows. Individuals with an elevated uric acid are also prone to the development of uric acid kidney stones. A new online gout calculator covering gout classification criteria is available at: [www.goutclassificationcalculator.auckland.ac.nz/](http://www.goutclassificationcalculator.auckland.ac.nz/).

Most individuals with gout have an idiopathic form. About 10% of gout is secondary to other problems, such as renal disease, acute leukemia, or similar myeloproliferative disorders. Alcohol and low doses of aspirin contribute to the retention of uric acid and can predispose to gout. Dietary factors contributing to gout include high-purine foods (e.g., red meat, shellfish, organ meats) and high-fructose corn syrup (e.g., in soda pop).

Individuals with gout frequently have other metabolic abnormalities, including diabetes and hyperlipidemia. These comorbid conditions are more important than gout in terms of risk assessment for insurance purposes.

Treatment of acute gout can utilize NSAIDs, colchicine, IL-1 antagonists (anakinra) and oral or intra-articular steroids. In those with recurring attacks, long-term control of gout is possible with the

use of urate-lowering therapies, such as allopurinol (Zyloprim®) or febuxostat (Uloric®). For the most severely affected gout patients, an intravenous drug, pegloticase (Krystexxa®), is approved in the U.S.

In addition to the monosodium urate crystals associated with gout, other crystals can cause arthritis. The most common of these is calcium pyrophosphate dihydrate deposition disease (CPPD). This causes a condition formerly known as pseudogout. It is most common in elderly females. It is often associated with calcification of joint cartilage, known as chondrocalcinosis. CPPD disease presents as an acute arthritis that can resemble infection or gout, or as a chronic arthritis, which can mimic OA or RA. Treatment includes anti-inflammatory drugs or local steroid injection. There is no proven preventive therapy and no associated increase in mortality.

### **Systemic Lupus Erythematosus (SLE)**

SLE is a chronic autoimmune disease in which the immune system is overactive. Abnormal antibodies are produced that react with the individual's own tissues. The cause of lupus is unknown. Genetics plays a role, as do environmental and hormonal factors. The prevalence of SLE varies but is estimated to be approximately 50 per 100,000 females and three per 100,000 males. Over 90% of affected patients are females. People of Afro-Caribbean and Asian background are affected more commonly and often have more severe disease.

As with rheumatoid arthritis, there is no one diagnostic test for SLE. Diagnosis is frequently based on American College of Rheumatology classification criteria. The latest 2017 version includes seven clinical and three immunologic domains:

Entry Criterion: History of a positive ANA BY Hep-2 immunofluorescence >1:80.

1. Constitutional Domain: Unexplained fever >38.3° C
2. Muco-Cutaneous Domain: any of non-scarring alopecia, Oral ulcers, Sub-acute cutaneous or discoid lupus or Acute cutaneous lupus
3. Arthritis Domain: Synovitis in two or more joints or tenderness in two or more joints or ≥30 minutes of morning stiffness
4. Neurologic Domain: Any of Delirium, Psychosis, Seizure
5. Serositis Domain: Pleural or pericardial effusion or Acute pericarditis
6. Hematological Domain: Any of Leukopenia, Thrombocytopenia, Autoimmune hemolysis
7. Renal Domain: Any of Proteinuria >0.5g 24 hours, Renal biopsy with Class II, III, IV or V lupus nephritis
8. Antiphospholipid Domain: Present (anti-cardiolipin antibody positive with medium or high units, or anti-β2-GP1 positive or lupus anticoagulant positive)
9. Complement Proteins Domain: Low C3 and/or Low C4
10. Highly Specific Antibodies Domain: Anti-dsDNA antibody and/or Anti-Smith antibody

Each domain contains a subgroup of weighted signs and symptoms. Only the highest scoring criterion in each domain is counted toward the total score. At least one clinical criterion must be present to be classified as SLE-positive. Anyone with an ANA titer of at least 1:80 and 10 points accumulated from the domains can be classified as having SLE.

The clinical course and prognosis are quite variable. Some individuals have a mild illness characterized by fever, fatigue, rash, and arthritis. Others have a very serious disease characterized by life-threatening renal or neurologic disease. Involvement of the heart, lungs, and other internal organs can also occur.

Treatment depends on the severity of the condition. Baseline treatment includes patient education and close follow-up by a rheumatologist, and other specialists as required. Non-steroidal anti-inflammatory drugs are useful for relief of arthritic symptoms. Hydroxychloroquine (Plaquenil®) is frequently used for rashes, arthritis, and fatigue and for prevention of more serious manifestations. Oral corticosteroids are required for severe inflammation of internal organs. Immunosuppressive drugs, such as azathioprine (Imuran®) and methotrexate (Rheumatrex®), can be used for arthritis symptoms or for steroid-sparing effects. Cyclophosphamide (Cytoxin®) orally or intravenously is employed only for severe renal or neurologic manifestations. Mycophenolate mofetil (Cellcept®) is increasingly used in lupus nephritis. The first biologic drug approved for SLE was belimumab (Benlysta®). Rituximab (Rituxan®) has also been studied in SLE. Newer therapies recently approved are anifrolumab (an interferon blocker), and voclosporin for lupus nephritis. Important adjunctive therapy includes management of any associated hypertension, infection, or thrombotic tendency, as well as control of cardiovascular risk factors.

In the past, systemic lupus had a very poor prognosis. Most individuals diagnosed had relatively severe disease, and five-year survival was less than 50%. More recent studies have shown increased survival rates. This reflects better recognition of the disease, inclusion of milder cases, better supportive therapy, and improved therapy of lupus flares. Five-year survival rates are now in the range of 86-88% and 10-year survival rates are in the range of 75-85%. Results from a single Canadian center showed 5-, 10-, 15-, and 20-year survival rates of 93%, 85%, 79%, and 68% respectively. The risk of death in those with systemic lupus is increased 4.9-fold compared to the general population. Causes of death include:

1. active lupus with end-organ damage such as heart, lungs, kidneys, and CNS (particularly in the early years of illness)
2. infection
3. atherosclerotic complications—Atherosclerosis is often the result of hypertension and lipid disorders resulting from long-term steroid therapy.

### **Systemic Sclerosis (Scleroderma)**

This is a chronic autoimmune disease that typically affects the skin and various internal organs. Scleroderma means “hard skin.” Characteristically, the skin becomes thickened over the fingers, but the arms, legs, trunk, and face can become involved as well. There are various forms of localized scleroderma that are not as serious as the systemic form.

In many individuals, the first symptom is Raynaud’s phenomenon, marked by cold-induced color changes in the hands, feet, and other distal parts of the body. These changes are due to spasm of the small blood vessels, as a response to cold or stress. Much more serious is internal organ involvement. Scleroderma renal crisis can cause severe hypertension and acute renal failure. Formerly it was often fatal, but now can be prevented readily with antihypertensive drugs such as angiotensin-converting

enzyme (ACE) inhibitors. Systemic sclerosis also causes scarring and fibrosis in the lungs (interstitial lung disease), heart, and gastrointestinal tract in some individuals, as well as pulmonary hypertension. These manifestations are all quite serious.

Systemic sclerosis is more common in females than in males. It can occur at any age, but most commonly in adults. There are 10-20 new cases of systemic sclerosis for every million people each year. The current survival rate is about 60-70% at five years. In a Canadian cohort study, the risk of death was increased 4.7-fold in systemic sclerosis patients compared to the general population.

The cause of systemic sclerosis is unknown. The most frequent causes of disability and death are lung, heart, and kidney involvement.

Diagnosis is based on typical clinical manifestations as well as the presence of certain specific antinuclear antibodies. There is no known cure. Treatment is symptomatic. Treatment of hypertension is one of the most important methods to prevent renal damage. Calcium channel blockers can be used to treat hypertension and Raynaud's phenomena. Angiotensin-converting enzyme (ACE) inhibitors are also used for these purposes. Esophageal symptoms are treated with proton pump inhibitors. Bacterial overgrowth in the bowel is treated with rotating courses of antibiotics. Pulmonary hypertension can be treated with endothelin-receptor antagonists and/or phosphodiesterase inhibitors. Pulmonary fibrosis can be treated with antifibrotic agents, such as nintedanib (OFEV®). Tocilizumab is a biologic therapy with some demonstrated efficacy in scleroderma.

### **Polymyositis and Dermatomyositis**

Polymyositis and dermatomyositis are inflammatory diseases of muscle. These are rare conditions of unknown etiology. About 10 new cases occur per one million individuals per year. They are more common in females than in males, as are most autoimmune disorders. Dermatomyositis is associated with a characteristic skin rash, which can include violet discoloration of the eyelids, as well as skin lesions on sun-exposed areas and over the knuckles. Polymyositis lacks this rash. Typically, there is muscle weakness in the shoulder and pelvic girdles as well as in the neck muscles. With more severe involvement, there can be difficulties with breathing and swallowing. There can be mild arthritis as well.

The diagnosis is based on a compatible clinical picture as well as signs of muscle inflammation, including an elevated CK (total CK and MM fraction) and aldolase levels. Electro-diagnostic studies, such as electromyography (EMG) testing, and MRI of involved muscles are also valuable. The diagnosis is confirmed by muscle biopsy. Polymyositis and dermatomyositis can be associated with an underlying malignancy that may not be clinically evident when the myositis first occurs. Thus, middle-aged, and older individuals presenting with this diagnosis should undergo a thorough search for an occult malignancy. Treatment includes high-dose oral steroids and immunosuppressive drugs. Tocilizumab is a biologic therapy with some demonstrated efficacy in myositis. IV immunoglobulin (IVIG) infusions have recently been approved and may also be used. The prognosis is variable. Many individuals survive for long periods with some degree of muscle weakness; others have a rapid, downhill course.

## Sjögren's Syndrome

Sjögren's syndrome is an inflammatory disease that can affect many different parts of the body, but most often affects the lacrimal (tear) and salivary glands. Individuals with this condition may notice irritation, a gritty feeling, or painful burning of the eyes. Dry mouth (or difficulty eating dry foods) and swelling of the glands around the face and neck are also common. Some experience dryness in the nasal passages, throat, vagina, and skin.

Between 400,000 and 3.1 million adults in the U.S. have Sjögren's syndrome. Symptoms most often appear between the ages of 45 and 55. Female to male ratio is 10:1. Half of those with Sjögren's also have rheumatoid arthritis or other connective tissue diseases, such as lupus.

Most of the complications of Sjögren's syndrome occur because of decreased tears and saliva. Individuals with dry eyes are at increased risk for infections around the eye and corneal damage. Dry mouth can cause an increase in cavities, gingivitis (gum inflammation), and oral yeast infections (thrush) that can cause pain and burning. Some individuals have episodes of painful swelling in the salivary glands.

Other parts of the body can be impacted. Pain and stiffness in the joints with mild swelling can occur in some individuals, even in those without rheumatoid arthritis or lupus. Rashes on the arms and legs related to inflammation in small blood vessels (vasculitis) and inflammation in the lungs, liver, and kidney can occur rarely. Numbness, tingling, and weakness also have been described in some patients.

The cause of Sjögren's syndrome is not known, but it is an autoimmune disorder. The decrease in tears and saliva seen in Sjögren's syndrome occurs when the glands that produce these fluids are damaged by inflammation.

Diagnosis is based on history of typical symptoms, physical examination, and blood tests. Special tests can assess decreases in tear or saliva production. An eye examination is helpful. Blood tests can determine the presence of typical antibodies, which include anti-nuclear antibodies (ANA), anti-SSA and SSB antibodies, and rheumatoid factor. Biopsies of minor salivary glands are used to make a diagnosis.

Dry eyes usually respond to artificial tears applied regularly during the day or to gels applied at night. Eye drops that reduce inflammation in the glands around the eyes, such as cyclosporine (Restasis), can be used to increase tear production. Drinking water, chewing gum, or using saliva substitutes can relieve dry mouth. Some individuals benefit from using prescription medications that stimulate saliva flow, such as pilocarpine (Salagen®) or cevimeline (Evoxac®). If patients develop yeast infections, anti-fungal therapies can be used. Humidifiers and nasal saline irrigation can improve nasal dryness.

Hydroxychloroquine (Plaquenil®) can be helpful in some individuals with Sjögren's syndrome by reducing joint pain and rash. Those with rare but serious systemic symptoms can require treatment with prednisone and/or immunosuppressive agents such as methotrexate (Rheumatrex®), azathioprine (Imuran®), mycophenolate (Cellcept®) or cyclophosphamide

(Cytoxan®). In addition, researchers are evaluating rituximab (Rituxan®) and other biological therapies to treat cases of more severe Sjögren's.

The vast majority of those with Sjögren's syndrome do not experience any serious complications. In a small number of individuals, Sjögren's syndrome can be associated with lymphoma, a cancer of the lymph glands.

### **Polymyalgia Rheumatica and Giant Cell Arteritis**

Polymyalgia rheumatica (PMR) and giant cell arteritis are related conditions that occur almost exclusively in individuals over the age of 55. Polymyalgia rheumatica is characterized by pain and stiffness involving the neck, shoulder girdle, and pelvic girdle muscles. Often there are systemic features including weight loss, fatigue, and low-grade fever. A very elevated ESR and CRP are typical, as well as anemia and slight elevation of alkaline phosphatase. In contrast to polymyositis, there is no true muscle weakness, and the CK is normal. The disorder mimics rheumatoid arthritis in some ways, though the symptoms tend to be more proximal and involve the muscles more than the joints. The etiology of PMR is unknown. The pathogenesis is inflammation of the small blood vessels in the muscle and likely around the joints as well.

Giant cell arteritis (GCA), or temporal arteritis as it is sometimes called, is a form of vasculitis involving inflammation of the large arteries. The temporal arteries are frequently involved, and this can lead to the devastating complication of blindness, which can be irreversible. However, other large blood vessels can be involved, and the presenting features might include claudication or organ dysfunction. Biopsy appearance is typical and is the basis of diagnosis. Ultrasound can also be used as a diagnostic tool.

Ten to fifteen percent of those with PMR have giant cell arteritis, whereas 40% of those with giant cell arteritis have associated PMR. Common symptoms of giant cell arteritis include pain in the jaw muscles on eating or speaking, as well as severe temporal headaches and tenderness of the scalp and in the area of the temples. The peak incidence of giant cell arteritis is in the 60–75-year-old age group. Females are affected three times as often as males. The annual incidence (i.e., the number of new cases per 100,000 of general population each year) is in the range of 20 per 100,000 over age 50 with a prevalence of about 2,000 per 100,000 over age 50.

The diagnosis of PMR is one of exclusion. It is based on a compatible clinical history associated with an elevated erythrocyte sedimentation rate (ESR). Frequently, the ESR is markedly elevated, approaching 100 mm/hour. A dramatic response to low-dose corticosteroid administration is also a diagnostic criterion. Before a diagnosis of PMR is made, diseases such as multiple myeloma or other neoplasms should be eliminated, along with inflammatory muscle diseases such as polymyositis, and other rheumatic diseases such as rheumatoid arthritis or other connective tissue diseases. Temporal artery biopsy is the diagnostic method of choice in giant cell arteritis.

Treatment with corticosteroids prevents blindness in giant cell arteritis and rapidly relieves the symptoms of polymyalgia rheumatica. Low-dose steroids may need to be continued for one to two years in those with PMR, although some individuals require indefinite treatment. Once treatment is initiated in giant cell arteritis, the risk of blindness drops dramatically. Higher doses of prednisone

are needed for the treatment of giant cell arteritis than for PMR. Tocilizumab, an IL-6 inhibitor, is a biologic therapy with demonstrated efficacy in GCA.

The complications of long-term steroid therapy include osteoporosis, diabetes, and hypertension. Worsening of glaucoma or cataracts can also occur. Polymyalgia rheumatica generally does not result in a reduction in life span. Since it occurs in an older population, PMR diagnosis should lead to cardiovascular risk screening and consideration of preventive strategies, such as the use of low dose aspirin.

## Vasculitis

Vasculitis describes a group of distinct disorders that are characterized by inflammation in the walls of blood vessels of various sizes. Thus, depending on which blood vessels are involved, the manifestations can occur in any organ in the body. These disorders can be devastating. Most of them are of unknown etiology, though some are linked to hepatitis B or hepatitis C infection. Polyarteritis nodosa (PAN) is one example of a disorder linked to hepatitis B infection in many cases. All of these disorders are rare and frequently life-threatening. Aside from PAN, other recognized disorders include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Antibodies to neutrophil cytoplasmic antigens (ANCA) are now a very useful diagnostic test for GPA and MPA. Temporal arteritis, which is discussed above under polymyalgia rheumatica, is also a form of vasculitis. These disorders are difficult to diagnose and depend on biopsy proof of inflammation in blood vessels. They are treated with high doses of oral steroids and immunosuppressive drugs. Other therapies can include plasma exchange and IV immunoglobulin infusions (IVIG). Rituximab is now approved for ANCA-associated vasculitis. The morbidity and mortality are high.

## Osteoporosis

Osteoporosis is a disorder characterized by a reduction in bone mass. The bone is normally mineralized, but the amount of bone is reduced, leading to high risk of fracture with minimal trauma. Considerable spinal deformity can result. Osteoporosis is very common, affecting one in five females over the age of 45, and 40% of females over the age of 75. It is more common in males than was previously thought.

Osteoporosis can be divided into several types: the most common is post-menopausal osteoporosis in females; a second type is age-related osteoporosis, which affects both females and males in the older age groups. Osteoporosis can also be secondary to a variety of endocrine disorders such as hyperthyroidism, hyperparathyroidism, or Cushing's syndrome. Gastrointestinal disorders that lead to malabsorption and inflammatory rheumatologic disorders, such as rheumatoid arthritis, are also associated with an increased risk of osteoporosis. Certain malignancies, such as multiple myeloma, and prolonged use of drugs, such as corticosteroids, heparin, and anticonvulsants, can result in osteoporosis as well.

Risk factors for primary osteoporosis include:

1. increased age
2. female gender
3. early menopause (whether natural or because of surgery)
4. smoking
5. heavy alcohol use.

Physical inactivity and thin body type are also predictors, as is a family history of osteoporosis.

Osteoporosis is often asymptomatic until a fracture occurs. Fractures typically occur in the spine, resulting in deformities such as thoracic kyphosis. Other common sites of fracture are the wrist and the hip. Hip fractures are particularly devastating, with mortality of 20% in the first year. Many older females who were previously independent will require ongoing nursing care or institutional placement after a hip fracture.

Bone mass and the risk of osteoporotic fracture can be best assessed by bone densitometry. The current standard method of assessment is known as DXA, or dual energy x-ray absorptiometry. The report of a DXA study provides measures of bone mineral density of the lumbar spine and femur. DXA test results are scored compared with the BMD of young, healthy people. This results in a measure called a T-score; worsening T-scores correlate with increased fracture risk. The scoring is as follows:

<b>DXA T-score</b>	<b>Bone mineral density (BMD)</b>
Not lower than -1.0	Normal
Between -1.0 and -2.5	Osteopenia (mild BMD loss)
-2.5 or lower	Osteoporosis

An online calculator, FRAX, which integrates risk factors including age, gender, BMI, prior fracture history, steroid use, and other comorbidities can be used to predict 10-year major and hip fracture risk to guide decisions about therapy. Prevention of osteoporosis involves making sure that the maximum bone mass is attained in individuals during their younger years.

Hormone replacement therapy (HRT), while effective for osteoporosis, is no longer recommended due to increased cardiovascular risk. The mainstay of osteoporosis therapy is bisphosphonate treatment. There are controversies regarding how long bisphosphonate therapy should be given, related to rare side effects such as osteonecrosis of the jaw and atypical femoral shaft fractures. Denosumab (Prolia®) is a biologic agent for osteoporosis therapy, given every six months by subcutaneous injection. Another newer agent with dual anti-resorptive and anabolic efficacy is romosozumab (Evenity®), which is given by injection monthly for 12 months, followed by other therapies as maintenance. Other agents used include raloxifene (Evista®), synthetic parathyroid hormone (teriparatide-Forteo®), and the newer abaloparatide (Tymlos®). Calcium and vitamin D supplements have a limited adjunctive role. Prevention of falls is also an important measure in reducing the frequency of osteoporotic fractures.

## Osteomalacia

Osteomalacia is a metabolic bone disease in which mineralization of the skeletal matrix is defective. Rickets is a similar disorder that occurs in children. Osteomalacia often presents insidiously. The symptoms include diffuse skeletal pain, as well as bone tenderness and altered gait. Proximal muscle weakness is often seen. The features of the underlying disease associated with osteomalacia can dominate the clinical picture. Fractures can occur with minimal trauma. On x-ray, pseudo-fractures are often seen. Bone scans can show increased uptake at these sites.

There are many causes of osteomalacia. Vitamin D deficiency or disorders of vitamin D metabolism are among the most common causes. Some of these are genetic and others are related to gastrointestinal disease with malabsorption or renal disease. Renal tubular acidosis and renal failure can be associated with osteomalacia. Drugs such as anticonvulsants can lead to impaired vitamin D availability and osteomalacia. Other causes of osteomalacia include some drugs and toxins such as aluminum, fluoride, and etidronate, and certain tumors, including multiple myeloma. Laboratory findings and treatments vary depending on the underlying disease.

## Paget's Disease of Bone

Paget's disease of the bone is also known as osteitis deformans. It is a metabolic disorder in which there is accelerated bone turnover. The bone that is formed is abnormal and weaker than normal bone. On x-ray, the Pagetic bone appears coarsened and thickened. There can be palpable bone enlargement on examination. Any part of the skeleton can be involved with the skull, pelvis, and spine frequently affected, as well as the larger long bones. The prevalence may be as high as 1% in those over the age of 40. The vast majority of those with Paget's disease are asymptomatic and the disease is detected incidentally when x-rays show Pagetic changes in bone, or when a serum alkaline phosphatase is found to be elevated on routine blood screening. Some individuals do develop clinical symptoms, including bone pain, as well as fracture through the weakened bone. Hearing loss can develop with skull involvement. Other complications, such as congestive heart failure, are very rare. Sarcomatous degeneration of the Pagetic bone can occur but is also quite uncommon.

In asymptomatic individuals, no treatment is required. In individuals with symptoms and elevated alkaline phosphatase, a course of a bisphosphonate drug, such as zoledronic acid, is often helpful. Calcitonin by injection can be given before orthopedic surgery in those with Paget's disease. Bone scans and measurements of serum alkaline phosphatase and other metabolic markers of bone turnover can be helpful in following individuals with Paget's disease. Life expectancy is generally not shortened in this condition.

There are excellent online resources on rheumatology, including:

1. Glossary of rheumatology terms - [www.rheumatology.org/Learning-Center/Glossary](http://www.rheumatology.org/Learning-Center/Glossary)
2. Rheumatology diseases and drugs - [www.rheuminfo.com](http://www.rheuminfo.com)
3. Other resources - [www.arthritis.ca](http://www.arthritis.ca) & [www.rheumatology.org](http://www.rheumatology.org).

## **Review Questions – ALU 201, Chapter 10**

1. An inflammatory disorder of the spine that can also involve the peripheral joints is:
  1. ankylosing spondylitis
  2. reactive arthritis
  3. polyarteritis nodosa
  4. Raynaud's phenomenon
2. All the following are types of vasculitis EXCEPT:
  1. polyarteritis nodosa
  2. granulomatosis with polyangiitis
  3. temporal arteritis
  4. granulomatous enteritis
3. Which of the following statements regarding systemic sclerosis is/are correct?
  - A. It is an autoimmune disease characterized by skin hardening.
  - B. It is effectively treated with penicillamine.
  - C. It can cause scarring and fibrosis in the lungs.

Answer Options:

1. A only is correct.
2. B only is correct.
3. A and C only are correct.
4. A, B, and C are correct.

4. Describe rheumatoid arthritis factors associated with a poor prognosis and the types of treatment used for this disease.
5. List the risk factors for primary osteoporosis and the preventative measures that can be taken throughout one's life.

6. A risk factor for the development of osteoporosis is:
1. older age
  2. late menopause
  3. vigorous physical activity
  4. overweight
7. A 69-year-old male smoker was diagnosed with rheumatoid arthritis 17 years ago. He has metatarsal-phalangeal joint involvement with minimal functional disability. His serology testing has a high rheumatoid factor (RF) titer. Recent laboratory testing indicated an abnormal C-reactive protein (CRP), low hemoglobin and hematocrit, and a normal erythrocyte sedimentation rate (ESR).
- The factor associated with the poorest prognosis for his rheumatoid arthritis is the:
1. abnormal CRP
  2. high RF titer
  3. diagnosis 17 years ago
  4. low hemoglobin and hematocrit
8. What clinical features, genetic marker, and extra-articular manifestations are commonly associated with ankylosing spondylitis?
9. Name the common domains used to diagnose systemic lupus erythematosus (SLE).
10. What are typical types of rheumatic disease and spondyloarthropathies? What criteria are used to diagnose and differentiate between these diseases? What lab tests are used, and why are lab tests not always valuable in evaluating musculoskeletal disorders?

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 1: ankylosing spondylitis – page 8.

### *Review Question 2*

Answer 4: granulomatous enteritis – page 16.

### *Review Question 3*

Answer 3: A and C are correct – pages 12-13.

### *Review Question 4*

Refer to pages 6-7.

### *Review Question 5*

Refer to pages 15-17.

### *Review Question 6*

Answer 1: older age – pages 16-17.

### *Review Question 7*

Answer 2: high RF titer– page 6.

### *Review Question 8*

Refer to page 8.

### *Review Question 9*

Refer to page 11.

### *Review Question 10*

Refer to page 2 and pages 7-9.



## **CHAPTER 11**

### **ADULT VALVULAR HEART DISEASE**

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Dedicated to the original author: Gordon R. Cumming, MD, FRCPC, FACC, FAHA, DBIM, former Vice President, Medical Director, The Great-West Life Assurance Company, adult and pediatric cardiologist, Professor, University of Manitoba, Winnipeg, Canada.

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## **ADULT VALVULAR HEART DISEASE**

### **Introduction – Heart Murmurs**

Auscultation of the heart, using a stethoscope, is the listening for sounds produced within the heart during the cardiac cycle. In addition to standard heart sounds, which reflect heart valve closures, murmurs, and other sounds can be heard. A heart murmur is a swishy noise produced by blood flow when turbulence is present.

Heart murmurs are common. As many as 80% of children develop a murmur between one and four years of age and 99% of these are functional, which means they are benign, innocent or normal murmurs. By age 20, up to 10% of individuals have a persistent, but normal, childhood murmur. However, a murmur can also suggest the possibility of valvular heart disease.

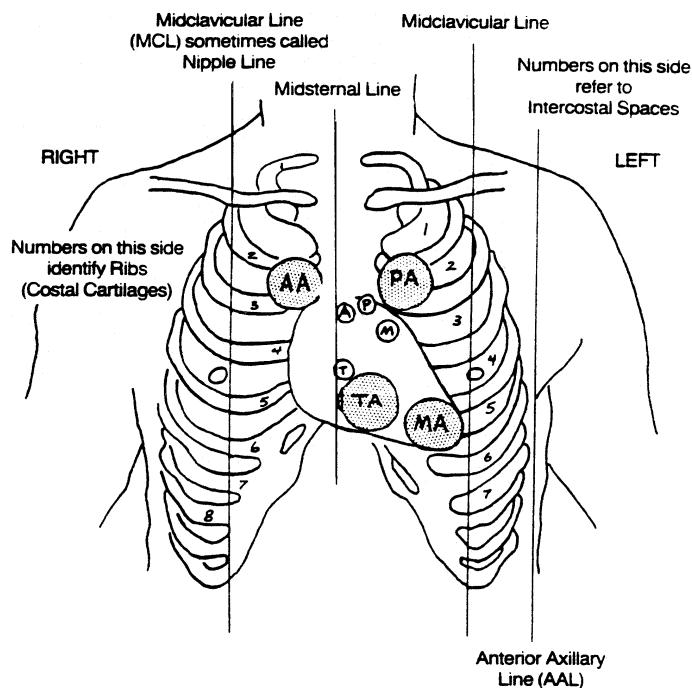
An experienced cardiologist can usually distinguish between a benign and a pathological murmur. The task has been simplified considerably since 1975 with the availability of the echocardiogram. An echocardiogram uses sound waves to create a moving picture of the heart. It can also be referred to by the abbreviation “echo,” or as a transthoracic echocardiogram (TTE), transesophageal echocardiogram (TEE), or Doppler ultrasound of the heart. (It is discussed later in this chapter.)

Before echocardiography became available, diagnosis for individuals with suspected or mild heart lesions was dependent on clinical skills without laboratory confirmation. Heart catheterization and angiography are invasive studies and were usually reserved for situations where lesions were thought to require surgical intervention.

It is no longer necessary for physicians practicing in modern facilities to have great auscultatory skills. If a doubtful murmur is heard, they simply arrange an echocardiogram. Minimal findings on the echocardiogram do not necessarily explain a murmur heard on auscultation. For example, mild mitral valve prolapse (MVP) with very mild mitral regurgitation is commonly reported but can be over-diagnosed in an essentially normal echocardiogram. The ordering physician can attribute the murmur to mitral regurgitation, while the murmur is a short innocent murmur along the left sternal edge, unrelated to the findings of MVP.

Underwriters cannot be expected to make a diagnosis from a physician’s mention of a murmur or a proposed insured’s mention of a murmur when the physician has not ventured a diagnosis nor has the individual been given a diagnosis. Proposed insureds still answer “yes” to the murmur question when their murmur has been gone for 20 years. Current physicians may have no knowledge of past murmurs. The recommendation of antibiotic coverage for dental procedures can suggest that the proposed insured’s murmur is organic. However, not infrequently, this coverage is recommended to be on the safe side when the heart is normal. The underwriter may only receive information that a murmur might be present; yet it would be economically unsound to require a detailed echocardiogram on all these cases. When available, the grade of the murmur and its timing in the cardiac cycle can provide additional helpful information.

**Figure 1. Where murmurs are heard.**



A, P, T, M show approximate locations of aortic valve, pulmonary valve, tricuspid valve, and mitral valve respectively. However, sounds originating at a valve are usually best heard in an area elsewhere than over the valve.

Sounds originating:

- 1) at the aortic valve seem to be carried up the aorta and are best heard at the aortic area, AA;
- 2) at the pulmonary valve seem to be carried up the pulmonary artery to the pulmonary area, PA;
- 3) at the tricuspid valve seem to be carried down the right ventricle to the tricuspid area, TA;
- 4) at the mitral valve seem to be carried down the left ventricle toward the apex to the mitral area, MA.

#### Grades of Heart Murmurs

Murmurs are graded on a one (I) to six (VI) scale. The starting point is a grade II murmur, one just loud enough that it is heard when the stethoscope is first placed on the chest. A murmur softer than this is grade I; a murmur louder than this is grade III and a very loud murmur is grade IV. Murmurs that can be heard with the stethoscope a few millimeters off the chest wall are grade V, and murmurs heard with the naked ear are grade VI.

A systolic murmur can be organic, meaning it is indicative of disease, although it should be noted that serious structural heart disease can exist in the absence of any murmur. A grade II systolic murmur can be normal (i.e., innocent) or abnormal (i.e., organic). A grade III systolic murmur in adults is usually organic, but normal murmurs in childhood can be this loud. A grade IV systolic murmur is always organic and can be accompanied by a palpable vibration called a thrill. Grade V and VI murmurs are uncommon.

Generally, the underwriter can assume that a grade I or II systolic murmur, with an attending physician either unaware of the murmur or aware but not concerned, is a benign systolic murmur. Individuals with a small ventricular septal defect (VSD), minimal pulmonary stenosis, a small

atrial septal defect (ASD), or mild mitral regurgitation have normal to near-normal longevity and missing these diagnoses is not really all that important for the physician or the underwriter.

There are a few exceptions to the above. Hypertrophic cardiomyopathy (HCM) can have a short grade II systolic murmur that can be called normal. Typically, this murmur is louder when the individual stands. The underwriter should be concerned with grade II murmurs with a family history of HCM. Bicuspid aortic valve can produce a grade I to II murmur in childhood or no murmur, but the individual can need aortic valve replacement by age 50. A systolic ejection click is usually present with this disorder and is the clinical clue to the diagnosis.

Diastolic murmurs, even if only grade I or II, can indicate significant disease. Mild mitral stenosis may not produce an easily heard murmur. Aortic regurgitation cases can have no murmur, or only grade I or II murmurs, even though the valve leak is significant.

**Table 1. Organic murmur location and probable lesion.**

Lesion	Murmur – type, location
Aortic Stenosis	Systolic – upper sternum radiating to carotid
Aortic Regurgitation	Diastolic – left sternal edge, high pitch, decrescendo
Mitral Stenosis	Diastolic – rumbling, apex, with opening snap
Mitral Regurgitation	Systolic – blowing, apex, radiating to axilla
Ventricular Septal Defect	Systolic – 3 <sup>rd</sup> and 4 <sup>th</sup> intercostal space next to sternum
Mitral Valve Prolapse	Late systolic – click, apex-not left sternal border

**Table 2. Characteristics of innocent or normal murmurs.**

<b>Location</b>	Left sternal edge
<b>Grade</b>	I or II, can be III in children but seldom in adults
<b>Change with posture</b>	Loudest supine, reduced or absent sitting
<b>Duration in heart cycle</b>	Systolic, short, mid-systolic
<b>Effect of exercise</b>	May increase the same as organic murmurs
<b>Association</b>	No abnormal heart sounds or clicks, normal TTE
<b>Normal EKG</b>	No help in deciding whether a murmur is normal or not

### Echocardiography in Valvular Heart Disease

Echocardiography is the most accurate test for assessing the severity of valvular disease as well as the need for surgery, the results, and follow up. An echocardiogram uses sound wave echoes recorded through a transducer to produce pictures of the heart. These pictures provide information on overall heart function, anatomy, size, and the presence of any cardiac masses, endocarditis, or any valvular, myocardial, pericardial, or congenital heart diseases.

Currently, echocardiographic evaluation includes M-mode examination to measure sizes of the atrial and ventricular chambers and of the aorta, wall thickness, ejection fraction (EF), and valve motion. In conjunction with M-mode, two-dimensional (2-D) imaging, presented in video format,

provides information on wall motion and anatomic details of valve leaflet structure and function. Additionally, Doppler echocardiography evaluates the speed and direction of blood flow through the heart valves as well as through any intracardiac shunts. Doppler quantification techniques for calculating velocity, pressure gradients, and valve areas are the basis for the key role of echocardiography in valvular heart disease assessment.

### Transthoracic Echocardiography (TTE)

TTE, or the standard echocardiogram, uses a transducer on the chest to direct ultrasound beams to the heart. These are obtained almost as a matter of routine for individuals with known or suspected heart disease. The original M-mode displays are complemented by two-dimensional (2-D) studies. Three-dimensional (3-D) studies are currently being developed, refined, and integrated. Doppler allows estimation of flow and pressure gradients. TTE after exercise is used to assess ventricular function. Contrast or bubble studies can be used to enhance ventricular borders and to assess atrial right to left shunts.

TTE with Doppler is the routine tool to assess valve stenosis, valve regurgitation, cardiac chamber enlargement and function, wall hypertrophy, and congenital heart anatomy. TTE diagnostic availability has eliminated most uncertainty regarding borderline murmurs.

Hypertrophy in hypertensive heart disease is best assessed by TTE. It is also used in familial screening for hypertrophic cardiomyopathy (HCM). TTE is also the starting point in investigating aortic root disease. For underwriting, aortic regurgitation requires TTE to assess aortic root anatomy and TTE should be considered for individuals with atrial fibrillation.

The focus of a stress echocardiogram is cardiac wall motion. Incidental findings such as valve abnormalities can be reported, but a detailed resting echocardiogram is needed for full assessment.

### Transesophageal Echocardiography (TEE)

TEE involves placement of the ultrasound transducer on an endoscope that is passed down the esophagus for a close look at the heart structures, without interference by lung tissue. It is useful in special situations, although swallowing the transducer is unpleasant for most individuals.

Transesophageal echocardiogram (TEE) can be used in place of a standard transthoracic echocardiogram (TTE) in the following cases:

1. when physical factors interfere with the test—individuals with barrel-shaped chests, those who are extremely obese, or individuals with emphysema, all of whom can have a poor transthoracic “window.”
2. when there are intra-cardiac factors – TEE is especially useful for visualization of vegetations of endocarditis, diagnosis of a small ASD or patent foramen ovale, and assessment of mitral valve prosthetic valve dysfunction.
3. when there is aortic root disease – better visualization to assess the aortic root and possible mild dissection.

## Echocardiographic Measurements

Echocardiographic measurements, usually obtained from 2-D guided M-mode dimensions, depend on body size. The usual reference point is body surface area although the correction for body size is often not done or provided on reports. For individuals with heights over six feet (183 cm) and under five feet and one inch (154 cm), dimensions are best related to body size.

**Table 3. Useful echocardiographic measurements in adults.<sup>1</sup>**

Measurement	Usual maximum
Left atrium (LA) anteroposterior diameter	40 millimeters (mm)
Left ventricular (LV) diastolic diameter	56 mm
LV systolic diameter	35 mm
Right ventricular (RV) mid diameter	33 mm
LV posterior wall thickness	10 mm
LV septal wall thickness	11 mm
RV wall thickness	3 mm
Aortic root	36 mm
LV mass, males	109 $\pm$ 20 grams/m <sup>2</sup>
LV mass, females	89 $\pm$ 15 g/m <sup>2</sup>

### *Left Ventricular Ejection Fraction*

Ejection fraction (EF) is a basic measurement of left ventricular function and is an important prognostic indicator in all types of heart disease, but it is important to realize its limitations. Mathematical models can be used to obtain systolic and diastolic volumes to calculate ejection fraction. However, in many echocardiography laboratories, EF is estimated and not measured directly. These estimates of EF are highly dependent on operator experience.

Normal LVEF is 55-65%. Normally, EF increases by 5% with exercise. Mild (EF 45-55%), moderate (EF 35-45%), or severe (EF < 35%) LV impairment can be reported. An EF of < 25% is generally considered within range for cardiac transplantation.

It is not uncommon to see ejection fractions on serial echocardiograms in the same individual ranging from 30% to 55% without clinical change. EF measures can vary between nuclear angiography, contrast angiography, and echocardiography by 20%. Thus, underwriting based on a single echocardiogram report of ejection fraction can lead to misclassification of the risk in either direction.

### *Valve Regurgitation on Echocardiogram*

Valves do not slam shut. Doppler is highly sensitive, and normal valves will show a trivial degree of regurgitation when viewed by Doppler. By convention, “trivial” indicates normal valve function and “mild” likely signifies an abnormal valve. However, if the echo report indicates “mild” regurgitation in all three of the mitral, tricuspid, and pulmonary valves, likely the valves are normal. A trivial degree of valve regurgitation occurs in the mitral valve in 75% of echocardiograms, at the tricuspid valve in 85%, and at the pulmonary valve in 70%. Trivial

regurgitation at the aortic valve increases from 5% at age 10 to 40% over age 50 in the normal population.<sup>2</sup>

### *Quality and Accuracy of Echocardiograms*

As with most tests, if the results of the echocardiogram report do not fit with the other information, it is reasonable to question the accuracy. Reports need to be compared to clinical history and other findings including physical examination, electrocardiogram (EKG), or x-ray reports. However, the echocardiogram is generally considered a far superior measure of severity than the clinical examination.

