Medical Staff Conference

Digitalis Toxicity—Turning Over a New Leaf?

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

LLOYD H. SMITH, JR, MD:* *It is routine to ask each chief medical resident at Moffitt Hospital to present a medical staff conference near the completion of his or her tour of duty in that important position. Not only does this tradition make us the beneficiaries of scholarly reviews, it also allows us the chance to express publicly our gratitude for a job well done. Dr Satinder Bhatia is completing four years as a member of this house staff, to which he came after his graduation from Emory University School of Medicine in Atlanta. From here he will go to the Brigham and Women's Hospital in Boston to pursue specialty training in cardiology. He has brought intelligence, dedication, maturity and style to this year of chief residency. We wish him the best in his new career. We look forward to a discussion that presages his career in cardiology—a review of digitalis toxicity.*

SATINDER J.S. BHATIA, MD:† Although it has been 200 years since the publication of the classic *Account of the Foxglove* by William Withering, MD, the efficacy of digitalis glycosides as positive inotropes continues to be debated. Withering's caution of the potential for digitalis toxicity is uncontested, however. His often-quoted description of digitalis toxicity states

> The foxglove, when given in very large and quickly repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow, increased secretion of urine with frequent motions to part with it and sometimes inability to retain it, slow pulse, even as low as 35 in a minute, cold sweats, convulsions, syncope, death.[1]

It is the objective of this review to update the manifestations (and management) of digitalis excess so accurately recorded 200 years ago.

I will focus primarily on toxicity due to long-term digoxin therapy. Digoxin is currently the fifth most prescribed drug in the United States. The drug has a high toxic-therapeutic ratio, with surveys of inpatients and outpatients showing an incidence of toxicity ranging from 6% to 29%.[2,3] Recognition of toxicity is imperative because the continuation of digoxin therapy has a high mortality. It appears that physician education is contributing to a decrease in the incidence and morbidity of toxicity, but toxicity continues at an unacceptably high rate.

Digoxin Pharmacokinetics

Digoxin tablets are passively absorbed from the small intestine, with effective absorption of 55% to 75%. Encapsulated liquid digoxin has an absorption rate of 90% to 100%.[5] Excretion of digoxin is primarily by glomerular filtration with a small element of hepatic metabolism and active tubular secretion.[4] The average elimination half-life is 1.5 days; it is prolonged in persons with a decreased glomerular filtration rate and slowed with acute massive ingestion. Protein binding of digoxin is in the range of 20% to 25%.[5]

The time course for achieving therapeutic concentrations varies with the route of administration. The serum concentration of digoxin rises more rapidly after intravenous than after oral administration.[4] Maintenance dose administration without a preceding loading regimen leads to steady-state levels in five to seven days. Although the administration of a loading dose more rapidly achieves therapeutic digoxin concentrations, the risk of toxicity is much increased. If administered intravenously, the dose of digoxin should be two thirds the dose given orally. The equivalent dose of the encapsulated elixir is three fourths the oral dose in milligrams. Dosage in obese patients should be based on lean body mass and not total body weight due to the minimal distribution of digoxin to adipose tissue.

Prevalence of Digoxin Toxicity

In Withering's era the prevalence of digitalis toxicity was estimated at 18% to 25%.[2] In the 1970s the reported incidence varied from 20% to 30%.[3] The incidences reported in the 1980s are lower, with prevalences of 6% to 18%.[2] The reasons for this trend may include the availability of the means to measure serum digitalis levels and the education of physicians in pharmacokinetics.[4]

Measuring and Interpreting Serum Digoxin Levels

The radioimmunoassay for digoxin became available in 1969 and defined the therapeutic range as 0.5 or 0.8 to 2.0 ng per ml.[6] The optimal time for measurement is just before the

*Professor of Medicine and Associate Dean, School of Medicine.

†Chief medical resident, Department of Medicine.

(Bhatia SJS: Digitalis toxicity—Turning over a new leaf?—Medical Staff Conference, University of California, San Francisco. West J Med 1986 Jul; 145:74-82)

ABBREVIATIONS USED IN TEXT

AV = atrioventricular
Ig = immunoglobulin
PAC = premature atrial complex
PVC = premature ventricular complex

next dose, or at least six hours after an oral dose and four hours after intravenous administration.[4] The ratio between myocardial and serum digoxin levels is fairly constant despite variation in total body digoxin content, providing a rationale for the use of serum levels to reflect myocardial content.[7] The causes of false-positive assays include spironolactone, hyperbilirubinemia, circulating γ-emitting radioimagers and renal failure. More than 60% of patients with chronic renal failure have been reported to have false-positive assay results to 1.0 ng per ml, possibly due to an endogenous circulating digoxin-like substance.[8]

Interpreting serum digoxin measurements has been hampered by the prevalence of two myths: one, a normal serum digoxin level implies that digoxin toxicity is absent and, two, an elevated serum digoxin level implies that digoxin toxicity is present. In a review of more than 1,000 patients, the mean serum digoxin level in nontoxic patients was 1.4 ng per ml, with the levels in patients with toxicity being twofold to threefold higher, but there was considerable overlap between the two groups of patients.[5] Approximately 10% of patients without toxicity had serum digoxin values of 2 to 4 ng per ml; 10% of patients with toxicity had serum concentrations of digoxin of less than 2 ng per ml.[9] Bayesian analysis reveals that the higher the serum digoxin level, the higher is the likelihood of toxicity.[10] For example, the risk of toxicity at a digoxin concentration of higher than 3.0 ng per ml was 12-fold the risk at a serum concentration of 0 to 0.99 ng per ml. Patients in atrial fibrillation are more resistant to digoxin toxicity and often require "toxic" doses for adequate rate control. Toxicity may appear on conversion to sinus rhythm. The diagnosis of digitalis toxicity is a clinical one, with serum digoxin values providing only part of the diagnostic information. The significance of a given digoxin value depends on the underlying tolerance of the myocardium to digitalis. Thus, although no serum digoxin level proves or disproves toxicity, a level higher than 3.0 ng per ml in the appropriate setting lends strong support to a diagnosis of digitalis excess.

