CECIL MEDICINE, 24TH EDITION

Edited by Lee Goldman and Andrew I. Schafer

PART 1: SOCIAL AND ETHICAL ISSUES IN MEDICINE

1: Approach to Medicine, the Patient, and the Medical Profession: Medicine as a Learned and Humane Profession
Lee Goldman
Editor: Goldman, Lee

2: Bioethics in the Practice of Medicine
Ezekiel Emanuel
Editor: Goldman, Lee

3: Care of Dying Patients and Their Families
Robert Arnold
Editor: Goldman, Lee

4: Cultural Context of Medicine
Victoria M. Taylor
Editor: Goldman, Lee

5: Socioeconomic Issues in Medicine
Steven Schroeder
Editor: Goldman, Lee

PART 2: PRINCIPLES OF EVALUATION AND MANAGEMENT

6: Approach to the Patient: History and Physical Examination
David Simel
Editor: Goldman, Lee

7: Approach to the Patient with Abnormal Vital Signs
David L. Schriger
Editor: Goldman, Lee

8: Statistical Interpretation of Data
Thomas Newman;Charles McCulloch
Editor: Goldman, Lee

9: Using Data for Clinical Decisions
Thomas Lee
Editor: Goldman, Lee

10: Measuring Health and Health Care

PART 3: PREVENTIVE AND ENVIRONMENTAL ISSUES

Michael A McGuigan
Editor: Goldman, Lee

PART 4: AGING AND GERIATRIC MEDICINE

22: Epidemiology of Aging: Implications of the Aging Society
Linda Fried
Editor: Goldman, Lee

23: Geriatric Assessment
David B. Reuben
Editor: Goldman, Lee

24: Common Clinical Sequelae of Aging
Kenneth Minaker
Editor: Goldman, Lee

25: Incontinence
Neil Resnick
Editor: Goldman, Lee

26: Neuropsychiatric Aspects of Aging
Sharon Inouye
Editor: Goldman, Lee

27: Delirium and Other Mental Status Problems in the Older Patient
Sharon Inouye
Editor: Goldman, Lee

PART 5: CLINICAL PHARMACOLOGY

28: Principles of Drug Therapy
Robert Diasio
Editor: Schafer, Andrew

29: Pain
Srinivasa N Raja;Steven P Cohen
Editor: Schafer, Andrew

30: Biology of Addiction
Steven E. Hyman
Editor: Schafer, Andrew

31: Nicotine and Tobacco
Tony P. George

PART 6: GENETICS

Editor: Schafer, Andrew

43: Gene and Cell Therapy
Karl Skorecki
Editor: Schafer, Andrew

PART 7: PRINCIPLES OF IMMUNOLOGY AND INFLAMMATION

44: The Innate and Adaptive Immune Systems
Cornelia Weyand;Jorg Goronzy
Editor: Schafer, Andrew

45: The Major Histocompatibility Complex
Peter K. Gregersen
Editor: Schafer, Andrew

46: Mechanisms of Immune-Mediated Tissue Injury
Jane Salmon
Editor: Schafer, Andrew

47: Mechanisms of Inflammation and Tissue Repair
Gary S. Firestein
Editor: Schafer, Andrew

48: Organ Transplantation
Megan Sykes
Editor: Schafer, Andrew

49: Complement in Health and Disease
David, R. Karp;V. Michael Holers
Editor: Schafer, Andrew

PART 8: CARDIOVASCULAR DISEASE

50: Approach to the Patient with Possible Cardiovascular Disease
Lee Goldman
Editor: Goldman, Lee

51: Epidemiology of Cardiovascular Disease
Michael Klag
Editor: Goldman, Lee

52: Cardiac Function and Circulatory Control
Andrew Marks
Editor: Goldman, Lee

53: Radiology of the Heart
Murray G. Baron;Arthur E. Stillman
Editor: Goldman, Lee

54: Electrocardiography
Leonard I Ganz
Editor: Goldman, Lee

55: Echocardiography
Catherine Otto
Editor: Goldman, Lee

56: Non-invasive Cardiac Imaging
Christopher Kramer
Editor: Goldman, Lee

57: Catheterization and Angiography
Morton Kern
Editor: Goldman, Lee

58: Heart Failure: Pathophysiology and Diagnosis
Barry Massie
Editor: Goldman, Lee

59: Heart Failure: Management and Prognosis
John JV McMurray;Marc A. Pfeffer
Editor: Goldman, Lee

60: Diseases of the Myocardium and Endocardium
William McKenna;Perry Elliott
Editor: Goldman, Lee

61: Principles of Electrophysiology
Hugh Calkins
Editor: Goldman, Lee

62: Approach to the Patient with Suspected Arrhythmia
Jeffrey Olgin
Editor: Goldman, Lee

63: Approach to Cardiac Arrest and Life-Threatening Arrhythmias
Robert Myerburg
Editor: Goldman, Lee