Quality of echocardiograms can vary, and many reports indicate the quality of the imaging. Some studies are technically difficult, and their results should be accepted with caution. Reports are likely to be more accurate when they are produced in a large volume medical facility with expert technologists and a cardiologist specializing in echocardiography. Ideally, specific measurements should be reported. Ejection fraction has a strong impact on prognosis, yet often it is roughly estimated and not measured.

### *Underwriting Assessment of Echocardiogram Reports*

Ideally, underwriting assessment should include a recent echocardiogram report. Serial echocardiograms, particularly in valvular heart disease, are helpful for comparison to determine disease progression.

In general, an echocardiogram report includes the reason for the test and a comment on the technical quality of the study. Quantitative measurements can be presented in table format with normal values also provided. The report also includes descriptive or qualitative findings related to chambers and their function, valves and their function, the aorta, vena cava, and pericardium. An interpretation summary or conclusion can also be included in the report.

The underwriting review should include assessment of whether the examination was technically complete, satisfactory, or whether there were some limitations and possible errors. The level of report detail should be noted, as well as comparison with any prior evaluations. Relevant information includes severity of the valve disorder and whether heart size and function are normal or abnormal. Complete review, rather than reliance on the summary, is encouraged for underwriting assessment to verify that subjective descriptions in the report correspond to risk classification in underwriting manuals. Common discrepancies include severity of valve lesions as measured by Doppler velocities and gradients, or severity of left ventricular hypertrophy as measured by wall thickness and size.

Determining the relevance of isolated or incidental echocardiographic findings can be challenging at time of underwriting. Findings need to be interpreted in conjunction with clinical evaluations including the indication for the test. Relevance will depend on body size, age, severity, associated conditions, and serial evaluations.

An echocardiogram, although reassuring, may not be essential for certain underwriting situations, such as:

1. diagnosis of a functional or innocent murmur
2. small VSD, which is a clinical diagnosis
3. possible mild mitral prolapse with systolic click only, female with soft murmur, no symptoms
4. mild mitral regurgitation with soft apical murmur, normal EKG, chest x-ray, no symptoms
5. possible mild aortic stenosis after the age of 60 with normal EKG and soft systolic murmur at base
6. most cases of angina pectoris and atypical chest pain
7. arrhythmias, such as symptomatic extrasystoles or paroxysmal supraventricular tachycardia with a clinically normal heart (while echocardiogram is helpful for assessment of atrial fibrillation).

Echocardiograms need not be repeated in individuals with mild structural disease unless clinical change is suspected.

### **Specific Valvular Heart Disease**

Heart valves are beautifully engineered structures that open to allow free flow of blood in the proper direction and close to prevent backflow of blood. Their purpose is to provide unidirectional flow. Valve disease is classified according to the functional change: stenosis for narrowing, insufficiency or regurgitation for leaking. Both functional alterations can occur together.

In the past, much of the valvular disease in adults was secondary to scarring from rheumatic fever (RF) in childhood, but RF declined markedly from 1950 to 1970 and is no longer the main cause of any of the valvular problems other than mitral stenosis.

Prevalence of valvular heart disease is estimated to be 2.5% in the United States.<sup>3</sup> Prevalence increases with age from 0.7% at ages 18 to 44 years to 13.3% in individuals aged 75 years and older. The number of cases of valve surgery has steadily increased. Several factors can explain the increase in reported heart murmurs and valvular heart disease despite the decrease in rheumatic fever:

1. More children have at least a few careful examinations, and minor murmurs will be mentioned to the parents; in the past, they likely were not.
2. The entire picture of valvular disease has changed with the introduction of echocardiography and the development of modern techniques that identify mild valvular thickening, mild stenosis, and mild regurgitation far better than clinical examination.
3. Because surgery is available past age 90, detailed diagnostic studies are carried out on more individuals with symptomatic disease and on most asymptomatic individuals if they see a doctor and are found to have a murmur.

4. Valvular disease increases with age and is part of the changes we see with increasing longevity.

### Aortic Sclerosis

Aortic sclerosis refers to a thickening of the aortic valve without significant stenosis or regurgitation. It is present in 25% of subjects by age 65, 30% by 80 and potentially 45% by age 90 years. Aortic sclerosis may lead to significant stenosis or regurgitation. In about half of aortic valve patients requiring surgery, sclerosis is the underlying cause. Aortic sclerosis is associated with an increased risk of coronary disease and stroke, and 50% of individuals with sclerosis have bicuspid aortic valve.<sup>4</sup>

### Aortic Stenosis

Aortic stenosis (AS) is defined as a narrowing of the aortic valve, which causes left ventricular outflow obstruction. A normal aortic valve has three leaflets or cusps. A stenotic valve can be thickened and deformed and can have one cusp (unicuspid) or two cusps (bicuspid). Obstruction caused by lesions below (subvalvular) or above (supravalvular) the aortic valve are less common and will not be discussed here.

#### *Causes*

The most common causes of valvular AS are:

1. congenital abnormal valve, either bicuspid or unicuspid, with calcification
2. normal tri-leaflet (tricuspid) valve with degenerative changes, eventual calcification, and fibrosis
3. rheumatic valve disease.

#### *Diagnosis of Aortic Stenosis*

Symptoms can include dyspnea, decreased exercise tolerance, syncope or dizziness, and angina. Symptoms usually do not develop until the AS is moderate or severe. On physical examination, there is an abnormal systolic murmur heard best in the aortic area (second intercostal space on the right). An EKG can show left ventricular hypertrophy by voltage with associated ST and T wave changes.

#### *Echocardiogram*

The following can be found on an echocardiogram with aortic stenosis:

1. aortic valve leaflets thickened and calcified with narrowing of the aortic opening during systole
2. abnormal valve, either bicuspid or unicuspid
3. left ventricular hypertrophy (posterior wall thickness in millimeters: normal 11; moderate hypertrophy 13; severe hypertrophy  $\geq 15$ )

4. aortic regurgitation and mitral regurgitation
5. with bicuspid aortic valve, dilatation of the aortic root can be present and detected on echocardiogram.

Doppler echocardiography provides excellent information on severity of aortic stenosis. The left ventricular-aortic gradient and valve area are the most important measures used to evaluate severity of AS. In the normal heart, left ventricular and aortic pressures are equal as the heart ejects blood out of the aorta. With a narrowing of the aortic valve, a pressure drop occurs across the valve, which is the pressure gradient. The gradient is dependent on the valve area and the velocity of systolic ejection. The Doppler gradient is a peak instantaneous gradient and is 10-20% higher than the peak-to-peak gradient measured by heart catheterization.

The table below lists the valve areas and gradients encountered in adults of average body size, according to severity.

**Table 4. Degree of aortic stenosis.**

State	Valve Area cm <sup>2</sup>	Peak Gradient Catheter mmHg	Mean Gradient mmHg	Doppler Velocity m/sec	Echo Gradient mmHg
Normal	> 3.0	0	< 0.5	< 1.0	0
Mild stenosis	2.0	<20	10	2.5	< 25
Moderate stenosis	1.5	40	10	3.5	< 50
Severe stenosis	< 1.0	50	30	> 4.0	> 50
Critical	< 0.8	> 50	> 35	> 4.5	> 70

When left ventricular function is normal, there is a direct correlation between valve area and gradient. However, with severely impaired left ventricular function, the ventricle is incapable of developing a high pressure, the gradient may be no more than 25 mmHg, and the severity of stenosis can be underestimated. There are pitfalls in assessing the aortic valve by echo and significant errors do occur in area calculations.

#### *Other Investigations*

Computed tomography (CT) can provide information on the degree of valve calcification, which correlates with the degree of stenosis on echocardiogram. Magnetic resonance imaging (MRI) can be used to measure valve area and blood velocity through the stenotic valve. Neither CT nor MRI replaces echocardiogram as the most valuable assessment for AS. Cardiac catheterization is less frequently performed with the availability of echocardiogram, although it can be seen, particularly with symptomatic individuals.

## *Course*

The degree of valve narrowing in AS develops slowly over several years. Mild AS gradually leads to progressive fibrosis and calcification. The natural history of mild and moderate aortic valve lesions is not well studied. The natural history, once symptoms have developed, is ominous, with either death or surgery in over 50% in five years.<sup>5</sup>

Progression depends on underlying etiology. Degenerative cases of AS take years to become severe and do not become significant until age 70 or even 80. Congenital bicuspid valves that gradually develop stenosis due to cusp thickening and calcification are generally asymptomatic until age 60. Congenital aortic stenosis, with or without prior surgical intervention, can cause significant problems between age 20 and 30 years.

Individuals seldom die before stenosis is severe, and even in severe cases, sudden death is uncommon. AS can be asymptomatic for years, even to age 75 or 80. The main indicator for surgical intervention is the history of symptoms, which is considered more reliable than accurate estimates of severity by echocardiogram. Once symptoms develop, surgical intervention is generally warranted. The average survival after the development of angina is three years and after the development of congestive heart failure 1.5 years. For asymptomatic individuals, the risk of sudden death is less than 1.0% per year.<sup>6</sup>

Serial echocardiograms at intervals of one to five years are used to follow the progressive narrowing that occurs in mild to moderate cases to assess candidates for surgical intervention. After the age of 40, the gradient can increase by 5-10 mmHg per year. Valve area is reduced in some individuals by over 0.3 cm<sup>2</sup> yearly and in others more slowly. Progression is more rapid after age 60, in the presence of hyperlipidemia, in smokers, and in those with associated coronary disease.<sup>7</sup>

Unfavorable features with AS include:

1. presence of any symptoms, such as angina or syncope
2. elevated blood pressure
3. abnormal heart rhythm, atrial fibrillation, frequent or complex ventricular ectopy, left bundle branch block (LBBB), or severe strain pattern on EKG
4. exercise EKG: very low fitness level and arrhythmias
5. current echocardiogram: LV wall over 16 mm, an ejection fraction <50%, or mitral disease.

## *Medical Treatment*

There is no satisfactory medical treatment. Any medical treatment is aimed at preventing bacterial endocarditis and rheumatic fever recurrence.

## *Surgical Treatment*

Indications for aortic valve replacement surgery for AS include:<sup>8</sup>

1. symptoms of severe AS; chest pain, dyspnea, heart failure, angina, syncope

2. severe AS in individuals having coronary artery bypass grafting
3. severe AS in individuals having surgery of the aorta or other heart valves
4. severe AS with a left ventricular ejection fraction less than 50%
5. aortic dilatation > 45 mm; surgical repair of both valve and aorta
6. heavily calcified aortic root; consider replacement of both valve and aortic root.

In recent years, over 50% of cases of aortic stenosis coming to surgery are due to degenerative disease: 35% are congenital, either bicuspid or unicuspids and less than 10% are rheumatic. Over 65% of cases are over age 65 years, and 85% of cases are male. The surgical risk of mortality in a good case is 2%.<sup>9</sup>

#### Ross Operation for Aortic Valve Disease (Pulmonary Autograft)

The Ross operation is an alternative to a mechanical or bioprosthetic valve. The aortic valve is replaced with the patient's own pulmonary valve (autograft), which is a three-cusp structure very similar to the normal aortic valve, and another tissue valve (homograft) is then used to replace the pulmonary valve.

This procedure was developed in 1967 by British surgeon Donald Ross. There was not a lot of enthusiasm for this procedure in the world-wide community of heart surgeons until the 25-year follow-up study of Ross cases published in 1992. This study demonstrated longevity and freedom of degeneration of the transplanted pulmonary valve in the aortic position as well as longevity of 15-25 years for the tissue valve replacing the pulmonary valve and low risk of replacement.<sup>10</sup>

The advantages of the procedure were:

1. anticoagulation required for mechanical valves was not needed
2. hemodynamics were better with very low gradients at rest or exercise
3. longevity of the transplanted new aortic valve
4. growth of the aortic autograft in children.

Surgical techniques gradually improved with significant improvement in mortality. The real impetus for this complicated procedure is the avoidance of embolization or bleeding related to anticoagulation. However, its technical complexity, complications with both the pulmonary autograft in the aortic position (dilation and failure with aortic regurgitation) and the homograft in the pulmonary position (stenosis), and simpler and effective alternatives (mechanical and bioprosthetic valves) have limited its use. Presently, its use is controversial and has been decreasing. Recent concerns of significant late autograft dilatation have limited its use even further. Cautious underwriting is recommended with full detailed echocardiogram and cardiac imaging reports with good visualization of the autograft in the aortic position, aortic annulus, ascending aorta, and the homograft in the pulmonary position.<sup>11</sup>

#### Transcatheter Aortic Valve Implantation (TAVI)

Transcatheter aortic valve implantation (TAVI; also known as transcatheter aortic valve replacement or TAVR) is an established alternative to surgical aortic valve replacement. Initially

reserved for individuals with severe symptomatic calcific aortic stenosis considered as unacceptably high surgical risk, it is now being considered for lower risk individuals. A recent registry-based study suggests TAVI as a reasonable option for select patients at low surgical risk who require valve replacement for bicuspid aortic stenosis. Any consideration of applicants following TAVI requires careful and thorough risk assessment, with refinement as more evidence becomes available.<sup>12</sup>

### *Course after Valve Replacement*

General post-surgical considerations after valve surgery are outlined in Table 7. Causes of death after surgery are outlined in Table 8.

### *Underwriting*

#### *Without Surgery*

Underwriting the asymptomatic case with mild or moderate AS requires a detailed echocardiogram report including valve area, peak and mean gradient, description of valve anatomy and calcium deposits, measurements of ascending aorta diameter and left ventricular function, and ideally serial echo studies five years apart. Echocardiogram and heart catheterization severity measures are listed in Table 5. Mild and moderate cases are associated with no symptoms, no decrease in exercise tolerance, no or mild left ventricular hypertrophy, and limited progression. As severe cases are usually treated surgically, underwriting is generally postponed until after intervention.

#### *With Surgery*

Underwriting valve surgery cases requires in-depth medical information, including preoperative, operative, and postoperative reports. A postoperative echocardiogram is essential. For accurate survival estimates after aortic valve replacement, ideally information on valve size needs to be obtained. One year after surgery there should be no paravalvular leak.

### Aortic Regurgitation

Aortic regurgitation (AR) is blood flow from the aorta to the left ventricle during diastole. This backward blood flow is due to incompetence and incomplete closure of the aortic valve. It is also called aortic insufficiency (AI).

### *Causes*

Aortic regurgitation has two main general causes: aortic valve leaflet (cusp) disease and deformity of the aortic root and aorta. The most common specific causes are a congenital bicuspid valve, bacterial endocarditis, and aortic root dilatation (e.g., age- and hypertension-related), Marfan syndrome, Ehlers-Danlos syndrome. Other causes of leaflet disease include other congenital heart diseases (e.g., aortic valve prolapse with VSD, congenital fenestration of aortic valve cusp), RF, ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, and

diet pill disease. Aortic disease also includes aneurysms of the ascending aorta caused by cystic medial necrosis or syphilis, and occasionally trauma.

### *Diagnosis of Aortic Regurgitation*

Symptoms can include fatigue, dyspnea, angina, or palpitations and, as with AS, are usually associated with severe disease. On physical examination, an abnormal high-pitched decrescendo diastolic murmur is heard at the left sternal border after the second heart sound. There is an increased pulse pressure, which is the difference between systolic and diastolic pressures. For example, rather than a normal pressure of 120/80 (pulse pressure = 40), pressure may be 130/50 (pulse pressure = 80). An electrocardiogram can show left axis deviation, Q waves, ST depression, and T-wave inversions.

### *Echocardiogram*

Findings on echocardiogram can include:

1. Aortic valve leaflets are thickened and calcified.
2. Abnormal bicuspid or unicuspid valve can be present.
3. Severity of regurgitation is based on several measurements. Doppler area of regurgitation jet graded 1-4, comparison of mitral inflow and aortic outflow, calculation of regurgitant area, and diameter of the aortic jet.
4. Ejection fraction with normal LV function should be in excess of 60%.
5. Measurements of the aortic root and ascending aorta—A markedly dilated aorta above 45 mm can require surgical intervention.
6. Measurements of left ventricular size—Normal AP diameter of the left ventricle is diastolic  $\leq 56$  mm and systolic  $< 36$  mm. Serious impairment of LV function is considered present when systolic diameter exceeds 45 mm; long-term prognosis is poor with a systolic diameter  $> 55$  mm or  $> 25$  mm/m<sup>2</sup>.

Doppler echocardiogram in asymptomatic individuals shows trivial AR in 5-10% of children and in 30-40% of individuals over age 75. This degree of “normal” aortic regurgitation is usually mild and not important unless there is associated myocardial weakness or hypertension. Mild AR is of little concern in an individual over age 70, but in the 30-year-old there is uncertainty about the likelihood of progression. It is helpful to have serial ultrasound studies over a period of 5 to 10 years to understand the likely course of the disease.

### *Other Investigations*

Magnetic resonance imaging (MRI) or computed tomography (CT) can be used to better assess the diameter of the aortic root and ascending aorta, as only the first 3 to 4 cm of the proximal aorta are seen on echocardiography. Generally, annual imaging is recommended for aortic root diameter greater than 40 mm.

Heart catheterization can be performed in potential candidates for valve replacement with coronary artery disease, severe LV dysfunction, or possible complex congenital heart lesions.

## *Course*

Both mild and moderate AR cases may be stable for years. Significant degrees of AR can be tolerated for years and, even when severe, survival without symptoms extends for another 10 years. However, acute worsening can occur after endocarditis. Progressive dilatation of the aortic root is another mechanism of deterioration.

**Table 5. Course of AR in relation to severity.**

	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
<b>Symptoms</b>	None	None	None to significant exercise intolerance
<b>Chest x-ray - heart enlargement</b>	None	Cardio-thoracic ratio (CTR) < 55%	CTR > 55%
<b>Pulse pressure</b>	$\leq 70$ mmHg	$\leq 70$	> 70
<b>EKG</b>	Normal	Borderline LVH	LVH, arrhythmias
<b>LV diameter, diastolic</b>	$\leq 56$ mm	57-65 mm	> 65 mm
<b>LV diameter, systolic</b>	$\leq 36$ mm	37-54 mm	> 55 mm
<b>Left atrial size</b>	Normal	Mildly enlarged	Enlarged
<b>Doppler</b>	1-2+	2-3+	3-4+
<b>Aortic root</b>	Normal	Normal or mild dilatation	Dilatation
<b>Course</b>	Generally well tolerated, with limited progression, can survive to age 80+	Usual progression, LV dysfunction, need for valve surgery	Heart failure, ventricular arrhythmias, sudden death unless valve replaced

The underlying cause of the regurgitation and the individual's age are key factors in determining disease course. An individual over the age of 60 with mild or moderate AR due to hypertension, mild aortic dilatation, or rheumatic damage from childhood who has remained stable is unlikely to have progression leading to valve surgery or early death. However, the 30-year-old with mild AR and an aortic diameter of 45 mm needs careful follow-up, as deterioration leading to surgery before age 60 is anticipated. In contrast, the 30-year-old with mild AR, bicuspid aortic valve, and normal aortic root diameter is likely to reach age 70+ before requiring intervention.<sup>13</sup>

Calcific aortic valve disease can cause dominant aortic regurgitation rather than aortic stenosis, and one out of four cases of calcific aortic valve disease coming to surgery has a significant amount of aortic regurgitation along with stenosis. Exercise capacity is not an indicator of AR severity. Some individuals with severe AR retain a good exercise capacity almost until the day that surgery is done.

AR is similar to AS in terms of the relationship between symptoms and prognosis. Once symptoms develop, surgical intervention is strongly recommended as heart failure and death are likely to occur. Delay can result in irreversible LV dysfunction.

Indications for aortic valve replacement or repair surgery for AR include:<sup>14</sup>

1. symptoms of AR, with or without LV dysfunction
2. severe AR, with development of symptoms on exercise testing

3. severe AR, without symptoms, but left ventricular ejection fraction less than 50%
4. severe AR in individuals having coronary artery bypass grafting
5. severe AR in individuals having surgery of the aorta or other heart valves.

### *Course after Valve Replacement*

General post-surgical considerations after valve surgery are outlined in Table 7. Causes of death after surgery are outlined in Table 8.

Unfavorable features with AR include:

1. moderate to severe left ventricular impairment that fails to improve completely - This is common in individuals who had AR, more so than with AS.
2. continued severe heart enlargement—echocardiogram LV diameter > 62 mm, chest x-ray cardiothoracic ratio (CTR) > 55%
3. ejection fraction < 50%
4. comorbid coronary artery disease
5. frequent ventricular ectopic beats or runs of ventricular tachycardia
6. deteriorating bioprosthesis—50% need replacing in 15 years, and many others will have valve leaks.

### *Underwriting*

#### *Without Surgery*

Underwriting the asymptomatic case with mild or moderate AR requires a detailed echocardiogram report including a description of valve anatomy, measurements of ascending aorta diameter and left ventricular function, and ideally serial echo studies five years apart.

Unfavorable features include:

1. signs of worsening over the past 10 years—elevated BP, increased heart size, EKG changes, increased regurgitation on Doppler report
2. underlying cause—Those with Marfan or Ehlers-Danlos syndromes are at risk for aortic rupture.
3. multiple valve involvement—higher surgical risk if both mitral and aortic valve replacement is required, and higher late mortality
4. comorbid coronary heart disease and/or significant cardiovascular risk factors
5. impaired LV function—decreased ejection fraction and/or diastolic dysfunction.

#### *With Surgery*

Underwriting valve surgery cases requires in-depth medical information, including preoperative, operative, and postoperative reports. A postoperative echocardiogram is essential.

## Mitral Stenosis

Mitral stenosis (MS) is the obstruction of blood flow from the left atrium to the left ventricle caused by narrowing of the mitral valve and creating a pressure gradient across the valve in diastole.

### *Causes*

Most cases are due to scarring of the mitral valve from rheumatic fever. Less commonly, infective endocarditis and severe mitral annular calcification cause MS. Rare causes include left atrial myxoma, congenital stenosis, carcinoid syndrome, systemic lupus erythematosus, rheumatoid arthritis, and endomyocardial fibrosis.

### *Diagnosis of Mitral Stenosis*

Symptoms can include dyspnea, decreased exercise tolerance, palpitations, cough, and chest pain. Atrial fibrillation, stroke, pulmonary edema, or pulmonary hemorrhage can also occur. On physical examination, there can be abnormal heart sounds, an opening snap of the mitral valve, and a rumbling low-pitched diastolic murmur best heard at the apex. With associated mitral regurgitation or aortic valve disease, other murmurs can be present. The electrocardiogram can show possible atrial fibrillation and right ventricular hypertrophy.

### *Echocardiogram*

The echocardiogram can provide the following information regarding MS:

1. Mitral valve leaflet deformities such as thickening, fibrosis, fusion, and calcification as well as other causes of stenosis can be identified.
2. In severe cases, the valve becomes funnel-shaped with extreme thickening and immobile leaflets.
3. Mitral valve area and estimates of extent calcification, leaflet motion restriction can be measured.
4. Heart chamber sizes, function, and other structures can be assessed.
5. Doppler echo measures the gradient across the valve and pressures, including an estimate of pulmonary artery pressure.
6. Associated mitral regurgitation and abnormalities of other valves can be present. About 30% of cases have associated aortic valve diseases, usually AR, and 6% of cases have rheumatic damage to the tricuspid valve.

**Table 6. Degree of mitral stenosis.**

State	Valve area (cm <sup>2</sup> )
Normal	4.0 – 5.0
Mild mitral stenosis	1.5 – 2.0
Moderate mitral stenosis	1.0 – 1.5
Severe mitral stenosis	< 1.0

### *Other Investigations*

A stress EKG or echocardiogram can be performed to assess exercise capacity, precipitate symptoms, and evaluate for pulmonary hypertension. Heart catheterization can be performed to directly measure pressures and gradients. Cardiac MRI is not currently used clinically.

### *Course*

Mitral stenosis develops insidiously after an episode of acute rheumatic fever, although the individual may not recall the clinical acute episode. MS is a progressive disease, with progressive calcification and fibrosis occurring at a variable rate. In North America, symptoms most commonly develop after age 35. In developing countries, MS can be found in the early teen years.

Generally, mild to moderate MS can produce dyspnea with exercise, and moderate to severe MS can be associated with symptoms at rest. Gradual limitation of exercise capacity due to dyspnea is the most common course. Individuals can gradually decrease their activities to avoid dyspnea and can deny symptoms, but an exercise test quickly reveals their limitation. Complications can change the individual's course acutely. Complications can include:

1. atrial fibrillation—This usually leads to marked dyspnea and hypotension.
2. pulmonary edema—Heavy exercise or pregnancy can lead to pulmonary edema with an acute episode of severe dyspnea.
3. thromboembolism—Systemic embolization can result in an acute stroke.
4. pulmonary hemorrhage—Massive pulmonary hemorrhage can occur because of pulmonary hypertension; this is, fortunately, less common with earlier intervention.

As seen with the aortic valve diseases, the onset and presence of symptoms are associated with a worse prognosis. The 10-year mortality rates are 14% for mild symptoms, 51% for moderate symptoms, and 82% for severe symptoms with limitations (e.g., shortness of breath on exercise). With MS, death is most commonly due to progressive right-sided heart failure. Other causes of death include stroke, endocarditis, and pulmonary embolism.<sup>15</sup>

### *Medical Treatment*

Medical treatment can relieve symptoms, but only definitive surgical intervention will relieve the obstruction. Medical treatment can include antibiotics for endocarditis and secondary rheumatic fever prevention, diuretics, digoxin and beta blockers to treat symptoms, or anticoagulants to prevent thromboembolic events.

### *Invasive Treatment*

Indications for percutaneous or surgical intervention for mitral stenosis include:

1. moderate to severe MS with symptoms
2. moderate to severe MS without symptoms but with pulmonary hypertension.

Percutaneous mitral balloon valvotomy (PMBV) is a newer procedure that is the treatment of choice for many cases of mitral stenosis. In PMBV, a heart catheterization is performed to access the mitral valve, and echocardiogram can also be performed to guide and monitor the procedure. A balloon, which is introduced via catheter, is inflated and then rapidly deflated, which opens the stenotic valve by separating the fused valve leaflets.

Surgical procedures include open valvotomy with valve repair, closed valvotomy (now rarely performed), and mitral valve replacement. Prior to 1985, closed mitral valvotomy was the most common procedure, and there are individuals still living today who had this procedure done 30-40 years ago. Since 1985, closed valvotomy has been largely replaced by PMBV, thus avoiding surgery. There was a period (1965-1975) when open mitral repair was common, but often the surgeon, once looking at the severity of the pathology, simply replaced the valve.

Generally, PMBV is recommended instead of surgery when the valve morphology (shape) is favorable, and the individual does not have left atrial thrombus or moderate to severe mitral regurgitation. Conversely, open valvotomy or mitral valve replacement surgery can be indicated with unfavorable valve morphology, left atrial thrombus or mitral regurgitation, and with severe calcification, complex lesions such as congenital MS, and other valve lesions.

#### *Course after Invasive Treatment*

In ideal cases, the valve area can be increased to 2.0-2.5 cm<sup>2</sup> after PMBV ballooning or palliative valvotomy. This is significantly less than the normal valve area of 4-5 cm<sup>2</sup> but is sufficient for improvement in symptoms and echocardiographic pressure and gradient measurements. Progressive fibrosis occurs after this and a repeat valvotomy or valve replacement is frequently needed within another 10-15 years and sometimes sooner. The palliative intervention can fail, and mitral regurgitation of a significant degree can occur.

Favorable long-term outcome is associated with a less deformed valve, normal ventricular function, better exercise tolerance, and success of improving valve area to 2.0 cm<sup>2</sup>. Less favorable long-term outcome is associated with older age, more severe MS prior to intervention, presence of mitral regurgitation, elevated pulmonary artery (right ventricular systolic) pressure, and atrial fibrillation.

General post-surgical considerations after valve surgery are outlined in Table 7. Causes of death after surgery are outlined in Table 8.

#### *Underwriting*

##### *Without Invasive Treatment*

Individuals with mild cases at older ages who are otherwise healthy and have valve areas over 1.5 cm<sup>2</sup> still exhibit significant mortality as the disease is usually progressive.

## With Invasive Treatment

Individuals over age 50 with valve areas close to  $2.0 \text{ cm}^2$ , with no pulmonary hypertension, no atrial fibrillation, no significant mitral regurgitation, no significant coronary artery disease, and no problems with other valves, are suitable for life underwriting. Only the best cases will qualify for insurance coverage. Individuals under age 50 and those with persistent atrial fibrillation are at increased risk for complications.

### Mitral Regurgitation

Mitral regurgitation (MR) is blood flow from the left ventricle to the left atrium during systole. This backward flow of blood is due to incompetence or incomplete closure of the mitral valve. It is also called mitral insufficiency (MI). A trivial leak or “whiff” of MR, also called “physiologic” MR, can occur across normal valves and can be seen on Doppler in up to 70% of normal adults.

#### *Causes*

MR can be caused by an abnormality of the mitral valve apparatus, which includes valve leaflets, annulus, chordae tendineae, and papillary muscles. These abnormalities can be a result of mitral valve prolapse, myxomatous degeneration, rheumatic heart disease, infective endocarditis, mitral annular calcification, ruptured chordae, degeneration with age, or a congenital cleft valve. MR can also be caused by other cardiac diseases including ischemic heart disease with papillary muscle dysfunction, left ventricular dysfunction and dilatation from any cause, and dilated or hypertrophic cardiomyopathy.

Other causes include systemic diseases such as Marfan or Ehlers-Danlos syndromes, scleroderma, systemic lupus erythematosus, rheumatoid arthritis, or amyloidosis. MR can be caused by radiation damage, damage at time of surgery, or by certain drugs including the diet pill Fen-Phen.

#### *Diagnosis of Mitral Regurgitation*

Symptoms include dyspnea, fatigue, decreased exercise tolerance, and palpitations. Physical examination can find a blowing, high-pitched holosystolic murmur best heard at the apex. An electrocardiogram can possibly show notched P waves, left ventricular hypertrophy, ST-T wave abnormalities, or atrial fibrillation.

An echocardiogram can provide the following information:

1. causes of the MR including abnormalities of the valve apparatus, cardiomyopathy, or left ventricular dysfunction
2. severity of regurgitation, which is based on Doppler color signal in the left atrium and will be grade 1–4 based on the volume of the signal into the left atrium
3. calculation of the effective regurgitation orifice (ERO)—A regurgitant orifice area of  $\geq 0.40 \text{ cm}^2$  indicates a high risk of future problems even in asymptomatic individuals.
4. left atrial size, which is usually increased

5. existence of left ventricular enlargement—With severe MR, left ventricular end-diastolic dimension (LVEDD) will be  $> 60$  mm and left ventricular end-systolic dimension will be  $> 45$  mm.
6. With good left ventricular function, EF should be 70% or 80% with MR, as the ventricle is emptying two ways: out through the aorta and back into the left atrium.
7. Left ventricular size and systolic function are usually normal in mild disease. With chronic severe MR, the left ventricle progressively dilates, and the EF decreases.

### *Other Investigations*

Heart catheterization can be performed to confirm echocardiographic findings or to identify coronary artery disease.

### *Course*

Because of the multiple causes and the complexity of mitral anatomy and function, the natural history of MR is much more variable than it is for aortic valve lesions or MS. However, as with other valve lesions, once MR is symptomatic, mortality risk increases with a mortality risk in five years of close to 35%.<sup>16</sup>

On the other hand, asymptomatic individuals with mild MR can remain asymptomatic for over 20 years from the point of diagnosis. When MR is classified as mild, the event-free survival in 10 years is over 95%, and, if moderate, is about 85%.

Mild MR can have a very favorable course. Mild MR by Doppler, without symptoms, has an effective regurgitation orifice (ERO)  $\leq 0.1 \text{ cm}^2$  with preserved mitral valve anatomy. It can be either the residual of rheumatic fever, post primum ASD repair, or be an incidental finding without known cause. This lesion can progress, but this progression is rarely of a degree to cause problems. Prior to echocardiography, the life insurance industry collected survival data on cases with blowing apical systolic murmurs, normal EKG, and chest x-ray. These cases represented mild MR, and long-term survival was favorable.

In contrast, mild MR with MVP and myxomatous change can result in progressive regurgitation. It is estimated that 2% will require surgery at the mean age of 57, and males outnumber females 3:1.

Symptomatic cases of MR and asymptomatic cases with severe MR by Doppler (with ERO  $\geq 0.4 \text{ cm}^2$ ) do poorly. Mortality in five years has exceeded 50%. Valve repair is indicated in all symptomatic cases. Which approach to take in an asymptomatic individual is controversial. Watchful waiting can be indicated in some individuals with chronic severe MR, including those individuals with LVEF  $> 65\%$  and LV end-diastolic LV diameter  $< 40$  mm. Regular follow-up with monitoring for symptoms and progression on echocardiography is warranted with intervention likely within the next few years.

Moderate MR with a Doppler grade 2-3+, an ERO  $< 0.4 \text{ cm}^2$ , and Class I New York Heart Association (NYHA) function can do well for years. Follow-up echocardiograms have found a

gradual increase in ERO of  $0.06 \text{ cm}^2$  per year in small studies with short-term follow-up. Echocardiogram findings, such as increasing left atrial diameter and an increase in the annular diameter are thought to indicate progression.

Rheumatic MR occurs at the time of the acute episode of rheumatic fever. Mild and moderate degrees of MR can remain stable without symptoms for many years. About 50% of individuals with MR after an attack of acute rheumatic fever will eventually lose their murmur and have mild degrees of residual valve scarring. They can either have no further problems or can have progressive valve scarring with return of MR or the development of MS. Individuals with moderately severe MR have a course like individuals with MS. The valve damaged by a previous rheumatic fever has some degree of fibrosis and rigidity of the valve leaflets in addition to some of the changes of MS, with shortening and fusion of the valve chorda. The regurgitation can be slowly progressive, and sudden worsening can occur with rupture of a chordae. Endocarditis is another complication that can rapidly increase the degree of regurgitation.

Also, mild MR due to complications of coronary disease is associated with increased mortality risk, and estimating longevity is difficult. Papillary muscle rupture occurs in 0.1% of cases of acute myocardial infarction. This produces severe MR requiring emergency valve replacement and is associated with a high acute mortality rate.

Chronic ischemic heart disease (IHD) can also lead to impaired papillary muscle function. Variable degrees of MR occur. With IHD and severe MR, one-year survival is about 50%. With IHD and mild or moderate MR, mortality risk is double compared to individuals with IHD but without MR. Some individuals with papillary muscle dysfunction will have worsening of MR and heart failure with physical activity, although the MR at rest appears relatively mild.

MR associated with dilated cardiomyopathy is due to annular dilatation, left ventricular dilatation, and dysfunction of papillary muscles and is associated with a high mortality risk.

### *Medical Treatment*

Medical treatment can relieve symptoms, but the only definitive treatment is surgical intervention. Medical treatment can include antibiotics for endocarditis prevention, diuretics, digoxin, angiotensin-converting enzyme (ACE) inhibitors to treat symptoms of volume overload, antiarrhythmic agents for atrial fibrillation if present, and oral anticoagulants to prevent thromboembolic events.

### *Surgical Treatment*

Indications for valve surgery for chronic MR include:

1. severe acute MR, defined by Doppler echocardiography, with symptoms
2. severe chronic MR with symptoms and with or without severe left ventricular dysfunction, LVEF  $<30\%$ , LV end-systolic dimension (LVESD)  $>55 \text{ mm}$
3. severe chronic MR without symptoms and with LVEF 30-60%, LVESD  $\geq 40 \text{ mm}$

4. severe chronic MR without left ventricular dysfunction but with new-onset atrial fibrillation or pulmonary hypertension (resting pulmonary artery systolic pressure >50 mmHg; with exercise >60 mmHg).

Mitral regurgitation cases coming to surgery in the last 10 years have had myxomatous disease with mitral valve prolapse in about 40% of patients, coronary artery disease complications in about 20%, rheumatic heart disease in 20%, endocarditis in 10%, and other causes in 10%.

When feasible and based on anatomy, mitral valve repair (i.e., mitral valvuloplasty) is preferred over mitral valve replacement in most cases. Repair is associated with better left ventricular function and avoids the complications associated with a prosthetic heart valve, including the need for long-term anticoagulation therapy. Valve replacement is usually indicated with extensive prolapse (involving more than one-third of the leaflet tissue), extensive calcification or degeneration of a leaflet or the annulus, and with extensive fusion of the chordae, calcification, or papillary muscle rupture.

Choices for mitral valve replacement include a mechanical valve, which requires life-long anticoagulation or a bioprosthetic valve that does not require anticoagulation but has limited durability. Bioprosthetic valves are generally recommended for individuals who are unable or unwilling to take oral anticoagulants (e.g., warfarin) and also for individuals age 65 or older as the limited valve durability is less of an issue at older ages. Mechanical valves are generally recommended for individuals under age 65 with atrial fibrillation since anticoagulants are warranted for both. Individual preference is a key factor for valve choice for individuals under age 65 in sinus rhythm. A bioprosthetic valve is likely to need replacement in this age group. More than 30% can require replacement of the valve by 12 years.

#### *Course after Valve Surgery*

Valve repair is associated with lower operative mortality, higher 10-year survival, and preserved LVEF compared to valve replacement.

Surgical mortality for mitral valve replacement is 5%. The subsequent course depends on whether good LV function was restored. Mortality in best cases of valve replacement is about three times normal. Survival with bioprosthetic valves is slightly better than with mechanical valves at 10 years, especially in the mitral position, but the mortality of a second operation is 5%-10%.

Mechanical valves today are much improved over the earlier models in hemodynamics. Large Bjork-Shiley valves have had a high rate of strut fracture. This mechanical valve is no longer implanted, and those cases where the valve remains in place should be underwritten carefully. Most of the mechanical valves on the market today have a mechanical failure rate of less than one per 10,000 in 10 years. Mortality ratios after valve replacement are very high up to age 40, but much lower after age 70, with the decline in ratio being due to the higher non-valve mortality in the older age groups.

General post-surgical considerations after valve surgery are outlined in Table 7. Causes of death after surgery are outlined in Table 8.

### *Underwriting*

The following describes characteristics of mild, moderate, and severe cases:

1. mild cases—a murmur only, normal rhythm, no LV enlargement by x-ray or echo - Doppler report shows only mild regurgitation; in favorable cases, mortality is no more than two times normal.
2. moderate cases—LV enlarged slightly by x-ray, LV diameter on echo to 60 mm (normal to 55 mm), LA enlarged on echo to 45 mm (normal to 40 mm), other factors favorable - The presence of atrial fibrillation increases the mortality risk.
3. severe cases—On x-ray, LV is enlarged ++ and LA is enlarged ++; on echo, LV is over 60 mm, LA is over 45 mm; Doppler shows severe regurgitation.