Digitalis-Drug Interactions

Many drugs have been reported to affect digoxin absorption.[5,11,12] This problem has been minimized by the use of more bioavailable preparations. Concurrent administration of antacids, bran, kaolin pectate, cholestyramine resin, colestipol hydrochloride, activated charcoal, sulfasalazine, neomycin or *para*-aminosalicylic acid can decrease digoxin absorption. This is minimized by administering digoxin two hours before the drug in question. Withdrawing the interacting drug without decreasing the digoxin dose can lead to enhanced absorption and toxicity. Increased intestinal motility due to the use of metoclopramide hydrochloride or cathartics may decrease digoxin absorption, whereas agents that decrease motility (atropine, propantheline bromide) have the opposite effect. Malabsorption and mucosal damage by cytotoxic drugs can decrease digoxin absorption as well.

Many drugs are reported to increase serum digoxin concentration. Quinidine causes such an increase in more than 90% of patients.[13] The effect is variable and ranges from none to sixfold, with an average increase in serum digoxin levels of twofold. This is due to a decrease in renal and nonrenal clearance and in the volume of distribution of digoxin. It has been postulated that the early rise in serum digoxin levels is due to displacement of digoxin from tissue stores, but the myocardial-serum digoxin ratio remains constant.[14] Studies in animals show that the increased serum digoxin concentration is not accompanied by a proportional increase in digoxin effect, as measured by percent inhibition of rubidium 86 uptake. Because total myocardial digoxin content increases appropriately, this implies that digoxin may be selectively displaced from active myocardial binding sites.[14]

The calcium channel blockers have a variable effect on serum digoxin concentration. Verapamil increases digoxin levels in more than 90% of patients by decreasing clearance and perhaps the volume of distribution of digoxin.[15] Nifedipine has no effect on serum digoxin levels and diltiazem hydrochloride causes a small but significant increase.[16] Amiodarone increases serum digoxin concentration by twofold by decreasing the clearance without changing the volume of distribution.[17] The increased digoxin concentration may be accompanied by signs and symptoms of digoxin toxicity. Other agents that can increase the serum digoxin concentration include spironolactone (inhibition of active tubular digoxin secretion) and antihypertensive agents (decreased renal blood flow and glomerular flow rate). Antibiotic therapy has an important effect in 10% of patients on digoxin therapy, perhaps because antibiotics eliminate the gastrointestinal bacteria that break down a proportion of ingested digoxin.[18] This effect appears minimal with the encapsulated elixir preparations. Thus, several commonly used drugs can increase the serum digoxin concentration and precipitate digoxin toxicity.

Factors Affecting Myocardial Sensitivity to Digoxin

Many conditions can precipitate digitalis toxicity (Table 1), either by decreasing the clearance or volume of distribution of digoxin—that is, increased serum digoxin concentration—or by decreasing myocardial tolerance for digoxin.[19] Renal failure is the most common reason for a rise in the serum digoxin level due to decreased renal excretion and volume of distribution. The loading and maintenance doses of

TABLE 1.—*Factors Affecting Myocardial Tolerance to Digitalis Glycosides*

Renal failure
Advanced age
Hypothyroidism/hyperthyroidism
Hypokalemia
Hypomagnesemia
Hypercalcemia, severe
Chronic pulmonary, heart disease
Cardiac disease—myocarditis, myocardial infarction, cardiomyopathy
CNS processes, such as cerebrovascular accidents
Decreased lean body mass (muscle digoxin depot)
Extracorporeal circulation
Concomitant drug administration

CNS = central nervous system

digoxin must, therefore, be reduced and the serum digoxin concentration monitored. Dialysis removes only a small fraction of total body digoxin stores. A supplemental digoxin dose after dialysis can increase the serum concentration of digoxin and cause toxicity. Patients of advanced age are more susceptible to toxicity due to an age-dependent decrease in glomerular filtration rate and renal digoxin excretion, decreased lean body mass and thus volume of distribution of digoxin and a possible increase in myocardial sensitivity to digoxin. Hypothyroidism increases serum digoxin concentration by decreasing the glomerular filtration rate and volume of distribution of the digoxin. The myocardium of patients with myxedema may have a reduced tolerance for digoxin. These changes are reversed with thyroid replacement. Hyperthyroid patients, on the other hand, have reduced serum digoxin levels due to an increase in renal digoxin clearance (glomerular filtration rate).

Electrolyte imbalance may also precipitate digoxin toxicity. Burch has defined a "digoxin-diuretic" cardiomyopathy to highlight the risk of diuretic-induced hypokalemia in patients receiving digoxin.[20] This concept can be extended to include diuretic-induced hypomagnesemia and hypercalcemia. Hypercalcemia can precipitate digoxin toxicity, but only at very high levels that may be transiently achieved during intravenous administration of calcium. Hypocalcemia increases myocardial digoxin tolerance. Intracellular hypokalemia can exist with normal serum potassium levels, with metabolic alkalosis serving as a clue to total body potassium depletion. Potassium competes with digitalis for myocardial receptor binding sites, and hypokalemia results in an increase in myocardial digoxin uptake, a decrease in sodium-potassium pump activity (increased digoxin binding to the sodium-potassium pump) and a decrease in tubular secretion of digoxin. The amplitude of digoxin-induced delayed afterdepolarizations is increased, and digoxin-induced atrioventricular (AV) conduction delay is prolonged. Thus, toxicity is seen at lower serum digoxin levels in the presence of hypokalemia.[21]

In digoxin-treated patients, hypomagnesemia is currently more common than hypokalemia. The causes include malabsorption of magnesium due to splanchnic vessel congestion, renal wasting due to hyperaldosteronism and diuretic therapy (blocked by potassium-sparing diuretics: spironolactone, triamterene, amiloride hydrochloride) and digoxin-induced impairment of tubular reabsorption of magnesium.[22] Like hypokalemia, hypomagnesemia increases myocardial digoxin uptake, decreases activity of the sodium-potassium pump and increases the amplitude of digoxin-induced afterdepolarizations. Hypomagnesemia can also exist with normal serum levels and can cause intracellular hypokalemia that is refractory to potassium replacement. Therapy for digitalis toxicity should thus include repletion of both potassium and magnesium stores. Thus, decreased magnesium stores, in a manner akin to hypokalemia, can precipitate digoxin toxicity at therapeutic levels.