64: Cardiac Arrhythmias with Supraventricular Origin
Peter Zimetbaum

Editor: Goldman, Lee

65: Ventricular Arrhythmias
William Stevenson
Editor: Goldman, Lee

66: Electrophysiologic Interventional Procedures and Surgery
Fred Morady
Editor: Goldman, Lee

67: Arterial Hypertension
Ronald Victor
Editor: Goldman, Lee

68: Pulmonary Hypertension
Valerie McLaughlin
Editor: Goldman, Lee

69: Congenital Heart Disease in Adults
Ariane Marelli
Editor: Goldman, Lee

70: Atherosclerosis, Thrombosis and Vascular Biology
Goran Hansson;Anders Hamsten
Editor: Goldman, Lee

71: Angina Pectoris
William Boden
Editor: Goldman, Lee

72: Acute Coronary Syndrome/Unstable Angina and Non-ST Elevation MI
Richard A. Lange
Editor: Goldman, Lee

73: ST-Elevation Myocardial Infarction and Complications of MI
Jeffrey Anderson
Editor: Goldman, Lee

74: Interventional and Surgical Treatment of Coronary Artery Disease
Paul Teirstein;Bruce Lytle
Editor: Goldman, Lee

75: Valvular Heart Disease
Blase Carabello
Editor: Goldman, Lee

76: Infective Endocarditis

PART 9: RESPIRATORY DISEASES

Jeffrey Drazen
Editor: Goldman, Lee

88: COPD
Dennis Niewoehner
Editor: Goldman, Lee

89: Cystic Fibrosis
Frank Accurso
Editor: Goldman, Lee

90: Bronchiectasis, Atelectasis, Cysts, and Localized Lung Disorders
Anne O'Donnell
Editor: Goldman, Lee

91: Alveolar Filling Disorders
Stephanie, M. Levine
Editor: Goldman, Lee

92: Interstitial Lung Disease
Ganesh Raghu
Editor: Goldman, Lee

93: Occupational Pulmonary Disorders
Susan Tarlo
Editor: Goldman, Lee

94: Physical and Chemical Injuries of the Lung
David C. Christiani
Editor: Goldman, Lee

95: Sarcoidosis
Michael Iannuzzi
Editor: Goldman, Lee

96: Acute Bronchitis and Tracheitis
Richard. P. Wenzel
Editor: Goldman, Lee

97: Overview of Pneumonia
Andrew H. Limper
Editor: Goldman, Lee

98: Pulmonary Embolism
Jeffrey Weitz
Editor: Goldman, Lee

PART 10: CRITICAL CARE MEDICINE

PART 11: RENAL AND GENITOURINARY DISEASES

121: Disorders of Magnesium and Phosphorus
Alan S. L. Yu
Editor: Goldman, Lee

122: Acute Kidney Injury
Bruce Molitoris
Editor: Goldman, Lee

123: Glomerular Disorders and Nephrotic Syndromes
Gerald B. Appel;Jai Radhakrishnan
Editor: Goldman, Lee

124: Tubulointerstitial Diseases
Eric G Neilson
Editor: Goldman, Lee

125: Obstructive Uropathy
Mark Zeidel
Editor: Goldman, Lee

126: Diabetes and the Kidney
Raymond Harris
Editor: Goldman, Lee

127: Vascular Disorders of the Kidney
Thomas D. DuBose, Jr.
Editor: Goldman, Lee

128: Nephrolithiasis
Gary C Curhan
Editor: Goldman, Lee

129: Cystic Kidney Diseases
M. Amin Arnaout
Editor: Goldman, Lee

130: Hereditary Nephropathies and Abnormalities of the Urinary Tract
Lisa Guay-Woodford
Editor: Goldman, Lee

131: Benign Prostate Disease and Prostatitis
Michael Barry;Mary McNaughton-Collins
Editor: Goldman, Lee

132: Chronic Kidney Disease
William Mitch
Editor: Goldman, Lee

PART 12:GASTROINTESTINAL DISEASES

Editor: Goldman, Lee

144: Inflammatory and Anatomic Diseases of theINtestine, Peritoneum, Mesentery, and Omentum
Charlene Prather
Editor: Goldman, Lee

145: Vascular Diseases of the GI Tract
Stephen Hauser
Editor: Goldman, Lee

146: Pancreatitis
Chris E. Forsmark
Editor: Goldman, Lee

147: Diseases of the Rectum and Anus
Robert D. Madoff
Editor: Goldman, Lee

PART 13: DISEASES OF THE LIVER, GALLBLADDER, AND BILE DUCTS

148: Approach to the Patient with Liver Disease
Paul Martin
Editor: Goldman, Lee

149: Approach to the Patient with Jaundice or Abnormal Liver Test Results
Paul Berk;Kevin Korenblat
Editor: Goldman, Lee

150: Acute Viral Hepatitis
Jean-Michel Pawlotsky;Heiner Wedemeyer
Editor: Goldman, Lee

151: Chronic Viral Hepatitis
Jean-Michel Pawlotsky;John McHutchinson
Editor: Goldman, Lee