Prognosis is often related to the underlying cause, with papillary muscle dysfunction due to coronary artery disease being very unfavorable. If due to myxomatous degeneration in a male, the lesion is usually progressive. If due to a congenital problem, most cases are stable.

### Mitral Valve Prolapse

Mitral Valve Prolapse (MVP) occurs when one or both mitral valve leaflets are too large or the chordae tendineae are too long. This results in uneven closure of the valve leaflets, which bulge back or prolapse into the left atrium. MVP is due to myxomatous degeneration in the mitral valve at the attachment of the chordae. MVP is also called the click-murmur syndrome, balloon or floppy mitral valve syndrome, and Barlow's syndrome.

### *Causes*

The cause of classic idiopathic MVP with myxomatous degeneration is uncertain. MVP with myxomatous degeneration can also be secondary to a connective tissue disorder including Marfan syndrome, Ehlers-Danlos syndrome, adult polycystic kidney disease, and osteogenesis imperfecta. MVP tends to run in families with an autosomal dominant inheritance pattern. It is associated with chest wall deformities (e.g., pectus excavatum, pectus carinatum) and found in Ebstein's anomaly, a congenital heart condition. MVP can also occur with papillary muscle dysfunction associated with myocardial ischemia, dilated cardiomyopathy, and hypertrophic cardiomyopathy.

### *Diagnosis of Mitral Valve Prolapse*

Symptoms can include chest pain, dyspnea, or palpitations. On physical examination, the auscultatory findings of MVP are quite specific. There is a mid-systolic click at the apex that moves towards the first heart sound on sitting. There can be an apical murmur, but typically that murmur occurs after the click in late systole. A murmur along the left sternal border may have been the reason for ordering an echocardiogram, but this type of murmur is not the type of murmur caused by MVP. When mitral regurgitation becomes moderately severe, the murmur of MVP can become pansystolic, as with any other cause of mitral regurgitation. When mild, the MVP clicks

and murmurs can be intermittent. Arrhythmias may or may not be proven with an EKG or Holter monitor.

### *Echocardiogram*

Echocardiogram – most useful to diagnose MVP – can demonstrate:

1. redundancy of the mitral valve leaflets
2. degree of prolapse or displacement of valve leaflets— $\geq 2$  mm leaflet displacement in classic MVP
3. severity of thickening of valve leaflets—leaflet thickness  $\geq 5$  mm in classic MVP
4. estimated severity of associated mitral regurgitation, if present by color flow Doppler
5. any abnormalities in leaflet length, annular diameter, and chordal length
6. left ventricular function.

### *Course*

It is unfortunate that the single term MVP is used to cover both mild cases that almost certainly will not progress, and the cases with myxomatous change that will progress to severe MR. Most individuals with MVP do well with no intervention needed during their lifetime. In most cases, this degenerative process is relatively mild, and any progression is very slow, if at all. About 2%, mostly male, will need mitral valve repair by age 58, and 5% percent by age 70.<sup>17</sup>

Favorable features of MVP unlikely to progress include the following:

1. female
2. apical click, no murmur
3. degree of prolapse on echocardiogram showing  $< 2.5$  mm prolapse in the maximal projection
4. valve thickening  $< 4$  mm on echocardiogram
5. valve regurgitation 2+ or less regurgitation and effective regurgitation orifice  $< 0.2 \text{ cm}^2$  on echocardiogram
6. no change with five years of follow-up
7. normal body build and habitus.

Unfavorable features of MVP with likely progression within the next 5-10 years include:

1. mitral regurgitation on echocardiogram, grade II-III, and effective regurgitant orifice  $\geq 0.3 \text{ cm}^2$
2. major degree of prolapse and myxomatous change, valve thickening
3. indication of progression on follow-up echocardiogram and clinical findings
4. enlarging left ventricle and definite left atrial enlargement
5. any symptoms
6. development of atrial fibrillation
7. progression of heart murmur to pansystolic in all postures
8. leaflet described as flail (i.e., having abnormal mobility) on echocardiogram.

MVP is an important cause of cardiac morbidity and mortality, accounting for 25% of mitral surgeries, 10% of endocarditis, and 1% of sudden deaths. The average age for mitral surgery for prolapse/myxomatous degeneration is 57 years. Therefore, lack of symptoms, a high exercise capacity, a normal EKG, and a grade II short murmur at age 35 is not necessarily a normal risk.

Severe myxomatous degeneration leads to major degrees of prolapse and can lead to rupture of the chordae tendineae. If the chordae rupture involves only one or two minor subleaflets, the degree of regurgitation is not severe. Localized rupture is found at surgery and autopsy in some individuals who have few symptoms. When rupture leads to a large portion of the leaflet becoming flail, acute mitral regurgitation occurs with acute heart failure. Individuals can survive with medical treatment in this circumstance, but most succumb within five years. Surgery is the best option.<sup>18,19</sup>

MVP-like changes occur with Marfan syndrome, hypertrophic cardiomyopathy, and Ehlers-Danlos syndrome. In these cases, the MR can be mild to severe.

Olmstead County study of MVP has the advantage of a large series (N=833) of controlled echocardiography assessment, 97% follow-up, mean 5.9 years, many followed for 10 years, and the inclusion of most cases in a defined population. There were 90 deaths (41 CVD) and a 10-year mortality of 19% (mortality ratio near normal at 1.08 for the entire series). By far, the most important determinant of mortality was the degree of mitral regurgitation on echocardiogram – moderate to severe. The additional factors related to death were ejection fraction below 50%, male gender, valve thickening, and left atrial diameter of 40 mm. The conclusion was that MVP was heterogeneous. Outcomes cannot be described as uniformly severe or universally benign. One of the problems in the study was the very wide age ranges,  $50 \pm 21$  for the whole group,  $65 \pm 18$  in those with MVP-related events.<sup>20</sup>

### *Treatment*

The reader is directed to the treatment section under mitral valve regurgitation.

### *Underwriting*

The first and most important message is that most cases reported to insurers are either mild or non-existent and mortality is normal or close to it. The proposed insured who reports a diagnosis of MVP, without a record in the attending physician's statement and without a murmur, likely does not have MVP. The MVP diagnosis may have been due to the over-diagnosis early in the use of echocardiography. However, MVP can accompany almost any significant cardiac pathology. It is important to recognize any associated impairments and consider their mortality risk.

Once significant MR occurs with MVP, the MR is likely to be progressive. If no MR is present at the time of underwriting, most cases of MVP have favorable mortality.

The following situations are commonly encountered:

1. An individual with a mitral click (an extra sound in mid-systole) has no murmur, no symptoms, no or only mild prolapse on echocardiogram, and trivial MR (which is normal) on Doppler. These cases are favorable.
2. An individual with chest pain goes to an MD, and a diagnosis of MVP is made. Findings include minor inferior T changes on EKG, minor mid-systolic murmur not typical for MVP, and mild prolapse reported on echocardiogram. Prolapse may or may not be present and likely has no relationship to the chest pain. If the individual is over age 40 or has cardiovascular risk factors, coronary artery disease (CAD) must be carefully evaluated. These cases exhibit no significant increased mortality if CAD or other cardiac pathology has been excluded.
3. An individual has palpitations. Arrhythmias may or may not be proven with an EKG or Holter monitor. The echo shows mild MVP with no MR. The relationship between mild MVP and arrhythmias is unproven. The MVP is unlikely to be associated with increased mortality, and the arrhythmias should be underwritten.
4. An individual has an MVP diagnosis based on a mid-systolic click with a late apical systolic murmur, louder on standing up. Echocardiogram is done to assess severity of MR, presence of any LA or LV enlargement, as well as any valve deformity. For mild to moderate valve deformity:
  - a. female age 15-40: minimal extra mortality
  - b. female > age 40: no extra mortality
  - c. male age 15-40: good chance of progression
  - d. male > age 40: no extra mortality.
5. An individual has a grade 2-3 pansystolic murmur and moderate to severe prolapse on echo, but no enlargement yet. Progression to severe MR is likely.
6. An individual has a grade 2-3 pansystolic murmur and moderate to severe prolapse on echo with definite enlargement. There are bulging or bulky leaflets with a pansystolic prolapse. Mitral valve replacement is very likely to be needed in this situation. This is more likely if the proposed insured is a male; the common age for replacement is 50-60 years. These cases are likely to exhibit high mortality until after valve replacement or repair.
7. An individual has definite MVP with a murmur, echo confirmation with or without heart enlargement, frequent ventricular ectopic beats, treadmill-test-induced non-sustained ventricular tachycardia, and arrhythmias controlled with a betablocker such as propranolol. This situation presents a difficult underwriting problem. There is a definite risk of sudden death, but whether this risk is one in 100 or one in 50 or even higher is impossible to predict.

### Tricuspid Valve Stenosis and Regurgitation

Tricuspid stenosis (TS) is rare, occurring occasionally after rheumatic heart disease or in carcinoid syndrome. Tricuspid regurgitation (TR) is common in cases of pulmonary hypertension, right ventricular dysfunction, and complex congenital anomalies such as Ebstein malformation. TR is common after surgery for tetralogy of Fallot and after endocarditis suffered by intravenous drug users. Trivial TR is present in 80% of normal individuals. TR is frequently found with

cardiac arrhythmias, such as atrial fibrillation or with congestive heart failure. Half the cases have some degree of tricuspid regurgitation.

### Pulmonary Valve Stenosis and Regurgitation

Pulmonary stenosis and pulmonary regurgitation are primarily congenital heart anomalies and will not be discussed in this chapter.

### **Valve Surgery – Special Considerations after Heart Valve Surgery**

#### Factors Influencing Outcome

Table 7 outlines several factors that affect outcome after valve replacement surgery. Causes of death after surgery are outlined in Table 8.

**Table 7. Factors in assessing post-surgical outcome.**

Heart Rhythm	Atrial fibrillation is unfavorable. Individuals with residual left atrial enlargement (>40 mm) are at greater risk of recurrent atrial fibrillation. High-grade ventricular ectopic activity is also unfavorable.
Left Ventricular Function	Impaired pre-operative ejection fraction (EF) and persistent EF < 45% are associated with adverse outcomes. Persistent heart enlargement by x-ray is another sign of poor LV function.
Anticoagulant Use	Any history of major bleeding or thromboembolism is unfavorable. INR should be in therapeutic ranges: 2.0-3.0 for aortic valve replacement and 2.5-4.0 for mitral valve replacement. Individuals with atrial fibrillation and valvular disease should be on warfarin (with or without mechanical valve).
Valve Type and Match - General	Ideally, valve size matches patient size. A smaller than ideal valve is referred to as valve prosthesis-patient mismatch. This is particularly important for the aortic valve as severe mismatch increases heart failure and mortality risk. Some mechanical and occasional tissue valves have high-pressure gradients by echocardiogram, particularly if there is a mismatch.
Valve Type and Match - Mechanical	Mechanical valves (e.g., Bjork-Shiley wide angle, Ionescu-Shiley, Edward-Duromedics Bileaflet) used from 1970-1985 are prone to mechanical failure with an unacceptable failure rate.
Valve Type and Match - Bioprostheses	Early tissue valves had limited long-term longevity. Tissue valves in individuals under age 65 are likely to need replacing in 10-20 years. Repeat surgery is associated with an operative mortality of 5-10%.
Associated Coronary Disease	Individuals with coronary artery stenosis >60% often will have had angioplasty or CABG at the time of valve surgery. Diffuse coronary disease, uncorrected coronary artery stenoses, and poorly controlled cardiovascular risk factors are higher risk.
Functional Capacity	Functional capacity and return to a productive life are markers for better long-term outlook. Associated depression is an adverse factor.

Multiple Valve Disease	In rheumatic valvular disease, often more than one valve is involved, and surgical strategy can be to only correct the most severe lesion. Associated tricuspid valve disease is an adverse sign.
Aortic Dilatation	Aortic valve disorders are often associated with dilatation of the ascending aorta. If the aortic diameter exceeds 45 mm, it is now felt that cases do better with repair with a sleeve or graft.
Pulmonary Hypertension	Right ventricular pressure >40 mmHg by echocardiogram is an adverse finding.
Comorbidity Factors	Significant comorbidities such as COPD, diabetes mellitus, or heavy smoking make mortality predictions more difficult. Warfarin (Coumadin®) therapy in individuals with prior gastrointestinal ulceration poses an obvious risk, as does hepatic disease.

**Table 8. Causes of death after valve surgery.**

Valve Related	<ul style="list-style-type: none"> <li>• Mechanical valve failure</li> <li>• Biological valve failure</li> <li>• Blood clots on valve</li> <li>• Paravalvular leaks</li> <li>• Valve/patient size mismatch</li> <li>• Endocarditis on valve</li> <li>• Surgery for valve replacement</li> <li>• Failure to replace other dysfunctional valves</li> </ul>
Heart Related	<ul style="list-style-type: none"> <li>• Worsening myocardial function and heart failure</li> <li>• Atrial fibrillation</li> <li>• Ventricular arrhythmias – tachycardia, fibrillation, sudden death</li> <li>• Uncorrected aortic aneurysm or aortic dilatation</li> <li>• Associated coronary heart disease not fully appreciated and corrected</li> <li>• Development of new coronary disease or progression previously mild</li> </ul>
Blood Clotting Disorders	<ul style="list-style-type: none"> <li>• Clots on valves</li> <li>• Embolism primarily to brain</li> <li>• Major hemorrhage from warfarin (Coumadin®) treatment 0.5% per year and half those fatal</li> <li>• anticoagulant complications with other surgeries</li> </ul>
Non-Cardiac Conditions	<ul style="list-style-type: none"> <li>• COPD, diabetes mellitus, stroke, cancer, others</li> </ul>

## **Summary**

The entire picture of valvular heart disease has changed significantly over the past 50 years. Only a generation ago, rheumatic fever was the most common cause of valvular heart disease until the introduction of antibiotics. Presently, valvular heart disease is more commonly a degenerative disease associated with older ages. Expert auscultation skills have been replaced by modern echocardiography, and diagnostic imaging continues to improve steadily. Advances have been made in understanding the natural history of valvular heart lesions and the optimal timing for intervention. Along with general advances in medical and surgical care, surgical devices for repair and replacement continue to be refined as well as both open and endovascular surgical approaches. Underwriters are likely to encounter valvular heart disease on a regular basis and need to be aware of diagnostic tools, interventions, course of disease, and prognosis.

## **Review Questions – ALU 201, Chapter 11**

1. One of the two most important measures of the severity of aortic stenosis is the:
  1. grade of the murmur
  2. degree of sclerosis
  3. hypertrophy of the left ventricle
  4. gradient across the valve
2. A transesophageal echocardiogram (TEE) is used to assess all of the following heart diseases EXCEPT:
  1. endocarditis
  2. aortic root disease
  3. atrial septal defect (ASD)
  4. coronary artery disease
3. Causes of death after heart valve surgery include which of the following?
  - A. blood clots on the valve
  - B. ventricular arrhythmias
  - C. brain embolism

Answer Options:

1. A only is correct.
2. A and B are correct.
3. B and C are correct.
4. A, B, and C are correct.

4. Which valvular heart disease is also known as mitral insufficiency (MI)? Review its causes, course, and treatment options.
5. Rheumatic fever (RF) is no longer the main cause of valvular heart disease other than which specific valvular heart disease? Review that specific valvular heart disease's other causes, its course, and treatment options.

6. Features of mitral valve prolapse indicating that it is unlikely to progress include which of the following?

- A. male gender
- B. absence of a murmur
- C. normal body habitus

Answer Options:

- 1. A only is correct.
- 2. C only is correct.
- 3. A and B only are correct.
- 4. B and C only are correct.

7. Common causes of aortic stenosis include all the following EXCEPT:

- 1. congenital abnormalities
- 2. aortic root dilation
- 3. valvular calcification
- 4. rheumatic valve disease

8. Describe TAVR and list the 2 conditions for which it is not used.

9. List at least five unfavorable features of mitral valve prolapse which indicate likely progression.

10. Describe and explain the difference in the murmur location and type for aortic stenosis, aortic regurgitation, and mitral regurgitation.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 4: gradient across the valve – page 9.

### *Review Question 2*

Answer 4: coronary artery disease – page 4.

### *Review Question 3*

Answer 4: A, B, and C are correct – page 28.

### *Review Question 4*

Refer to pages 19-22.

### *Review Question 5*

Refer to page 7 and pages 15-18.

### *Review Question 6*

Answer 4: B and C only are correct - pages 24-25.

### *Review Question 7*

Answer 2: aortic root dilation – page 8.

### *Review Question 8*

Refer to pages 11-12.

### *Review Question 9*

Refer to page 25.

### *Review Question 10*

Refer to page 3.

## **CHAPTER 12**

### **HEMATOLOGICAL DISORDERS**

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## **HEMATOLOGICAL DISORDERS**

### **Introduction**

Hematology is the study of blood. Blood consists of two components that can easily be separated by centrifugation. The fluid component, called plasma, is a complex mixture of water, proteins, carbohydrates, lipids, electrolytes, and clotting factors. The cellular components of blood consist of red blood cells, white blood cells, and platelets. Hematology is most concerned with the cellular elements and with the pathological conditions resulting from changes in the quantity and quality of these cells. These changes can be related to impairments of blood forming organs, other organ systems, or from transient physiologic changes unrelated to disease.

Blood serves the human body in many ways. Nutrients are supplied to the various tissues as blood circulates through the complex network of arteries and veins. The most important of these nutrients is oxygen, which is carried by the red blood cells. Blood also carries end products of metabolism to the organs of excretion. White blood cells and circulating antibodies form a natural defense against microorganisms and foreign antigens. Platelets and coagulation factors in the plasma maintain hemostasis. Plasma and cellular components exchanging elements result in a dynamic equilibrium.

### **Hematopoiesis**

The bone marrow, one of the largest organs of the body, is the principal site of blood cell formation. The bone marrow contains the precursors of developed cell lines. These precursors of red blood cells, white blood cells, and platelets multiply and mature in the bone marrow, differentiating into their appropriate cell lines prior to release into the peripheral blood.

Hematopoiesis is the term given to the production of blood cells. At birth and throughout life, the bone marrow is the only site of normal hemopoietic activity. As an individual ages, the hemopoietic tissue or red marrow is slowly replaced by fatty tissue or yellow marrow. This occurs from the periphery of the body inward toward the axial skeleton. At adulthood, hemopoietic marrow is found in the vertebrae, sternum, ribs, skull, and pelvic bones. While the number of bone cavities containing red marrow decreases at adulthood, the increased size of these hemopoietic cavities compensates for the loss of some marrow sites. Bone marrow samples for diagnostic studies are usually taken from the posterior iliac crest or from the sternum.

It is postulated that all cell lines develop from pluripotential stem cells. These stem cells can differentiate into the precursors of red blood cells, white blood cells, and platelets. The differentiation to a specific cell line can be triggered by physiologic changes that cause a demand for increased production of one cell type. Stem cells committed to red blood cell production become cells called erythroblasts. These cells undergo four mitotic divisions with one erythroblast eventually producing sixteen mature red blood cells (erythrocytes). As the cell nears maturity, it extrudes its nucleus, and it is released into the peripheral circulation. The newly released cell is called a reticulocyte. A normal mature red blood cell is a biconcave disk saturated with hemoglobin. This shape allows maximum oxygen saturation as well as the ability to navigate the microcirculation of organ systems without damage to the cell.

The principal factor in the regulation of red blood cell production appears to be the hormone erythropoietin, which is produced in the kidney. When oxygen transport to the tissues is impaired, as it is in anemia, cardiovascular disorders, or the low oxygen environment of high altitude, erythropoietin activity is increased. This causes stem cells to commit to the red blood cell line, as well as to increase the rate of cell division, and to trigger the early release of reticulocytes. The bone marrow has the capacity to adjust its red blood cell production to ten or more times the normal rate.

### **Hemoglobin Synthesis and Degradation**

The main function of the red blood cell is the transport of oxygen to the tissues; hemoglobin is the carrier substance. The hemoglobin molecule consists of a heme portion containing iron and a globin portion. The globin portion consists of two pairs of chains composed of amino acids, the building blocks of proteins. Genetic variations in the structure of these chains are responsible for the various hemoglobinopathies such as sickle cell or thalassemia. Heme combines with oxygen and carbon dioxide reversibly. In the lung, where oxygen tension is high, hemoglobin is 95% saturated with oxygen. In the tissues, where oxygen tension is low, the oxygen dissociates readily.

The life span of a normal red blood cell is approximately 120 days. As the life cycle comes to an end, the cell is removed from the circulation by the reticuloendothelial system. This system is composed of the spleen, liver, bone marrow, and lymph nodes. Special cells called macrophages engulf or phagocytize the aging red blood cells in the bone marrow. Misshapen cells are removed by the spleen. Following phagocytosis, the hemoglobin molecule is broken down into iron, protoporphyrin, and globin. Protoporphyrin undergoes further degradation to eventually become bilirubin. Iron is reincorporated into newly synthesized heme or is stored for future use.

### **The Complete Blood Count**

The complete blood count (CBC) is a most useful laboratory test for the evaluation of hematological processes and disorders. It is one of the most frequently ordered of all blood tests. Significant findings in a CBC give valuable information concerning a patient's diagnosis, response to treatment, prognosis, and recovery. The CBC is used as a diagnostic tool in the emergency room or physician's office when a patient presents with symptoms of fatigue, jaundice, or outright acute blood loss. The CBC is useful when following a course of treatment for anemia, such as post-transfusion or during iron therapy treatment. The severity of an anemia and the appropriate prognosis can be directly related to the corresponding blood counts. The CBC is also used as a screening test. It can be done routinely with hospital pre-admission testing, in the emergency room, during routine physicals, and even with employment physicals. CBC testing is also performed frequently due to the ease of specimen procurement through venipuncture and the small amount of specimen needed. It is important for underwriters to understand that when a physician orders a CBC, it is not necessarily to diagnose anemia.

The CBC consists of two parts. The tests in the first part, sometimes called the hemogram, include:

1. white blood cell count (WBC)
2. red blood cell count (RBC)
3. hemoglobin (HGB)
4. hematocrit (HCT)
5. red blood cell indices (MCV, MCH, MCHC)
6. platelet count (PLT).

The second part of the CBC includes:

1. white blood cell differential
2. red blood cell morphology.

### White Blood Cell Count

The main function of white blood cells is to fight infection. White blood cells, also called leukocytes, defend the body against foreign organisms by phagocytosis of bacteria and production of antibodies. An increased number of white blood cells is termed leukocytosis while reduced levels are referred to as leukopenia. There are many causes of leukocytosis including:

1. acute bacterial infection (the most common cause) with white counts in the 15,000 to 30,000 range—Counts as high as 45,000 can be seen with pneumococcal pneumonia.
2. physical stimuli such as heat, cold, pain, surgery, malignancies, and drug reactions
3. emotional stimuli such as stress.

Leukocytosis of a temporary nature must be distinguished from leukemia in which the elevated cell count is permanent and progressive. Leukopenia (a reduction in the number of white blood cells) is often seen with viral or rickettsial infection or with an overwhelming bacterial infection.

### Red Blood Cell Count

The red blood cell count determines the total number of erythrocytes per volume of blood. Normal values differ for males and females with males having higher values. Decreased red blood cell counts are seen in anemia. Anemia, by definition, is a decrease in the number of circulating erythrocytes, and/or the quality of these cells. Anemia can be caused by:

1. a decrease in red blood cell production or reduction in hemoglobin level
2. an increase in red blood cell destruction
3. dietary insufficiencies
4. actual blood loss.

Increased red blood cell counts are seen in polycythemia. Anemia and polycythemia will be covered in more detail later in this chapter.

## Hemoglobin

Hemoglobin is the main component of erythrocytes. It serves as the vehicle for both oxygen and carbon dioxide transport. Normal values differ for males and females. The oxygen-carrying capacity of blood is directly proportional to the hemoglobin concentration rather than the number of red blood cells. Some red blood cells contain more hemoglobin than others. For this reason, the hemoglobin value tends to be more important in the evaluation of anemia than the red blood cell count. Decreased hemoglobin values are found in anemia from any cause, including hyperthyroidism, liver cirrhosis, severe hemorrhage, hemolytic reactions, and cancer. Increased hemoglobin levels are seen in polycythemia, pulmonary disorders, and congestive heart failure. There is a tendency for smokers to have elevated hemoglobin levels.

## Hematocrit

The hematocrit, also called the packed cell volume, is the volume of erythrocytes compared to the volume of whole blood in a sample. The word hematocrit means “to separate blood,” which underscores the mechanism of the test. Blood is centrifuged and red cells are forced to the bottom of a capillary tube. The hematocrit is then calculated as the height of the packed cells compared to the total height of the specimen and is expressed as a percentage. Decreased hematocrit values are again seen in anemia. Increased values, as with red blood cell counts and hemoglobin, are seen with polycythemia, severe dehydration, and hemoconcentration. Very often the hemoglobin and hematocrit tests (i.e., H & H) are done separately without the remainder of the CBC tests.

## Red Blood Cell Indices

The red blood cell indices (MCV, MCH, MCHC) are calculated values determined from the same blood sample used for the red blood cell count, hemoglobin, and hematocrit values. The indices are used to define cell size (i.e., normocytic, macrocytic, microcytic) and hemoglobin content (i.e., normochromic, hypochromic). Traditionally, these quantities have been used as a basis for the classification of anemias. These parameters were originally estimated qualitatively after examining red blood cells on a peripheral blood smear. Automated procedures now replace subjective impressions with objective quantitative standards.

Using the MCV, a description of the red blood cell size is the best index for the classification of anemia. Microcytic cells are seen in iron deficiency anemia and thalassemia. Macrocytes can appear in liver disorders, alcoholism, and folic acid and vitamin B12 deficiencies. Underwriters should note that a medical history of vague physical symptoms with elevated MCV and GGTP might be associated with alcohol-related problems. It is possible to have both microcytes and macrocytes in a blood sample with a normal MCV. This occurs because the MCV is a calculated average. Examination of the blood smear will uncover the variation in size.

The MCH is the average weight of hemoglobin in each individual red blood cell. The MCHC is a measure of the average concentration of hemoglobin in red cells. Decreases in content and concentration of hemoglobin are seen with iron deficiency anemia and thalassemia. An increased hemoglobin concentration can indicate spherocytosis, in which the red cell is shaped like a sphere rather than the normal biconcave disk.

### Platelet Count

The platelet count is also considered a part of the CBC. Platelets will be covered in greater detail later in this chapter.

**Table 1. Normal CBC Values.**

WBC	4500-11,000/cu. mm.
RBC	4.6-6.2 million/cu. mm. (Male)
	4.2-5.4 million/cu. mm. (Female)
HGB	14-18 gm/dl (Male)
	12-16 gm/dl (Female)
HCT	41-52% (Male)
	37-47% (Female)
MCV	82-98
MCH	27-31
MCHC	33-37
PLT	150-350 thousand/cu. mm.

**Table 2. WBC Differential Normal Values.**

50-70%	Neutrophils
20-40%	Lymphocytes
0-7%	Monocytes
0-5%	Eosinophils
0-1%	Basophils

### WBC Differential

Following the quantitative determination of hematological values, the white blood cell differential is performed. A stained blood smear is examined, and 100 consecutive white blood cells are counted and identified. Each of the five types of normal leukocytes (i.e., neutrophils, lymphocytes, monocytes, eosinophils, basophils) and any abnormal cells is noted as a percentage. Increased or decreased numbers of specific white blood cells correspond with certain disease states or conditions. White blood cell disorders will be covered later in this chapter.

## RBC Morphology

The stained blood smear used in the differential provides an excellent opportunity to study the morphology of the red blood cells. It is the best way to observe variations and abnormalities in erythrocyte size, shape, structure, hemoglobin content, and staining properties. Study of a stained blood film together with a hemoglobin value will yield most of the information that would have been obtainable with a complete hematological examination.

Normocytes, or normal size erythrocytes, appear as uniform, circular, homogeneous discs ranging from six to eight microns. Cells smaller than six microns are microcytes, while those larger than eight microns are macrocytes. Anisocytosis is the term used to describe an abnormal variation in cell size. The degree of anisocytosis, microcytosis, or macrocytosis is noted as slight, moderate, or marked.

Variation in red blood cell shape is called poikilocytosis. Red blood cells can take on numerous abnormal shapes. The normal erythrocyte shape is round. Abnormal cells can appear oval-shaped, pear-shaped, helmet-shaped, target-shaped, or teardrop-shaped. These abnormal cells are frequently named for their physical shape, as is the case with sickle cells, target cells, spherocytes, and ovalocytes. Cell fragments are called schistocytes. Red blood cells can also contain inclusion bodies with diagnostic significance.

## **Interpreting the CBC**

If an underwriter is presented with CBC information as outlined above, it can be organized for a simplified analysis. The following items should be considered by the underwriter:

1. source of the CBC results – e.g., an M.D. exam, or a blood study with the application
2. reason the test was done – a diagnostic purpose, treatment follow-up, or a screening test
3. age of the result – current studies are more useful; older tests can reflect a problem that has been resolved.
4. whether a diagnosis has been made – medical records should be checked.
5. whether there is a pattern to the results over time – All CBC results should be organized chronologically to follow the pattern of any potential problem, such as an anemia. The abnormality can have been a one-time problem and now resolved, or the blood levels can be getting lower with each test.

## Using the CBC with Anemias

With an anemia, the CBC numbers should be analyzed using only the hemoglobin, MCV, and MCH. The hemoglobin value is proportional to the oxygen-carrying capacity of blood and is, thus, the most important parameter. Hemoglobin values below 12.0 require further investigation and a value below 10.0 should be considered clinically significant. Next, the MCV and MCH should be checked to classify an anemia as normocytic, microcytic, or macrocytic, and normochromic or hypochromic.

Although the following information is not completely diagnostic, it can serve as a helpful guideline when dealing with and identifying commonly classified anemias.

1. Anemias with normal MCV and MCH are called normocytic and normochromic and include anemia of chronic disease, acute blood loss, and aplastic anemia.
2. Anemias with decreased MCV and MCH (microcytic, hypochromic) are almost always iron deficiency anemia. Very low MCV (below 60) is commonly seen with thalassemia.
3. Anemias with elevated MCV (macrocytic) can be due to folic acid deficiency, vitamin B12 deficiency, or a problem with intrinsic factor that transports vitamin B12 to the intestine. Elevated MCV can also be due to excess alcohol intake.

The complete blood count provides an important series of parameters used in the diagnosis and treatment of hematologic disorders. The diagnosis of anemia should be considered a symptom. Once the anemia is identified and classified, the appropriate classification will lead to a subsequent diagnosis and correct underwriting action.

### **Anemia, an Overview**

Anemia is one of the most common problems encountered in the study of medicine and, therefore, is a subject of utmost importance to the underwriter. Just as with a cold or fever, anemia is a sign or symptom of an underlying disease process that must be identified. These signs and symptoms show a great deal of variation in their relationship to the degree of anemia. For example, acute hemorrhage can cause circulatory collapse, shock, or even death from sudden blood volume loss. On the other hand, a chronic blood loss anemia of equal severity can show no symptoms due to the ability of the human body to adapt to the deficit over a period.

Careful assessment of clinical history, physical examination, and laboratory evaluation are essential to the diagnosis and classification of anemia. The clinical history can provide background information regarding any determinant that can lead to the development of anemia. These factors include:

1. age
2. sex
3. racial and geographic derivation
4. occupations
5. lifestyle
6. family history of bleeding disorders.

A physical exam is done to detect the pathophysiological mechanisms of anemia. Mildly anemic patients can be asymptomatic but, as the anemia worsens, can develop fatigue, malaise, dyspnea on exertion, and possibly headache, faintness, and vertigo. The skin, eyes, tongue, lymph nodes, spleen, liver, and nervous system all hold clues to the potential diagnosis of anemia.

Aside from the CBC, there are many other blood studies that can assist in the diagnosis of anemia. These include the reticulocyte count, blood volume studies, stool for occult blood, serum

iron, ferritin, total iron binding capacity, vitamin B12 and folic acid levels, and bone marrow aspiration and examination.

Anemia can be classified in two different manners. The morphologic classification is based on microscopic observation and works well with the simplified analysis discussed earlier in the reading. Anemias are divided into:

1. normocytic/normochromic anemia (acute blood loss, aplastic, anemia of chronic disease such as renal insufficiency or rheumatoid arthritis)
2. microcytic/hypochromic anemia (iron deficiency, thalassemia)
3. macrocytic anemia (vitamin B12, folic acid deficiency).

Anemias can also be classified by their causes (pathophysiologic classification). General groupings are:

1. blood loss anemia (acute blood loss, iron deficiency)
2. anemia due to decreased production (vitamin B12, folic acid, aplastic, thalassemia)
3. anemia due to increased destruction (hemolytic anemia, sickle cell, thalassemia).

This following section discusses anemias based on their causes.

### **Acute Blood Loss Anemia**

Anemia due to blood loss is a common clinical experience. Blood loss anemia can be due to acute blood loss or chronic blood loss, and the blood loss can be internal or external. Acute blood loss can occur following trauma or can be due to a disease process that significantly damages vascular integrity. Severe blood loss due to hemorrhage will acutely decrease total blood volume to the point of causing cardiovascular collapse. This loss of total blood volume becomes more important than the loss of circulating red blood cells. When blood loss is gradual, the total blood volume is restored by expansion of the plasma volume. Acute blood loss anemia is characteristically a normocytic, normochromic anemia.

Acute blood loss can be due to hemorrhage of the gastrointestinal tract due to malignant tumor, ulcer, diverticulosis, or esophageal varices. Obstetrical problems such as ectopic pregnancy and placenta previa can also result in hemorrhage. Other causes of severe acute blood loss include ruptured aortic aneurysm, trauma resulting in spleen rupture, and bleeding associated with hemophilia.

Subsequent to acute blood loss from accidental trauma in which there is no underlying disease process, the individual can recover by increased red blood cell production in the bone marrow or by administration of packed cells by transfusion. When the hemoglobin returns to normal and there has been no adverse reaction to transfusion, the individual can be considered to have no extra mortality risk. When blood loss is due to a disease process, the underwriter must assess based on the appropriate cause.

## **Iron Deficiency Anemia**

Iron deficiency is the most common cause of anemia worldwide and can initially mimic the symptoms of blood loss anemia. It afflicts individuals of all ages and socioeconomic backgrounds, although it is more common in females, the very young, and those with poor diets. Iron deficiency is apparent in infants with unsupplemented milk diets, in adolescent females due to growth requirements, inadequate diet, and menstrual blood loss, and in pregnant females because the growing fetus requires large amounts of iron. Iron deficiency in adults is usually caused by chronic blood loss due to ulcer, esophageal varices, carcinoma, menstrual bleeding, hemorrhoids, or ulcerative colitis. Malabsorption of iron is rare.

Iron deficiency anemia can be described as a three-stage process:

1. Storage iron is decreased or absent while serum iron levels and hemoglobin and hematocrit levels are normal. This is called iron depletion.
2. Low serum iron concentration without the presence of anemia occurs. This is called deficiency without anemia.
3. Iron deficiency anemia, which is characterized by decreased serum iron, hemoglobin, and hematocrit occurs.

In the early stages of a chronic blood loss anemia, the body will be depleting iron storage as noted above. There can be a mild anemia or none at all. Red blood cell counts, hemoglobin and hematocrit readings may be reduced, but not necessarily to an anemic level. Without serial testing to confirm a slow blood loss, it can be difficult to identify a decreasing trend. The peripheral blood smear and the red blood indices would mimic an acute blood loss with a normocytic, normochromic picture.

Individuals often miss these early symptoms of chronic blood loss anemia as the body slowly adapts to lower blood counts. As mentioned earlier, patients may simply feel a bit tired or fatigued with some tasks. They often fail to correlate their fatigue with bright red blood on toilet tissue from hemorrhoidal bleeding or dark black stools from bleeding in the upper digestive tract. Menstrual bleeding can cause chronic blood loss anemia in premenopausal females. Conditions such as ulcerative colitis or esophageal varices, which can arise at any age, have the potential to cause blood loss that could cause anemia.

Malignancies in the GI tract are more common in older adults, aligning with the recommendation for routine colonoscopies starting at age 50. A reducing blood count may be the first sign of a malignancy. Only an elevated carcinoembryonic antigen (CEA) level, which is usually not done as a screening test, might offer an advanced notice of a cancerous growth.

In the later stages of iron deficiency anemia, the peripheral blood smear will have a characteristic microcytic, hypochromic appearance. The red blood cells can appear as mere rings of hemoglobin in severe cases. The MCV, MCH, and MCHC are all low. Serum iron levels are reduced, while the total iron binding capacity (TIBC), a measure of transferrin present in the circulating blood, will be elevated. Examination of the bone marrow will show depletion of iron stores.

Prior to an underwriting decision, the cause of the anemia must be thoroughly investigated. A determination must be made whether the cause has been identified and resolved or whether the source of chronic blood loss still exists. The significance of blood loss from a malignant tumor or from esophageal varices versus incidental hemorrhoidal bleeding is obvious. The underwriter should always exercise caution due to the possibility of undiagnosed malignancy.

Treatment with oral iron must wait until an accurate diagnosis is made. Response to iron therapy can be monitored with the reticulocyte count.

### **Megaloblastic Anemia**

Megaloblastic anemia is an imprecise term used to designate a group of anemias having similar characteristics of morphology and function. DNA and RNA synthesis is impaired, reducing mitotic divisions in the bone marrow. This results in fewer but larger red blood cells, a macrocytic anemia. Vitamin B12 and folic acid are essential elements of DNA and RNA synthesis. Any deficiency or inability of these elements to reach the bloodstream will result in megaloblastic changes.

A *lack of vitamin B12* also interferes with myelin synthesis that can result in neurological symptoms. Complaints of weakness, anorexia, pallor, and tingling in the extremities are common. Dietary deficiencies of vitamin B12 are rare as the body requires only minimal amounts of this vitamin. Stores in the liver would take three to six years to become depleted. Upon ingestion, vitamin B12 is bound to intrinsic factor (a protein produced in the stomach). This vitamin B12-intrinsic factor complex migrates to the terminal ileum where it is absorbed into the plasma and transported to the liver. Vitamin B12 deficiency is caused by any of several mechanisms. These include inadequate amounts of intrinsic factor due to gastrectomy, resection of the terminal ileum, or bowel disorders such as Crohn's disease. *Pernicious anemia* is an autoimmune disorder that causes a lack of intrinsic factor. This disorder is believed to be caused by antibodies directed against the mucosal cells of the stomach that produce intrinsic factor.

A *deficiency of folic acid* can be due to diet, malabsorption, or inadequate utilization due to anticonvulsive drugs. Folic acid is found in green, leafy vegetables and fruits. It is absorbed in the jejunum and is stored in the liver, but only in quantities sufficient for three months of bodily needs. Dietary deficiencies do exist and are often seen in the elderly and in chronic alcoholics.

Proposed insureds with a history of B12 deficiency must be evaluated for complications involving the spinal cord and neurological damage. Folic acid deficiency should be reviewed for alcohol involvement. Diagnosed pernicious anemia should be evaluated for additional autoimmune disorders.