Chronic pulmonary disease is a well-identified precipitant of digitalis toxicity.[5,23] Factors contributing to this include hypoxia, hypercapnia, endogenous and exogenous catecholamines, hypokalemia, vagotonic (suctioning, acidosis, infections) and vagolytic (atropine) stimuli, advanced age and decreased lean body mass. Underlying severe cardiac disease (myocarditis, myocardial ischemia or infarction, cardiomyopathy/amyloidosis) also reduces the myocardial threshold for toxicity. Acute cerebrovascular accidents can precipitate toxicity by increasing central sympathetic outflow. Extracorporeal circulation may increase myocardial sensitivity in the first 24 hours after an operation. Concomitant drug therapy may potentiate the cardiac effects of digitalis. Administering sympatholytic, vagotonic or sympathomimetic medications may increase digoxin conduction block and ectopic impulse formation. Patients with sinus node dysfunction are particularly sensitive to combination antiadrenergic therapy, such as with clonidine, methyldopa, reserpine and β-blockers. Succinylcholine chloride decreases, while halothane increases, myocardial digoxin tolerance. Finally, although digoxin pharmacokinetics are normal in patients with cirrhosis, patients with obstructive jaundice may be more sensitive to the vagotonic effects of digoxin, possibly due to retained bile acids with a structural similarity to digoxin.

Digitalis and Myocardial Infarction

Myocardial ischemia and infarction are generally accepted as causing a decrease in myocardial tolerance to digoxin. Although several clinical studies have failed to show that an acutely infarcted myocardium is more susceptible to digitalis arrhythmias,[24] studies in animals have clearly shown that ischemic myocardium is more sensitive to digitalis toxicity, with the site of initiation of digitalis-induced ventricular tachycardia being localized to the infarcted and peri-infarcted area.[25] Compounding this increased potential for toxicity is the finding that digoxin is a weak inotrope for the treatment of peri-infarction congestive heart failure. The reasons for a lack of significant digoxin effect include digoxin-induced peripheral vasoconstriction (increased afterload) and bulging of the ischemic or infarcted myocardium with decreased effective forward cardiac output. Digoxin may also cause coronary vasoconstriction and an increase in myocardial oxygen demand; digoxin has been shown to increase the size of experimental myocardial infarction.[26] Thus, in the setting of peri-infarction congestive heart failure, digoxin has possible enhanced toxicity and limited efficacy as an inotrope and may worsen myocardial ischemia.

The effect of digoxin therapy on survival after myocardial infarction is likewise controversial. Three nonrandomized studies show the use of digoxin to be an independent risk factor for mortality,[27-29] but more recent reports were unable to assign any additional mortality risk to its use.[30,31] In all the studies, the patients receiving digoxin were hemodynamically more compromised. Definition of the role of digoxin therapy in the peri-infarction period must thus await the outcome of randomized trials.

Extracardiac Symptoms of Digitalis Toxicity

The extracardiac symptoms of digoxin excess are nonspecific and are often mistakenly attributed to underlying congestive heart failure, thus delaying recognition. Lely and Van Enter reported that 28% of patients had symptoms for more than three weeks before diagnosis.[32] In as many as 50% of patients, cardiac arrhythmias are not preceded by extracardiac symptoms. There is a poor correlation between serum digoxin concentration and the extent of symptoms, although in general, as the serum digoxin level rises, so does the prevalence of symptoms. Symptoms are primarily of the ocular,

neuropsychiatric and gastrointestinal systems. The goals of clinical diagnosis are to identify the subgroup of patients with digoxin toxicity but without extracardiac symptoms, and the subset without toxicity who have the symptoms attributable to toxicity.

Of the extracardiac manifestations, anorexia is often the earliest symptom and is followed in two to three days by nausea and vomiting due to stimulation of the area postrema of the medulla. Abdominal pain and bloating may be nonspecific symptoms or may be due to nonocclusive mesenteric ischemia from digitalis-induced vasoconstriction. Such ischemia may be relieved by verapamil. Ocular symptoms (alteration of red and green perception, predominance of yellow-green vision), consistent with a diagnosis of retrobulbar neuritis, may persist for two to three weeks after digitalis therapy is discontinued. Neuropsychiatric symptoms range from ubiquitous neuromuscular complaints (fatigue, muscle weakness) and subtle alterations of personality to outright delirium and psychosis, often termed "foxglove frenzy" or "digitalis delirium."

Significant digitalis toxicity may produce hyperkalemia that can be refractory to therapy. The level of potassium elevation is directly correlated with mortality.[33] Mechanisms include total body inhibition of the sodium-potassium pump and increased congestive heart failure with decreased glomerular filtration rate. Hyperkalemia can worsen digitalis-induced AV block and increase the pacing threshold of a ventricle with a digitalis toxic reaction.[34]

Cardiac Manifestations of Digitalis Toxicity

Increased congestive heart failure may be the initial manifestation of toxicity in as many as 7.5% of patients.[35,36] This may occur independent of arrhythmias or ischemia and subsides with discontinuation of digitalis therapy. Rapid intravenous digoxin administration can abruptly increase afterload via peripheral vasoconstriction and precipitate pulmonary edema. Digitalis-induced dysrhythmias may produce palpitations, angina, syncope or a low-output state. In the setting of atrial fibrillation, a subtle alteration of the cardiac rhythm may be the only clue to toxicity.

Digitalis-Induced Dysrhythmias

Many of the toxic effects of digitalis are mediated via the autonomic nervous system (Table 2).[5,37,38] At the level of the sinus node, atrial myocardium and AV node, the primary digitalis effect is parasympathomimetic and antiadrenergic. Adrenergic stimulation is the primary cause of toxicity at the level of His-Purkinje fibers and ventricular myocardium. Delayed afterdepolarizations seen in atrial fibers, Purkinje's fibers and ventricular muscle are transient late depolarizations that follow repolarization of the action potential. Inhibition of the sodium-potassium pump by digitalis leads to increased intracellular sodium, which in turn leads via the sodium-calcium exchange system to an increase in intracellular calcium. The calcium overload triggers an oscillatory release of calcium from intracellular stores and a secondary transient inward current of sodium resulting in the afterpotentials. If of sufficient amplitude, the afterpotentials can trigger another action potential and result in coupled beats or tachycardia, referred to as triggered activity.[5,38] Amplitude of the afterpotentials can be increased by digitalis, hypokalemia, hypercalcemia and catecholamines (via a β-receptor-mediated increase in intracellular calcium) and reduced by manganese, magnesium and verapamil. At the ventricular level, ectopy may also be due to enhanced automaticity (accelerated phase 4 depolarization) and reentry mechanisms.

Dysrhythmias, often multiple, occur in 80% to 90% of patients with digitalis toxicity.[35] Approximately a third of patients have arrhythmia as their initial manifestation of toxicity.[36] A characteristic feature of digitalis toxicity is the concurrent occurrence of enhanced impulse formation and depressed conduction.[39] Otherwise healthy patients primarily manifest deficits of conduction that are cholinergically mediated, whereas disorders of impulse formation with or without depressed conduction develop in patients with underlying myocardial disease.

Wellens has outlined four criteria for the electrocardiographic diagnosis of digitalis toxicity[39]: (1) appearance of a slow heart rate in a patient with a fast or normal heart rate; (2) appearance of a fast heart rate in a patient with a normal heart rate; (3) appearance of a regular rhythm in a patient with an irregular rhythm; (4) appearance of a regularly irregular rhythm. No arrhythmia is unique to digitalis toxicity. Any change in rhythm (or clinical state) in a patient receiving digitalis should suggest toxicity. Although a digitalis effect on the electrocardiogram has often been equated with toxicity, such changes may be present in the absence of toxicity and absent in two thirds of cases of toxicity.[35]

Table 3 catalogues the arrhythmias considered most suggestive of digitalis toxicity and those unlikely to be digitalis

TABLE 2.—*Mechanisms of Digitalis Toxicity*

Site of Action of Digoxin	*Toxic Electrophysiologic Effect*
Sinus node	Antiadrenergic, direct drug effect
Atrium	First-degree direct drug effect, increased automaticity, triggered activity
Atrioventricular node	First-degree direct effect, cholinergic
Purkinje's fibers and ventricular muscle	Increased automaticity, delayed afterdepolarizations, reentry mechanism

TABLE 3.—*Catalogue of Digitalis-Induced Arrhythmias*

Arrhythmias Most Suggestive of Digitalis Toxicity
- Bidirectional ventricular tachycardia
- Bigeminal ventricular rhythm
- Multiform premature ventricular complexes
- Atrial tachycardia with block
- Nonparoxysmal AV junctional tachycardia with or without exit block
- Supraventricular rhythm (atrial fibrillation) with ventricular ectopy
- Nonconducted premature atrial complexes
- Ventricular tachycardia with exit block

Arrhythmias Unlikely to Be Digitalis Induced
- Mobitz II second-degree AV block
- Parasystole
- Sinus tachycardia
- Paroxysmal AV junctional tachycardia
- Nonparoxysmal ventricular (idioventricular) tachycardia
- Multifocal atrial tachycardia
- Atrial flutter or fibrillation with rapid ventricular response
- Complete infranodal AV block
- Bilateral bundle branch block of varying degree

AV = atrioventricular

induced.[35,39-41] Nonparoxysmal AV junctional tachycardia is considered the most specific digoxin-induced arrhythmia. Bidirectional tachycardia, nonconducted premature atrial complexes (PACs) and bigeminal ventricular rhythm are virtually diagnostic of intoxication. Reviewed below are the most common digitalis-induced arrhythmias.

Disorders of Sinus Node Impulse Formation and Conduction

Disorders of sinus node impulse formation and conduction can manifest as sinus bradycardia or sinoatrial block (first, second [Mobitz I or II] or third degree), and a sudden reduction of the heart rate to less than 50 per minute is suggestive of toxicity.[35] Bradycardia is more common with acute overdose in patients without underlying heart disease, is cholinergically mediated and is reversible with atropine therapy.

Atrioventricular Block

Risk factors for the development of AV block include ischemic rheumatic disease, preexisting conduction system disease, a recent cardiac operation, acute inferior wall myocardial infarction and significant overdose in patients without underlying heart disease. First-degree AV block represents the earliest manifestation of toxicity, with a reported incidence of 15% to 25%; the actual incidence may be higher, as several authors do not consider it a manifestation of toxicity. The incidence of second-degree block is about 6%. Only Mobitz type I AV block has been reported. Third-degree AV block is uncommonly associated with syncope because of the acceleration of subsidiary pacemakers. The identification of retrograde P waves is a clue to this diagnosis because digitalis-induced AV block is often greater than ventriculoatrial block.[39]

Nonparoxysmal Atrioventricular Junctional Tachycardia

Nonparoxysmal AV junctional tachycardia represents up to 50% of digitalis-induced dysrhythmias and may be the most specific manifestation of toxicity. The ventricular response is 70 to 140 per minute, often occurs with exit block and may increase with exercise.[39] Carotid sinus massage produces minimal or no slowing of the rate. It is often precipitated by hypokalemia and is more common in the presence of underlying atrial fibrillation and advanced age. The differential diagnosis includes acute inferior wall myocardial infarction, rheumatic fever, a recent surgical procedure including coronary artery bypass grafting, anesthesia and myocarditis.[35] Therapy is indicated for hemodynamically significant tachycardia or a ventricular response of more than 90 per minute.[12]

'Paroxysmal' Atrial Tachycardia With Block

"Paroxysmal" atrial tachycardia with block, first described by Sir Thomas Lewis in 1906, accounts for 10% of digitalis-induced arrhythmias.[42] One third to one half of cases may be due to digitalis excess and 60% of these may be precipitated by recent hypokalemia. On examining the neck veins, the jugular a-wave rate is greater than the apical rate. The atrial rate is usually 150 to 250 with 2:1 AV block. Ventricular ectopy may be seen in 50% of cases. Carotid sinus massage may increase the degree of AV block. Prompt therapy is recommended because this arrhythmia has a reported mortality of 28% to 70%. The sequence of conversion is a decrease in the atrial rate, followed by 1:1 AV conduction and eventual conversion to sinus rhythm at a critical atrial rate.

Ventricular Ectopy

Ventricular ectopy is the most frequent digitalis-induced dysrhythmia, with a frequency of 50%. Premature ventricular complexes (PVCs) are nonspecific but some patterns are more suggestive of digitalis excess. These include multiform, bidirectional and bigeminal PVCs, as well as PVCs occurring after carotid sinus massage. Varying QRS morphology associated with a fixed PVC coupling interval is diagnostic of digitalis excess. The association of a supraventricular rhythm such as atrial fibrillation with complex ventricular ectopy is virtually pathognomonic of digoxin excess. Therapy is indicated for complex ectopy including multiform, "frequent," late diastolic (R on T), bigeminal and bidirectional PVCs.

Ventricular Tachycardia

Ventricular tachycardia is an infrequent manifestation of digitalis excess (10%) but has a high mortality of greater than 50%.[35] The rate is often faster than tachycardia precipitated by ischemia and may not be preceded by warning ventricular ectopy. Bidirectional tachycardia is considered pathognomonic of toxicity.[35,39] It occurs at a rate of 140 to 180 per minute and is recognized by a right bundle branch block morphology and alternating left and right axis deviation. The origin of the tachycardia may be atrioventricular or ventricular. The prognosis is grave with frequent evolution to ventricular fibrillation and sudden death.