### **Aplastic Anemia and Pure Red Cell Aplasia**

*Aplastic anemia* is a bone marrow disorder characterized by a reduction of hemopoietic tissue, replacement of hemopoietic tissue, and depletion of all cell lines (pancytopenia). The reduction of functional bone marrow can be caused by radiation, toxins, drugs, or autoimmune suppression of stem cells. Benzene exposure and recent use of the antibiotic isoniazid (INH) for tuberculosis

are probably the most common toxic causes of aplastic anemia. Other toxins that can cause aplastic anemia include arsenic, DDT, and anticonvulsive drugs. Aplastic anemia presents with pancytopenia, a hypocellular bone marrow, and no abnormal cells in the peripheral blood.

*Pure red cell aplasia* is a similar disorder except that only the red blood cell precursors are hypoplastic. It can be an acquired disease, or a rare, congenital disorder called Blackfan-Diamond syndrome. Pure red cell aplasia can be caused by the same or similar toxic substances as those causing aplastic anemia. It can also be seen with lupus erythematosus, chronic lymphocytic leukemia, or lymphoma. A normocytic, normochromic anemia is the only sign of this disorder.

Because of the lack of clinical signs, an individual is usually first diagnosed when the disease has progressed so far that only the late consequences of pancytopenia are present. These include weakness and fatigue due to anemia, fever, and infection due to neutropenia, and hemorrhage and bruising due to thrombocytopenia. Treatment includes the transfusion of blood components and possible bone marrow transplantation.

Aplastic anemia has a poor prognosis. The disease process can be brief and overwhelming or can be a prolonged smoldering disease lasting many years. The overall mortality is 65-70% with a median survival of about three months. Those individuals exposed to toxins do better than those with idiopathic or congenital anemia. Early identification of the toxic substance, leading to a reversal of the hypoplastic marrow, is favorable. When the disease shows steady progression or follows an attack of hepatitis, mortality is high. The most common cause of death is hemorrhage or infection. Due to the poor prognosis, underwriters must be very careful when evaluating these proposed insureds. The most favorable situations are those where the cause has been clearly diagnosed and the anemia has been resolved for several years.

## Hemolytic Anemias

A hemolytic process is defined as a situation in which there is shortened red blood cell survival. Anemia will develop if the rate of cell production is not sufficient to compensate for the decrease in cells resulting from excessive destruction. Red blood cell survival must be extremely short for the bone marrow to be outdone. Hemolysis can be due to intracorporeal or extracorporeal defects. Intracorporeal defects are usually hereditary and result from abnormalities of the cell membrane, hemoglobin molecule, or enzymatic defects. Extracorporeal defects are usually acquired and can be caused by immune or nonimmune mechanisms, infections, or severe burns. Hemolysis can occur extravascularly in the spleen, liver, or bone marrow, or intravascularly in the circulatory system.

### Hereditary Spherocytosis

Hereditary spherocytosis is the most common of a group of hemolytic anemias involving the cell membrane. Often called congenital hemolytic jaundice, it is a disease of autosomal dominant inheritance. Red blood cells become sphere-shaped and are destroyed in the spleen. Anemia may or may not be present based on the compensatory ability of the bone marrow, although jaundice can be present due to excess red blood cell destruction. Splenectomy is the most common treatment and is almost invariably curative. The operative mortality of splenectomy is low, but

the lack of a spleen leads to a significant increase in the risk of acquiring serious infections. This is most apparent in young children. Children who have had a splenectomy present a higher mortality risk until age 15-18. Other proposed insureds should be evaluated based on the recency of the problem and any recurrence of anemia, symptoms, or crisis.

### G-6-PD Deficiency

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is a hereditary abnormality in which the activity or stability of the enzyme G-6-PD is markedly diminished. A G-6-PD deficiency can result in hemolytic anemia following administration of oxidant drugs, during infection, in response to stress, from ingestion of fava beans, or inhalation of pollen. Drugs that cause hemolytic episodes include antimalarials, aspirin, sulfa drugs, and antibiotics. The deficiency has an X-linked recessive pattern of inheritance with expression in males. Basic treatment is usually accomplished by avoiding the oxidant drugs. Underwriters must ascertain the number of episodes and their recency and verify that the G-6-PD deficiency has been confirmed as the cause of the anemia.

### **Hemoglobinopathies**

Hemoglobinopathies are hereditary disorders involving the polypeptide chains of the globin portion of the hemoglobin molecule, resulting in hemolytic anemias. Hemoglobin A is the hemoglobin of normal adults. There are four clinically important abnormal hemoglobins: S, C, D, and E. Individuals can inherit a gene for a hemoglobinopathy from one or both parents.

### Sickle Cell Disease

Homozygous hemoglobin S (i.e., inheritance from both parents) is the cause of sickle cell disease, a serious chronic hemolytic anemia that first manifests itself in early childhood and is often fatal before age 30. Worldwide, sickle cell disease is found almost exclusively in the black population. Individuals are in reasonably good health until a crisis occurs. When oxygen is reduced, the abnormal hemoglobin molecule polymerizes into crystals. These crystals deform the cell to a sickle shape that is unable to pass through the capillary system. This results in blood vessels tangled with sickled cells causing infarction or tissue death in organs. The cells are vulnerable to trauma and are readily destroyed in the spleen.

Underwriters must firmly establish whether the diagnosis is sickle cell disease or heterozygous sickle cell trait (with inheritance from only one parent). Individuals with sickle cell trait do not present extra risk provided they have not experienced any crises. This diagnosis can be determined using hemoglobin electrophoresis, a definitive test. Screening tests will only indicate the presence of hemoglobin S but will not differentiate between the disease and the trait. Children and young adults present the greatest risk due to numerous complications and a high mortality rate. Mortality risk is lower if proposed insureds have gone long periods without a crisis. Underwriters should be alert when underwriting a family policy for the possibility of children developing the disease when both parents have the trait.

## Thalassemia

Thalassemia is caused by decreased synthesis of one of the polypeptide chains that make up hemoglobin. Imbalanced chain production leads to ineffective red blood cell production. The anemia of thalassemia is due to both decreased red cell production and hemolysis. The homozygous form, called *thalassemia major*, occurs when genes for thalassemia are inherited from both parents. The heterozygous form is called *thalassemia minor*. The expression of the disorder is not as definitive as with sickle cell anemia where the homozygous disorder is severe, and the heterozygous disorder is of little consequence. The rate of hemoglobin synthesis will vary, making it difficult to differentiate the severe heterozygote from the mild homozygote. Diagnosis is by hemoglobin electrophoresis.

The most common types of thalassemia are characterized by decreased production of beta chains. *Beta thalassemia major* is also called Cooley's anemia. Clinical findings include severe hemolytic anemia, jaundice, and splenomegaly that become evident in childhood. Conditions can vary, with clinical problems arising during periods of stress such as pregnancy. *Beta thalassemia minor*, also known as beta thalassemia trait, is probably the most common of the thalassemias and presents with mild anemia, low MCV (60-70), and an increased red blood cell count.

There is no definitive treatment for any of the thalassemia syndromes. Therapy is only supportive, with blood transfusion, folic acid administration, and splenectomy being the only useful forms of treatment. Iron overload is a danger with multiple transfusions. Splenectomy will eliminate the source of hemolysis, but it does not improve the basic defect of hemoglobin synthesis. Most cases of thalassemia major are associated with substantially increased morbidity and mortality. Cases in which there have been no anemic crises for at least five years are more favorable.

## **Polycythemia**

Polycythemia is a general term that literally means "many cells." There are three types of polycythemias: polycythemia vera, secondary polycythemia, and relative polycythemia.

### Polycythemia Vera

Polycythemia vera is a myeloproliferative disorder of the bone marrow that can terminate in acute granulocytic leukemia. There is an absolute increase in the peripheral red blood cell count, the hemoglobin, and the hematocrit, as well as an increase in red blood mass and the viscosity of the blood. Increased platelet counts can lead to a high incidence of thrombosis with multiple systemic complications. Polycythemia vera is a disease involving all cellular elements of the blood rather than the red blood cell series alone. Approximately 30% of all patients will develop leukemia. Management of the disorder is often accomplished by periodically drawing off blood (i.e., phlebotomy).

## Secondary Polycythemia

Polycythemias from other causes are known as secondary polycythemias. These polycythemias are usually due to lack of oxygen or because of hormonal problems. Decreased oxygen tension in the lung increases erythropoietin production and subsequent red blood cell production. This hypoxia can be caused by respiratory disorders such as emphysema or chronic bronchitis, or by high altitude. Decreased alveolar oxygen tension results in incomplete arterial oxygen saturation. There is a direct relationship between the severity of this oxygen deficit and the degree of red blood cell elevation. Several forms of heart disease characterized by a venoarterial shunt or valvular disorder, certain renal and neoplastic disorders, and testosterone administration can also cause secondary polycythemia. Testosterone replacement therapy creates a polycythemia response in 2-40% of patients with a possible risk of venothromboembolism.

## Relative Polycythemia

There are several other benign physiological variations that tend to affect the red blood cell count. Dehydration causes hemoconcentration, which will artificially increase the red cell count. This can be seen with excessive vomiting, diarrhea, severe burns, stress, or exercise. The increased body fluid content in pregnancy dilutes the normal number of erythrocytes causing a low count. Drug reactions can increase or decrease the erythrocyte count. Smokers can also exhibit an elevated hematocrit level due to diminished plasma volumes caused by the diuretic effect of nicotine.

## **White Blood Cell Disorders**

There are five types of normal leukocytes: neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Neutrophils, eosinophils, and basophils are termed granulocytes. These three distinct cell lines originate from a common precursor stem cell and differentiate until specific granulation in the cells' cytoplasm appears. These granules are released to neutralize infections and foreign substances.

### Neutrophils

Neutrophils are the most numerous of white cells, comprising 50% to 70% of circulating leukocytes. Neutrophils are also called polymorphonuclear neutrophils, PMNs, polys, segmented neutrophils, and segs. As the neutrophil precursors mature, the nucleus undergoes several changes resulting in a nucleus with pinched off segments connected by a fine filament. This multinucleated cell gives rise to the name segmented neutrophils. The phase just prior to segmentation is called a band or stab. Bands usually comprise only 1-5% of the cells in a normal differential. An increase in bands, termed a shift to the left, will occur when there is an increased demand for neutrophils and the bone marrow is releasing these cells prematurely, such as when there is a bacterial infection.

Neutrophils are most important in fighting bacterial infection and inflammation. They are attracted to areas of tissue invasion by microorganisms and are capable of phagocytizing, neutralizing, and destroying bacteria and yeasts. Neutrophils can also digest inert foreign particles

and inflammatory debris and can be thought of as scavenger cells. A marked decrease in the neutrophil population alone (neutropenia) can occur due to a variety of causes. Predominant causes include the association with other secondary disease processes or drug-induced reactions.

### Eosinophils

The eosinophilic granulocyte, or eosinophil, has a similar structure to that of the neutrophil, with the striking difference that the cytoplasm contains large granules that stain a bright red orange. Eosinophils make up only 1-5% of circulating leukocytes. There is a close association between eosinophils and allergies. Allergic diseases such as bronchial asthma, hay fever, angioneurotic edema, and urticaria will precipitate an eosinophilic response. An eosinophilic response pushes the cells from the bone marrow into the peripheral blood and then into nearby tissues. Eosinophils are found in the sputum in bronchial asthma, nasal discharge in hay fever, and in urticarial skin lesions. Pronounced eosinophilia will occur in tissues invaded by parasites. Eosinophilia of various degrees can also be seen in infectious diseases, leukemias, and during drug reactions.

### Basophils

Basophils are also easily recognizable cells although quite rare, comprising less than 1% of circulating leukocytes. The basophil contains heparin and histamine and appears in allergic states, chronic granulocytic leukemia, and following irradiation. Although rare, these cells appear to play an important role in the immune system, responding to bacteria and parasites, recognizing, engulfing, and destroying foreign organisms. The release of histamine dilates blood vessels, improves blood flow, promotes healing, and provides other immune cells better access to an infection site. The release of heparin prevents blood clotting at the location.

### Lymphocytes

The lymphocyte is the second most abundant white blood cell. Lymphocytes constitute 20% to 40% of all leukocytes and are even more abundant in children. When the number of lymphocytes exceeds the number of neutrophils in the differential, it is termed a reverse differential.

Most circulating lymphocytes are either T lymphocytes or B lymphocytes. They cannot be differentiated by size or staining technique on a standard blood smear. During fetal life, lymphocyte precursors originate in the bone marrow and are programmed to function in one of two ways. Those lymphocytes influenced by the thymus are called T cells, while those influenced by a “bursal equivalent” (exact anatomic site is unknown) are termed B cells. T cells function in cell-mediated immunity, delayed hypersensitivity, graft rejection, and defense against intracellular organisms such as tuberculosis and brucellosis. B cells function in humoral immunity or the production of antibodies.

Lymphocytosis, an increase in lymphocytes, most often occurs when the blood shows neutropenia. In other words, the lymphocyte count is increased due to a decrease in neutrophils. This is termed relative lymphocytosis. Absolute lymphocytosis is present with certain bacterial

and viral infections, during recovery from acute infections, with infectious mononucleosis, and with chronic lymphocytic leukemia (CLL).

Infectious mononucleosis is a common disorder caused by the Epstein-Barr virus (EBV) that mostly affects younger individuals. Symptoms include fatigue, sore throat, swollen lymph glands, and fever. Complications of splenomegaly and inflamed liver are rare and most cases resolve on their own.

### Monocytes

The monocyte is the largest cell of normal blood. It is transported in the bloodstream and migrates into the tissues where it functions as a macrophage. Macrophages ingest and destroy particles, debris, and bacteria. Monocytes constitute up to 7% of the peripheral leukocyte population. Monocytosis is present during the recovery stage of acute infections and with hematologic disease, lymphoma, and monocytic or granulocytic leukemia.

## **Leukemia**

Leukemia is a malignant disorder characterized by the uncontrolled proliferation of one or more types of immature or abnormal leukocytes. Leukemias were originally classified based on the course of the disease process. Acute leukemia meant an estimated survival of less than six months, subacute referred to a survival of six months to less than one year, and chronic leukemia meant survival of more than one year. As treatment methods advanced, this classification method became outdated. The acute and chronic definitions are now based on the presence of immature cells. Acute leukemias are characterized by a predominance of immature cells while chronic leukemias have a proliferation of mature-looking cells.

Leukemias have an impact on morbidity and mortality from several different origins. A proliferation of abnormal cells in the bone marrow will crowd out the normal cell lines. Depleted red blood cell production results in anemia, reduced platelet production will lead to bleeding disorders, and depleted white blood cell production will make the body more prone to infection. Treatment itself can have an adverse effect as chemotherapy destroys all bone marrow cells, leading to results similar to those described above. Leukemic infiltrates can also play a role as leukemic cells spread to other organs including the brain, spinal cord, lungs, heart, liver, spleen, and kidneys.

There are four common leukemias: acute and chronic lymphocytic leukemia and acute and chronic myelogenous leukemia:

1. acute lymphocytic leukemia – Acute lymphocytic leukemia is most common in children and is the most curable.
2. chronic lymphocytic leukemia – Chronic lymphocytic leukemia is a disorder of morphologically mature but immunologically immature lymphocytes and is manifested by the progressive accumulation of these cells in the blood, bone marrow, and lymphatic tissues. This leukemia has a middle age to elderly onset with males twice as likely to be affected.

3. acute myelogenous leukemia – Acute myelocytic (myelogenous) leukemia is characterized by the presence of myeloblasts in the peripheral blood. Between 60% and 70% have a complete remission with remission being inversely related to age.
4. chronic myelogenous leukemia – Chronic myelocytic (myelogenous) leukemia is one of the myeloproliferative disorders, which include polycythemia and thrombocythemia. It has a gradual onset at older ages and is not curable with conventional chemotherapy.

## **Platelets and Blood Coagulation**

Platelets (thrombocytes) are the smallest of the formed elements in the blood. Platelets in the peripheral circulation represent pinched-off portions of a megakaryocyte. Megakaryocytes are large, multinucleated cells found in the bone marrow. One megakaryocyte will release several thousand platelets. Platelets are nonnucleated, round or oval, disc-shaped structures responsible for the preservation of capillary integrity and coagulation. Approximately two-thirds of all platelets are found in the circulating blood while one-third are harbored in the spleen. The average life span of a platelet is 7.5 days. Normal platelet counts range from 150,000 to 350,000 per cubic millimeter.

### Platelet Disorders

Abnormally increased numbers of platelets (thrombocythemia, thrombocytosis) occur in numerous clinical situations. Cancer, chronic myelogenous leukemia, polycythemia vera, acute infections, trauma, and post-splenectomy are common conditions in which platelet counts increase. Platelets can also be elevated following strenuous exercise or physical activity.

Decreased platelet counts (thrombocytopenia) are seen in idiopathic thrombocytopenic purpura (ITP), hemolytic, aplastic, or pernicious anemia, during cancer therapy, and from drug toxicity. There are many drugs that either cause thrombocytopenia or affect the ability of the platelet to function. Examples include quinidine, gold salts, indomethacin (Indocin®) and heparin. Alcohol and aspirin both affect platelet function adversely. Aspirin has been used therapeutically as an antiplatelet agent to prevent thrombosis in heart patients.

ITP is a disorder of unknown cause characterized by marked thrombocytopenia and large skin discolorations (i.e., petechiae and ecchymosis) due to subcutaneous hemorrhages. It is often encountered in children following a viral infection. The disease course is often acute, and the prognosis is favorable. Adults tend to develop a more chronic disease course with relapses and the need for treatment with steroid drugs.

### Hemostasis

Hemostasis is the prevention of blood loss. There are several hemostatic mechanisms. The first response to injury of a blood vessel is vasoconstriction, the rapid contraction of a vessel wall to retard the rate of blood loss. Platelets release serotonin causing the vessels to constrict. Vasoconstriction alone can be sufficient to achieve hemostasis if the injury is minor. Exposed collagen fibers from the injury cause platelets to adhere. Adenosine diphosphate (ADP) is then released, which causes the platelets to aggregate. The aggregated platelets at the site of injury

form a platelet plug. Coagulation factors in the plasma and from the platelets initiate a cascade of reactions culminating in a fibrin clot. A fibrin clot is essential for sustained hemostasis.

The coagulation cascade is a complex process of chemical events in which clotting factors are activated and then, in turn, activate the next factor in the process. The clotting factors have been identified with Roman numerals. Factor VIII is best known for its association with hemophilia.

The precise number of platelets necessary for hemostasis has not been established. Platelet counts below 20,000 per cubic millimeter can cause spontaneous bleeding, prolongation of bleeding time, small pinpoint bruises on the skin (petechiae), or larger bruises (ecchymoses). Individuals with severe platelet deficits show signs and symptoms of gastrointestinal bleeding, hemolysis, hematuria, vaginal bleeding, nosebleeds, and bleeding gums.

There are several common laboratory tests that can be used to monitor anticoagulant therapy or to make a diagnosis of a factor deficiency: the prothrombin time (PT), the activated partial thromboplastin time (APTT), and the international normalized ratio (INR). Common anticoagulants used medically include heparin and Coumadin®. Coumadin® (generic name warfarin) impairs the synthesis of vitamin K, which is needed to produce Factors II, VII, IX, and X. Coumadin® therapy requires routine monitoring using the INR or the prothrombin time test. Newer anticoagulants Xarelto® and Eliquis® are Factor X inhibitors used for the treatment and prevention of deep vein thrombosis and acute pulmonary embolism, and to reduce the risk of stroke in people with nonvalvular atrial fibrillation. Routine monitoring is not required.

## **Coagulation Disorders**

Coagulation disorders can involve a number of the factors of blood coagulation:

1. defects in the ability of platelets to function thus leading to aggregation disorders
2. deficiency or inactivity of coagulation factors causing a break in the cascade chain
3. defects in which the system overreacts, resulting in a hypercoagulable state.

### Hemophilia A

Hemophilia A, caused by a deficiency of factor VIII, is one of the most commonly discussed coagulation defects. It is an inherited disorder with an X-linked recessive inheritance pattern. This means that it is transmitted on the X chromosome and only exhibits the bleeding disorder trait when there is no other normal X chromosome present. This causes females to be the carriers while the disease process develops predominantly in males.

### Hemophilia B

Hemophilia B (Christmas disease) is a similar disorder caused by a lack of factor IX. Individuals with these disorders will have initial platelet plug formation but lack the ability to develop a fibrin clot. This leads to a delay of several hours or days before a bleeding episode ends. Bleeding can persist for several days or weeks. Due to this defect in the maintenance stage of hemostasis, bruises, ecchymoses, and deep subcutaneous and intramuscular hematomas occur

frequently, whereas petechiae and purpura do not occur. Recurrent hemarthrosis can result in joint damage. Any organ in the body can be a site of bleeding with hemorrhage always having lethal potential.

### Von Willebrand's Disease

Von Willebrand's disease, also called pseudohemophilia, is a hereditary disorder of hemostasis transmitted as an autosomal trait and characterized by a prolonged bleeding time. Von Willebrand's involves both platelet and factor VIII deficiencies resulting in problems with platelet adhesion and fibrin formation. Bleeding is usually mucosal and cutaneous with easy bruising and nosebleeds occurring. This condition tends to be exhibited more often in females, with menorrhagia and postpartum bleeding being the most common symptoms.

### Hypercoagulable States

As opposed to the many conditions in which there is a deficiency or defect in the coagulation process, certain hypercoagulable states can exist when the body does not turn off the coagulation function. These hypercoagulable states can increase the incidence of transient ischemic attacks (TIAs), cerebrovascular accidents (CVAs), retinal infarcts, deep vein thrombosis, pulmonary emboli, and spontaneous abortions.

In the normal coagulation cascade, a blood clot forms only at the site of trauma. Braking mechanisms are in place to prevent the ongoing cascade process from continuing clot formation beyond the site of trauma. These braking systems, including plasmin, antithrombin III, protein C, and protein S, not only prevent excessive clot formation when injury occurs, but also prevent spontaneous inappropriate clot formation. If these braking functions are defective, blood clot formation can occur unchecked.

The presence of antiphospholipid antibodies including lupus anticoagulants and anticardiolipin antibodies can stimulate clot formation causing thrombosis in either arteries or veins. In addition, the presence of factor V Leiden, a variant of the normal factor V, will cause blood to have an increased tendency to clot. This autosomal dominant disorder most often results in blood clots in the legs. These conditions are treated with aspirin or an anticoagulant such as Coumadin®, Xarelto®, or Eliquis® to eliminate recurrent deep vein thrombosis.

### Hematology Flow Chart

#### **White Blood Cells = WBC's = Leukocytes**

Increased levels = Leukocytosis

    Increased Neutrophils = Neutrophilia

        Seen in bacterial infection

    Increased Lymphocytes = Lymphocytosis

        Seen in viral or bacterial infections

Decreased levels = Leukopenia

    Seen in viral response

    Seen in drug-induced response

## **Red Blood Cells = RBC's = Erythrocytes**

Increased levels = Polycythemia

Polycythemia vera

A myeloproliferative disorder

Secondary polycythemia

Related to pulmonary disorders, lack of oxygen, CHF

Relative polycythemia

From dehydration or smokers

Decreased levels = Anemia

Decreased RBC production

Thalassemia

Cancer, leukemia

Dietary

Increased RBC destruction

Hemolytic anemia

Hereditary spherocytosis

Hemoglobinopathies

Blood Loss, acute or chronic

Decreased levels with MCV elevated

Folic acid or B12 deficiency

Pernicious anemia

Alcoholism

Decreased levels with MCV decreased

Iron deficiency anemia

Decreased levels with MCV normal

Acute blood loss

Aplastic anemia

Chronic disease

## **Platelets = Thrombocytes**

Increased levels = Thrombocytosis

Cancer, leukemia

Polycythemia vera

Following splenectomy

Strenuous physical activity

Decreased levels = Thrombocytopenia

ITP or post viral infection

Anemias

Cancer therapy or drug toxicity

## **Review Questions – ALU 201, Chapter 12**

1. Which of the following statements regarding hemophilia A is correct?
    1. It is caused by a factor IX deficiency.
    2. It develops predominantly in males.
    3. It is transmitted on the Y chromosome.
    4. It is also known as Christmas disease.
  2. Aplastic anemia is characterized by all the following EXCEPT:
    1. replacement of hemopoietic tissue
    2. depletion of cell lines
    3. reduction of hemopoietic tissue
    4. hypercellular bone marrow
  3. Which of the following statements regarding polycythemia vera is/are correct?
    - A. Hemoglobin and hematocrit levels are often decreased at diagnosis.
    - B. Treatment can involve periodic phlebotomy.
    - C. Most individuals will develop aplastic anemia.
- Answer Options:
1. B only is correct.
  2. C only is correct.
  3. A and B only are correct.
  4. A, B, and C are correct.
4. Describe the hypercoagulable state, its significance to underwriting, and how it is usually treated.
  5. Compare and contrast polycythemia vera and secondary polycythemia.

6. A malignant disorder characterized by the uncontrolled proliferation of abnormal white blood cells is:
  1. thalassemia
  2. leukemia
  3. von Willebrand's disease
  4. idiopathic thrombocytopenic purpura
7. Hematopoiesis is the:
  1. depletion of platelets
  2. production of blood cells
  3. transportation of oxygen
  4. prevention of blood loss
8. List and discuss four of the five items that should be considered by an underwriter when reviewing a CBC report.
9. Name five primary causes of iron deficiency anemia in adults.
10. Compare and contrast the causes and disorders associated with thrombocytosis and thrombocytopenia.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 2: It develops predominantly in males – page 18.

### *Review Question 2*

Answer 4: hypercellular bone marrow – page 10.

### *Review Question 3*

Answer 1: B only is correct – page 13.

### *Review Question 4*

Refer to page 19.

### *Review Question 5*

Refer to pages 13-14.

### *Review Question 6*

Answer 2: leukemia – page 16.

### *Review Question 7*

Answer 2: production of blood cells – page 1.

### *Review Question 8*

Refer to pages 6-7.

### *Review Question 9*

Refer to pages 9-10.

### *Review Question 10*

Refer to pages 17-18.



## **CHAPTER 13**

### **CORONARY ARTERY DISEASE**

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## CORONARY ARTERY DISEASE

### Introduction

Over the past several decades, advances in the understanding and treatment of acute and chronic coronary artery disease (CAD) have led to a steady decline in the mortality of this impairment. Nevertheless, heart attacks occur in over 700,000 people in the United States every year. It remains the most common cause of death in adults overall and, tragically, the most common cause of premature death in adults before the age of 65. In 15-20% of adults with CAD, their first symptom is their last symptom, in that they fall victim to the syndrome of sudden unexpected death as the first manifestation of this impairment. Despite these sobering statistics, CAD mortality rates have been falling since 1969 and the number of people alive with CAD (and seeking life insurance) has been increasing each year. This presumably reflects the awareness and treatment of CAD risk factors, the improving survival rates of the acute coronary syndromes, and technical advances in revascularization strategies, as well as advances in the medical treatment of the aging population.

Ongoing medical research has increased our understanding of the etiology and pathogenesis of atherosclerosis and its clinical sequelae. Indeed, risk factor analysis and intervention are major weapons in the fight against atherosclerotic disease. The association of serum lipids with clinical CAD dates back to the 1940s and 1950s when total cholesterol and triglycerides were linked to atherosclerotic disease in both cross-sectional and prospective studies. In the 1960s and 1970s, focus shifted to the serum lipoprotein cholesterol fractions, emphasizing the protective value of high-density lipoprotein (HDL) and the proatherogenic association of low-density lipoprotein (LDL) cholesterol. Apolipoproteins (e.g., B, A<sub>1</sub>, E, Lp[a]), metabolic products (homocysteine), and serum inflammatory markers (C-reactive protein) have also been found to be additional markers of CAD. Genetic markers can also be included as even stronger predictors of later atherosclerotic sequelae. Similar trends can be identified for other risk factors such as hypertension, diabetes, and obesity.

The past several decades have also witnessed rapid advances in the medical treatment of coronary artery disease. Cardio-selective beta-blockade and calcium channel blockers are used extensively, as well as angiotensin-converting enzyme (ACE) inhibitors and, more recently, antiplatelet, and anticoagulant drugs such as clopidogrel (Plavix®).

Finally, significant progress in the treatment of CAD has been in revascularization (i.e., restoring blood flow to obstructed or blocked coronary arteries). Microsurgical bypass graft implantation techniques (CABG surgery), balloon angioplasty (PTCA), and most recently, drug-eluting (DES) coronary stenting have all proven effective in the treatment of the angina syndromes and myocardial infarction.

### Medical Risk Assessment in CAD

The major determinants of prognosis in patients with CAD are:

1. *coronary obstruction* – The prognosis of CAD is dependent on the number of coronary vessels obstructed by plaque, as well as the severity of obstruction (or occlusion) at each

site, an indication of the amount of myocardium at risk. This relationship will be explored further following an overview of angiography and the coronary circulation.

2. *left ventricular function* – The normal heart can pump over half of its blood volume with each stroke. This is measured by ventriculography, echocardiography, or nuclear scan as the ejection fraction, and is normally 50% or greater. Left ventricular dysfunction (abnormal function), particularly in the setting of myocardial ischemia or infarction, is an important factor in predicting survival outcomes.
3. *presence of ischemia* – In addition to a clinical history consistent with angina, there are invasive and non-invasive cardiac studies that serve to further define the frequency and severity of ischemic episodes. Evidence of ongoing ischemia will usually predict reduced survival in the absence of medical or surgical intervention.
4. *risk factor analysis* – Increased understanding of the pathophysiology of atherosclerosis will highlight the importance of CAD risk factor evaluation. Risk factor analysis includes:
  - age and gender
  - genetic predisposition such as the familial dyslipidemias
  - lipids, including cholesterol, triglycerides, and apo-lipoprotein sub-fractions
  - obesity
  - hypertension
  - diabetes
  - homocysteine and c-reactive protein (CRP).

Risk factor assessment and control are crucial, both in apparently healthy individuals (primary prevention) as well as in individuals with known CAD (secondary prevention), to reduce CAD risk. Not surprisingly, risk factor analysis is essential to critically interpret the results of cardiac testing in the insurance applicant.

## The Coronary Circulation

### Coronary Artery Anatomy

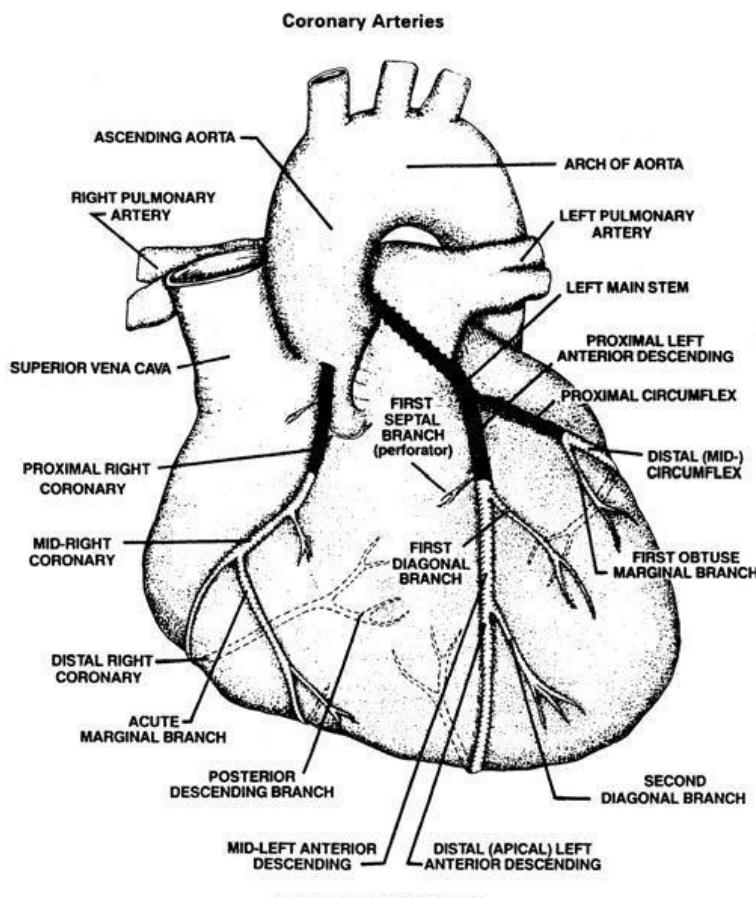
The coronary arteries are major blood vessels that emerge from the aortic root to supply the heart muscle with oxygen and nutrients. Reference is usually made to left and right systems based on where the take-off from the aorta occurs. (See Figure 1.)

1. *Left main artery*: The left main coronary artery (LMCA) arises from the upper portion of the left aortic sinus. It then usually bifurcates by giving off the left circumflex artery (LCx) at right angles and continues in a straight line as the left anterior descending artery (LAD). Any significant obstruction of blood flow within the left main artery could result in severe myocardial damage.
2. *Left anterior descending artery*: The left anterior descending (LAD) artery supplies the anterior and septal walls of the left ventricle. It gives rise to the septal perforating arteries that go deep into the muscular septum and to the diagonal arteries that course over the anterolateral free wall of the left ventricle. The LAD and its branches are usually considered the most important coronary artery system after the LMCA and obstruction or occlusion of this system could also result in extensive myocardial injury.

3. *Left circumflex artery*: The left circumflex (LCx) artery is responsible for blood supply to the lateral ventricular wall. The artery can terminate in one or more large obtuse marginal (OM) branches, which course over the lateral to posterolateral left ventricular free wall. In 10-15% of cases, the LCx gives rise to a posterior descending artery, providing circulation to the inferior and posterior walls of the left ventricle.
4. *Right coronary artery*: In 85% of cases, the posterior descending artery arises from the right coronary artery, supplying the inferior and posterior wall of the left ventricle as well as the right ventricle.

The term “dominance” is often used to describe the anatomic configuration of the blood supply to the posterior descending artery. Right dominance, with the posterior descending artery emerging from the right coronary artery, occurs in 85% of cases; the left circumflex (i.e., left dominance) provides the posterior descending circulation in the remaining 15%. Even in the setting of right dominance, however, the left circumflex artery will supply a very significant portion of the left ventricle. In most cases, therefore, obstructive disease of the LCx is considered more of a risk than isolated RCA disease.

**Figure 1. Coronary artery anatomy.<sup>1</sup>**



Modified from Lincoln National Reinsurance Manual 1986

## The Pathology of Atherosclerosis and Myocardial Ischemia

### *The pathology of atherosclerosis*

The coronary arterial wall (Figure 2) is composed of three layers:

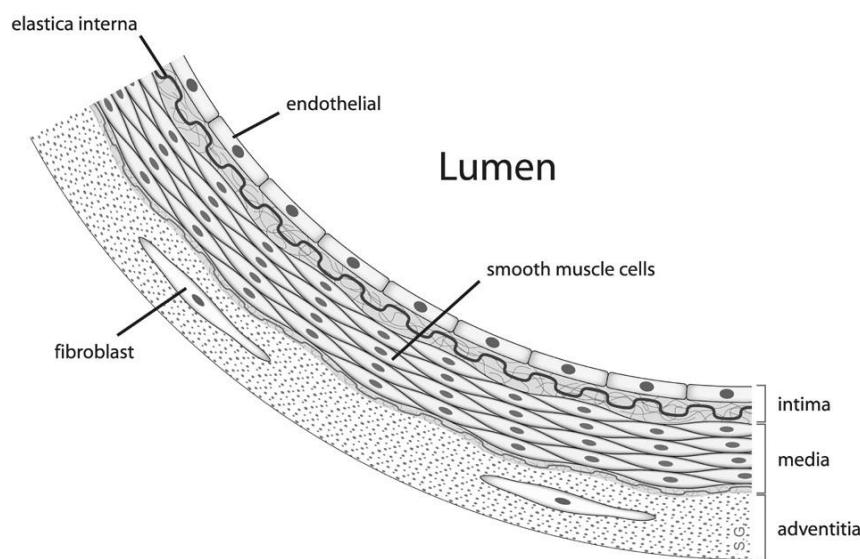
1. intima
2. media
3. adventitia.

The intima is the innermost layer and is in direct contact with the flowing blood. The open space through which blood flows is known as the lumen. The most important structure in the intima is the endothelium, a layer of endothelial cells lining the whole vascular wall. The normal endothelium plays an important role in protecting against atherosclerosis. It acts as a selective barrier to prevent plasma lipid accumulation within the vessel wall and has also been shown to prevent blood clot formation and arterial spasm.

The media is the middle layer of the vascular wall. Its smooth muscle cells and connective tissue are responsible for the vasodilatory properties of the blood vessel.

The adventitia is the outermost layer of the vascular wall. It consists of fibroelastic tissue without smooth muscle cells. It also houses nutrient vessels (i.e., vasa vasorum) of the vascular wall and nerve fibers. In addition to carrying nutrients to the inner layers of the vessel, the adventitia gives the vascular wall a fair amount of stability by connecting the artery to its surrounding tissue.

**Figure 2. Coronary artery wall layers.<sup>2</sup>**

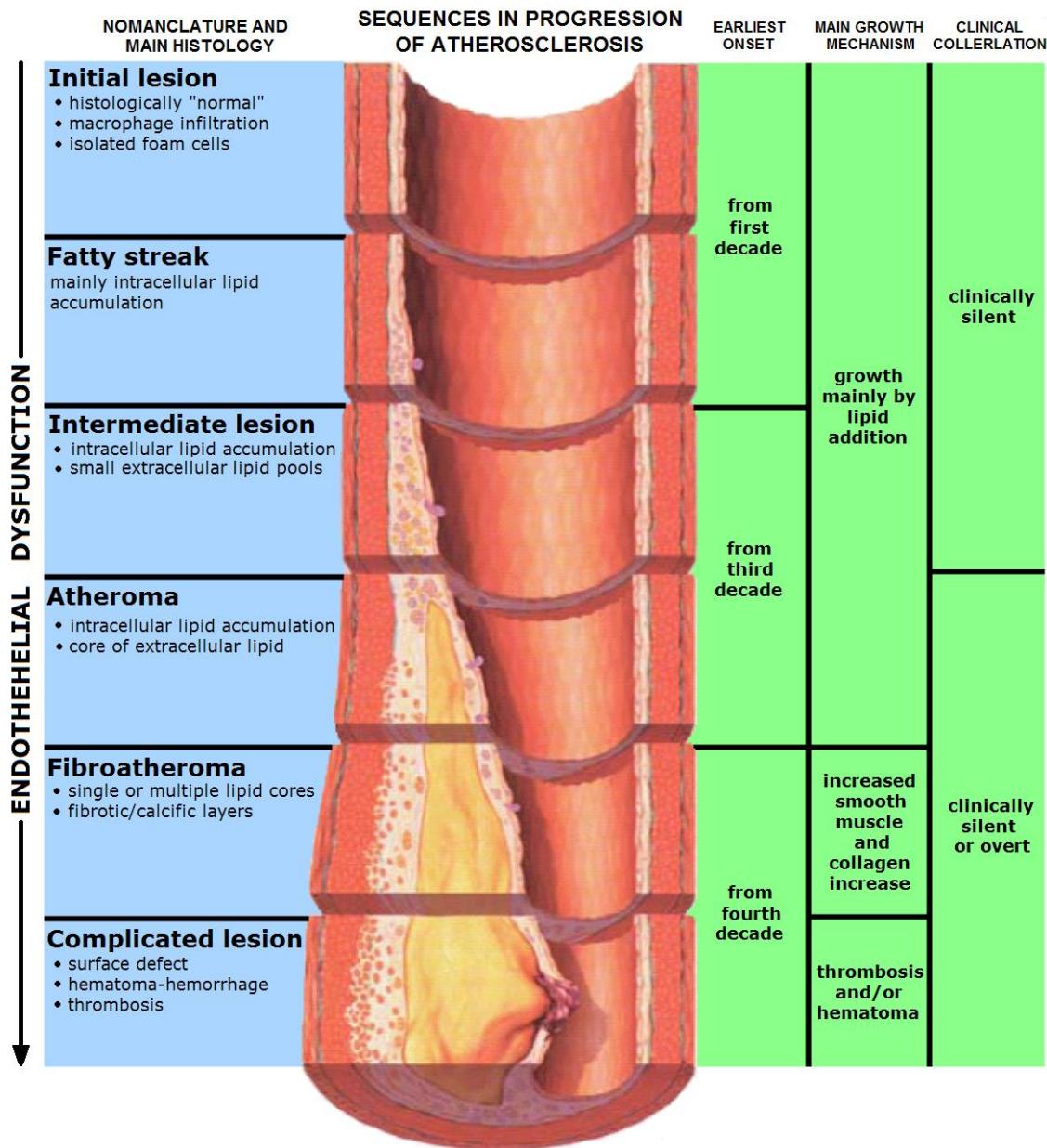


Atherosclerosis affects mainly the medium-sized coronary arteries on the epicardial (outer) surface of the heart.