Miscellaneous Dysrhythmias

Atrial fibrillation and flutter are uncommonly due to digitalis, especially if associated with a rapid ventricular response. Nonconducted (blocked) PACs are very suggestive of digitalis toxicity.[35] Frequent PACs may precipitate atrial fibrillation. Ventricular fibrillation is usually a preterminal event with a mortality of virtually 100%.

Digitalis Toxicity in Patients With Atrial Fibrillation

Patients in atrial fibrillation are often maintained on "toxic" doses and are thus susceptible to clinical toxicity. Clues to the diagnosis of digitalis toxicity in the presence of atrial fibrillation are as follows: slow ventricular response, complete AV block with junctional escape rhythm at a rate of 45 to 55 per minute, nonparoxysmal AV junctional tachycardia at a regular rate of 70 to 100 per minute, a tendency toward rhythm regularity, accelerated junctional rhythm with variable exit block resulting in a rapid irregular (or regularly irregular) rhythm and bidirectional tachycardia; all of above can occur without ventricular ectopy.[43] Of note is that the presence of a regular rhythm does not imply the presence of sinus rhythm, and the presence of irregular rhythm does not assure the presence of atrial fibrillation. Thus, electrocardiographic confirmation is necessary before altering therapy for atrial fibrillation.

Digitalis Toxicity in Patients With Pacemakers

The most important clue to toxicity is an altered atrial mechanism in the presence of an underlying pacemaker rhythm.[44] Independent retrograde P waves at a rate of 70 to 130 per minute suggest nonparoxysmal AV junctional tachy-

cardia; a rate of 40 to 60 per minute suggests AV junctional escape rhythm. Sinus bradycardia and sinoatrial block may be present. Atrial tachycardia is diagnosed by the recognition of independent upright P waves at a rate of 160 to 250 per minute. Premature ventricular complexes and ventricular tachycardia/fibrillation may also be present with an underlying pacemaker rhythm.

Therapy for Digitalis Intoxication

Therapy for digitalis toxicity is indicated for hemodynamically significant bradyarrhythmias or tachyarrhythmias, for arrhythmias with malignant potential and for hyperkalemia. Specific indications for treatment are ventricular ectopy (multiform, bigeminy, bidirectional), ventricular tachycardia (including bidirectional), ventricular fibrillation, atrial tachycardia with block, symptomatic bradyarrhythmias and nonparoxysmal junctional tachycardia at a rate of more than 90 per minute.

Therapy should begin with discontinuation of digoxin and diuretics (to replete potassium stores). The patient should be placed at bed rest to avoid sympathetic stimulation and exacerbation of digitalis arrhythmias. Monitoring is essential because multiple rhythms of variable hemodynamic significance may occur over time. Conservative therapy may be adequate for many of the digitalis dysrhythmias. The agents most useful in treating significant digitalis toxicity are reviewed below.

Potassium Chloride

Increasing extracellular potassium results in increased sodium-potassium pump activity and consequently decreased intracellular calcium and secondary afterdepolarizations. Potassium replacement is often the initial therapy of choice for ectopic rhythms (ventricular ectopy, ventricular tachycardia, atrial tachycardia with block and nonparoxysmal AV junctional tachycardia). It is contraindicated by renal failure, preexisting hyperkalemia and depressed AV conduction (greater than first-degree AV block). Hyperkalemia, by decreasing the resting membrane potential, can potentiate digoxin's effect on AV conduction.[34] The dose of potassium required to produce AV block, which is reduced in the presence of digoxin, however, is still more than the dose required to eliminate ectopic rhythms. A given dose of potassium chloride can produce a greater than expected increase in serum potassium levels due to inhibition of the sodium-potassium pump. Administering potassium chloride in glucose can paradoxically decrease serum potassium levels further by increasing intracellular potassium movement; administration in saline may be necessary.

Diphenylhydantoin

Given prophylactically, phenytoin is the best agent to retard the development of digitalis toxic dysrhythmias. Phenytoin appears to act in the central nervous system by depressing central sympathetic outflow. It suppresses digitalis-induced enhanced automaticity and delayed afterdepolarizations without reversing digitalis inotropism. It may also reverse digoxin-induced depression of AV and sinoatrial conduction.[12] Hypotension is the main adverse effect of intravenous administration of phenytoin. Phenytoin is administered by intravenous infusion at a rate of 100 mg every five minutes until the desired effect, toxicity or a total dose of 1,000 mg. This is followed by oral dosing of 400 to 600 mg per day until the toxicity is resolved.[12] There is often a critical dose at which arrhythmias are suppressed. Indications for phenytoin therapy are atrial tachycardia with block, ventricular ectopy, ventricular tachycardia and nonparoxysmal AV junctional tachycardia.

Lidocaine

In a manner similar to phenytoin, lidocaine suppresses digoxin-induced automaticity and delayed afterdepolarizations without depressing AV conduction.[12] In a patient with advanced AV block, however, suppressing the ectopic focus can precipitate ventricular standstill. Indications include ventricular ectopy or tachycardia and atrial tachycardia with block.

Magnesium

Intravenous administration of magnesium can suppress digitalis-induced ventricular arrhythmias in animals and in clinical use.[45] The use of magnesium is contraindicated in renal failure, hypermagnesemia and advanced AV block but is indicated for ventricular ectopy and tachycardia and perhaps for AV junctional tachycardia.

Atropine

Atropine is useful for reversing digoxin-induced AV and sinoatrial conduction delay. It is particularly effective in patients without underlying heart disease and with significant ingestion. Therapy is indicated for symptomatic bradyarrhythmias complicated by hypotension, angina, heart failure or bradycardia-dependent ventricular ectopy.

Isoproterenol

Indicated for temporary treatment of symptomatic bradycardias before pacemaker therapy, the use of isoproterenol can precipitate malignant ventricular ectopy, increase the amplitude of delayed afterdepolarizations and potentially worsen hypokalemia via a β_2-receptor effect.

Second-Line Antiarrhythmic Agents

Several antiarrhythmic agents have been relegated to second-line agents (Table 4) due to their potential for toxicity (worsened ventricular ectopy or AV conduction). Most are negative inotropes as well.

Treatment of Hyperkalemia

The treatment of hyperkalemia includes potassium exchange resins, glucose-insulin, bicarbonate, hemodialysis and antidigoxin Fab fragments. Calcium is relatively contraindicated because it can increase afterdepolarizations, and transient severe hypercalcemia sensitizes the myocardium to digoxin.

Carotid Sinus Massage

Digitalis sensitizes the heart to the vagal effect of carotid massage, and the maneuver in intoxicated patients can precipitate ventricular asystole, advanced AV block and malignant ventricular arrhythmias that are refractory to countershock.[46] There is no defined role for carotid massage as therapy for digitalis-toxic rhythms.

TABLE 4.—*Potential Uses and Toxicity of Second-Line Drugs for Digoxin Toxicity*

Drug	May Increase AV Block	May Increase Ventricular Ectopy	Negative Inotrope	Potential Indications
Procainamide hydrochloride or quinidine	Yes	No	Yes	Ventricular ectopy, ventricular tachycardia, atrial tachycardia with block, AVT
β-Blockers	Yes	No	Yes	Ventricular ectopy, ventricular tachycardia, atrial tachycardia with block
Verapamil	Yes	No	Yes	Atrial tachycardia with block, AVT, ventricular ectopy, ventricular tachycardia
Amiodarone	Yes	No	Yes	Ventricular tachycardia (refractory dysrhythmia)
Isoproterenol	No	Yes	No	Bradycardia (refractory dysrhythmia)
Bretylium tosylate	No	Yes	No	Ventricular tachycardia, ventricular fibrillation (refractory dysrhythmia)

AV = atrioventricular, AVT = nonparoxysmal atrioventricular junctional tachycardia

Pacemaker Therapy

Initiation of pacing is recommended for hemodynamically significant bradycardia refractory to atropine. Placement or displacement of a pacing catheter can precipitate ventricular arrhythmias in ventricles made "prefibrillatory" by the use of digitalis.[47] If AV conduction is intact, atrial pacing is preferable to minimize the risk of pacemaker-induced ventricular fibrillation. Overdrive pacing of triggered activity can result in "overdrive acceleration" of the underlying arrhythmia.

Cardioversion

Digitalis decreases the energy threshold for producing postcardioversion dysrhythmias by 2,000-fold.[48] Countershock can lead to refractory ventricular dysrhythmias. The extent of arrhythmias correlates with the energy level used and the level of digitalization. Postulated mechanisms for arrhythmias are the release of catecholamines from cardiac nerve endings and alteration of cardiac membranes leading to intracellular potassium egress. In patients (or animals) without overt evidence of toxicity, cardioversion does not precipitate arrhythmias.[49]

Recommendations include the use of the lowest effective energy setting and pretreatment with potassium chloride, phenytoin, lidocaine, quinidine or β-blockers. If β-blockers are administered to block catecholamine effect, atropine should be given to prevent postcardioversion asystole.

Dialysis (Renal, Gastrointestinal)

Hemodialysis, peritoneal dialysis and charcoal hemoperfusion are ineffective measures for reducing the total body digoxin content. Serial administration of activated charcoal by mouth may decrease the half-life of digoxin.

Immunologic Therapy for Digitalis Toxicity

About 20 years after the first report of the isolation of antidigoxin antibodies, an immunologic antidote has been established as the therapy for advanced, life-threatening digitalis toxicity. In 1966 Butler and Chen reported the initial isolation of antibodies to digoxin in rabbits.[50] Subsequently, sheep antidigoxin immunoglobulin (Ig) G molecules and Fab fragments were shown to reverse experimental digoxin-induced dysrhythmias, inotropism, inhibition of rubidium 86 transport and cellular electrophysiologic effects.[51,52] After the report of the first human case of reversal of life-threatening digoxin toxicity with Fab fragments in 1976, the experience in a multicenter trial has been extended to 63 patients.[53]

Table 5 outlines the mechanism of action of sheep antidigoxin antibodies.[54] Fab fragments have several advantages over intact IgG in that they have decreased immunogenicity due to loss of the Fc segment and smaller molecular weight leading to more rapid and effective distribution and reversal of toxicity. In addition, Fab-digoxin complexes are rapidly excreted by glomerular filtration, whereas IgG-digoxin is slowly degraded by the reticuloendothelial system. On intravenous infusion of Fab, intravascular and interstitial digoxin is bound, resulting in undetectable free (active) digoxin and more than a tenfold increase in total serum digoxin (bound plus free) content. A concentration gradient is thus created, leading to egress of intracellular digoxin. Fab fragments also bind digoxin molecules recently dissociated from receptor sites and prevent their reassociation because the affinity of digoxin is tenfold higher for Fab than for its receptor site. Reversal of digoxin toxicity is evident within one half to one hour. The excretion half-life of Fab-digoxin complexes is 16 to 20 hours. Antidigoxin Fab fragments are also useful for digitoxin even though their affinity for digitoxin is tenfold less.

For administering Fab fragments, the dose is calculated to be stoichiometrically equal to total body digoxin content. Calculations differ for acute and chronic ingestion and for digoxin and digitoxin use. The calculated dose of Fab is diluted in normal saline and, after confirmation of the absence of immediate hypersensitivity (serial skin testing, test intrave-

TABLE 5.—*Sequence of Reversal of Advanced Digoxin Toxicity by Digoxin-Specific Fab Antibody Fragments*

Sheep immunized with digoxin-serum albumin conjugate
IgG sheep antidigoxin antibody isolated
Antiserum digested with papain
Digoxin-specific Fab fragments purified, isolated
Fab administered intravenously to digoxin-intoxicated patient
Fab fragments bind intravascular digoxin, diffuse into interstitial space and find free interstitial digoxin
Decreased free (active) extracellular digoxin; increased bound (inactive) extracellular digoxin; significantly increased serum digoxin concentration by radioimmunoassay; undetectable free serum digoxin by equilibrium dialysis
Concentration gradient favoring egress of intracellular digoxin—subsequently bound by Fab fragments in extracellular space
Fab fragments bind freshly dissociated digoxin molecules and prevent their reassociation with membrane receptors
Reversal of adverse electrophysiologic effects of digoxin, usually seen within ½ to 1 hour of Fab administration; hyperkalemia rapidly reversed
Excretion of Fab-digoxin complexes by glomerular filtration with half-life of 16 to 20 hours

nous dose), is administered intravenously over 15 to 30 minutes.