The classic *atheroma or plaque* appears as a rounded, raised lesion, white with a yellow core. Usually these plaques cause some degree of stenosis, narrowing the vascular lumen. Microscopically, they are composed of a fibrotic cap and a necrotic core containing cellular debris, extracellular lipids, cholesterol crystals, calcium deposits, and blood-borne material. These deposits of calcium contribute to the sensitivity of coronary calcium scans (i.e., electron beam CT or EBCT) in detecting early atherosclerosis. By increasing their content of lipid material, these plaques can rupture through the thin fibrotic cap or can fissure with subsequent exposure of the internal constituents of the atherosclerotic plaque to the flowing blood. Because of the highly thrombogenic properties of these components, the ruptured or fissured plaques represent a major risk for mural or occlusive thrombosis, the so-called *complicated plaque*.

Fissuring or rupture of complicated atherosclerotic plaques with subsequent occlusive thrombi plays a fundamental role in development of the acute ischemic syndromes. In addition, emerging evidence suggests that vicious cycles of plaque disruption, thrombosis, and scarring can also be important in the progression of atherosclerosis in asymptomatic individuals and in those with stable angina.

**Figure 3. Clinical and pathological progression of atherosclerosis.<sup>3</sup>**



While plaque progression can be slow in some lesions, it is probable that for most, the progression from early lesion to occlusion is very rapid by means of *plaque rupture*, resulting in blood clot formation that occludes the coronary artery. A rapidly progressive coronary lesion produced by plaque rupture and resultant thrombosis can also be responsible for myocardial ischemia, infarction, and sudden cardiac death. This new lesion could potentially lead to decreased blood flow, myocardial hypoperfusion, and increasing susceptibility to fatal ventricular arrhythmias.

The possibility of stabilizing or retarding the progression of human atherosclerosis or even causing its regression is one of the current challenges. Several approaches are being pursued:

1. One is aimed at reducing risk factors, especially cholesterol levels. Preliminary evidence suggests that lipid-lowering therapy can act on the lipid-laden plaques more prone to rupture, possibly preventing their progression and inducing their regression thereby reducing the risk of acute coronary events.
2. Because thrombus formation seems to be an important factor in the initiation of an acute cardiac event and in the progression of disease after the acute event has subsided, another promising medical approach is the use of antithrombotic therapy.

### *Myocardial Ischemia*

The basic process by which CAD produces morbidity and mortality and alters quality of life is acute myocardial ischemia. Myocardial ischemia occurs when myocardial oxygen supply cannot meet myocardial oxygen demand in a region of the ventricle. Coronary artery disease is often called ischemic heart disease (IHD) because it is only when the coronary atherosclerotic process causes ischemia that it manifests clinically.

Myocardial infarction (MI) refers to the irreversible myocardial cell injury and death that occurs following prolonged ischemia. Muscle necrosis occurs when an ischemic episode is prolonged beyond 30-40 minutes. Almost all acute myocardial infarctions result from coronary atherosclerotic lesions, generally with superimposed thrombosis.

Myocardial oxygen supply is determined by the amount of oxygen delivered by coronary blood flow. Since oxygen extraction by the myocardium is nearly maximal at rest, myocardial oxygen supply is very dependent on the ability to increase coronary artery size and, thus, blood flow (coronary flow reserve).

While a complex host of factors will determine myocardial oxygen supply, myocardial oxygen demand is rather simply controlled by:

1. heart rate
2. contractility of the myocardium
3. left ventricular wall tension.

Brief periods of oxygen supply/demand imbalance (as short as several minutes) will promptly result in myocardial ischemia. At the same time, reversible regional myocardial wall motion abnormalities and perfusion defects appear, detectable with echocardiography and radionuclide imaging (thallium or sestamibi (SPECT)).

More prolonged (30-60 minutes) disruptions in the myocardial supply and demand balance, such as that resulting from coronary thrombosis, will result in myocardial injury and cell death (myocardial infarction). Ischemic injury will usually produce cardiac dysfunction when cardiac

testing will reveal a reduced ventricular ejection fraction. More extensive cardiac dysfunction can progress to “heart failure” and death.

## **Angina Syndromes**

Individuals with CAD can be classified into several clinically and prognostically distinct categories. History, initial findings, and early course distinguish these various CAD or anginal syndromes.

### Stable Angina Pectoris

Patients with stable angina pectoris have chest pain with effort, exercise, or during other conditions in which myocardial oxygen demand is increased. This occurs in a predictable manner and is usually relieved promptly by rest or sublingual nitroglycerin. When studied angiographically, one or more coronary stenoses, often calcified, are usually found.

#### *Classification of Severity of Stable Angina Pectoris*

The severity of stable angina is classified according to the degree of physical activity required to bring on chest discomfort. A classification system, developed by the Canadian Cardiovascular Society, is commonly used worldwide and is as follows:

<u>Class</u>	<u>Description</u>
I.	No angina with ordinary physical activity such as walking or stair climbing.
II.	Angina with walking more than two blocks or climbing one flight of stairs at a normal pace; angina walking uphill, in the wind or cold, with undue emotional stress, or after meals.
III.	Angina walking one or two blocks on the level at a normal pace.
IV.	Inability to perform any physical activity without angina.

An association of the chest pain with exercise, effort, and emotion, and of relief with rest or nitroglycerin, is presumptive evidence that the chest pain represents typical angina pectoris. This implies a 90% likelihood of angiographically significant disease involving at least one major coronary artery.

If the clinical features are atypical, or if an estimate of severity and prognosis is required, then further cardiac testing can be indicated. The resting EKG is normal in 25-50% of individuals with stable angina pectoris. Even when abnormal, the findings such as ST-T changes or bundle branch block are nonspecific. For this reason, tests that provoke myocardial ischemia pharmacologically or with exercise are utilized.

While the ultimate goals are the prevention of myocardial infarction and death, relief of chest pain and improvement in the quality of life are important objectives in the management of stable angina. The approach to these goals is based on the:

1. frequency and severity of ischemic episodes

2. level of left ventricular function
3. clinical assessment of risk factors and comorbid conditions.

Individuals who appear to be at high risk, or who present with symptoms unresponsive to medical management, are considered for revascularization therapy (e.g., coronary angioplasty or bypass grafting). Successful coronary revascularization offers high probability (over 85%) for relief or improvement of symptoms over an intermediate period (i.e., five to ten years). In addition, individuals with anatomical factors such as left main stenosis or three-vessel CAD with reduced ventricular function (ejection fraction 35% or less) have significantly improved survival for up to 15 years after revascularization. People with less severe anatomy can be expected to experience symptom relief, but survival benefit with revascularization is less certain.

### Variant Angina Pectoris (Prinzmetal's Angina)

In 1959, Prinzmetal described an unusual syndrome of cardiac pain that occurs almost exclusively at rest, usually is not precipitated by physical exertion or emotional stress and is associated with electrocardiographic ST-segment elevation. This syndrome, now known as Prinzmetal's angina or variant angina, can be associated with:

1. acute myocardial infarction
2. severe cardiac arrhythmias, including ventricular tachycardia and fibrillation
3. sudden death.

Variant angina pectoris has been demonstrated convincingly to be due to coronary artery spasm. Spasm is a transient, abrupt, marked reduction in the diameter of an epicardial coronary artery resulting in myocardial ischemia. This reduction in the diameter can usually be reversed by nitroglycerin and can occur in either normal or diseased coronary arteries.

The history differs from that of typical angina in that the principal finding is angina at rest. The key to the diagnosis of variant angina lies in the development of ST-segment elevations with pain. Exercise testing in individuals with variant angina is of limited value since the responses are so variable. The coronary anatomy in individuals with variant angina has been defined both at autopsy and during coronary angiography. Severe proximal coronary atherosclerosis of at least one major vessel occurs in approximately two-thirds of these individuals, and, in those individuals, spasm usually occurs within one centimeter of the organic obstruction. The remaining individuals have normal coronaries in the absence of ischemia.

During the first six months after their presentation, many with variant angina go through an acute, active phase with frequent episodes of angina and cardiac events. Over this period, nonfatal myocardial infarction occurs in up to 20% of these individuals and death in up to 10%. Those who have serious arrhythmias or conduction disturbances during attacks have higher maximal ST-segment elevations and are at higher risk for sudden death. In addition, those individuals with severe fixed obstructive coronary artery lesions, upon which coronary artery spasm is superimposed, are at a greater risk for persistent anginal syndromes, acute myocardial infarction, and death. Long-term survival in variant angina at five years is excellent (89-97%) but will be adversely affected by the extent and severity of CAD.

## Cardiac Syndrome X

Cardiac syndrome X is the syndrome of angina or angina-like chest pain with a normal coronary angiogram. It is an important clinical entity to be differentiated from classic CAD (and from the metabolic syndrome X of early diabetes). It can also be differentiated from variant angina by the absence of EKG changes or provokable arterial spasm at angiography.

In contrast to the prognosis in individuals with coronary atherosclerosis, the survival in cardiac syndrome X is usually excellent, and it is important for the underwriter to recognize this. This group of individuals can constitute up to 20% of those undergoing coronary angiography because of the strong suspicion of angina. True myocardial ischemia can be demonstrated in some of these individuals by special tests.

The cause of the syndrome is unknown. Several studies have demonstrated an abnormally reduced capacity to increase coronary flow in response to increased myocardial oxygen demand (i.e., abnormal vasodilator reserve). This abnormality appears to affect the smaller resistance vessels that are not visible angiographically, while the large proximal conductance vessels appear to be normal. Such individuals can have positive exercise stress tests.

## Silent Myocardial Ischemia

Silent myocardial ischemia is defined as episodes of asymptomatic ischemia, with objective evidence of coronary insufficiency provided by exercise testing or Holter monitoring, usually occurring in someone with known CAD. While not a new topic, silent ischemia has generated considerable interest recently. This is largely the result of the advances in ambulatory 24-hour monitoring that revealed that many people with CAD and relatively stable angina had frequent episodes of asymptomatic, ischemic-type ST-segment depression during daily life. Surprisingly, these silent episodes occurred at relatively low activity and heart rates compared with data from treadmill exercise tests for the same individuals, suggesting that changes in myocardial oxygen supply, as well as demand, might be responsible for these asymptomatic episodes of ischemia. Similar ST-segment changes were seen in people hospitalized for unstable angina even after apparent relief of chest pain. Additional studies confirmed that episodes of silent ischemia occurred in many people, from those who were totally asymptomatic to those who were post-myocardial infarction.

A characteristic daily variation in the frequency and duration of silent ischemic episodes has been documented. Increased activity is seen shortly after waking, with higher peaks around noon, plateaus in the afternoon, and minimal activity late at night and in the early morning hours. This variation is the same as the variation observed in the frequency of acute MIs and out-of-hospital deaths, suggesting a common mechanism between transient ischemia and these life-threatening events.

Silent myocardial ischemia is classified as follows:

1. Type 1 occurs in individuals who are apparently well and totally asymptomatic. Detection is usually by means of an exercise EKG, and the prevalence ranges from 2.5-12% in

different studies. In the absence of intervention, mortality risk in these people compared to those with no exercise EKG abnormalities is increased by 200%-500%, depending on association with other known CAD risk factors.

2. Type 2 is seen in individuals who have been asymptomatic after a proven acute myocardial infarction. In this group, the one-year mortality can range up to 25% if not treated or revascularized. It is the presence of ischemia, rather than the presence or absence of symptoms, that appears to be prognostically important.
3. Type 3 is seen in individuals with angina in whom episodes of both symptomatic and silent ischemia are detected. The mortality in individuals with unstable angina and silent ischemia is significantly increased and represents a very high-risk group. In those with stable angina, left untreated, the presence of silent ischemia increases the mortality by a factor of two to four times.

### **Acute Coronary Syndromes**

The acute coronary syndromes encompass a range of clinical syndromes that includes new or worsening chronic angina, “rest” angina, and, finally, acute myocardial infarction. Current definitions of these acute syndromes rely on the diagnostic electrocardiogram (EKG) and cardiac enzyme pattern on initial presentation:

1. non-ST elevation syndromes—Within this group are those individuals classified as having unstable angina without infarction as well as those with non-Q wave infarctions (to be discussed with classic infarctions in the following section).
2. ST elevation syndromes—This is the classic pattern for acute myocardial infarction. Infarct Q waves on EKG can develop during or after the acute event.

#### Unstable Angina without Infarction

Most often, unstable angina is an active intracoronary process (i.e., thrombus formation and/or vasospasm) leading to acute reduction in myocardial blood flow and oxygen supply. An inappropriate increase in myocardial oxygen needs, such as with severe anemia, fever, or hypoxia, can also cause a rapidly aggravating anginal syndrome. As a group, if untreated, within three months, 15-20% will experience refractory angina, MI, or death. Fifty-seven percent of individuals who enter the hospital with a myocardial infarction give a history of recent, unstable angina.

The early classification used for unstable angina was based on a description of the symptoms and included three subgroups:

1. new onset angina in a person previously free of symptoms
2. crescendo angina and pain at rest occurring in someone with known stable angina
3. acute coronary insufficiency, with episodes of chest pain at rest, 15 minutes or more in duration, not related to any previous precipitating factors.

More recently, this descriptive classification of unstable angina has been extended to include the clinical background for its presentation (e.g., unstable angina after myocardial infarction, post-bypass, or post-angioplasty). In these circumstances, unstable angina possesses specific clinical

characteristics, has a different natural history, and can require a different treatment. Finally, special forms of unstable angina can also be individualized because of their distinctive nature; these include Prinzmetal's variant angina and cocaine intoxication.

Most individuals with unstable angina have multivessel CAD, similar in severity to those with chronic stable effort angina. In approximately 10% of individuals with unstable angina, coronary angiograms show no significant obstruction. Presumably, most of these people have coronary artery spasm as the basis for ischemia.

The pathophysiology and coronary angiographic morphology of unstable angina have been intensely studied in recent years. Many of these individuals have acute active angiographic lesions with eccentricity, overhanging edges, or irregular scalloped borders. Some appear to be sites of ulceration or ruptured plaques. Such lesions are rarely seen in people with stable angina pectoris. In addition, thrombi are commonly seen. These arteriographic impressions have been confirmed by direct coronary angioscopy.

Individuals suspected of unstable angina pectoris are placed at rest, usually in a hospital. Acute myocardial infarction is ruled out by serial enzyme and EKG studies. Most data suggest that the more extensive and severe that the EKG changes are during chest discomfort, the more likely complications are to develop.

Nitrates, both intravenous and oral, are the mainstays of the initial treatment of unstable angina. Along with nitrates, calcium channel blockers and beta-blockers have been shown to be useful in reducing the number of ischemic episodes. Both aspirin and heparin are useful in reducing complications, emphasizing the importance of platelets and thrombosis in the unstable phase.

In almost all cases, coronary angiography is usually performed, with further therapeutic options, including coronary stenting and CABG surgery, determined based on the individual's response to therapy and the angiographic findings.

In summary, both the evaluation and treatment of unstable angina are like those for stable angina but are greatly accelerated. The unstable phase is over when the individual's symptoms have disappeared or become predictable. It is assumed that the active endothelial lesions heal in two to three months, and the individual has entered the stable phase with an improved prognosis.

### Myocardial Infarction

In the United States, over 700,000 people suffer from acute myocardial infarction (MI) annually and approximately one-fourth of all deaths are due to MI. More than 50% of the deaths associated with MI occur within one hour of the event and are attributable to arrhythmias, most often ventricular fibrillation. Before the introduction of thrombolytic therapy for MI, the mortality rates during hospitalization and the year following infarction were in excess of 10%. However, in the past 20 years there has been a significant decline in the mortality from MI due to both a 25% decrease in incidence of MI and a similarly marked fall in case fatality rate once an MI has occurred.

In general, the diagnosis of MI is based on a clinical presentation characterized by prolonged and severe chest pain. However, at least 25-30% of all MIs are probably silent or unrecognized. These are detected only by interval electrocardiograms showing residual Q wave evidence of MI. Approximately one-half of silent MIs are truly asymptomatic and one-half cause mild or atypical symptoms that the patient does not recognize as being due to infarction. Those in the elderly age group, with diabetes or with hypertension, are at highest risk for silent infarction.

In all cases, the diagnosis of MI must be supported by objective laboratory findings. These findings include electrocardiographic or serum enzyme evidence of myocardial necrosis. Over the past 10 years, serum enzymes and isoenzyme levels have become the final arbiters by which acute myocardial necrosis is documented and the diagnosis of MI is confirmed or excluded. If MI is suspected, levels of creatine kinase (CPK) and its MB fraction (CPK-MB), as well as myoglobin and cardiac-specific troponins (T and I), are measured and repeated approximately eight to 24 hours later.

The cardiac troponins are the most sensitive and specific biomarkers and can be elevated when other biomarkers are not. In very early MI presentations, the serum troponin elevation can precede all other enzyme evidence of MI. Troponins are not detected in the peripheral circulation under normal circumstances. Even minor elevations of troponin concentrations are thought to indicate myocardial necrosis. In short- and long-term follow-up studies, the magnitude of troponin elevations has correlated with the risk of death and the composite risk of death or nonfatal MI, irrespective of whether the individuals had ST elevation or non-ST elevation acute coronary syndrome.

### *EKG Changes in MI*

In most individuals with myocardial infarction, some change can be documented when serial electrocardiograms are compared. The EKG changes are those of ischemia, injury, and cellular death (necrosis) and are, within limits, reflected by T wave changes, ST-segment elevation, and the appearance of Q waves, respectively.

Myocardial infarctions often present with ST elevation on the ECG and are classified as STEMI (ST elevation MI). A global cardiology task force established a new sub-classification of STEMI by cause:

1. Type 1: Myocardial infarction caused by acute plaque disruption and thrombosis – the most common cause of acute MI.
2. Type 2: Myocardial infarction due to oxygen supply/demand imbalance – this includes coronary artery dissection and vasospasm
3. Type 3: Myocardial infarction in the setting of chronic stable or unstable angina
4. Types 4 and 5: Myocardial infarctions occurring after procedures such as stenting or CABG surgery.

Compared with individuals with STEMI infarctions, those infarctions presenting without ST elevation (non-STEMI or NSTEMI) appear to have a smaller infarction size and a reduced early mortality; however, they appear to be at a higher risk for re-infarction and continuing angina. One-

year mortality is similar in both types of MI. STEMI infarctions also have a high likelihood of coronary thrombus at early angiography (85% of patients studied within four hours of onset of symptoms) compared with those who have NSTEMI infarction (30% or less). Thus, the individual with NSTEMI infarction has limited initial damage but a high frequency of residual ischemia and its attendant risk.

### *Treatment of MI*

Management of individuals with MI has undergone remarkable evolution over the past several years. Coronary angiography and other complex manipulations can now be done in a relatively rapid and safe manner in the individual with MI. The time interval between onset of abrupt coronary occlusion and the institution of any intervention to limit damage is critical. Clinical trials to date have confirmed that the larger the evolving MI is, the sooner that reperfusion is attempted, and the higher the patency rate achieved, the greater will be the benefit on mortality and left ventricular function, provided chronic vessel patency is maintained. The risks of this therapy are low and are less in younger patients than in older patients.

Treated in the past with thrombolytic agents, reperfusion of the infarct-related artery is now usually achieved by a catheter-based strategy. Percutaneous coronary intervention (PCI) includes angioplasty and stent insertion. PCI has assumed an important role particularly in the treatment of those with a STEMI. There is little evidence of benefit with PCI in the acute coronary syndromes of unstable angina and NSTEMI infarctions.

### *Post-MI Period*

Mortality in the first year after an MI, especially in the first six to nine months, is 6-10% (versus 2-4% overall annual mortality in CAD without recent MI). Within the post-MI population, up to one-third of people have coronary anatomy (i.e., left main or three-vessel disease) for which coronary artery bypass graft (CABG) surgery has been shown to improve prognosis. Individuals with post-MI angina should have coronary angiography on an urgent basis. In addition, a large percentage of people with previous infarction merit early coronary angiography because of higher likelihood of diminished LV function and multiple lesions. Individuals with a prior MI have significantly increased mortality in the year following a recurrent infarction.

In the remaining individuals, many will be experiencing their first infarction and will be minimally or completely asymptomatic. Most will have ejection fractions in the normal or near normal range, the exception being those people who have suffered a larger anterior MI as their first event. In this large group, post-MI exercise testing has been shown to be superior to coronary angiography to identify individuals at risk for recurrent infarction and death.

Risk stratification is determined from clinical findings (e.g., age, previous MI, presence or absence of heart failure, and ventricular arrhythmias) and noninvasive studies. If a symptom-limited exercise test performed two to four weeks after the infarction is available, this can be a cost-effective method for determining low- and high-risk individuals. High-risk groups are identified based on low exercise capacity, failure to have systolic blood pressure (BP) rise, and presence of ischemic ST-segment depression at a low workload, whether accompanied by angina

or not. The first-year mortality can range up to 25% in such people in the absence of intervention. In those who have good exercise tolerance, who have no exercise-induced ST change and a good BP response, the risk of cardiac events is 12% annually.

The second component of risk stratification post-MI is residual LV function. Individuals with an ejection fraction of 50% or greater have a low event rate of approximately 5% over the next five years. Long-term post-infarct survival decreases when the ejection fraction (EF) falls below 50%, and significantly deteriorates in those with ejection fractions less than 35-40%. Unfortunately, a severely reduced ejection fraction also predicts a high surgical mortality and poor long-term survival, despite revascularization.

### Sudden Cardiac Death

Sudden cardiac death (SCD) is a major health problem in the United States, accounting for more than 300,000 deaths each year, and is a major cause of death for people with CAD. It is usually defined as death from cardiac disease within one hour of the onset of symptoms in someone who was not expected to die. Most sudden cardiac deaths are due to arrhythmias occurring in the presence of chronic coronary or structural heart disease. Other, less frequent causes include cardiomyopathy and inherited repolarization abnormalities. The factors that produce fatal arrhythmic events are complex but usually include a triggering acute event, superimposed on an arrhythmogenic substrate. The anatomic substrate for sudden cardiac death is most frequently a chronically abnormal myocardium harboring various degrees of fibrosis. In most cases, the underlying cause is coronary artery disease. At autopsy, significant narrowing of two or more coronary arteries is usually seen. Evidence of acute myocardial infarction is found at autopsy in 40-70% of victims of sudden cardiac death, but various acute triggers can ultimately precipitate a malignant arrhythmia. These triggers include acute myocardial ischemia, hemodynamic factors, electrolyte abnormalities, autonomic influences, and even drug interactions.

Although non-arrhythmic sudden cardiac deaths have been described, most EKG-documented sudden cardiac deaths appear to be arrhythmic. Among arrhythmias, ventricular tachycardia and fibrillation seem to be the initiating electrical disturbance in most cases.

A high degree of correlation exists between the level of left ventricular function and the propensity toward future arrhythmic SCD. Patients with an LV ejection fraction of less than 30% are at significantly greater risk than those who have ejection fractions of 30% or more.

Management of survivors of an SCD episode includes a detailed evaluation including:

1. definition of coronary anatomy by angiography
2. LV function
3. electrophysiologic testing (EPS).

All reversible triggers, such as acute ischemia and electrolyte abnormalities, need to be addressed as well to remove the arrhythmogenic substrate. When no effective medical regimen is identified, antiarrhythmic therapy includes:

1. radiofrequency ablation

2. surgical suppression of the arrhythmia
3. implantation of an automatic internal cardiac defibrillator (AICD).

Indeed, there is a recent trend toward earlier AICD implantation without EPS testing. This is clinically justified as a potentially safer, more cost-effective strategy, but certainly makes medical risk assessment more difficult.

Most survivors of out-of-hospital cardiac arrest remain at significant risk for a recurrence and fewer than one-quarter will have evidence of an acute myocardial infarction. A cardiac arrest unassociated with a reversible cause such as a myocardial infarction or electrolyte disturbance is associated with a risk of recurrence of up to 35% within the first year.

### **CAD: Medical Treatment and Revascularization**

#### Medical Therapy for Angina Pectoris

Medical therapy with beta-blockers, and calcium channel blockers offers a diverse choice of drugs to relieve symptoms of stable angina pectoris. It has now been shown that drugs that improve exercise tolerance and relieve symptoms will favorably improve outcomes. For all drugs, there is a wide individual variation in drug dose required for optimum symptomatic response while keeping side effects to a minimum. Newer preparations are designed to provide better dosing schedules and bioavailability with fewer side effects.

Many physicians use a beta-blocker as initial therapy for stable angina, due to its relatively low cost as well as its cardioprotective effects in post-myocardial infarction studies. Most beta-blockers are generally well tolerated and are effective in reducing angina frequency and improving exercise tolerance. The choice between the agents is based largely on side effects and personal preference. Important but uncommon adverse effects of beta-blockers include excessive bradycardia, heart block, heart failure, aggravation of claudication, asthma, and depression.

Calcium channel blockers are popular for chronic therapy in classic stable angina pectoris. In addition, these agents are useful in vasospastic (i.e., Prinzmetal's variant) angina and angina suspected to be related to limited coronary vasodilator reserve (i.e., cardiac syndrome X). The calcium channel blockers are available in oral and intravenous forms, both as short-acting and long-acting preparations and are a diverse group of drugs with different chemical, pharmacologic, and physiologic actions. Anti-ischemic agents from these three drug classes (nitrates, beta-blockers, and calcium blockers) are frequently used as combination therapy to enhance their effects or minimize their side effects.

The previous discussion of the pathophysiology of myocardial ischemia stressed the important role of thrombosis and platelet aggregation, especially in the conversion of chronic stable CAD to the acute ischemic syndromes of unstable angina, myocardial infarction, and sudden cardiac death. Despite this, therapy with anticoagulants has not yet been shown to have a role in the treatment of stable angina pectoris. Aspirin, when used as an antiplatelet agent, can reduce the risk of myocardial infarction and cardiac death in stable angina patients, particularly in association with

other antiplatelet agents such as clopidogrel. The implications of these findings for long-term mortality assessment await further studies.

### Percutaneous Transluminal Coronary Angioplasty

Revascularization with percutaneous transluminal coronary angioplasty (PTCA) is an effective method to treat individuals with CAD. A balloon-tipped catheter is inserted percutaneously into the coronary circulation. The balloon, inflated at high pressure at the site of a coronary stenosis, creates a fracture of the plaque and splits the plaque from the wall of the vessel to allow an increase in the area through which blood can flow. The limitations of the early forms of angioplasty equipment confined PTCA to selected individuals with anatomically suitable single-vessel disease. As the equipment has become more sophisticated and operators more experienced, it has become possible to manage more complex, multivessel coronary disease with PTCA.

### Coronary Stenting

The major limitations to balloon angioplasty (PTCA) alone are related to the significant restenosis rate and need for repeat revascularization procedures. To address these problems, increasingly sophisticated coronary artery stents have been developed. These stents are devices with metal structural supports infused with anti-coagulant medication (i.e., drug-eluting stents) that are inserted at sites of atherosclerotic narrowing. Once in place, the stent provides structural support and improved arterial flow, often to near-normal levels.

In the United States, stents are currently implanted post-balloon angioplasty in most angioplasty procedures. Most studies have shown marked improvement in early restenosis rates with the newer generation of coronary stents.

### Coronary Artery Bypass Graft Surgery

Given the prevalence of CAD and its considerable cost to society, the selection of the optimal approach to treatment for everyone is an important health care issue. Several large clinical trials have compared medical therapy with coronary artery bypass graft surgery (CABG). These studies demonstrated that surgery improved survival and reduced the risk of myocardial infarction mainly for patients with left main or three-vessel coronary disease, particularly when their disease was accompanied by left ventricular dysfunction.

Since PTCA with stenting is now performed even in patients with multivessel coronary disease, it must be compared with CABG. The operative mortality for elective CABG has fallen consistently and is about 1-3% in most centers. The internal mammary artery (IMA) bypass graft is a superior conduit with improved long-term patency when compared with vein bypass grafts. Recent studies indicate an IMA patency rate of over 90% at 10 years is likely, while 50% of vein bypass grafts are likely to occlude within 10 years.

For individuals with less extensive CAD, bypass surgery offered no survival advantage over the already excellent results with medical therapy. However, it did effectively relieve severe angina that proved refractory to medical therapy.

The indication for CABG that is least controversial is that of angina pectoris unrelieved by medical therapy and not amenable to PTCA. Other indications for CABG that have been clearly accepted include left main coronary artery stenosis of more than 50%, failed PTCA, and triple-vessel coronary disease, especially when large amounts of myocardium are at risk due to proximal stenoses. CABG is also often used in double-vessel CAD not amenable to PTCA, especially if the LAD artery is involved and a large amount of myocardium is at risk. Less often, individuals with single-vessel CAD can be candidates for CABG, especially those with a very proximal LAD lesion before the first septal perforator, just beyond the left main coronary artery, not amenable to PTCA, and with evidence of ischemia in the anterior wall and septum.

Numerous studies have confirmed the long-term survival benefit of CABG surgery. Most recently, studies on post-CABG patients reported a survival rate of 85%-90% at 5 years. Symptomatic improvement has been demonstrated in 70% of patients and complete absence of angina pectoris in 50% after five years. However, about 30% require repeat revascularization by 10 years. Reoperation CABG is somewhat riskier, with perioperative mortality somewhat higher than first-time surgery—1-2% first-time versus 5-7% reoperation mortality.

### Comparing PTCA and CABG

The differences between PTCA and CABG are obvious. Successful PTCA is less traumatic, less costly initially, and requires a shorter hospital stay than CABG. PTCA of multiple vessels, though, can leave individuals with incomplete revascularization, and long-term follow-up of these individuals has indicated a higher recurrence of symptoms.

The degree of left ventricular dysfunction is the factor most likely to predict preoperative and long-term mortality. CABG prolongs survival in high-risk patients when compared with medical therapy alone, but does not “cure” CAD, since these individuals can develop progressive disease in other vessels not grafted or within the bypass grafts themselves.

In individuals with unstable angina, CABG is quite successful. Relief of angina pectoris is excellent and prolonged. As with chronic stable angina, however, the beneficial effect diminishes with time. Late return of symptoms after CABG usually indicates disease of the bypass graft or progression of disease in previously uninvolved native vessels. The recurrence of angina is not influenced by the existence of stable or unstable symptoms before surgery. Late myocardial infarction rate is low and late survival of these individuals is good, similar to findings in people with chronic stable angina after CABG. However, operative mortality in individuals with unstable angina is approximately twice that expected with those who have stable angina pectoris before surgery.

During the early phase of an acute MI, it is logistically impossible to admit, assess, and prepare a person for emergency CABG within the six-hour time frame for acceptable myocardial salvage. Thrombolytic therapy, with the option of emergent PTCA/stenting, remains the mainstay of therapy in this situation.

At present, many people with single- and multivessel CAD are now being offered PTCA and coronary stenting as an alternative to medical therapy rather than as an alternative to CABG.

PTCA, therefore, has achieved widespread acceptance for single-vessel and multivessel CAD, while data to support this therapeutic protocol are only recently being published.

### CAD in Females

Myocardial infarction is the number one killer of North American females. In fact, in many studies, the post-MI death rate in females surpasses that of males. Females present a unique set of problems in terms of risk factor modification, acute presentation, and subsequent management.

The same factors that affect the risk of CAD in males apply to females; however, not all risk factors are equivalent between the sexes. Some risk factors, such as menopausal status and hormone use, are unique to females. MIs are rare in pre-menopausal females, but the incidence increases sharply with menopause and is two to three times that of pre-menopausal females the same age. Normally, females' risk lags 10 years behind that of males; however, 10 years after menopause, the ischemic event rate approximates that of males. As compared to the gradual increase in cardiac risk seen in natural menopause, the risk rises sharply if surgical menopause is induced by a total hysterectomy with removal of the ovaries.

Post-surgical and post-menopausal hormone replacement therapy (HRT) has been recommended in the past, in part based on theoretical protective effects on atherogenic risk. While previous observational studies had suggested a protective role for estrogen replacement, these results have yet to be confirmed in a published randomized trial. One large study, the Heart and Estrogen/Progestin Replacement Study (HERS), included the troubling finding of increased coronary disease events in known CAD patients in the first year after initiation of HRT therapy. Additional analysis showed that this increased CAD risk was confined to older women more than 10 years after menopause. There also appears to be a slightly increased atherogenic risk in females taking oral contraceptives; this risk is only clinically significant in females who smoke or who have known thrombotic disease.

It has been recognized for many years that stress testing for CAD is associated with a lower sensitivity and specificity in females than in males. However, when the age, symptom, and EKG status of the individuals have been properly classified, the predictive value of stress testing in females compares favorably with males when coronary angiography is used as the gold standard.

Several studies have suggested that coronary artery bypass surgery is less successful in females, related to operative mortality and graft closure and angina post-operatively. Subsequent studies have suggested that these results can be explained by factors other than gender, including age, disease severity, body size, and coronary vessel size. In contrast to earlier reports, most recent studies have shown similar PTCA success rates for males and females. After successful angioplasty, females have similar symptomatic improvement, decreased requirement for additional revascularization, restenosis, and similar survival rates as males.

Recent studies have also suggested that there appears to be a referral bias that works against females in their selection for thrombolytic therapy, cardiac catheterization, and revascularization. The lower prevalence of CAD in females often leads the clinician to look for other causes of chest pain. Also, CAD in females often presents with atypical symptoms such as abdominal bloating or

breathlessness. Recognition of this will probably result in a more aggressive approach to the early and later management of CAD in females.

### CAD in the Elderly

Aging produces a variety of changes in cardiac structure and function. These include increased arterial and myocardial stiffness, fibrosis, and cell loss within the cardiac conduction system, thickening and calcification of cardiac valves, and reduction in the maximal heart rate. The elderly are more likely to require cardiac medications and yet are also more likely to experience medication side effects and adverse drug interactions.

CAD is the number one cause of death in those over age 65. While traditional risk factors identify elderly individuals at risk for CAD, these factors lose some of their predictive power in the elderly. Advanced age is such a potent risk factor for CAD that it weakens the relative effect of other clinical variables.

Advanced disease is often displayed as disease in more than one site. The elderly with non-coronary atherosclerosis (for example, cerebrovascular disease, peripheral vascular disease, abdominal aortic aneurysm) are much more likely to have CAD, whether or not it is clinically apparent. Many of these individuals die from CAD rather than their non-coronary atherosclerotic vascular disease.

The original report from the Framingham Heart Study indicated that the predictive power of both total cholesterol and LDL-cholesterol waned with age. However, more recent data from the same study have shown that HDL-cholesterol and total cholesterol/HDL ratio maintain their association with CAD incidence in both sexes between the ages of 65-84 years. Several subsequent studies have supported this conclusion. There are also reports suggesting reduction in cardiac events with statin lipid-lowering therapy up to age 75.

There is now good evidence that both systolic and diastolic hypertension are formidable risk factors for stroke and CAD in the elderly and that treatment can be effective. There appears to be particular risk associated with an elevated pulse pressure (i.e., systolic minus diastolic blood pressure), which may be related to increased arterial shear stress. Isolated systolic hypertension is the most common form of hypertension in people between the ages of 65 to 89, affecting two-thirds of individuals with hypertension. The recent report of Systolic Hypertension in the Elderly Program demonstrated that treatment of these individuals results in a significant reduction in cardiovascular disease events.

Smoking is the third major risk factor for CAD. There is now good evidence that smoking cessation reduces the risk of cardiovascular events in the elderly, just as it does in the young and middle-aged.

The likelihood of having extensive CAD increases progressively with advancing age. In the Coronary Artery Surgery Study (CASS), the incidence of left main disease was 15% vs. 9%, and three-vessel disease was 61% vs. 46% in patients over age 65 versus those aged 64 or younger.

Angina is more likely to be attributed to less significant causes of chest pain in the elderly. Acute myocardial infarction is more difficult to diagnose in the elderly and many MIs occur with virtually no symptoms.

PTCA and coronary stenting in the elderly has a primary success rate comparable to results observed in younger groups. However, angina is more likely to recur in the elderly and to recur sooner than it would after CABG surgery. Procedure-related morbidity and mortality increases with age. Long-term results after CABG in the elderly mirror those seen in the younger populations. Most studies conclude that there is higher perioperative mortality for CABG in the elderly. Data from the CASS show perioperative mortality for CABG of 1.5% for those under age 65, about 5% for those aged 65-74, and about 10% for those over age 75. However, those elderly CAD patients who successfully undergo CABG surgery and who experience an uneventful recovery period have been shown to have excellent subsequent survival, often equivalent to those of similar age with no known CAD.

### **Cardiac Testing and Angiography**

Angina, myocardial ischemia, and myocardial infarction have been correlated with the presence of angiographically significant CAD (i.e., 50-70% narrowing of one or more coronary arteries). Whereas the likelihood of significant CAD in the asymptomatic male population might be 5%, the individual with typical angina will have a 90% likelihood of angiographically significant CAD. At times, the chest pain history is that of “atypical” angina and will include some, but not all, of these classic features. The pain can occur with exercise, for example, but be sharp rather than dull and achy. Atypical angina predicts only about a 50% chance of CAD, with the chest complaint often eventually attributed to non-cardiac causes. Finally, non-anginal chest pain identifies a clinical history in which the symptoms described in no way resemble that of classic angina; the prevalence of CAD in this group approaches that of the general population.

Underwriting mortality risk assessment in those individuals with known angina or CAD is relatively straightforward compared to the greater challenge in assessing those who are asymptomatic or with atypical symptoms on presentation. In these situations, CAD risk factor assessment along with the results of cardiac testing are useful tools, confirming (or excluding) the presence of CAD and providing an estimate of disease severity.