The multicenter trial of Fab therapy reported by Wenger and co-workers showed resolution of advanced toxicity in 52 of 56 analyzed patients.[53] Of the 63 studied patients, 33 had accidental or suicidal overdose. No response was seen in three patients, but the diagnosis of digitalis excess was uncertain in these cases. In all, 52 patients had complete resolution of toxicity. A response to Fab infusion was usually seen within 30 minutes. Based on this experience, current indications for Fab therapy include acute, massive digitalis overdose, life-threatening arrhythmias or conduction deficits unresponsive to conventional therapy and refractory hyperkalemia. In the multicenter trial, no correlation was found between the level of hyperkalemia and outcome, implying a significant impact of Fab on mortality.

Theoretical concerns about infusion of heterologous antibodies have not materialized. No patient in the multicenter trial had an adverse hypersensitivity response.[53] The following concerns, however, remain:

- An anamnestic immune response with repeat Fab administration.
- Dissociation of digoxin from Fab-digoxin complexes with recrudescence of toxicity in patients with a prolonged elimination half-life of Fab-digoxin—that is, in cases of renal failure; no recrudescence has been seen to date in patients with a decreased glomerular filtration rate.
- Reversal of digoxin inotropic response may be detrimental in patients with compromised ventricular function, but additional digoxin can restore the inotropic effect.
- Possible delayed serum sickness.

To circumvent the difficulty of preparing large quantities of Fab fragments from many sheep and to improve standardization, a somatic cell fusion technique has been developed to produce "in vitro" monoclonal antibodies to digoxin. Lechat and associates showed the efficacy of monoclonal IgG and Fab fragments in reversing toxicity in guinea pigs.[55] Monoclonal IgG fully reversed toxicity in six of eight animals. Monoclonal Fab fragments, however, more rapidly reversed toxicity in all ten animals so treated. No clinical experience has been reported, but the potential of such therapy is obviously of tremendous academic and practical value.

Conclusion

Withering's cautions about the potential toxicity of digitalis remain as pertinent today as when first published in 1785. The incidence of toxic reactions remains high, affecting almost one of every five patients treated with digitalis glycosides. Physician education has contributed to a decline in the incidence of toxicity, but the mortality of unrecognized toxicity remains high. Several therapies are available for the diverse dysrhythmias induced by digoxin. Immunologic therapy, when widely available, will have a significant impact on the mortality due to digitalis toxicity. Therapy will be effective, however, only if toxicity is first recognized. In conclusion, in 1986 we have realized Withering's dream of an effective digitalis antidote, and we can see more light; yet, due to a lack of rapid recognition of intoxication, there is still more tunnel ahead.

REFERENCES

1. Withering W: An account of the Foxglove, and some of its medical uses: With practical remarks on dropsy, and other diseases. London, GGJ & J Robinson, 1785
2. Aronson JK: Digitalis intoxication. Clin Sci 1983; 64:253-258
3. Beller GA, Smith TW, Abelmann WH, et al: Digitalis intoxication—A prospective clinical study with serum level correlations. N Engl J Med 1971; 284:989-997
4. Doherty JE, de Soyza N, Kane JJ, et al: Clinical pharmacokinetics of digitalis glycosides. Prog Cardiovasc Dis 1978; 21:141-158
5. Smith TW, Antman EA, Friedman PL, et al: Digitalis glycosides: Mechanisms and manifestations of toxicity. Prog Cardiovasc Dis 1984; 26:413-416; 26:495-523; 27:21-56
6. Smith TW, Butler VP, Haber E: Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. N Engl J Med 1968; 281:212-216
7. Doherty JE, Perkins WH, Flanigan WJ: The distribution and concentration of tritiated digoxin in human tissues. Ann Intern Med 1967; 66:116-124
8. Graves SW, Brown B, Valdes R Jr: An endogenous digoxin-like substance in patients with renal impairment. Ann Intern Med 1983; 99:604-608
9. Haber E: Antibodies and digitalis: The modern revolution in the use of an ancient drug. J Am Coll Cardiol 1985; 5:111A-117A
10. Eraker SA, Sasse L: The serum digoxin test and digoxin toxicity: A Bayesian approach to decision making. Circulation 1981; 2:409-420
11. Marcus FL: Pharmacokinetic interactions between digoxin and other drugs. J Am Coll Cardiol 1985; 5:82A-90A
12. Bigger JT Jr, Strauss HC: Digitalis toxicity: Drug interactions promoting toxicity and the management of toxicity. Semin Drug Treat 1972; 2:147-177
13. Bigger JT Jr, Leahey EB: Quinidine and digoxin—An important interaction. Drugs 1982; 24:229-239
14. Warner NJ, Barnard JT, Bigger JT Jr: Tissue digoxin concentrations and digoxin effect during the quinidine-digoxin interaction. J Am Coll Cardiol 1985; 5:680-686
15. Klein HO, Lang R, Weiss E, et al: The influence of verapamil on serum digoxin concentration. Circulation 1982; 65:998-1003
16. Kuhlmann J: Effects of nifedipine and diltiazem on plasma levels and renal excretion of beta-acetyldigoxin. Clin Pharmacol Ther 1985; 37:150-156
17. Nademanee K, Kannan R, Hendrickson J, et al: Amiodarone-digoxin interaction. J Am Coll Cardiol 1984; 4:111-116
18. Lindenbaum J, Rund DG, Butler VP, et al: Inactivation of digoxin by the gut flora: Reversal by antibiotic therapy. N Engl J Med 1981; 305:789-794
19. Surawicz B: Factors affecting tolerance to digitalis. J Am Coll Cardiol 1985; 5:69A-78A
20. Burch GE: Of the digoxin-diuretic cardiomyopathy. Am Heart J 1979; 97:540
21. Shapiro W: Correlative studies of serum digitalis levels and the arrhythmias of digitalis intoxication. Am J Cardiol 1978; 41:852-859
22. Iseri LT, Freed J, Bures AR: Magnesium deficiency and cardiac disorders. Am J Med 1975; 58:837-846
23. Doherty JE, Kane JJ, Phillips JR, et al: Digitalis in pulmonary heart disease (cor pulmonale). Drugs 1977; 13:142-151
24. Lown B, Klein MD, Barr I, et al: Sensitivity to digitalis drugs in acute myocardial infarction. Am J Cardiol 1972; 30:388-395
25. Iesaka Y, Aonuma K, Gosselin AJ, et al: Susceptibility of infarcted canine hearts to digitalis toxic ventricular tachycardia. J Am Coll Cardiol 1983; 2:45-51
26. Marcus FL: Use of digitalis in acute myocardial infarction. Circulation 1980; 62:17-19
27. Bigger JT Jr, Weld FM, Rolnitzky LM, et al: Is digitalis treatment harmful in the year after acute myocardial infarction? Circulation 1981; 64:83
28. Moss AJ, Davis HT, Conard DL, et al: Digitalis-associated mortality after myocardial infarction. Circulation 1981; 64:1150-1156
29. Bigger JT Jr, Fleiss JL, Rolnitzky LM, et al: Effect of digitalis treatment on survival after acute myocardial infarction. Am J Cardiol 1985; 55:623-630
30. Ryan TJ, Bailey KR, McCabe CH, et al: The effects of digitalis survival in high risk patients with coronary artery disease. Circulation 1983; 67:735-742
31. Madsen EB, Gilpin E, Henning H, et al: Prognostic importance of digitalis after acute myocardial infarction. J Am Coll Cardiol 1984; 3:681-689
32. Lely AH, Van Enter CHJ: Noncardiac symptoms of digitalis intoxication. Am Heart J 1972; 83:149-152
33. Bismuth C, Gaultier M, Conso F, et al: Hyperkalemia in acute digitalis poisoning: Prognostic significance and therapeutic implications. Clin Toxicol 1973; 6:153-162
34. Fisch C, Knoebel SB, Feigenbaum H, et al: Potassium and the monophasic action potential, electrocardiogram, conduction and arrhythmias. Prog Cardiovasc Dis 1966; 8:387-418
35. Chung EK: Digitalization and digitalis arrhythmias, chap 23, Principles in Cardiac Arrhythmias, 3rd Ed. Baltimore, Williams & Wilkins, 1983, pp 648-682
36. Von Capeller D, Copeland CD, Stern TN: Digitalis intoxication: A clinical report of 148 cases. Ann Intern Med 1959; 50:869-878
37. Gillis RA, Quest JA: The role of the nervous system in the cardiovascular effects of digitalis. Pharmacol Rev 1979; 31:19-97
38. Rosen MR: Cellular electrophysiology of digitalis toxicity. J Am Coll Cardiol 1985; 5:22A-34A
39. Wellens HJJ: The electrocardiogram in digitalis intoxication, chap 10, *In* Yu PN, Goodman IF (Eds): Progress in Cardiology, Vol 5. Philadelphia, Lea & Febiger, 1976, pp 271-290
40. Chung EK: Digitalis induced cardiac arrhythmias: A report of 180 cases. Jpn Heart J 1969; 10:409-427
41. Ewy GA: Digitalis intoxication: Diagnosis and therapy, chap 40, *In* Ewy GA, Bressler R (Eds): Cardiovascular Drugs and the Management of Heart Disease. New York, Raven Press, 1982, pp 657-674
42. Lown B, Wyatt NF, Levine HD: Paroxysmal atrial tachycardia with block. Circulation 1960; 21:129-143