### **Screening with NT-proBNP**

Brain natriuretic hormone (BNP) and its metabolite NT-proBNP, are relatively new laboratory markers that have been found to be useful in clinical and insurance medicine. Although originally isolated in brain tissue, BNP is synthesized predominantly by the cardiac ventricles in response to cardiac stress. Early studies confirmed an association between increased BNP levels and heart failure. More recently, clinical BNP testing has found a role in the treatment and monitoring of patients with a wide variety of cardiac impairments, including heart failure, congenital heart disease, aortic and valvular heart disease, and cardiomyopathy.

Not long thereafter, researchers began to explore the possibility that BNP could be useful as a screening tool for cardiac disease in asymptomatic people. Favorable results in this arena led to

interest from insurance companies in the use of BNP as an underwriting requirement. NT-proBNP was chosen for insurance screening based on its longer half-life and greater stability in collection and transport. Initial reports suggest that NT-proBNP levels can effectively identify increased mortality risk in proposed insureds, providing value over and above that of classic risk factor analysis.

Serum NT-proBNP levels vary with age, gender, build, and renal function and so require underwriting guidelines that take these into account. Ultimately, underwriting cardiac mortality risk should benefit from the additional prognostic information that NT-proBNP screening provides.

### Exercise Stress Tests

Exercise stress tests, the most frequently performed tests for diagnosis and assessment of CAD, are usually done on a treadmill using standardized protocols (e.g., Bruce, Balke, Naughton) of walking speed and gradients. The individual starts at low workloads and progresses to higher ones, with blood pressure and pulse monitored throughout and multi-lead EKGs obtained prior to, during, and after exercise. The test is terminated by:

1. reaching a “maximal heart rate,” determined individually by age and gender
2. marked EKG changes early in exercise
3. significant blood pressure changes, either markedly hypertensive, or severely hypotensive
4. reproduction of typical chest pain.

Myocardial ischemia is indicated by EKG ST-segment depression, radionuclide imaging defects, or wall motion abnormalities on echocardiogram.

An exercise EKG is considered positive if there is horizontal or downsloping ST-segment depression of 1 mm or greater, 0.08 seconds after the J point. False positive results can occur, in which the individual, despite an abnormal test, is found to be free of CAD. Possible explanations for false positive tests include:

1. ventricular hypertrophy
2. mitral valve prolapse
3. conduction abnormalities (e.g., bundle branch blocks and WPW syndrome).

False negatives are also seen in which 10%-15% of individuals with important coronary artery disease fail to demonstrate diagnostic EKG abnormalities. Possible explanations for false negative tests include:

1. failure to achieve an adequate heart rate (“submaximal” test)
2. baseline EKG changes that limit interpretation of exercise tracings
3. medications that suppress the development of ischemia

Other parameters measured during the standard exercise protocol (Table 1) can improve both the diagnostic and prognostic utility of the test.

**Table 1. Important stress testing parameters.**

Exercise duration (Bruce protocol stage; MET level)
ST-segment change with exercise
Blood pressure response to exercise
Symptoms with exercise (chest pain, leg cramps)
Ejection fraction, resting and exercise
Thallium/SPECT defects
Echocardiographic wall motion abnormalities.

Attempts to improve the diagnostic accuracy of exercise testing have led to the use of supplementary radionuclide and echocardiographic/Doppler imaging during testing (Table 2). Myocardial distribution of radio-isotopes following intravenous injection at rest, during exercise, or following administration of a coronary vasodilator (e.g., dipyridamole and adenosine) is related to regional blood flow and myocardial viability. Reversible defects on nuclear scans generally reflect ischemic myocardium, whereas nonreversible defects often indicate scarring from previous myocardial infarction. Technetium 99M (Tc99M) labeled agents, such as Tc99M sestamibi (SPECT), demonstrate improved imaging characteristics and have replaced thallium as the imaging agents of choice for most myocardial perfusion studies.

**Table 2. Sensitivity and specificity of exercise tests for CAD.**

TEST	SENSITIVITY	SPECIFICITY
<b>Exercise</b>		
Exercise EKG	66%	84%
Exercise Echo	81%	89%
Exercise Nuclear (SPECT)	90%	72%
<b>Pharmacologic</b>		
Dobutamine	81%	83%
Dipyridamole nuclear	90%	70%
Adenosine nuclear	89%	83%

Alternatively, echocardiography/doppler studies can be done during exercise and compared with resting studies. Myocardial ischemia is detected:

1. as a decrease in left ventricular ejection fraction during exercise
2. by the development of regional ventricular wall motion abnormalities not present at rest.

In individuals who cannot undergo exercise testing, myocardial ischemia has been diagnostically induced with a variety of pharmacologic agents, among them dipyridamole and adenosine. Imaging, either radionuclide or echocardiographic, is required for this type of testing, as the usual heart rate, blood pressure, and EKG findings of exercise testing are absent with the pharmacologic approach. In reliable laboratories, these pharmacologic stress tests have proven equal in value to standard exercise testing in the detection of myocardial ischemia.

## Positron Emission Tomography (PET)

Positron emission tomography (PET) is a very accurate method for identifying how much the heart has been damaged by infarction and how much is still viable. Until recently, it had been confined to research applications, but its use in clinical medicine is increasing. The test is performed by the injection of radionuclide "tracer" and then detection of radioactive decay by use of a scanner. This differs from a thallium scan or radionuclide angiography in the radiation-emitting substances used. The advantage of PET is the higher resolution or detail leading to improved localization of areas of decreased blood flow. Disadvantages are the limited availability and relatively high cost of the tracers and imaging equipment. PET may also be performed as a "stress test" after the administration of intravenous dipyridamole, which acts to increase cardiac workload.

## Computed Axial Tomography (CAT Scanning)

Computed tomography (CAT or CT) is now widely used in cardiac diagnosis. The CT scan is a computer-assisted imaging method that assembles anatomically accurate pictures from a huge number of standard x-rays. Recent developments in rapid CT systems that allow for up to 256 cardiac image "slices" per second have eliminated the blurring that occurs with a regular CT scan of the heart. The results are two important cardiac testing modalities – the coronary calcium scan and the CT angiogram.

### Coronary Calcium Scanning (EBCT)

Ultrafast CT scanners (also referred to as electron beam CT or EBCT) take x-ray images of the heart so quickly that they can freeze the motion of the heart and snap the pictures between beats, avoiding the blurring that would occur with normal CT scans. Conventional scanners require about two seconds to form an image, during which time the heart has contracted twice. The ultrafast CT scanner can take a picture in a tenth of a second.

EBCT scans can detect atherosclerosis before the buildup of arterial plaque has advanced enough to disrupt blood flow. While it cannot show actual plaque, it can show flecks of calcium in coronary arteries, which appear as bright white flakes on the dark gray x-ray films. It is these calcium deposits that are associated with plaque and coronary artery disease.

### CT Angiogram (CTA)

The CT angiogram represents the next step in the evolution of CAT scan imaging in CAD. Rapid sequence images timed to the cardiac cycle and reconstructed by computer are able, for the first time, to reveal coronary artery anatomy *non-invasively* (i.e., without resorting to arterial catheters as in cardiac catheterization). Current generation scanners can detect small non-obstructive atherosclerotic plaques as well as flow-limiting larger stenotic coronary lesions. Coronary obstructions identified on CTA require further confirmation and quantitation with conventional coronary angiography before proceeding with revascularization. Dense calcium particles in the arterial walls will reduce the image quality. Another limiting factor is the significant radiation exposure that occurs during the CT imaging process. However, the CT

angiogram represents a major advance in cardiac testing, particularly when the coronaries are “clean,” thus excluding the presence of significant CAD in those presenting with chest pain or shortness of breath.

### Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) produces cross-sectional images of anatomy by placing individuals in a strong magnetic field and bombarding them with radio waves. A super-conducting magnet circles around the body, causing the hydrogen nuclei in the body to align with the magnetic field. Hydrogen nuclei emit their own signals, which are then converted to computerized images. MRI can visualize the heart and large vessels in the abdomen and chest. It is an effective tool for cardiac diagnosis, with improved resolution and anatomic clarity leading to rapid expansion in the use of the MRI. Aortic aneurysms, lesions in the aorta and other large arteries, congenital heart abnormalities, chest tumors, pericardial diseases, and myocardial scar from prior infarction are all well-visualized. Intra-luminal masses (tumors or clots) are easily shown. Special MRI techniques are available that can illustrate abnormal blood flow patterns that allow for MRI angiographic studies of the cerebral and peripheral vessels. MRI imaging is now performed along with exercise testing but does not yet have the resolution required for identification of coronary stenoses. In addition, the strong magnetic fields, however, limit the use of the MRI to those who do not have pacemakers, metallic objects or implants, or certain prosthetics.

### Coronary Angiography

Although noninvasive procedures (such as exercise electrocardiography, radioisotope tests, and echocardiography) are important tools in CAD risk assessment, they do not define coronary anatomy. Coronary angiography is the “gold standard” to define the extent of CAD. A specialized catheter is passed into the coronary artery and radiographic contrast material is injected into the artery while a special x-ray or video film is taken. Coronary angiography identifies the presence, site, extent, and severity of coronary obstruction. When obstruction is present, angiography identifies atherosclerosis, thrombus, spasm, or various combinations. More specifically, coronary angiography can identify anatomic characteristics (such as left main stenosis, severe three-vessel disease with abnormal left ventricular function) associated with high risk for death if left untreated. Equally important is the exclusion of the CAD diagnosis as a cause of chest pain in patients with normal coronaries at angiography. One rare exception to this conclusion is cardiac syndrome X, in which chest pain occurs without objective evidence of atherosclerotic disease.

The degree of stenosis is recorded as a reduction in the lumen diameter expressed as a percentage, with total occlusion being 100%. From the standpoint of surgically significant disease, a stenosis with greater than 50-70% reduction in diameter (10-40% in the left main stem coronary artery) is a lesion that can produce myocardial ischemia. Lesions in series or a long stenosis are of added importance.

A complete cardiac catheterization study usually includes ventriculography with injection of contrast medium directly into the left ventricle. This procedure is used to assess left ventricular size and function, the presence and degree of regional wall motion abnormalities, and the presence and severity of mitral regurgitation. In the past, this test had been the gold standard for left

ventricular analysis, but has, for the most part, been supplanted by newer radionuclide and echocardiogram/Doppler techniques.

### *Myocardium at Risk*

Coronary angiography will establish the severity and location of coronary artery obstructions. *Severity of obstruction* refers to the extent of stenosis and is expressed as a percentage of the coronary artery diameter. A 50-70% stenosis or greater is usually considered significant, implying that the artery has been narrowed to one-quarter of its normal diameter with a concomitant severe decrease in blood flow. *The location of an obstruction* will be described in relation to the origin of that coronary artery. Thus, a proximal lesion implies that the stenosis is close to the origin of the artery. Somewhat further along, after significant branching has occurred, lesions are referred to as mid lesions. Finally, distal lesions are those that occur near the terminal portions of the imaged artery.

Ultimately, the prognosis in CAD will be directly related to the amount of damage that could occur, termed the “myocardium at risk,” should a coronary lesion undergo sudden and total occlusion. This, in turn, is linked to coronary stenosis severity and location. Complicated clinical scoring systems have been developed to quantitate the amount of myocardium at risk, but, in general, several broad rules apply:

1. Prognosis in CAD is related in large part to the *number* of coronary arteries with significant stenoses. Survival is best in single-vessel disease where obstruction is limited to one artery and is intermediate in two-vessel or double-vessel disease. Involvement of three vessels or triple-vessel disease carries the worst prognosis and usually is an indication for stenting or bypass.
2. Lesions in the left main artery are almost always prognostically significant. An occlusion in that artery could potentially cut off circulation to both the left anterior and left circumflex systems and would result in a massive myocardial infarction.
3. Proximal lesions are associated with greater risk than mid or distal lesions.
4. LAD lesions are usually associated with a large amount of myocardium at risk, as this artery provides blood flow to the functionally important anterior, septal, and apical walls of the left ventricle.
5. The importance of LCx and RCA stenoses depends, in part, on the dominance of the system as well as severity and location. In general, there is less myocardium at risk linked to lesions in these arterial systems.

## **Review Questions – ALU 201, Chapter 13**

1. When myocardial oxygen supply cannot meet demand, it is:
  1. angina
  2. hypoxia
  3. ischemia
  4. infarction
  
2. All the following findings on a post-myocardial infarction exercise test can help identify individuals at high risk for a recurrent event EXCEPT:
  1. angina symptoms
  2. low exercise capacity
  3. rising systolic blood pressure
  4. ischemic ST-segment depression at low workloads
  
3. Possible explanations for a false positive result on an exercise stress test include which of the following?
  - A. ventricular hypertrophy
  - B. mitral valve prolapse
  - C. bundle branch block

Answer Options:

1. A and B only are correct.
2. A and C only are correct.
3. B and C only are correct.
4. A, B, and C are correct.

4. Name the medical treatment and revascularization options for coronary artery disease.
  
5. Describe the characteristics of coronary obstruction that can be identified by coronary angiography.

6. A coronary artery lesion that would typically place the most myocardium at risk would be located:

1. mid
2. distal
3. proximal
4. dorsal

7. Which of the following statements regarding adenosine stress testing is/are correct?

- A. Its results are typically less accurate than the results of standard exercise testing.
- B. It is used for individuals who are unable to undergo standard exercise testing.
- C. It requires concurrent radionuclide or echocardiographic imaging.

Answer Options:

1. A only is correct.
2. B only is correct.
3. B and C only are correct.
4. A, B, and C are correct.

8. What is coronary angiography and explain its value as a CAD risk assessment tool?

9. Identify five broad rules generally applied to quantitate the amount of myocardium at risk.

10. Identify three medical therapy options for angina pectoris and when they are typically used.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 3: ischemia – page 7.

### *Review Question 2*

Answer 3: rising systolic blood pressure – page 14.

### *Review Question 3*

Answer 4: A, B, and C are correct – page 22.

### *Review Question 4*

Refer to pages 15-18.

### *Review Question 5*

Refer to pages 24-25.

### *Review Question 6*

Answer 3: proximal – page 25.

### *Review Question 7*

Answer 3: B and C only are correct – page 23.

### *Review Question 8*

Refer to pages 24-25.

### *Review Question 9*

Refer to page 26.

### *Review Question 10*

Refer to pages 16-17.



## **CHAPTER 14**

### **NON-CARDIAC BLOOD VESSEL DISORDERS**

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## **NON-CARDIAC BLOOD VESSEL DISORDERS**

### **Introduction**

The scope of this chapter includes diseases of the blood vessels except for the coronary and cerebrovascular blood vessels and pulmonary embolism. This chapter covers non-coronary atherosclerotic and non-atherosclerotic peripheral vascular disease, aneurysms, dissections, venous disease, and select vasculitis syndromes.

The vascular system consists of three highly specialized components: the arterial, venous, and lymphatic systems. The arterial system consists of vessels of varying size and carries oxygenated blood to the tissues of the body after it leaves the heart. The venous system is responsible for transporting deoxygenated blood back to the heart and lungs. The lymphatic system is a separate vessel system and is responsible for carrying excess fluid from the tissue spaces back to the bloodstream.

### **Anatomy and Physiology**

Understanding the peripheral arterial system and its diseases requires knowledge of vascular structural elements and their arrangement within vessel walls. Vessels above a certain lumen diameter generally consist of three defined layers: the intima, media, and adventitia.

1. The intima is a single layer of endothelial cells on the innermost section of the vessel wall.
2. Media refers to the middle section of the vessel wall and consists of smooth muscle cells surrounded by collagen and elastic tissue.
3. Adventitia, the outermost covering of the vessel wall, consists of a mixture of collagen, elastic tissue, smooth muscle, nerve fibers, vasa vasorum, and lymphatic vessels that accommodate lymphatic flow to nourish and remove metabolic waste products from the vessel wall.

The structural elements most common to arterial vessels consist of five separate tissue components:

1. endothelium
2. basement membrane
3. elastic tissue
4. collagen
5. smooth muscle

The endothelium is comprised of a flat layer of endothelial cells lining the entire vascular system. Below the endothelium is the basement membrane, composed of various proteins and polysaccharides that serve as a support structure and transport medium for various materials. Elastic tissue encompasses the endothelium and basement membrane. Collagen (a major protein of the white fibers of connective tissue, cartilage, and bone) resists stretching and thereby prevents over-distention of the vasculature. Smooth muscle provides the contracting component of the vascular system that regulates vasoconstriction and dilation.

The vascular system is further subdivided into elastic arteries (the aorta and major pulmonary arteries), muscular arteries (the renal and femoral arteries), arterioles, and capillaries. Elastic arteries contain large amounts of elastic tissue, which enables them to distend and recoil during

systole and diastole to help propel blood. The muscular arteries are mainly comprised of smooth muscle cells and control blood flow to the periphery and major organs. These arteries are capable of constricting and dilating to allow varying degrees of blood flow to certain tissues according to their needs. Muscular arteries are major regulators of systemic blood pressure.

Arterioles are small arteries, which lead, in turn, to capillaries. Capillaries, the smallest blood vessels, have an endothelium but no intima. Red blood cells pass single file through the capillary bed at a very slow pace. This combination of slow movement and thin capillary walls is ideally suited for the exchange of substances between the tissues and blood. Blood eventually passes into the post-capillary venules and, sequentially, through the collecting venules and the small, medium, and large veins, thus transporting the blood back to the right side of the heart via the vena cavae.

Veins have larger diameters, larger lumens, and thinner, more distensible walls making the venous system capable of holding approximately two-thirds of the total blood in the body. In the extremities, where blood flows against gravity, a system of valves prevents reverse flow or pooling of blood.

Lymphatics are thin-walled, endothelial-lined channels that collect excess fluid in the tissue (i.e., interstitial tissue fluid) and inflammatory cells, transporting them back to the blood.

### Atherosclerosis

Atherosclerosis is a pathologic condition that causes coronary, cerebral, aortic, and peripheral arterial diseases. It develops primarily in elastic arteries (e.g., aorta, carotid, and iliac arteries) and large and medium-sized muscular arteries (e.g., popliteal arteries). It begins as fatty streaks in childhood and lesions can advance with age. The first phase, intimal thickening with accumulation of lipid-filled macrophages (called foam cells), is followed by lipid accumulation in and around cells to produce the fatty streak. Fatty streaks transition into atherosclerotic plaques and these plaques can then develop a well-defined lipid core covered by a fibrous cap. Advanced lesions may have a necrotic lipid core with calcification, and more advanced lesions may also have hemorrhage. Table 1 summarizes The American Heart Association (AHA) classification of atherosclerotic lesions.

**Table 1. The American Heart Association lesion classification system for atherosclerosis.**

AHA grade	Criteria	Description
0	Normal artery	Normal tissue
1	Isolated macrophage foam cells (MFC) which contain lipid	Initial lesion
2	Numerous MFC, fine particles of extracellular lipid	Fatty streak
3	Numerous MFC with pools of extracellular lipid	Intermediate: fatty plaque, raised fatty streak
4	Numerous MFC with well-defined core of extracellular lipid	Atheroma, fibrous plaque, or raised lesion

5	Numerous MFC, well-defined core or multiple cores of extracellular lipid, reactive fibrotic cap, vascularization, or calcium	Fibroatheroma, fibrous plaque, or raised lesion
6	All the above plus surface defect, hematoma, hemorrhage, or thrombosis	Complicated lesion

General risk factors for atherosclerosis align with risk factors for cardiovascular disease. Established risk factors for atherosclerosis include advancing age, cigarette smoking, dyslipidemia (e.g., increased non-HDL cholesterol, triglycerides, lipoprotein (a), high blood pressure, diabetes mellitus, family history of premature atherosclerosis, and evidence of inflammation [markers including high sensitivity C-reactive protein (hsCRP)]).

### **Atherosclerotic Peripheral Arterial Disease**

Peripheral arterial disease (PAD) is an occlusive disease of the aorta, the iliac arteries, and the arteries of the lower extremities. Prevalence is estimated at about 10 million Americans.

PAD is a marker for systemic disease of atherosclerosis and confers sharply increased risks for coronary, cerebrovascular, and renovascular disease. Ten-year cardiovascular disease mortality in patients is 6.6 times that in age-matched controls. Estimates of cerebrovascular disease prevalence range from 0.5% to 52%, depending on the method of detection.

#### Clinical Presentation

PAD usually presents with gradual onset of lower extremity claudication characterized by aching, tiredness, or burning pain, and frequently goes unrecognized for an extended period. The symptoms are usually brought on by walking and are relieved by rest. The most common presentation is calf claudication, secondary to femoral-popliteal artery atherosclerosis. Often, the treating physician will erroneously attribute the symptoms to arthritis, muscular pain, or aging. Misdiagnosis as an orthopedic back problem is especially common when the aortoiliac artery is involved since that causes hip, thigh, or buttock pain. Claudication can also present as the hip or leg “giving out” after a certain period of ambulation. Leriche syndrome is a clinical syndrome characterized by intermittent claudication, impotence, and decreased or absent femoral pulses. This syndrome usually correlates with narrowing of the distal aorta.

Physical exam of an affected limb often reveals decreased pulses, atrophic changes of the skin, decreased capillary refilling, loss of hair, discoloration of the skin, and vascular bruits. While vascular bruits can indicate the presence of disease, they do not correlate with its severity. The posterior tibial pulse (found behind the ankle bone) is always present in individuals who do not have PAD. Any decrease in or absence of this pulse is the most reliable clinical sign of the presence of PAD.

#### Diagnosis

Making the diagnosis of PAD with symptoms of claudication requires careful history taking, with special attention to differentiating true claudication from pseudoclaudication due to lumbar canal stenosis. True claudication is manifested by pain when walking a certain distance that is relieved when the individual stops. It does not occur while the individual is merely standing. With

pseudoclaudication, pain persists when standing and can necessitate sitting or changing position to obtain relief.

Historically, physicians have been taught to look for the classic “5 Ps” on physical exam: pulselessness, paralysis, paraesthesia, pain, and pallor. These signs can be applicable in more advanced disease but are not sensitive enough to make a diagnosis early in the disease process.

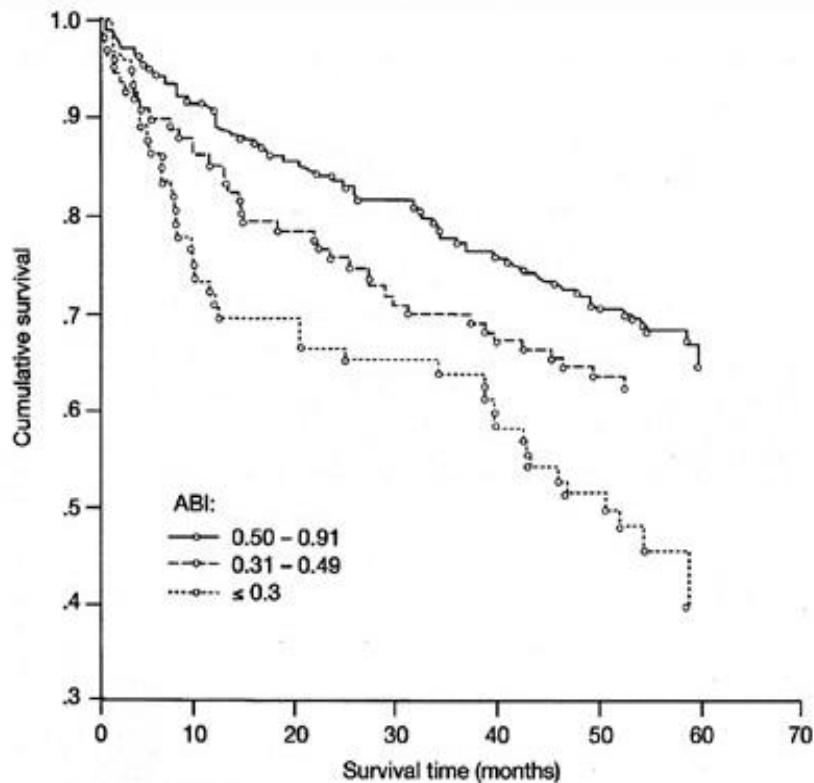
#### *Ankle-Brachial Index Test*

The most accurate, quick, and non-invasive way to diagnose PAD is by ankle-brachial index (ABI). The ABI is 95% sensitive and 99% specific for angiographically-measured lower extremity arterial stenosis of 50% or greater.

The hallmark of arterial insufficiency of the lower extremity is a decrease in the ankle-brachial index, especially after exercise. The ABI is determined through Doppler wave ultrasound assessment received from blood pressure measurements in the arm and ankle. The index is determined by dividing ankle systolic blood pressure by arm systolic blood pressure. The test is usually performed at rest and after treadmill exercise. Completion of a standard exercise protocol without pain or symptoms virtually excludes the diagnosis of PAD. A normal ABI is  $> .91$ . An index of 0.9 or less indicates the presence of obstructive disease and 0.4 or less suggests severe disease.

The ABI can be used to identify individuals with an increased risk of cardiovascular events and total mortality. Studies show that more severe disease, as evidenced by the lower ABI value, is associated with greater risk of total mortality and cardiovascular mortality than mild disease, as referenced in Figure 1.<sup>1</sup>

**Figure 1. Relationship between ankle-brachial index (ABI) and mortality.**



#### *Exercise Treadmill Testing*

Exercise testing is utilized in individuals with typical symptoms of claudication with normal resting ABI measurements. ABI is measured at one-minute intervals for five minutes after exercise. Exercise induces a systolic pressure gradient across the area of stenosis resulting in a fall in the ABI in recovery.

#### *Segmental Limb Pressures*

The level and extent of PAD can be determined by segmental limb pressures. Blood pressure cuffs are applied at various levels based on the results of ABI testing and location of the clinical symptoms of claudication. Each cuff is inflated individually, and a pressure gradient difference is determined. A 20 mmHg or greater reduction or difference in pressure between the segments along the same leg, or when compared to the same level in the opposite leg, is considered significant.

#### *Segmental Volume Plethysmography*

Plethysmography is used in conjunction with segmental limb pressures to locate the level of disease. A transducer detects volume change in a limb as a pneumatic cuff is placed at various levels and then inflated. The volume change is converted into a pressure pulse wave. Variations in the contour of the pressure pulse wave reflect disease severity. In severe disease, the amplitude of the wave is blunted or flattened.

### *Ultrasonography*

The quality of ultrasound testing of the vascular system and evaluating blood flow through vessels has improved greatly in recent years. Ultrasound methods include gray-scale imaging, Doppler pulse and continuous-wave spectral imaging, and Doppler color flow imaging.

Gray scale imaging is used to assess the morphology of the vessel, to determine the presence of plaque, and to assess the characteristics of the plaque. Color flow imaging is useful in evaluating subtotal occlusion of blood vessels and aneurysms and localizing areas of stenosis.

### *Magnetic Resonance Imaging and Angiography*

MRI and MRA are widely used techniques for evaluating the blood vessels of the vascular system, especially when surgical intervention is contemplated. Magnetic resonance techniques are very sensitive and specific in evaluating arterial wall morphology and possible dissection.

### *Angiography*

The definitive diagnostic tool is still angiography. The use of contrast material in angiography increases risk to the individual and is usually reserved for severe cases of peripheral vascular disease when surgical intervention is contemplated.

## Treatment

Treatment modalities include lifestyle, medical, and surgical interventions. Medical treatment is also directed at reducing the major morbidity and mortality of co-morbid conditions, especially cardiovascular and cerebrovascular disease. Surgical intervention is usually reserved for severe cases that are not responsive to risk factor modification, exercise, and drug therapy.

### *Lifestyle Modification*

Cardiovascular risk factor modification - smoking cessation, lipid-lowering therapy, and control of blood pressure, blood sugar, and weight - is an important cornerstone for management of PAD. Individuals who stop cigarette smoking reduce progression of disease, reduce risk of amputation, and improve symptoms of limb ischemia at rest.

Modification of diet - primarily by reducing saturated fat intake and increasing fresh fruits and vegetables - has been shown to benefit PAD. In particular, the Mediterranean diet, which consists of mainly plant-based nutrition with a high percentage of fresh fruits, legumes, vegetables, omega 3 fatty acids (fish), and monounsaturated fats such as olive oil, shows correlation with improved vascular and cardiovascular health.

Consistent exercise, primarily walking, improves exercise tolerance and symptoms of lower extremity vascular disease. A meta-analysis showed the significant delay in onset of claudication. Consistent exercise training that lasted at least 30 minutes and was performed three times a week proved most beneficial.<sup>2</sup>

Exercise appears to reduce red blood cell aggregation, improve muscle metabolism, improve endothelial function, reduce local inflammation, and can induce vascular angiogenesis (formation of new blood vessels), all mechanisms that can improve symptoms of claudication.<sup>3</sup>

### *Medical therapy*

Pharmacologic therapy has a well-established role in the treatment of PAD. Antiplatelet agents, such as aspirin and dipyridamole, decrease claudication with ambulation and increase resting limb blood flow. Clopidogrel (and ticlopidine, which is not available in U.S.), both inhibitors of platelet aggregation, modestly increase walking distance. Cilostazol, a phosphodiesterase inhibitor, suppresses platelet aggregation and induces vasodilatation. Pentoxifylline (Trental®) is approved for treatment of intermittent claudication and appears to increase pain-free walking by up to 67% in most studies.<sup>4</sup>

### *Interventions*

Intervention, including percutaneous procedures or surgical bypass, can be used for individuals with significant claudication. Major advancements in percutaneous procedures, such as percutaneous transluminal angioplasty (PTA), balloon angioplasty, and stenting, have resulted in a dramatic increase in these procedures in recent years. A landmark study, published in 1993, showed no significant difference in outcome between angioplasty and surgical bypass for peripheral disease after a median follow-up of four years.

The main indications for utilizing angioplasty for peripheral vascular disease are:

1. persistent claudication that significantly reduces the ability of the individual to perform activities indent of daily living
2. pain at rest
3. tissue loss.

PTA is utilized traditionally for focal, short segment occlusions. More recently, technology allows PTA to be applied to more extensive disease segments. It can also be used in individuals who are poor surgical candidates.

The greatest success rate for PTA has been found when it is utilized for aortoiliac stenosis. In uncomplicated disease, the five-year patency rate is 70%. The use of intravascular stents for aortoiliac occlusive disease is usually limited to a suboptimal angioplasty result and is not routinely employed as part of the PTA procedure.

When employed for femoral-popliteal occlusive disease, the restenosis rate is greater than 50% at two years in some studies, making femoropopliteal surgical bypass a more appropriate choice of intervention. Stenting also carries a high restenosis rate and has not been shown to improve outcome.

Complications from PTA include direct arterial injury leading to groin hematoma (2 to 4%), pseudoaneurysm (0.3 to 2%), or arteriovenous fistula (0.1 to 0.3%). The actual dilatation of the vessel can result in distal embolization (2%), thrombotic occlusion (2%), and rarely, arterial rupture.

Surgical bypass and graft placement in occlusive disease are also used to relieve persistent claudication and improve the level of activities of daily living, but it is generally reserved for more severe disease. Individuals who benefit the most from elective surgical revascularization are generally under 70 years of age, nondiabetic, and have little evidence of disease distal to the primary lesion. Of note, individuals under 40 years of age with aggressive atherosclerotic disease

had a 71% failure rate for initial vascularization and averaged a 10-year mortality rate of 31% after initial surgery.

One study of 5,285 individuals who underwent surgery and were followed for greater than 25 years, revealed the following predictors of mortality in all age groups:

1. age, with a relative risk of 1.62 for each 10-year increase in age
2. male sex, relative risk 1.55
3. diabetes mellitus, relative risk 1.71
4. systemic hypertension, relative risk 1.51.

Diabetes mellitus was the only predictor of recurrence of symptoms or progression of disease. Aspirin therapy prior to surgery and life-long aspirin therapy after surgery is recommended. The addition of dipyridamole can provide additional benefit in the prevention of graft failure.

### **Non-atherosclerotic peripheral vascular disease**

#### Thromboangiitis Obliterans (Buerger's Disease)

Thromboangiitis obliterans, a vasculitis strongly linked to cigarette smoking, is characterized by segmental, thrombosing, acute and chronic inflammation of small and medium vessels. Most individuals have a hypersensitivity to intradermally injected tobacco extracts. Historically a disease of males who were heavy smokers, it is increasingly reported in females, reflecting smoking increases. The disease usually begins before age 35.

The disease affects mainly the tibial and radial arteries, leading to vascular insufficiency. Later complications include chronic ulcerations and gangrene of the fingers and toes. Clinically, in contrast to atherosclerosis, individuals experience significant pain at rest, reflecting the small vessel and neural involvement. Angiography demonstrates smooth, tapered, segmental lesions. Abstinence from tobacco use in the early stages of the disease often prevents further attacks or the development of late complications.

### **Aneurysms**

An aneurysm is a localized, abnormal dilatation of a blood vessel. When an aneurysm is bounded by the components of the vessel wall, it is considered a true aneurysm. Atherosclerotic, syphilitic, and congenital vascular aneurysms are considered true aneurysms. In contrast, a false aneurysm is a breach in the vascular wall leading to an extravascular hematoma that freely communicates with the vessel lumen.

The two most important causes of aortic aneurysms are atherosclerosis and cystic medial degeneration of the arterial media. Arterial aneurysms can also be caused by systemic diseases (e.g., vasculitides), trauma, and mycotic (fungal) infections.

#### Abdominal Aortic Aneurysms

Abdominal aortic aneurysms (AAA) are usually caused by the atherosclerotic process of plaque formation. Plaque forming in the intima eventually starts to erode the media or muscular layer of the vessel wall, thus weakening the media with eventual aneurysmal formation. Although atherosclerosis and hypertension predispose an individual to the development of an aortic aneurysm, recent attention has focused on a genetic predisposition to an altered balance of collagen

degradation and synthesis, providing a susceptible substrate on which atherosclerosis and hypertension could act to weaken the vessel wall.

Risk factors for development of AAA include age over 60 years, male sex, family history, tobacco use, presence of other large vessel aneurysms, coronary artery disease, and peripheral arterial disease. Aneurysms typically expand at a rate of 0.2 to 0.3 cm per year, but 20% expand more rapidly. The most important clinical factor affecting aneurysmal growth is elevated blood pressure. As aneurysms grow, they can impinge on adjacent structures such as a blood vessel or ureter or erode into a vertebral body. The risk of rupture is directly related to the size of the aneurysm. Risk varies from zero for a small AAA (less than 4.0 cm in diameter) to 1% per year for aneurysms measuring 4.0 to 4.9 cm in diameter, 11% per year for aneurysms between 5.0 and 5.9 cm in diameter, and 25% per year for those larger than 6.0 cm.

### *Diagnosis*

Most abdominal aortic aneurysms are asymptomatic and can progress without symptoms. Diagnosis requires a high level of clinical suspicion, with imaging confirmation. Symptoms, when present, may include pain in the abdomen, back or flank and limb ischemia, which are associated with increased risk for rupture.

Asymptomatic AAAs are often detected by screening or as an incidental finding on imaging done for other reasons. A pulsatile abdominal mass, discovered on physical exam or by the individual, is often the first indication of an aneurysm. As an aneurysm enlarges, the individual may experience abdominal, flank, or back pain. Abdominal ultrasound and computed tomography (CT) are excellent imaging modalities used to identify aneurysms. Magnetic resonance imaging (MRI) can also be used.

### *Management*

The Society for Vascular Surgery recommends surveillance of unrepaird AAA by ultrasound imaging based on aneurysm diameter.

**Table 2. Society for Vascular Surgery AAA surveillance schedule.**

AAA diameter (cm)	Surveillance interval
Less than 3.0	10 years
3.0 – 3.9	3 years
4.0 – 4.9	1 year
5.0 – 5.4	6 months

The major complication of AAA is rupture, which is associated with high operative mortality. Elective AAA repair is most effective to prevent rupture. In general, elective repair is indicated for asymptomatic AAA of 5.5 cm diameter or more, AAA that is rapidly expanding and AAA associated with peripheral artery disease that is being re-vascularized. Intervention is individualized and can be either endovascular or open surgical repair.

In general, endovascular repair is associated with less short-term (i.e., 30-day) morbidity and mortality compared to conventional surgical repair. However, endovascular repair is also

associated with higher re-intervention rates and with an ongoing risk for rupture and the need for indefinite imaging surveillance.

### *Underwriting AAA*

AAA management includes optimal control of cardiovascular risk factors, including smoking cessation. Smaller unrepaired AAAs may be detected on imaging done for another reason. The need for ongoing surveillance depends on size of the aneurysm. Underwriting of smaller unrepaired AAAs requires imaging reports with a description of the aneurysm and its diameter. Ideally, evidence of monitoring according to recommended intervals and serial measures should be available to assess for any aneurysm expansion. For repaired aneurysms, cardiovascular risk factor control remains important as does regular surveillance for all endovascular repairs.

### Thoracic Aneurysms

Thoracic aneurysms can be classified based on their anatomic location. The four basic categories are:

1. ascending thoracic aneurysms
2. aortic arch aneurysms
3. descending aortic aneurysms
4. thoracoabdominal aneurysms.

Thoracic aneurysms occur most commonly in the sixth and seventh decades of life and are twice as likely to occur in males. Thoracic aneurysms are commonly seen in atherosclerotic vessels, and the most common risk factor associated with thoracic aneurysms is hypertension, seen in approximately 60% of cases.

When seen in younger individuals, thoracic aneurysm is most often associated with Marfan syndrome and, to a lesser degree, with connective diseases such as Ehlers-Danlos syndrome. A strong association exists between thoracic aneurysms and bicuspid aortic valve and aortic coarctation. Thirty to forty percent of those with bicuspid aortic valve also have coarctation of the aorta. In a study of young males with bicuspid aortic valve, over half also had enlargement of the aortic root and dilatation of the ascending aorta.

Although many aneurysms are not seen on chest x-ray, it is a common way to identify an incidental asymptomatic aneurysm. Mediastinal widening and enlargement of the aortic knob, when seen, warrant further investigation. CT scan and MRI with contrast are the recommended imaging procedures to diagnose thoracic aneurysms.

Surveillance of unrepaired TAA with serial imaging is recommended, with echocardiography, computed tomographic (CT) angiography, or magnetic resonance (MR) angiography. Imaging modality choice depends on aneurysm location, ideally using the same technique (and center) serially for optimal comparison. Imaging six months after the initial diagnosis to ensure the stability of the aneurysm diameter and extent is recommended. Further imaging is recommended annually if there is no expansion or extension or modified to more frequent surveillance with instability or based on etiology, site, and diameter of the aneurysm at presentation. For example, recommendations for ascending (thoracic) aortic or aortic root aneurysms include annual CT or MR angiography for aneurysms 3.5 to 4.4 cm and every six months for aneurysms 4.5 to 5.4 cm in size.

Surgical intervention is indicated with an accelerated growth rate of greater than or equal to 1.0 cm per year in aneurysms less than 5.0 cm in diameter. Surgical intervention is also indicated when end-diastolic diameter is 5.0 to 6.0 cm for an ascending aneurysm and 6.0 to 7.0 cm for a descending aneurysm, found by radiologic intervention.