43. Kastor JA: Digitalis intoxication in patients with atrial fibrillation. Circulation 1973; 57:888-896

44. Chung EK: Artificial pacing and digitalis toxicity, chap 10, Manual of Artificial Cardiac Pacing. Baltimore, University Park Press, 1983, pp 115-118

45. Cohen L, Kitzes R: Magnesium sulfate and digitalis toxic arrhythmias. JAMA 1983; 249:2808-2810

46. Lown B, Levine SA: The carotid sinus. Circulation 1961; 23:766-789

47. Bismuth C, Motte G, Conso F, et al: Acute digitoxin intoxication treated by intracardiac pacemaker: Experience in 68 patients. Clin Toxicol 1977; 10:443-456

48. Lown B, Kleiger R, Williams J: Cardioversion and digitalis drugs: Changed threshold to electric shock in digitalized animals. Circ Res 1965; 17:519-531

49. Mann DL, Maisel AS, Atwood JE, et al: Absence of cardioversion-induced ventricular arrhythmias in patients with therapeutic digoxin levels. J Am Coll Cardiol 1985; 5:882-890

50. Butler VP, Chen JP: Digoxin-specific antibodies. Proc Natl Acad Sci USA 1967; 57:71-78

51. Curd J, Smith TW, Jaton JC, et al: The isolation of digoxin-specific antibody and its use in reversing the effects of digoxin. Proc Natl Acad Sci USA 1971; 68:2401-2406

52. Lloyd BL, Smith TW: Contrasting rates of reversal of digoxin toxicity by digoxin specific IgG and Fab fragments. Circulation 1978; 58:280-283

53. Wenger TL, Butler VP Jr, Haber E, et al: Treatment of 63 severely digitalis-toxic patients with digoxin-specific antibody fragments. J Am Coll Cardiol 1985; 5:118A-123A

54. Butler VP: Antibodies as specific antagonists of toxins, drugs, and hormones. Pharmacol Rev 1982; 34:109-114

55. Lechat P, Mudgett-Hunter M, Margolies MN, et al: Reversal of lethal digoxin toxicity in guinea pigs using monoclonal antibodies and Fab fragments. J Pharmacol Exp Ther 1984; 229:210-213

Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Contralateral Breast Surgery Following Mastectomy

QUESTION:

Following mastectomy with breast reconstruction, is a surgical procedure on a disease-free, contralateral breast to attain symmetry considered accepted medical practice?

If so, is it considered a cosmetic procedure?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery and Plastic Surgery, reconstruction of a disease-free contralateral breast to restore symmetry is considered established medical practice following mastectomy with breast reconstruction. This reflects the commonly accepted goals of breast reconstruction which are to provide a contour as natural looking and feeling as possible, to create a natural looking nipple/areola complex and to obtain acceptable symmetry with the opposite breast.

When the contralateral breast is excessively large, in size or volume, or droops severely (ptosis), it is usually impossible to match these characteristics with the newly reconstructed breast. To restore symmetry, therefore, reduction mammoplasty of a large breast, mastopexy of a drooping breast and augmentation mammoplasty of an unusually small breast may be necessary. Patients with a high risk of cancer developing in the contralateral breast who need size or shape correction to achieve symmetry may be considered for mastectomy and immediate reconstruction.

Because the breasts are paired organs and symmetry is the natural state, contralateral breast reconstruction is considered a restoration of the normal condition. In this sense, the procedure is reconstructive, not cosmetic.

For the psychological well-being and physical appearance and functioning of many women, breast reconstruction following mastectomy is essential. Contralateral breast reconstruction is understood to be an integral part of this surgical care.