### Vasculitis

Vasculitis is a group of rare diseases with inflammation of the blood vessels. Causes are generally unknown although some are secondary to other diseases. Information at time of underwriting should include specific diagnosis, symptoms, and treatment. Vasculitis may be associated with high mortality and morbidity risk. The current naming of vasculitides is listed in Table 3.

**Table 3. The Vasculitides, International Chapel Hill Consensus Conference.**

Large vessel	Medium vessel	Small vessel	Variable vessel	Single organ	Other
Takayasu arteritis Giant cell (temporal) arteritis	Polyarteritis nodosa Kawasaki disease	ANCA-associated: Microscopic polyangiitis (MPA), Granulomatosis with polyangiitis (GPA, Wegener's), Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) Immune complex small vessel: Anti-glomerular basement membrane disease, Cryoglobulinemic vasculitis, IgA vasculitis (Henoch-Schönlein purpura), Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)	Behçet's syndrome Cogan's syndrome	Primary central nervous system vasculitis	Associated with systemic disease: Lupus, rheumatoid, sarcoid, others Associated with probable etiology: Hepatitis C or B, syphilis, drug-associated, cancer-associated

#### Arteritis- small and medium vessels

The small and medium vessel vasculitides are a complex heterogeneous group of disorders that involve inflammation and destruction of blood vessel walls. This section will review the major vasculitides that affect the small and medium vessels.

#### *Polyarteritis Nodosa*

Polyarteritis nodosa (PAN) is a prime example of a medium vessel vasculitis (MVV) affecting the arteries that contain muscular walls. The damage caused by inflammation leads to aneurysmal formation. PAN usually begins with nonspecific symptoms that can include malaise, fatigue,

fever, and weight loss, though it can take weeks to months to clearly manifest itself as a vasculitis. The organ systems most involved are skin, peripheral nerves, gastrointestinal tract, and kidneys. Most individuals with PAN have a vasculitis neuropathy in the form of a mononeuritis multiplex (MM) that produces symptoms of foot drop or wrist drop. The classic symptom of postprandial periumbilical pain or “intestinal angina” is a hallmark of the disease. Anemia, thrombocytosis, high erythrocyte sedimentation rate (ESR), and microscopic hematuria are common. The diagnosis of PAN requires a tissue biopsy or an angiogram demonstrating microaneurysms. Sural nerve biopsy can be highly diagnostic when MM is suspected. Immunosuppression in the form of corticosteroids and cyclophosphamide (Cytoxan®) can affect a remission or cure in one-third of cases treated.

#### *Kawasaki Syndrome*

Kawasaki syndrome (KS), an acute vasculitis of childhood, is the number one cause of acquired heart disease among children in the United States and Japan. It is a systemic vasculitis that has a predilection for the coronary arteries. Morbidity and mortality most often are due to cardiac sequelae in the form of coronary aneurysms. The peak incidence is at age two years and younger and the syndrome recurs in 2-4% of cases. KS begins with prolonged fever accompanied by rash, conjunctival injection, and oral lesions. Arthritis may be present 10 to 14 days after the onset of fever, as is periungual desquamation (i.e., peeling of the skin around the fingertips).

Treatment is directed at preventing coronary artery aneurysms. Coronary artery aneurysms will develop in 15-25% of those affected, unless treatment, in the form of IV gamma globulin, is instituted in the early stages of the disease. Aneurysms are easily detected by transthoracic echocardiography. Smaller aneurysms usually regress over five years. Despite regression, there are case reports of young adults suffering myocardial infarction more than a decade after the initial disease.<sup>5</sup>

#### *Granulomatosis with polyangiitis (GPA, Wegener's Granulomatosis)*

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG), is a vasculitis of the small and medium vessels, affects approximately one in 20,000-30,000 people. Most individuals are adults, and the disease is not gender specific. WG affects primarily the lungs and kidneys, but that is not overtly apparent early in the course of the disease. Most individuals initially seek care for recurrent upper or lower respiratory symptoms usually attributed to asthma or infection. Persistent symptoms and complications such as recurrent epistaxis, mucosal ulcerations, nasal septal perforation, and nasal deformity, usually lead to more extensive evaluation. Pulmonary infiltrates are present in 50% of cases. Seventy-five percent of individuals will eventually develop glomerulonephritis. A blood test to identify the autoantibody anti-neutrophil cytoplasmic antibody (ANCA), and in conjunction with an active urinary sediment, elevated ESR, unexplained anemia, and recurrent symptoms, help form the diagnosis. In cases where the ANCA is negative, a biopsy of an involved site can be needed to support a definitive diagnosis. With the use of immunosuppressive agents, remission can be achieved in 75% of individuals. Unfortunately, approximately 50% will relapse and develop active disease.<sup>6</sup>

## Arteritis - Large Vessels

### *Giant Cell Arteritis (Temporal Arteritis)*

Giant cell arteritis (GCA) is characterized by inflammatory changes in one of the branches of the aorta, occurring almost exclusively in individuals older than 50 years. The disease incidence increases progressively with age and is higher in females. GCA is also known as temporal arteritis because extracranial branches of the carotid branches are targeted preferentially. In 80-90% of individuals, vasculitis is detected in the extracranial tree, most often in the superficial temporal, vertebral, ophthalmic, and posterior ciliary arteries.

GCA presents with two major symptomatic complexes: signs of vascular insufficiency resulting from impaired blood flow and signs of systemic inflammation. Individuals complain of throbbing, sharp or dull headaches, usually severe enough to prompt an evaluation. Typically, they notice temporal tenderness. On exam, the involved vessels are thickened, tender and, at times, nodular. Pulses are reduced or absent. Vision loss is a serious complication and can occur when the ophthalmic artery is involved. Loss of vision is sudden, painless, and usually permanent. Amaurosis fugax, or fleeting visual blurring, can precede partial or total blindness. About one-half of individuals experience claudication with prolonged talking or chewing.

In about 15%, GCA targets the large arteries, most notably the carotid, subclavian and axillary arteries. Termed the aortic arch syndrome, this variant typically presents with claudication of the upper arms, absent pulses, paresthesia, Raynaud's phenomenon, and occasionally gangrene. Nonspecific blood tests, such as an elevated ESR, help support the clinical suspicion of GCA. A positive biopsy of the affected vessel is the procedure of choice. Corticosteroids effectively treat the symptoms of GCA with a significant concomitant reduction in the rate of blindness.<sup>7</sup>

### *Takayasu's Arteritis (TA)*

This large vessel vasculitis classically involves the aortic arch and its main branches but can also involve the coronary and pulmonary vessels in half the cases. Inflammation of the vessels results in intimal thickening with subsequent stenosis and/or aneurysm. Complete occlusion of an upper extremity artery can occur, hence the name "pulseless disease." TA affects females, usually under the age of 40 years, with higher incidence rates in the Asian population.

Classic constitutional symptoms of myalgias, fever, malaise, weight loss, and anorexia are often misdiagnosed as infection. Eventually, clinical patterns of ischemia become apparent based on the pattern of involved arteries. Carotid and vertebral artery involvement can cause dizziness, tinnitus, syncope, stroke, and visual disturbances. Inflammation and stenosis of the subclavian arteries would present with arm claudication, pulselessness, and discrepant blood pressures. Aortitis (inflammation of the aorta) can lead to aortic regurgitation and ischemic coronary disease.

Vascular imaging provides the best diagnostic evidence and is often combined with angioplasty. Corticosteroids remain the therapy of choice for management of TA. Aggressive surgical intervention has led to improved prognosis in recent years. Long-term studies found stable clinical conditions in two-thirds of patients.<sup>8</sup>

## **Review Questions – ALU 201, Chapter 14**

1. The risk factor strongly linked to thromboangiitis obliterans (Buerger's disease) is:
  1. genetics
  2. hyperlipidemia
  3. cigarette smoking
  4. sedentary lifestyle
2. Peripheral arterial disease can cause occlusion of all of the following vessels EXCEPT the:
  1. aorta
  2. vena cava
  3. iliac artery
  4. femoral-popliteal artery
3. Which of the following statements regarding Wegener's granulomatosis is/are correct?
  - A. It is a vasculitis of the large vessels.
  - B. The majority of affected individuals are adults.
  - C. It primarily affects the lungs and kidneys.

Answer options: 1. A only is correct.

2. B only is correct.
3. B and C only are correct.
4. A, B, and C are correct.

4. Compare and contrast polyarteritis nodosa (PAN) and granulomatosis with polyangiitis.
5. List three of the four basic categories of thoracic aneurysms.

6. Which of the following statements regarding abdominal aortic aneurysms is/are correct?
- A. They can be caused by atherosclerosis
  - B. They usually develop before age 50.
  - C. Hypertension affects aneurysmal growth.

Answer options:

- 1. A only is correct.
- 2. B only is correct.
- 3. A and C only are correct.
- 4. A, B, and C are correct.

7. The smallest blood vessels in the vascular system are:

- 1. venules
- 2. arterioles
- 3. lymphatics
- 4. capillaries

8. Briefly describe the six types of atherosclerotic lesions.
9. List at least three risk factors for atherosclerosis.
10. Discuss diagnosis methods and treatment options for thoracic aneurysms.

## **Answers and Sources of Review Questions**

*Review Question 1*

Answer 3: cigarette smoking – page 8.

*Review Question 2*

Answer 2: vena cava – page 3.

*Review Question 3*

Answer 3: B and C only are correct – page 12.

*Review Question 4*

Refer to pages 11-12.

*Review Question 5*

Refer to page 10.

*Review Question 6*

Answer 3: A and C only are correct – pages 8-9.

*Review Question 7*

Answer 4: capillaries – page 2.

*Review Question 8*

Refer to pages 2-3.

*Review Question 9*

Refer to page 3.

*Review Question 10*

Refer to pages 10-11.

## **CHAPTER 15**

### **PHARMACOLOGY**

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# **PHARMACOLOGY**

## **Introduction**

Pharmacology can be simply defined as the study of medications (for purposes of this chapter this includes pharmaceutical drugs, street drugs, and ethanol alcohol). The pharmacology industry is continually growing and expanding due both to competition and to the progress of medical technology. For this reason, there is no reasonable way to list all of the available medications on the market today. If attempted, that list would no doubt be obsolete by the time it was printed. It should be fully understood that the lists of medications within this chapter are in no way exhaustive. In addition, while medications listed are described based on their originally intended and Food and Drug Administration (FDA) approved uses, they are often used “off-label.” Underwriters should always research medications with which they are unfamiliar to determine their effects on the body, their common uses, and any potential off-label uses when assessing the risk.

### **Pharmacology and the Underwriter**

Medications taken by proposed insureds provide information about their potential medical impairments. Medications can indicate the severity of the impairment or the stage to which the health issue has progressed. For example, when a proposed insured reveals that he suffers from headaches and reports that the treatment consists of aspirin, this tells the underwriter that the headaches are not severe. On the other hand, if that individual reveals the medication is oxycodone HCl (Oxycontin®), a potent narcotic used for pain, it will indicate a more serious medical impairment. Further, a situation in which a client reports having asthma but does not reveal any prescription medication use, could indicate a very mild case of asthma or a life-threatening impairment that is going unmedicated.

### **Basic Categories of Medications**

A medication is any substance that can produce biological changes in the body, whether those changes are therapeutic or damaging. Once the substance is delivered into the body and is therapeutic in nature, it can be considered a medication.

Prescription (Rx) medications require a prescription from a licensed physician (e.g., M.D., D.O.). Dentists can write prescriptions but are limited as to which medications they can prescribe. Optometrists can only prescribe eye medications. Other health professionals who can prescribe medications on a limited basis are physician assistants (PA), nurse practitioners, and psychiatrists. Chiropractors are not allowed to write prescriptions.

Over the counter (OTC) medications are those medications that do not need a doctor's prescription to be purchased. These medications are generally self-prescribed, and often an individual has not consulted with a health professional prior to their use. In the U.S., the FDA is the federal government agency that determines whether a medication must be prescribed by a doctor for distribution or can be purchased as an OTC medication.

Supplements are considered products that are not sold as therapeutic medications. The FDA does not regulate dietary supplements and medicinal herbs. Unlike prescription and OTC medications, dietary supplements can be made, marketed, and sold without providing the FDA with proof they are safe or successful in their therapeutic claims. If the supplement proves harmful, the FDA must intervene through the court system to have the supplement regulated.<sup>1</sup> An example of this type of intervention by the FDA was the withdrawal of ephedra, a well-known dietary weight loss supplement, from the market.

Medications or drugs that can be addictive are classified by dependency and abuse potential and are regulated by schedules. Table 1 provides an overview of the schedule system with examples of medications in each category.

**Table 1. U.S. Drug Schedules and Examples.<sup>2</sup>**

<i>Schedule</i>	<i>Example</i>
Schedule I - highest potential for abuse	heroin, LSD
Schedule II - high potential for abuse	morphine, methadone
Schedule III - moderate potential for abuse	codeine, Tylenol-3®
Schedule IV - lower potential for abuse	Valium®, Xanax®
Schedule V - lowest potential for abuse	OTC cough medicine with codeine

Medications have three categories of names. N-Acetyl-para-aminophenol is the *chemical* name for the *generic* acetaminophen, which is more easily recognized as Tylenol®, the *trade* name. In this chapter, generic names are presented without the first letter capitalized and trade names are capitalized and followed by the registered trade name symbol: ®. It is important to realize that new medications are introduced to the market almost daily. While the generic names of medications do not often change, the newer trade names of medications do. In addition, trade names can vary by country. For these reasons, this chapter will mainly refer to medications by their generic name only. Please see Appendix 1 for example trade names of each generic medication referenced.

### **Basic Pharmacokinetics and Pharmacodynamics**

Two processes describe how a medication is utilized in the body – pharmacokinetics and pharmacodynamics.

*Pharmacokinetics* is the study of how a medication moves through the body and, thus, how it gets to target tissues. These functions include absorption and distribution of the medication, including how the medication is metabolized and then excreted by the body. Administration route (e.g., oral vs. IV administration), dosage, and dosing schedule are determined by how a specific medication moves through the body and the target location for effectiveness. For example, for a cough drop, one drop in a buccal administration (in the cheek) every few hours is the most effective method and dosage to deliver that medicine.

*Pharmacodynamics* describes how the medication changes the body. The nature and intensity of the response in the body determine the dynamic action or impact of the medication on the body.

Responses can be altered by tolerance, placebo effect, and other body variables, as well as by the dosage and potency of the medication.

Medication metabolism varies in individuals. Age, gender, body mass, and genetic makeup are examples of variations in individuals that affect the way a chemical works in the body. Diseases can alter the way in which the body metabolizes a medication, especially when the disease affects the kidneys and liver.

### **Administration of Medications**

Medications are administered or introduced into the body by several routes. Table 2 describes the methods of medication administration currently used. The speed and degree of absorption determine the time of onset and the intensity of the effect of the medication. This dictates the best way(s) of introducing the medication into the body. For example, intravenous administration promotes speed of distribution of the medication, while taking a pill by mouth (oral administration) slows the process of medication absorption and, therefore, the medication's effect.

**Table 2. Administration of Medications.**

<i>Administration</i>	<i>Description</i>	<i>Example</i>
Intravenous (IV)	Into the vein	IV drips
Intramuscular (IM)	Into the muscle	Immunizations
Subcutaneous (SC)	Under the skin	Insulin
Oral (PO)	By mouth	Pills, capsules, tablets
Inhalation	Breathing the medication into the nose or mouth	Inhalers, oxygen, anesthesia
Buccal or sublingual	In the cheek or under the tongue	Organic nitrates (nitroglycerin)
Nasal	Breathing or placing the medication into the nose	Nasal decongestants
Anal, vaginal, colonic	By anal cavity, vagina, or into the colon	Suppositories
Topical application	Onto the skin	Medicated creams
Intrathecal	Into the spinal canal	Pain medication, anesthesia
Intraperitoneal	Into the peritoneum	Chemotherapy, antibiotics
Intra-articular	Into the joint	Anti-inflammatories
Intra-arterial	Into the artery	Vasodilators
Transdermal	Through the skin	Birth control and nicotine patches

### **Medication Interactions and Side Effects**

No medication is perfect. All medications have side effects and often a decision must be made regarding whether the positive effects outweigh the negative effects. Lehne defines a side effect as "a nearly unavoidable secondary medication effect produced at therapeutic doses."<sup>3</sup> Excessive

dosing that causes adverse effects is considered drug toxicity. Examples of other adverse responses to medications are:

1. Allergic reactions are an immune response (e.g., penicillin-induced hives).
2. Idiosyncratic effects are uncommon responses to a medication secondary to a genetic predisposition – (e.g., succinylcholine is used to produce temporary flaccid paralysis of skeletal muscle; an individual can become paralyzed for hours if genetically predisposed to this effect).
3. Iatrogenic refers to medication error (e.g., due to incorrect administration or dosage).
4. Physical dependence occurs when the body adapts to repeated use of a substance and thus becomes addicted to a medication, such as morphine.
5. Carcinogenic effect means cancer-causing (e.g., cyclosporine, an immunosuppressant used for the prophylaxis of organ transplant rejection, is a known human carcinogen).
6. Teratogenic effects are medication-induced birth defects (e.g., fetal alcohol syndrome).

Individuals often take more than one medication at the same time. This can trigger mild to severe side effects. However, it can be advantageous. For example, Maalox® (milk of magnesia and aspirin) protects the stomach and reduces the gastric irritation produced by aspirin when it is taken alone. Some medications interact with others, resulting in one of three effects:

1. The effect of the medication is intensified. For example, drinking alcohol while taking a sedative will result in an additive interaction in which the nervous system is further depressed. This interaction can be quite dangerous.
2. The medication has reduced effects. For example, calcium reduces the absorption of tetracycline (an antibiotic), which decreases its effect. This is why it is important for some medications to be taken with food, while some medications are to be taken on an empty stomach.
3. The two medications combined produce a new effect not seen in either of the original medications. For example, the interaction between monoamine oxidase inhibitors (a type of antidepressant) and foods rich in tyramine (such as aged cheese, yeast extracts, and Chianti wine) can raise blood pressure to a life-threatening level.

**The underwriter can refer to Appendix 2 for resources and websites to find information regarding medication-to-medication or drug-to-drug interactions.**

### **Issues of Medication Compliance**

When a proposed insured reports a medication on an application, it is assumed he or she is taking the medication. However, medication compliance is an issue of which the underwriter must be continually aware. As many as 40% or more of elderly individuals fail to take their medicines as prescribed. Some individuals never fill their prescriptions, some fail to refill their prescriptions, and some do not follow the prescribed dosing schedule.<sup>4</sup> This could obviously change the status of the proposed insured's life expectancy and mortality.

## **Medications That Affect the Circulatory System**

The heart is assisted by pressure gradients within the vascular system, which are dependent upon the following factors: the diameter and length of the blood vessels (especially arteries and arterioles) and the resistance to blood flow. Examples of resistance include increased blood thickness (viscosity) and atherosclerosis. The body regulates pressure gradients and blood flow through a complicated feedback system that involves the autonomic nervous system (ANS), the renin-angiotensin system (RAS), and the kidneys. Simplified, the ANS controls the heart, the RAS controls the constriction of arterioles and veins, and the kidneys regulate blood volume. The presence of pedal edema suggests volume overload. Pharmacological strategies are used to manipulate or control these systems in the presence of heart diseases. Measuring an individual's blood pressure is a common way to assess the effectiveness of this system.

Many types of pharmacological treatments can be used for the same condition, while one medication can often be used to treat several different circulatory problems. Examples of each class of medication will be provided, but it is more important to know how each type of medication affects the circulatory system. With this foundation, the underwriter can determine how the treatment can be useful in reported conditions and extrapolate what circulatory problems can exist based on a list of medications alone.

### Angiotensin-Affecting Medications

Angiotensin II is the chemical that causes the muscles surrounding blood vessels to contract, which increases blood pressure. Blocking the function of angiotensin is not only helpful in regulating blood pressure but can also help to regulate blood volume. For this reason, these medications are most used to treat hypertension. However, it is not uncommon to see these medication classes used in heart failure or coronary artery disease.

*Angiotensin-converting enzyme inhibitors*, or ACE inhibitors as they are more commonly known, inhibit the RAS from producing angiotensin II. Unfortunately, ACE inhibitors sometimes produce a chronic cough as a side effect and must be discontinued. Examples include lisinopril and enalapril.

*Angiotensin receptor blockers* (ARBs) block angiotensin II from binding to the angiotensin receptors and are often used as a substitute for ACE inhibitors when side effects occur. Common ARBs include losartan and candesartan.

### Beta Blockers

Beta blockers decrease the heart rate and contractile force, which decreases the cardiac oxygen demand. These effects reduce blood pressure and promote dilation of blood vessels to improve blood flow.

These medications are commonly used in angina pectoris, heart failure, hypertension, and as a cardioprotective agent following myocardial infarction or intervention for coronary artery disease. Slowing the heart rate can also be helpful in treating some dysrhythmias, such as atrial fibrillation

and supraventricular tachycardia. In addition, beta blockers are used to treat migraines, glaucoma, benign tremor, and anxiety disorders. Commonly used medications in this class include atenolol and metoprolol.

### Calcium Channel Blockers

As their name suggests, calcium channel blockers block calcium channels in the heart and blood vessels. This reduces cardiac muscle contraction, which results in lower cardiac output. The reduction in calcium in the blood vessels promotes vasodilation. Many medications of this class reduce the conduction velocity of the electrical impulse of the heart.

Calcium channel blockers are particularly effective in the treatment of hypertension. Like beta blockers, the reduction in cardiac oxygen demand from the reduced contractility is helpful in counteracting the symptoms of ischemic heart disease (angina) and some arrhythmias. Common examples include diltiazem and verapamil.

### Anti-Arrhythmic Agents

There are several other medication classes that are specifically used to treat dysrhythmias or arrhythmias.

*Potassium channel blockers* prolong the recovery of the heart between beats or repolarization. These medications are commonly used to treat atrial fibrillation as well as other atrial and ventricular arrhythmias. Examples include amiodarone and sotalol.

*Sodium channel blockers* work very similarly to calcium channel blockers by slowing the electrical impulse in the heart and are used to treat various atrial and ventricular arrhythmias. One added benefit of this medication class, however, is that their effects do not interfere with the activity of normal heart pacemakers. The most common example is flecainide.

*Cardiac glycosides* can be used to treat refractory atrial fibrillation and atrial flutter after beta blockers and calcium channel blockers have failed. The only medication in this class still used is digoxin, also known as digitalis. Digoxin used to be the standard treatment for congestive heart failure but is now used primarily in individuals still symptomatic despite treatment with other medications.

### Vasodilators

Generically, a vasodilator is a class of medications that relaxes smooth muscle within the vessel walls. Most of these medications act on both arteries and veins, but some are more specialized and target one type. An example of a vasodilator that affects only the arteries is hydralazine. It is also used to reduce afterload (arterial resistance) in those with congestive heart failure and is occasionally used in combination with other agents for refractory hypertension.

*Organic nitrates* can affect both types of blood vessels, but at normal therapeutic doses the venous dilation predominates and reduces preload (venous resistance). They are most used to treat

angina pectoris but can be combined with other agents, like hydralazine, to treat congestive heart failure. Examples include nitroglycerine and isosorbide.

*Diuretics* encourage the kidneys to decrease blood volume by increasing urinary output, which in turn lowers blood pressure. Diuretics are also a mainstay in the treatment of heart failure. The primary side effect of most diuretics is the loss of potassium, which can require replacement (e.g., K-dur, KCl). Common examples of diuretics include furosemide and hydrochlorothiazide (HCTZ), which is often combined with other medications to create brand-name medications (e.g., Diovan HCT®, Zestoretic®).

*Potassium-sparing diuretics* are specifically aldosterone antagonists but also diuretics. Aldosterone, a hormone produced by the adrenal cortex, increases the reabsorption of sodium and water by the kidney and thus increases blood volume. However, aldosterone also increases excretion of potassium, which can lead to hypokalemia. Potassium-sparing diuretics inhibit these effects, resulting in the reduced absorption of sodium and water without the associated loss of potassium. These medications are usually used in combination with other diuretics to treat hypertension or volume overload conditions, like heart failure. They can also be used to treat other conditions such as ascites in individuals with liver failure and hyperaldosteronism due to adrenal tumors. Examples include spironolactone and triamterene.

### Blood Thinners

Coagulation and platelet aggregation promote the formation of clots to stop bleeding. Both a thrombus, which adheres to the artery wall, and an embolus, which travels to another site, are blood clots that can obstruct blood flow.

*Anticoagulants* act by blocking substances that promote clotting, such as fibrinogen. They are used to treat pathologic clot formation (e.g., heparin) and prevent recurrence once an individual is stabilized after an embolic event (e.g., warfarin). Low molecular weight heparin, such as enoxaparin, is frequently used to prevent clotting post-operatively in high-risk individuals who have undergone hip or knee replacement surgery. A new class of anticoagulants includes dabigatran (Pradaxa®) and is a direct thrombin inhibitor used to prevent stroke in those with atrial fibrillation. Those taking warfarin and heparin require frequent blood tests to adjust the level of anticoagulation, whereas those taking dabigatran do not.

*Anti-platelet medications* inhibit platelet formation at the site of vascular damage. These medications prevent the development of platelet thrombi and are most used to prevent stroke and myocardial infarction (MI) and after invasive cardiovascular procedures, such as stent placement. Examples include aspirin and clopidogrel bisulfate (Plavix®).

*Thrombolytics* are a class of medications that are used to break down clots once they have formed. They are often used in an emergency, such as acute MI, stroke, pulmonary embolism, or acute arterial thrombosis. Examples include tissue plasminogen activators (tPAs), such as alteplase.

## Lipid Medications

Lipid metabolism is an important factor in the prevention and control of most cardiovascular conditions. Pharmacologic intervention is used when diet and exercise are insufficient to lower LDL cholesterol to safe levels.

*Statins* inhibit cholesterol production in the liver. Side effects include elevated liver enzymes and myalgias (muscle aches). Common statins prescribed are atorvastatin, rosuvastatin, and simvastatin.

*Nicotinic acid*, or vitamin B<sub>3</sub>, is the most potent therapy available to increase HDL cholesterol levels and may have additional vascular benefits.<sup>5</sup> This substance is marketed under the name niacin.

*Bile-acid binding resins* bind to bile, one of the richest sources of cholesterol, in the intestine and eliminate it from the body through feces. Examples include colestipol and cholestyramine.

*Ezetimibe* works differently than other lipid-lowering agents by inhibiting absorption of cholesterol in the intestine.<sup>6</sup> This is marketed under the brand name Zetia.

*Fibrates* are medications specifically used to decrease triglyceride levels and have been shown to assist in increasing HDL levels.<sup>7</sup> Common examples include gemfibrozil and fenofibrate.

## **Medications That Affect the Digestive System**

### Acid Blockers

The most common problem seen with the digestive system is an increase in acid production. This leads to symptoms of reflux, commonly known as indigestion or heartburn. Diet plays an important role in acid indigestion and often lifestyle changes can result in an alleviation of symptoms without the use of medications.

*Antacids* are alkaline compounds that neutralize stomach acid and are often the first line of defense in controlling increased acid since most of these medications are available over the counter (OTC). Reduced acid is also useful in preventing or controlling gastroesophageal reflux disease (GERD), gastritis, and other causes of dyspepsia (discomfort after eating). Commonly used antacids in the U.S. include Alka-Seltzer® and Mylanta®.

*Proton pump inhibitors (PPIs)* are antisecretory agents that enhance the mucosal lining of the digestive tract. Specifically, they block the enzyme in the stomach wall that produces acid. The reduction in acid prevents ulceration and helps heal existing ulcers in the esophagus, stomach, and duodenum. Examples of PPIs include omeprazole and pantoprazole. Some of these medications are now available OTC.

Like PPIs, *histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub> antagonists)* reduce the amount of acid in the stomach. They are also used to treat ulcers, gastritis, and reflux and some are available over the

counter. In OTC strength, these medications are used to relieve or prevent indigestion, heartburn, or sour stomach. Examples include famotidine and ranitidine.

### Intestinal Agents

Poor diet or disease processes can contribute to abnormal bowel habits. Constipation represents too little water in the fecal matter or an increase in the absorption rate of liquids. Conversely, diarrhea is the state of having too much liquid in the feces or inadequate absorption. In healthy individuals, this balance can be regulated by a correct amount of fiber in the diet.

A *laxative* is a general term for a medication that will work to increase the movement of fecal matter through the colon. Psyllium husks and methylcellulose are bulking agents, which cause stool to be bulkier and retain more water. Stool softeners, such as docusate, allow water and fat to be incorporated into the stool so it can move more easily. Lubricants and hydrating agents help to move already formed stool through the colon. Stimulants, such as bisacodyl, can alter water and electrolyte secretion and stimulate peristaltic action and can be dangerous with overuse.

*Antidiarrheal agents* are employed to decrease the amount of liquid in the colon and slow down the production of feces. Opioids activate the intestinal opioid receptors, resulting in constipation. Loperamide is the most common opioid used for this purpose since it does not cross the blood-brain barrier in significant amounts.

More severe intestinal disorders require different types of medications. Inflammatory bowel disease (IBD) can be treated by many different types of medications, determined by the severity of the disease. Sulfasalazine and one of its metabolites, 5-aminosalicylic acid (5-ASA) or mesalamine, are *disease-modifying antirheumatic drugs (DMARDs)*. These medications are thought to have an anti-inflammatory effect that provides topical relief inside the intestine. *Glucocorticoids*, such as prednisone or hydrocortisone, can help to reduce inflammation by suppressing the immune system.

### Additional Gastrointestinal Medications

Gastrointestinal distress can be caused by bacterial infections. For example, a bacterium called *Helicobacter pylori* causes some cases of peptic ulcer disease. *Antibiotics* are used to treat any form of bacterial infection and will be discussed in greater depth later in this chapter.

*Bismuth* can also be used to fight *H. pylori*. In addition, this medication is helpful as both an antacid and an antidiarrheal agent.

Cytoprotective medications, or *mucosal protectants*, can work either by coating the gastric mucosa at sites of ulceration by forming an adherent complex with proteins. Examples include sucralfate and misoprostol. *Prokinetic medications* suppress vomiting and increase gastrointestinal motility. This is especially helpful with cases of GERD and chemotherapy-induced nausea and vomiting. Examples include metoclopramide and prochlorperazine.

*Anticholinergics* are medications that selectively block the binding of acetylcholine to its receptors. These prevent involuntary muscle contracting within the gastrointestinal system, making them useful in gastritis, GI spasm, diverticulitis, and ulcerative colitis. The most commonly used anticholinergic for GI issues is hyoscyamine.

*Antineoplastics* and other anti-viral medications can be used to treat chronic viral hepatitis. While there is no cure for chronic hepatitis B and C, these medications can result in a sustained virological response. Hepatitis B has historically been treated solely with interferon alfa-2b, but newer anti-virals such as lamivudine can help fight the virus and slow liver damage.<sup>8</sup> In hepatitis C, success rates with interferon and ribavirin combined are only 45% in genotype 1, but as high as 75% with genotype 2 or 3 patients. However, adding protease inhibitors, such as boceprevir, the success rates improve to 65-70% in genotype 1 patients.<sup>63,64</sup>

*Ursodeoxycholic acid* is one of the secondary bile acids. When used as a pharmaceutical, it reduces cholesterol absorption and helps to dissolve gallstones. However, this medication is not commonly used, as laparoscopic cholecystectomy is usually the treatment of choice for cholecystitis.

The pancreas produces enzymes that aid in digestion. In severe pancreatic insufficiency oral enzyme replacement can be required with the use of supplements such as *pancrease*.

## Medications That Affect the Endocrine System

The endocrine system functions using hormones. Most endocrine disorders are simply a deficiency or an overproduction of a particular hormone. Therefore, treatment mainly consists of supplementing hormones or suppressing them, depending on the individual's need.

### Pituitary Gland

The pituitary gland is often referred to as the “master gland” since it produces eight major hormones that control the release of hormones produced by other endocrine glands. The anterior pituitary, which is controlled by the hypothalamus, produces six of these control hormones and the remaining two are produced by the posterior pituitary gland. Table 3 summarizes these hormones, abbreviates their function, and gives common pharmaceutical therapy for each.

**Table 3. Pituitary gland hormones, function, and pharmaceutical therapy.<sup>9</sup>**

HORMONE	FUNCTION	MEDICATION
Growth hormone (GH)	Stimulates growth in tissues and organs	somatrem
Corticotropin (adrenocorticotropic hormone/ACTH)	Acts on the adrenal cortex to promote release of hormones	See adrenal glands
Thyrotropin (thyroid-stimulating hormone/TSH)	Acts on the thyroid gland to release hormones	See thyroid gland

Follicle-stimulating hormone (FSH)	Acts on the ovaries to promote follicular growth or the testes to promote sperm growth	urofollitropin
Luteinizing hormone (LH)	Acts on females to promote ovulation and men to promote androgen production	menotropins (50% FSH & LH)
Prolactin	Stimulates milk production in females after giving birth	For excessive secretion: bromocriptine
Oxytocin*	Promotes uterine contractions	oxytocin
Antidiuretic hormone (ADH)*	Acts on the kidneys to retain water	vasopressin

\*Considered posterior pituitary hormones and produced by the hypothalamus

### Adrenal Glands

There are three classes of steroid hormones produced by the adrenal cortex that are also synthetically produced for therapeutic reasons. When these medications are introduced into the body, they are in much higher dosages than occur naturally. The three classes of steroid hormones of the adrenal cortex are:

1. glucocorticoids that influence carbohydrate metabolism (see section on diabetes)—Cortisol (hydrocortisone) is the most important glucocorticoid naturally produced by the adrenal cortex. Typically, glucocorticoids are not the sole medication being prescribed, but are given as a supplement for more serious cases of various disorders, such as autoimmune disorders, asthma, and gastrointestinal disorders. The most commonly used glucocorticoid is prednisone.
2. mineralocorticoids that influence salt and water balance (i.e., kidney function)—Aldosterone is the most important mineralocorticoid naturally produced by the adrenal cortex. Fludrocortisone is an example of this medication.
3. androgens that are involved with the development of sex characteristics but are not as powerful as testosterone in males—Androstenedione is a naturally produced androgen of the adrenal cortex and is often synthetically produced and abused by athletes.

Cushing's syndrome (overproduction of adrenal hormone) can be caused by different pathologies, but when it results from excessive corticosteroid production, the steroid synthesis inhibitor aminoglutethimide is often prescribed. Addison's disease is an adrenocortical insufficiency and is treated with replacement therapy, such as hydrocortisone and cortisone.

### Thyroid Gland

The thyroid gland produces hormones that are essential to heart function, growth, and development. An example of a hormone produced by the thyroid gland is thyroxine, which is necessary for normal body metabolism. When the thyroid gland does not produce sufficient thyroid hormone (i.e., hypothyroidism), supplementation with a synthetic version, such as levothyroxine, is required.

Hyperthyroidism is an overactive thyroid gland and is classified as either Graves' disease or toxic nodular goiter (Plummer's disease). When the thyroid overproduces its hormone, surgical removal, or destruction of thyroid tissue with radioactive iodine is the most common therapeutic option. A third option is antithyroid medications, such as methimazole.

### Reproductive System

*Sex hormones* can be used to treat several different disorders. Primarily, they are used to treat a deficiency, such as testosterone for hypogonadism in males and progestins or estrogen for hormone replacement therapy (HRT) in females. Female sex hormones are also combined to create oral contraceptive pills (OCP). Examples of these medications include testosterone gel for males, medroxyprogesterone acetate for HRT in females, and drospirenone for OCP.

*Gonadotropin-releasing hormone (GnRH) agonists* overstimulate the pituitary gland to release FSH and LH, which causes that production to shut down temporarily. This is helpful in treating disorders that feed on excess hormones, such as endometriosis and advanced prostate cancer. Leuprolide and nafarelin are examples of this class of medication.

*Female reproductive agents* or infertility medications can range among multiple classes. The treatment chosen will depend on the reproductive needs for the individual. Clomiphene and menotropins, which are ovulation stimulants, promote follicular maturation and ovulation. Gonadorelin is useful in treating gonadotropin deficiency and can help treat amenorrhea. Bromocriptine is a dopamine agonist that works to correct amenorrhea and excess prolactin secretion.

*Phosphodiesterase type 5 (PDE5) inhibitors* work in conjunction with sexual arousal to increase the vasodilatory effect of nitrous oxide in the penis, resulting in firmer erections. Examples include sildenafil and tadalafil.

### *Prostate*

*5-alpha-reductase inhibitors* block the enzyme that promotes prostate growth. A commonly used medication in this class is finasteride.

*Alpha blockers*, or alpha-adrenergic blockers, relax certain muscles to help small blood vessels remain open, which helps to improve urine flow. Because of the vasodilation effect, alpha blockers are also useful in treating hypertension and Raynaud's disease. Examples of medications commonly used to treat the symptoms of benign prostatic hypertrophy include alfuzosin and tamsulosin.

### Pancreas

One of the most important enzymes that the pancreas produces is insulin, which regulates blood sugar. Type 1 diabetes mellitus results when the pancreas can no longer produce its own insulin, which must then be replaced by injection. In addition to insulin supplementation, regular

monitoring of blood glucose, diet, exercise, and control of cardiovascular risk factors is necessary to avoid microvascular and macrovascular complications. Insulin injections or insulin pumps are used to deliver the medication to the body. Three types of insulin used in Type 1 diabetes are:

1. short-acting (lispro insulin)
2. intermediate-acting (neutral protamine hagedorn (NPH) insulin)
3. long acting (ultralente insulin).

Type 2 diabetes results in a relative insulin deficiency while cells no longer respond appropriately to the presence of insulin. Many find diet and exercise changes to be sufficient treatment. If these two lifestyle changes are not successful in controlling the disease, oral hypoglycemics and/or insulin treatments can be initiated. Hypoglycemics are used to lower blood glucose levels and include sulfonylureas such as glipizide, and metformin.<sup>10</sup>

### **Medications That Affect the Immune System**

Like issues that affect the endocrine system, pharmacology can help support the immune system when it is insufficient or becomes overwhelmed. Similarly, medications can be used to help suppress or control the immune system when inappropriate antibody production becomes harmful to the body.

#### **Immune Support**

When the immune system is weak, opportunistic diseases overcome the body and one is susceptible to infections. There are vaccines available to prevent several diseases. However, the second leading cause of death in the world is infectious disease.<sup>11</sup>

*Antibiotics*, also known as antibacterials, are a class of medication that is used to treat infections caused by bacteria. Overuse of antibiotics has led to some bacteria acquiring resistance to the medications. An example of a broad-spectrum antibiotic is amoxicillin; an example of a cephalosporin is cephalexin; and the macrolides include azithromycin.

While not as prevalent or effective as antibiotics, some specific *antiviral medications* do exist. The common HIV-AIDS medications are used to block replication of the virus and include protease inhibitors such as saquinavir and fusion inhibitors such as enfuvirtide. Truvada® is a combination of two nucleoside reverse transcriptase inhibitors. It is currently being used in treatment of HIV, post-exposure prophylaxis (PEP), and pre-exposure prophylaxis (PrEP). The herpes simplex virus can be treated with valacyclovir. Influenza is best treated with prevention (i.e., immunization), although treatment for those who have contracted the flu include amantadine.

*Antifungal medications* are classified for treating infections caused by fungi, whether systemic (as seen in those with AIDS) or localized, as in athlete's foot. The prototype for systemic anti-fungal medication is amphotericin B and fluconazole. Fluconazole and nystatin are prototypes for the superficial fungal infections.

Protozoans are single-celled animals that cause widespread diseases throughout the world, the most serious being malaria. The prototype *anti-malarial medication* is chloroquine hydrochloride.

*Anthelmintics* are medications that destroy helminths, which are parasitic worms that are different in structure from protozoans. Mebendazole is used to fight roundworms and pinworms.

### Immune Control

In autoimmune diseases, the immune system falsely identifies normal body tissue as an antigen and attacks. In addition, when foreign body tissue is introduced into the body, such as with therapeutic transplantation, the immune system can mobilize to destroy it. When the immune system acts inappropriately in these ways, pharmacologics can be employed to save the healthy tissue.

*Glucocorticoids* can be used to suppress various allergic, inflammatory, and autoimmune disorders and can help prevent acute transplant rejection. The most common type of this steroid used is prednisone.

*Calcineurin inhibitors* work to stop T-cells from trying to actively fight transplanted tissue or other ailments as a threat to the body. These medications can also be used in conjunction with other immunosuppressants to treat other autoimmune disorders such as rheumatoid arthritis, lupus, and psoriasis. An example is cyclosporine.

*Disease-modifying antirheumatic drugs (DMARDs)* slow down the progression of rheumatic disease. Originally the class was defined as any medication that reduced any of the findings thought to indicate the presence of rheumatic disease (e.g., elevated erythrocyte sedimentation rate, positive rheumatoid factor). More recently the definition of DMARDs has been updated to be any medication that reduces the rate of damage to bone and cartilage. Some DMARDs are mild chemotherapeutic agents, using immunosuppression as their main therapeutic benefit. While most commonly used in rheumatic arthritic diseases, these medications have been found to be useful in many connective tissue diseases (e.g., lupus, Sjogren's), psoriasis, and Crohn's disease. The most common DMARD used is methotrexate. Another common example is hydroxychloroquine. While it is not as strong as other DMARDs, it has fewer side effects.

A subgroup of DMARDs is *tumor necrosis factor (TNF) inhibitors*, or anti-TNF medications, which are administered by injection. They work by neutralizing the immune system's signals that lead to joint damage. Anti-TNF medications are thought to have fewer side effects than other DMARDs but could result in potentially serious infections. Examples include etanercept and infliximab.

### **Medications That Affect the Musculoskeletal System**

For everyday muscle and joint aches and pains, most individuals use OTC *nonsteroidal anti-inflammatory drugs (NSAIDs)* for relief. However, some conditions are very specific or better treated with prescription medications that are specifically designed to alleviate the related symptoms.

## Pain Medications

NSAIDs are medications that control pain, inflammation, and fever. The prototype for the many NSAIDs on the market today is aspirin. First generation OTC NSAIDs include ibuprofen and naproxen sodium. Examples of first-generation prescription NSAIDs are naproxen and diclofenac, the latter of which can be administered topically as a gel. The major advantage of these first generation NSAIDs is that they inhibit prostaglandin, which is a powerful pain-producing agent. However, prostaglandin also protects the GI tract, so chronic use of NSAIDs is one of the major causes of peptic ulcer disease.

The second generation of NSAIDs has been able to control fever, pain, and inflammation without disrupting the activity of prostaglandins in the gut. These *COX-2 inhibitors* have mostly been removed from the market due to an increased risk of cardiovascular events. The only example of this class of medication still available in the U.S. is celecoxib.<sup>63</sup>

While glucocorticoids do not treat pain, their powerful reduction in inflammation often results in a reduction or resolution of associated pain. Steroids carry more risks of serious side effects and are, therefore, preferred to be used for short-term therapy. Cortisone injections are frequently used with common musculoskeletal disorders, such as tendonitis and arthritis.

When pain is severe, *narcotic*, or *opioid analgesics* can be used. Narcotics work by attaching to the opioid receptors in the brain, altering an individual's perception of pain and inducing a feeling of well-being. Note that these medications do not actually eliminate pain or its source. Narcotics also have an addictive potential, which is why they are highly regulated. Examples of narcotics used for pain are hydrocodone and morphine.

A new approach is to inject joints with a synthetic liquid that mimics synovial fluid (sodium hyaluronate) to reduce knee pain caused by osteoarthritis.

## Gout Treatment

Gout is a joint disease, in which uric acid crystals are deposited in the joint, causing severe pain. Medications for gout work by blocking uric acid production and reducing inflammation. Examples of this class of medication include allopurinol, which can also be used for kidney stones, and colchicine. Other pain medications and NSAIDs are also used to alleviate the symptoms of gout.

## Muscles

*Muscle relaxants* work through the central nervous system (CNS), relaxing all the muscles of the body. In most cases, any injury to the back results in spasm of the many small muscles that move and support the back and trunk. Muscle injury is often treated with physical therapy. Examples of CNS muscle relaxants are cyclobenzaprine and metaxalone.

*Antispasmodics* work by blocking the receptors responsible for contraction of smooth muscle. Spasticity refers to movement patterns that are disrupted as groups of muscles are unable to work

smoothly together. Multiple sclerosis, cerebral palsy, and spinal cord injury exemplify muscle disorders that generate spasticity. Both muscle relaxants and antispasmodics can be used to alleviate these symptoms. Examples include baclofen and dantrolene.

*Benzodiazepines* can also be used as a muscle relaxant and antispasmodic. They will be addressed later in this chapter.

### Bone Density

While not life-threatening, bone loss can lead to frailty and bone fractures, particularly in the elderly. The first choice for prevention and mild cases of osteopenia and osteoporosis are supplemental calcium and vitamin D. Weight-bearing exercise and good nutrition decrease the risk of osteoporosis. Bone mass increases through one's life, peaks around the age of fifty, and then decreases afterward. Post-menopausal females lose bone mass at an even faster pace.

*Bisphosphonates* are a class of medication that inhibits the digestion of bone, thereby slowing bone loss. These can be used prophylactically or to treat osteopenia or osteoporosis. Examples include risedronate and alendronate. In more severe cases, an injection of zoledronic acid will be given as treatment. This medication is also used to treat other bone disorders, such as Paget's disease.

*Hormone replacement therapy (HRT)* is used to prevent many menopausal symptoms, including bone loss. Specifically, estrogens are used not only to stop the bone loss associated with menopause but also to increase bone density. An example of a conjugated estrogen treatment is estradiol.

Raloxifene is a specific type of endocrine-metabolic agent that reduces loss of bone tissue. Not only is it useful in preventing or treating osteopenia and osteoporosis, but also reduces the risk of some breast cancers in postmenopausal females.<sup>12</sup>

## **Medications That Affect the Nervous System**

### Antiepileptics

Antiepileptics (AEDs), also known as anticonvulsants or anti-seizure medications, are most used to treat epilepsy and control seizure activity. They work by suppressing the rapid and excessive firing of neurons that trigger a seizure. When prevention of a seizure does not occur, AEDs can prevent the spread of a seizure within the brain and protect against possible excitotoxic effects. In addition to epilepsy, these medications are frequently used to treat bipolar disorders and neuropathic pain. Examples include carbamazepine, topiramate, and phenytoin.

*Valproates* are a subclass of AEDs that are derived from the naturally occurring valproic acid. This substance blocks certain chemicals in the brain that make it useful as a broad-spectrum anticonvulsant. In addition, it acts as a mood stabilizer, making it effective for use in many neuropsychiatric conditions, but most commonly it is used to treat manic episodes found in bipolar

disorder. It has also been found to be useful in preventing migraine headaches and in some cases of neuropathic pain. The most common example of this type of medication is sodium valproate.

*GABA analogues* were originally designed to be used in the treatment of epilepsy but are used more frequently in the treatment of neuropathic pain. The exact process of how these work is not yet fully understood. These medications are most used to treat fibromyalgia, post-surgical pain, and other types of neuropathies and neuritis. Common examples include gabapentin and pregabalin.

### Central Nervous System Depressants

*Barbiturates* depress the central nervous system by inhibiting the transmission of information between neurons. This results in numerous effects including reduced anxiety, respiration, blood pressure, heart rate, and rapid eye movement (REM) sleep. These medications are used to treat many different conditions including anxiety, insomnia, and seizures. Because of their serious addictive potential, they are not as commonly used except for the treatment of epilepsy, particularly with phenobarbital.

*Benzodiazepines* have predominantly replaced barbiturates in pharmacology. These medications have sedative, hypnotic (i.e., sleep-inducing), anxiolytic, anticonvulsant, muscle relaxant, and amnesic action. While these uses are widespread, the most common conditions benzodiazepines are employed for are anxiety and panic disorders, insomnia, seizures, and alcohol withdrawal. In general, they are safe and effective for short-term use, but they do still carry an addictive potential. Common examples include alprazolam and clonazepam.

*Hypnotics*, also known as *sedatives* or *soporifics*, are medications that induce sleep. While many of the medications already mentioned can have hypnotic effects, these medications are designed specifically for that purpose and are used for insomnia and in surgical anesthesia. Examples include zolpidem and eszopiclone.

### Antidepressants

Antidepressants are psychiatric medications used to alleviate the symptoms of mood disorders, such as depression and anxiety. Depression is the most common psychiatric illness.<sup>13</sup> While depression itself is not life-threatening, it is a risk factor for suicide.

*Selective serotonin reuptake inhibitors (SSRIs)* are the most prescribed antidepressants. They work by blocking the reabsorption of the neurotransmitter serotonin after being released in the brain. Both serotonin and norepinephrine have been highly implicated in depression and anxiety, and it has been shown that facilitation of their activity has beneficial effects on these mental disorders.<sup>14</sup> Examples of SSRIs include paroxetine and escitalopram oxalate, which are predominantly used for depression disorders, and citalopram, which is more commonly used in anxiety disorders.

*Serotonin-norepinephrine reuptake inhibitors (SNRIs)* work similarly to SSRIs but block both neurotransmitters from being reabsorbed. An older example of this type of medication is tricyclic

antidepressants (TCAs). Unfortunately, the desired mechanism came with numerous side effects, resulting in their being used only when other medications have failed. Examples include nortriptyline and desipramine. However, newer generation SNRIs have fewer side effects and include venlafaxine and duloxetine.

Bupropion is an antidepressant medication that is in its own class. It is thought to work as a norepinephrine-dopamine reuptake inhibitor. It is simply considered to be a non-tricyclic antidepressant. It is used to treat depressive disorders and is also useful in smoking cessation.

*Monoamine oxidase inhibitors (MAOIs)* block the reuptake of serotonin, norepinephrine, and dopamine. Unfortunately, these medications also affect other neurotransmitters in the brain and digestive system, causing significant side effects. These were the first antidepressants developed but are only used when other antidepressants have been ineffective or for those with atypical depression. Examples include isocarboxazid and phenelzine.<sup>15</sup>

### Antimanic Agents

Aside from some of the anticonvulsants, the only antimanic agent currently available is lithium. Lithium is a naturally occurring substance in the body but, in therapeutic doses, can even out mood swings, which is particularly useful in the presence of the bipolar disorders. It is probably more effective in preventing mania than depression, but it has a very important anti-suicidal effect not shown in other stabilizing medications, such as anticonvulsants.<sup>16</sup> Lithium is most used in bipolar disorder, but can be used for major depressive disorder, borderline personality disorder, and schizophrenia.

### Antipsychotics

Antipsychotic medications, or neuroleptics, are primarily used to manage psychosis and are generally classified as either first generation or typical antipsychotics or second generation or atypical antipsychotics. Both tend to block receptors in the dopamine pathways in the brain but encompass a wide range of receptor targets. These medications have several significant and harmful side effects and result in withdrawal symptoms if stopped abruptly. An example of a typical antipsychotic is haloperidol. Risperidone and olanzapine are examples of atypical antipsychotics. There is now a third generation that is thought to reduce the susceptibility to metabolic symptoms seen in some other atypical antipsychotics; the only successful medication in this class so far is aripiprazole.<sup>65</sup>

### Headache Control

Mild headaches that occur from episodes such as intoxication, stress, fatigue, or illness are often treated successfully with OTC medications. When headaches are more severe, NSAIDs and opioid analgesics are often the first line of defense and usually work well to control cluster and tension headaches, as well as some migraines. Migraines are a special type of headache that is poorly understood and do not always respond to normal pain control.

*Triptans* are an abortive therapy for migraines, meaning they do not prevent migraines but can treat them when they occur. They work by narrowing blood vessels in the head that become dilated during a migraine. Examples include sumatriptan and rizatriptan.

*Ergot alkaloids* stimulate serotonin, decrease inflammation, and reverse blood vessel dilation around the brain, relieving the symptoms of a migraine or cluster headache. Examples include ergotamine and dihydroergotamine.

Beta blockers and calcium channel blockers are often used to prevent migraines and/or cluster headaches. In addition, amitriptyline – a tricyclic antidepressant – has been found to be useful in the prophylaxis of these types of headaches.

### Parkinson's Disease Treatment

*Dopamine agonists* essentially supplement reduced dopamine in the brain to treat Parkinson's disease. The medication treatment strategy is to both increase the level of dopamine while decreasing the level of acetylcholine. Levodopa works very well in the beginning stages of the disease but is less effective in later stages. Additional medications used include carbidopa, amantadine, and bromocriptine.

### Detoxification Agents

*Opioid antagonists* are used to treat an acute overdose of opioids, as they counteract the actions of the excessive substance. An example of this medication is naloxone.

As previously stated, the use of opioids comes with a significant risk of addiction. Unfortunately, there is no treatment for addiction except for abstinence. However, because of the powerful, physical dependence this medication creates in the body, withdrawal symptoms can be severe enough to be fatal. The medication methadone is also an addictive opioid but is much less so than other medications in this class. It is often used as a substitute for heroin and other morphine-like medications to help wean the body off opioids altogether. In addition, methadone can also be used for chronic pain conditions.

When the addictive substance of concern is alcohol, there are a few more pharmacological alternatives to help with treatment. Disulfiram interferes with the metabolism of alcohol resulting in unpleasant physical effects when ingested. Acamprosate can be useful in restoring the chemical balance in the brain that is disrupted in an individual who is addicted to alcohol, once alcohol intake has ceased. Naltrexone works similarly to acamprosate but is useful in those with either alcohol or opioid dependence.

### Dementia Treatment

*Cholinesterase inhibitors* work by increasing the amount of acetylcholine in the brain, which can help reduce the symptoms of different types of dementia, including Alzheimer's disease. Examples of this class of medication include donepezil and rivastigmine. Memantine is a newer

medication which blocks NMDA receptors in the glutamatergic system. Unfortunately, the pharmaceutical treatments available can help in certain cases, but tend to have mixed results.<sup>66,67</sup>

### **Medications That Affect the Respiratory System**

Obstruction to normal exchange of air in and out of the lungs is always a mortality issue. Even with proper care, medication, and lifestyle changes, such as cessation of smoking, respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) still increase mortality risk.

*Oral antihistamines*, or histamine antagonists, are used to treat inflammation by blocking the production of histamine, which results from the introduction of an allergen into the body. Histamine results in swelling and vasodilation to eliminate the offending protein, which results in sneezing, runny nose, and nasal itching. The first antihistamines developed caused drowsiness; an example is diphenhydramine. The second generation does not cause sedation; examples include cetirizine and fexofenadine.

*Leukotriene inhibitors* block the chemicals that are released in the body when an allergen is inhaled. Leukotrienes cause swelling in the lungs and tightening of the muscles around the airways, which can result in asthma symptoms. These medications are useful in preventing allergy symptoms as well as asthma attacks. A common example is montelukast.

*Sympathomimetics* (oral and intranasal), also known as decongestants, mimic the effects of transmitter substances of the sympathetic nervous system such as catecholamines, epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine. These are used to decrease nasal congestion as well as to treat sinusitis and the common cold. An intranasal example is mometasone furoate; an oral example is pseudoephedrine.

*Antitussives* suppress coughing, possibly by reducing the activity of the cough center in the brain.<sup>17</sup> Codeine, an opioid, is a common cough suppressant. Benzonatate is an example of a non-narcotic cough medicine. When a cough is productive (i.e., produces phlegm or mucus), an expectorant or *mucokinetic* agent will be used in an attempt to remove mucus from the respiratory tract. An example of an expectorant is guaifenesin.

### **Bronchodilators**

Bronchodilators, as their name suggests, are any agent that will dilate the bronchial tree, decreasing resistance in the respiratory airway, thereby increasing airflow to the lungs.

*Short-acting beta<sub>2</sub> agonists* relax the muscles lining the bronchi and bronchioles within five minutes and are intended for prevention or to abort acute exacerbations, because of exercise or cold-air exposure. These medications are considered “rescue inhalers” and are not intended for frequent use. For this reason, frequent use can indicate a poorly controlled condition. Common examples include albuterol and pirbuterol.

*Long-acting beta<sub>2</sub> agonists* work in the same way as the short-acting class but are intended for daily use to improve lung function. These are useful in treating more serious and chronic respiratory diseases such as asthma, bronchiectasis, and chronic obstructive pulmonary disease (COPD). An example is formoterol. These medications can be combined with an inhaled corticosteroid to improve the anti-inflammatory function, such as in Advair®, which is a combination of salmeterol and fluticasone (a steroid).

*Anticholinergics* relax and enlarge the airways and can also protect them from spasms that can suddenly cause the bronchial tree to become narrower (bronchospasm). In addition, they can also reduce the amount of mucus produced by the airways.<sup>18</sup> Short-acting anticholinergics are used for those with stable chronic respiratory disorders who have intermittent symptoms, whereas long-acting medications are used for those with persistent symptoms. These medications are the stronger of the bronchodilators and so are most seen in more severe conditions, such as COPD. Examples include ipratropium, which is short-acting, and tiotropium, which is long-acting.

*Glucocorticoids* are commonly used to reduce inflammatory respiratory diseases, such as asthma. Oral steroids are often given to suppress a particularly severe or medication-resistant acute respiratory illness or exacerbation of a chronic illness.

### **Medications Used in the Treatment of Cancer**

The three major strategies in treating cancer are surgery, radiation therapy, and medication. Solid tumors, such as breast cancer, are most treated with radiation and/or surgery. Disseminated cancers, such as leukemia, some lymphomas, and metastasized cancers, are treated with medications. Pharmaceutical therapy can also be used in combination with surgery and radiation to prolong life and reduce symptoms.

*Cytotoxic agents* are medications that kill the cells directly. Examples are the alkylating agents, such as nitrogen mustards and cyclophosphamide, or the alkylating-like platinum analogues, such as cisplatin.

*Hormones and hormone antagonists* act through specific receptors on target tissues. For example, antiestrogens, like tamoxifen, block estrogen receptors in the breast in an effort to reduce growth of residual cancer cells. Also in this category are androgens and antiandrogens, estrogens, glucocorticoids, aromatase inhibitors, and progestins.

*Biologic response modifiers* modify the tissues infiltrated by the cancer cells (e.g., immunostimulation), which increases the immunity of the tissue to fight the cancer cells. An example is interferon alpha-2a.

### **Supplements and Herbal Therapy**

As stated in the introduction of this chapter, supplements are considered a form of alternative medicine, which means they are not sold as therapeutic medications. The FDA does not regulate dietary supplements and medicinal herbs, so efficacy and safety are always questionable. Still, many individuals use herbal remedies alone or as supplements to treat illness for various reasons.

They are typically used in pill form or powder to be eaten with food. Some herbal medicines are discussed in this section, but the underwriter must be aware that there are thousands of different plant-derived (e.g., roots, bark, leaves, fruits, berries, and flowers) products used to promote health and fight symptoms of illness.<sup>19,20</sup> Examples of popular supplements or herbal therapies include:

*Turmeric* is a spice commonly used in cooking, but its active ingredient curcumin helps support a healthy inflammation response during exercise. This supplement is often taken to control inflammation and chronic pain.

*Garcinia Cambogia* is used for weight loss and is thought to help reduce appetite and block fat production.

*CoQ10* is a compound produced by the body, but production decreases with aging. Lower levels are often found in chronic disease and supplementation is felt to help prevent oxidative damage and improve circulation.

*Probiotics* is a general term referring to any live culture beneficial bacteria. Eating live probiotics is felt to improve gut health, which may support the immune system. Probiotics are found in fermented foods, kefir, kombucha, yogurt, and also sold in pill form.

*Ginkgo biloba* is used to improve memory, increase concentration, and reduce dizziness. It is also used to treat senility, dementia, and Alzheimer's disease. Those using SSRIs, like fluoxetine, find it counteracts the side effect of impotence.

*Ginseng* is used to support digestion, relieve stress, enhance the immune system, and reduce fatigue.

*Saw palmetto fruit* is used to reduce the urinary symptoms of benign enlargement of the prostate gland.

*St. John's wort* is used to relieve depression and anxiety and reduce inflammation.

*Glucosamine* and *chondroitin* are natural substances found in the cells of joints, and supplementation is used to reduce the symptoms and delay the progression of joint degeneration. Glucosamine is an amino sugar found in cartilage and other connective tissue. Chondroitin helps cartilage retain water.

*Fish oil (omega-3 fatty acids)* is used to regulate cholesterol, thus reducing the risk of cardiovascular disease. Similarly, *red yeast rice* has been sold as a natural cholesterol-lowering agent and is found to be clinically identical to lovastatin.<sup>21</sup>

*Black cohosh* is used to alleviate symptoms of menopause.

*Evening primrose oil* is used for the symptoms of menopause, but also for eczema and to reduce inflammation in conditions such as rheumatoid arthritis. It is important for the underwriter to

determine the specific reason this supplement is being used, as it is often used by individuals with cancer or diabetes.

*Milk thistle* is used as a remedy for liver and gallbladder ailments. It is also used by those with cancer to slow tumor growth by limiting cell division and reducing the blood supply to the tumor.

*Echinacea* is used to stimulate the immune system and fight infections.

### **Medical Marijuana**

While the use of marijuana for medicinal purposes dates back thousands of years,<sup>22</sup> its use as an alternative form of medication has recently resurfaced and become prevalent throughout the world. In the U.S., medical marijuana began being used in the state of California for varying conditions in 1996 and several states very quickly approved similar legislation. Currently, the District of Columbia and thirty-eight states have decriminalized medicinal use of marijuana and many others have pending legislation. In addition, Alaska, Arizona, California, Colorado, Connecticut, Illinois, Maine, Massachusetts, Michigan, Montana, Nevada, New Jersey, New Mexico, New York, Oregon, South Dakota, the District of Columbia, Vermont, Virginia and Washington as well as some individual cities in other states have legalized recreational use for all residents age 21 and over.<sup>23</sup> Medical marijuana has been available in Canada since 2001.<sup>24</sup>

Because marijuana is not a legal substance federally, it is not prescribed like other medications. Instead, individuals in the U.S. must obtain a recommendation from a licensed physician to legally purchase or grow marijuana for medicinal purposes. While some physicians will provide this recommendation directly to their patients, many will refer them to clinics specifically established for this purpose. In most cases, no testing or diagnoses are made at these clinics, and the recommendation for medical marijuana use is based on medical records and diagnoses from other practitioners as well as details of previous treatments attempted. The recommendation is then taken to an accredited marijuana dispensary or individual distributor where the patient can purchase marijuana products of their choosing, up to the limit set by the city or state governing the decriminalization.

The most common methods of marijuana administration are inhalation, ingestion, or topical. Topical applications typically have minor amounts of tetrahydrocannabinol (THC), do not enter the blood stream, and are unlikely to have any effect on underwriting. Most individuals choose inhalation, either through smoking or vaporization, for several reasons. It is easier to regulate the dose in this form, the drug takes effect more quickly, and it is more cost effective.<sup>25</sup> There are many ways to ingest marijuana (e.g., cooked in food, infused in oils, in capsules). However, ingested marijuana has a different effect than inhaled marijuana as some of the THC, the active ingredient in the herb, is destroyed by liver metabolism, and a potent THC metabolite is formed. Because of this change, it is very difficult to regulate dosage, and individuals must wait until the drug has taken effect before determining if more is needed. Ingested marijuana can take up to two hours to take effect.<sup>26</sup>

While most uses for medical marijuana are based on anecdotal evidence and “folk medicine,” there have been some studies that have proven its medicinal benefits. The list of potential uses is quite extensive, but the most common uses are as follows:

1. acute and chronic pain – Multiple drug trials have shown marijuana to be safe and effective for many different types of pain including neuropathic pain, fibromyalgia, arthritis, migraines, other types of headaches, musculoskeletal disorders, dysmenorrhea, and pain from HIV, strokes, and many other conditions.<sup>27,28,31</sup> Marijuana has also proven to be a safer alternative to opioids, which are known to have a risk of significant morbidity.<sup>29</sup>
2. epilepsy – Historically, seizure control is the oldest known use for marijuana. Anecdotal evidence for this condition is very strong and has led to the creation of a specialized strain that controls intractable seizures and is primarily used in children. However, actual studies have been limited and show marijuana to only be useful in some types of seizures and possibly only those that cannot be controlled by other medications. Studies have shown that THC limits the spread of epileptogenic activity inside the brain as well as increasing the effects of other anticonvulsants.<sup>30,31,32,33,34</sup>
3. gastrointestinal disorders – The appetite-stimulating effect of marijuana is particularly useful in cases of anorexia and cachexia. Cannabinoid receptors have been detected in enteric nerves and can be activated pharmacologically to provide gastroprotection and reduce gastric and intestinal motility as well as intestinal secretions. Marijuana has been found to be helpful in treating nausea, vomiting, gastric ulcers, irritable bowel syndrome, inflammatory bowel disease, secretory diarrhea, paralytic ileus, and gastroesophageal reflux disease. Some cannabinoids are already being used clinically as antiemetics.<sup>31,35</sup>
4. spasticity – Marijuana was found to reduce symptoms and pain in those with multiple sclerosis who have treatment-resistant spasticity or excessive muscle contractions. In addition, success has been found in treating pain, paresthesia, tremor, ataxia, bowel and bladder control, and other movement disorders.<sup>31,34,36</sup>
5. psychiatric conditions – Marijuana has been noted to provide sedative, hypnotic, anxiolytic, antidepressant, antipsychotic, and anticonvulsant effects. Therapeutic uses have been found in many mental health conditions including anxiety, depression, insomnia, stress, bipolar disorder, and even schizophrenia. It has also been found to be helpful in the treatment of dependency and withdrawal from benzodiazepines, opiates, and alcohol.<sup>31,34,37</sup>
6. cancer – THC has been found to slow the growth of some tumors, prevent angiogenesis, and even cause the death of specific types of cancer cells<sup>34,38,39,40,41,49</sup>
7. others – Marijuana can be used to treat inflammation, glaucoma(reduces intraocular pressure), asthma(the use of marijuana corresponds to therapeutic doses of common bronchodilator medications), pruritus and allergies through immunomodulatory action, neurogenerative diseases(e.g., Parkinson’s, Tourette’s, dementia), obesity, osteoporosis, fertility, cardiovascular disorders, metabolic syndrome-related disorders, and neurological damage following a stroke or other injury to the nervous system, and many more.<sup>31,34,42,43</sup>

While thousands of those using medical marijuana are currently finding relief with this drug for varying conditions, these successes are largely anecdotal. Most of the studies that have been conducted were cursory, proving a possible benefit only. Almost every study cites the need for additional research to determine optimal dosage for each indication.

Most pharmaceutical medications have possible side effects, some of which can be rather severe. Potential adverse effects of marijuana are often cited as a concern for legalization/decriminalization. Most of the “known” side effects of marijuana were assumptions based on what was already known about chronic alcohol and tobacco use.<sup>44</sup> Many of these assumptions have been disproven or their significance dramatically reduced after studies were conducted (e.g., addiction,<sup>45,46,47,48</sup> cancer,<sup>49,50,51,52</sup> respiratory disorders,<sup>45,53,54,55,56,57</sup> mental health,<sup>45,58,59</sup> cognitive decline<sup>45,60</sup>). Others still have not been thoroughly studied, and it is not known whether these possible adverse effects are attributable to marijuana alone and what the quantitative relationship is between frequency and duration of use and actual risk.<sup>44</sup> It has been well established for decades that marijuana use itself has no significant effect on mortality except in HIV-positive males.<sup>61</sup>

Proponents on both sides of the debate about medical marijuana agree that additional studies and actual clinical trials are needed not only to determine appropriate administration methods and dosage amounts as well as methods of separating therapeutic agents from those that produce the well-known “high,” but also to accurately determine both short-term and long-term risks. While many researchers are eager to begin these studies and trials, approval has been difficult due to the medication’s current Schedule I status. As of June 2014, the FDA is reviewing marijuana to determine if the Schedule I status should remain but has yet to release an update.<sup>68</sup> In 2014, 22.2 million Americans were users of marijuana.<sup>62</sup> As medicinal and recreational marijuana becomes more accepted socially and legally, more of these users will be forthcoming about their use on applications. Underwriters should expect to see more of these cases as time goes on.

## **Summary**

Most diseases are treated with medications as classes, and the specific medication from the class used is not usually relevant to the underwriting of the case. As an example, proton pump inhibitors are used for the treatment of GERD and/or peptic ulcer disease. There are several individual medications within the class of proton pump inhibitors on the market now, such as lansoprazole and omeprazole. Which of these medications being used would not affect the underwriter’s decision; only the extent of the disease and the degree of control achieved through treatment would be pertinent? Understanding the class of medication and how it is used is far more important than knowing each individual medication itself.

**APPENDIX**  
*(For students' information only; this material will not be tested.)*

**Appendix 1. Trade Names of Generic Medications Referenced in Chapter.**

<b>Generic Medication</b>	<b>Trade Name Example(s)</b>
acamprosate	Campral®
albuterol	Proventil®
alendronate	Fosamax®
alfuzosin	Uroxatral®
allopurinol	Zyloprim®
alprazolam	Xanax®
alteplase	Activase®
amantadine	Symmetrel®
aminoglutethimide	Cytadren®
amiodarone	Cordarone®
amitriptyline	Elavil®
amoxicillin	Amoxil®
amphotericin B	Fungizone®
aripiprazole	Abilify®
atenolol	Tenormin®
atorvastatin	Lipitor®
azithromycin	Zithromax®
baclofen	Lioresal®
benzonatate	Tessalon®
bisacodyl	Dulcolax®
bismuth	Pepto-Bismol®
boceprevir	Victrelis®
bromocriptine	Parlodel®
bupropion	Wellbutrin®
candesartan	Atacand®
carbamazepine	Tegretol®
carbidopa	Sinemet®
celecoxib	Celebrex®
cephalexin	Keflex®
cetirizine	Zyrtec®
chloroquine hydrochloride	Aralen®
cholestyramine	Questran®
cisplatin	Platinol®

<b>Generic Medication</b>	<b>Trade Name Example(s)</b>
citalopram	Celexa®
clomiphene	Clomid®
clonazepam	Klonopin®
clopidogrel bisulfate	Plavix®
codeine	Robitussin®
colchicine	Colcyrs®
colestipol	Colestid®
cyclobenzaprine	Flexeril®
cyclophosphamide	Cytoxan®
cyclosporine	Sandimmune®
dabigatran	Pradaxa®
dantrolene	Dantrium®
desipramine	Norpramin®
diclofenac	Voltaren®
dihydroergotamine	Migranal®
diltiazem	Cardizem®
diphenhydramine	Benadryl®
disulfiram	Antabuse®
docosate	Colace®
donepezil	Aricept®
drospirenone	Yaz®
duloxetine	Cymbalta®
enalapril	Vasotec®
enfuvirtide	Fuzeon®
enoxaparin	Lovenox®
ergotamine	Cafergot®
escitalopram	
oxalate	Lexapro®
estradiol	Premarin®
eszopiclone	Lunesta®
etanercept	Enbrel®
ezetimibe	Zetia®
famotidine	Pepcid®
fenofibrate	Tricor®
fexofenadine	Allegra®
finasteride	Proscar®
flecainide	Tambocor®
fluconazole	Diflucan®
fludrocortisone	Florinef®

<b>Generic Medication</b>	<b>Trade Name Example(s)</b>
fluoxetine	Prozac®
formoterol	Symbicort®
furosemide	Lasix®
gabapentin	Neurontin®
gemfibrozil	Lopid®
glipizide	Glucotrol®
gonadorelin	Lutrepulse®
guaifenesin	Mucinex®
haloperidol	Haldol®
hydralazine	Apresoline®
hydrocodone	Lortab®, Vicodin®
hydrocortisone	Cortenema®
hydroxychloroquine	Plaquenil®
hyoscyamine	Levsin®
ibuprofen	Motrin®, Advil®
infliximab	Remicade®
interferon alfa-2a	Roferon-A®
interferon alfa-2b	Intron A®
interferon alfa-2b & ribavirin	Rebetron®, Peginterferon®
ipratropium	Atrovent®
isocarboxazid	Marplan®
isosorbide	Isosordil®
lamivudine	Epivir®
lansoprazole	Prevacid®
leuprolide	Lupron®
levodopa	Dopar®
levothyroxine	Synthroid®
lisinopril	Prinivil®
lithium	Eskalith®
loperamide	Imodium®
losartan	Cozaar®
lovastatin	Mevacor®
mebendazole	Vermox®
medroxyprogesterone acetate	Provera®
menotropins	Menopur®, Pergonal®
mesalamine	Rowasa®
metaxalone	Skelaxin®

<b>Generic Medication</b>	<b>Trade Name Example(s)</b>
metformin	Glucophage®
methadone	Dolophine®
methimazole	Tapazole®
methotrexate	Rheumatrex®
methylcellulose	Citrucel®
metoclopramide	Reglan®
metoprolol	Lopressor®
misoprostol	Cytotec®
mometasone furoate	Nasonex®
montelukast	Singulair®
nafarelin	Synarel®
naloxone	Narcan®
naltrexone	Depade®
naproxen	Naprosyn®
naproxen sodium	Aleve®
niacin	Niaspan®
nitrogen mustards	Mustargen®
nortriptyline	Pamelor®
nystatin	Nystex®
olanzapine	Zyprexa®
omeprazole	Prilosec®
oxytocin	Pitocin®
pantoprazole	Protonix®
paroxetine	Paxil®
phenelzine	Nardil®
phenobarbital	Solfoton®
phenytoin	Dilantin®
pirbuterol	Maxair®
pregabalin	Lyrica®
prochlorperazine	Compazine®
pseudoephedrine	Sudafed®
psyllium husks	Metamucil®
raloxifene	Evista®
ranitidine	Zantac®
risendronate	Actonel®
risperidone	Risperdal®
rivastigmine	Exelon®
rizatriptan	Maxalt®
rosuvastatin	Crestor®

<b>Generic Medication</b>	<b>Trade Name Example(s)</b>
salmeterol	Serevent®
saquinavir	Fortovase®
sildenafil	Viagra®
simvastatin	Zocor®
sodium hyaluronate	Hyalgan®
sodium valproate	Depakote®
somatrem	Protropin®
sotalol	Betapace®
spironolactone	Aldactone®
succinylcholine	Anectine®
sucralfate	Carafate®
sulfasalazine	Azulfidine®
sumatriptan	Imitrex®
tadalafil	Cialis®
tamoxifen	Nolvadex®
tamsulosin	Flomax®
testosterone	Androgel®
tiotropium	Spiriva®
topiramate	Topamax®
urofollitropin	Fertinex®
ursodeoxycholic acid	Urso®, Actigall®
valacyclovir	Valtrex®
vasopressin	Pitressin®
venlafaxine	Effexor®
verapamil	Covera-HS®, Verelan PM®, Calan®
warfarin	Coumadin®
zoledronic acid	Reclast®
zolpidem	Ambien®

## **Appendix 2. Resources and Websites**

### *Resources*

1. The Physician's Desk Reference (PDR)
2. Physicians General Rx book, published by Mosby
3. The Merck Manual<sup>1</sup>
4. Miller-Keane Encyclopedia and Dictionary of Medicine
5. Nursing, and Allied Health<sup>2</sup>

### *Websites*

1. <http://www.fda.gov/cder/ob/default.htm> - a list of FDA-approved generic equivalents.
2. <http://www.rxlist.com> - provides a “sounds-like” search and information regarding specific medications.
3. [http://my.webmd.com/hw/index/index-drug\\_data-f.asp](http://my.webmd.com/hw/index/index-drug_data-f.asp) - an alphabetical listing of medications.
4. <http://www.druginfonet.com/> - provides medication and disease information for healthcare needs.
5. [http://www.gettingwell.com/drug\\_info/index.html](http://www.gettingwell.com/drug_info/index.html) - online Physicians' Desk Reference (PDR) Family Guide.
6. <http://www.drugs.com/> - prescription drug information for consumers and professionals.
7. <http://ods.od.nih.gov/> - dietary supplements and herbs database.

## **Review Questions – ALU 201, Chapter 15**

1. Lithium is primarily prescribed for:
    1. bipolar disorder
    2. insomnia
    3. schizophrenia
    4. seizures
  2. All of the following are used to treat inflammation EXCEPT:
    1. glucocorticoids
    2. nonsteroidal anti-inflammatories (NSAIDs)
    3. hydrochlorothiazide
    4. antihistamines
  3. Medications used to treat hypertension include which of the following?
    - A. beta blockers
    - B. potassium channel blockers
    - C. angiotensin-converting (ACE) inhibitors
- Answer Options:
1. A only is correct.
  2. A and B only are correct.
  3. A and C only are correct.
  4. B and C only are correct.
4. Explain the difference between pharmacokinetics and pharmacodynamics.
  5. List three different types of diseases that glucocorticoids can be used to treat and explain why they can affect so many different conditions.

6. A medication used for the treatment of Parkinson's disease is:
1. haloperidol
  2. phenobarbital
  3. nitrogen mustard
  4. levodopa
7. Subcutaneous medications are administered:
1. onto the skin
  2. into the skin
  3. under the skin
  4. into the artery
8. Describe how beta blockers affect the body and list three conditions for which they are prescribed.
9. When one medication interacts with another medication in the body, what are the possible effects?
10. List the conditions for which benzodiazepines are most commonly prescribed and identify a potential risk associated with their use.

## **Answers and Sources of Review Questions**

### *Review Question 1*

Answer 1: bipolar disorder – page 18.

### *Review Question 2*

Answer 3: hydrochlorothiazide – pages 7, 14, 20, 21.

### *Review Question 3*

Answer 3: A and C only are correct – pages 5-6.

### *Review Question 4*

Refer to page 2.

### *Review Question 5*

Refer to pages 9, 11, 14, 15, 21.

### *Review Question 6*

Answer 4: levodopa – page 19.

### *Review Question 7*

Answer 3: under the skin – page 3.

### *Review Question 8*

Refer to pages 5-6.

### *Review Question 9*

Refer to page 4.

### *Review Question 10*

Refer to page 17.