152: Toxin- and Drug-Induced Liver Disease
William Lee
Editor: Goldman, Lee

153: Inherited and Metabolic Hepatic Disorders
Bruce R Bacon
Editor: Goldman, Lee

PART 14: HEMATOLOGIC DISEASES

165: Hemoglobinopathies: The Thalassemias
Maria Cappellini
Editor: Schafer, Andrew

166: Sickle Cell Disease and Associated Hemoglobinopathies
Martin Steinberg
Editor: Schafer, Andrew

167: Megaloblastic Anemias
Asok C. Antony
Editor: Schafer, Andrew

168: Aplastic Anemia and Related Conditions
Grover Bagby
Editor: Schafer, Andrew

169: Polycythemias, Essential Thrombocythemia and Primary Myelobfibrosis
Ayalew Tefferi
Editor: Schafer, Andrew

170: Leukopenia and Leukocytosis
Nancy Berliner
Editor: Schafer, Andrew

171: Approach to the Patient with Lymphadenopathy and Splenomegaly
James Armitage
Editor: Schafer, Andrew

172: Disorders of Phagocyte Function
Michael Glogauer
Editor: Schafer, Andrew

173: Eosinophilic Syndromes
Marc Rothenberg
Editor: Schafer, Andrew

174: Approach to the Patient with Bleeding and Thrombosis
Andrew Schafer
Editor: Schafer, Andrew

175: Thrombocytopenia
Charles Abrams
Editor: Schafer, Andrew

176: Von Willebrand's Disease and Abnormalties of Vascular Function
William Nichols
Editor: Schafer, Andrew

PART 15: ONCOLOGY

188: Myelodysplasia Syndrome
Alan List;Rami Komrokji;Eric Padron
Editor: Schafer, Andrew

189: The Acute Leukemias
Frederick R Appelbaum
Editor: Schafer, Andrew

190: The Chronic Leukemias
Hagop Kantarjian;Susan O'Brien
Editor: Schafer, Andrew

191: Non-Hodgkin's Lymphomas
James Armitage
Editor: Schafer, Andrew

192: Hodgkin's Lymphomas
Joseph Connors
Editor: Schafer, Andrew

193: Plasma Cell Disorders
S. Vincent Rajkumar
Editor: Schafer, Andrew

194: Amyloidosis
Morrie Gertz
Editor: Schafer, Andrew

195: Tumors of the CNS and Intracranial Hypertension and Hypotension
Lisa DeAngelis
Editor: Schafer, Andrew

196: Head and Neck Cancer
Marshall R. Posner
Editor: Schafer, Andrew

197: Lung Cancer and Other Pulmonary Neoplasms
David S Ettinger
Editor: Schafer, Andrew

198: Neoplasma of the Esophagus and Stomach
Anil Rustgi
Editor: Schafer, Andrew

199: Neoplasms of the Large and Small Intestine
Charles Blanke;Douglas Faigel

Editor: Schafer, Andrew

200: Pancreatic Cancer
Margaret Tempero
Editor: Schafer, Andrew

201: Pancreatic Endocrine Tumors
Robert T. Jensen
Editor: Schafer, Andrew

202: Liver and Biliary Tract Tumors
Lewis Roberts
Editor: Schafer, Andrew

203: Tumors of the Kidney, Bladder, Ureters, and Renal Pelvis
Dean Bajorin
Editor: Schafer, Andrew

204: Breast Cancer and Differential Diagnosis of Benign Lesions
Nancy Davidson
Editor: Schafer, Andrew

205: Gynecologic Cancers
Maurie Markman
Editor: Schafer, Andrew

206: Testicular Cancer
Lawrence Einhorn
Editor: Schafer, Andrew

207: Prostate Cancer
Eric Small
Editor: Schafer, Andrew

208: Bone Tumors: Primary and Metastatic Lesions
Karen H. Antman
Editor: Schafer, Andrew

209: Sarcomas of Soft Tissue
George D. Demetri
Editor: Schafer, Andrew

210: Melanoma and Nonmelanoma Skin Cancers
Lynn Schuchter
Editor: Schafer, Andrew

211: Cancer of Unknown Primary Origin

John Hainsworth
Editor: Schafer, Andrew

PART 16: METABOLIC DISEASES

212: Approach to Inborn Errors of Metabolism
Louis Elsas II
Editor: Schafer, Andrew

213: Disorders of Lipid Metabolism
Clay F. Semenkovich
Editor: Schafer, Andrew

214: Glycogen Storage Diseases
Joseph I. Wolfsdorf;David A. Weinstein
Editor: Schafer, Andrew

215: Lysosomal Storage Diseases
Ellen Sidransky;Donna Krasnewich
Editor: Schafer, Andrew

216: Homocystinuria and Hyperhomocysteinemia
Bruce Barshop
Editor: Schafer, Andrew

217: The Porphyrias
Karl Anderson
Editor: Schafer, Andrew

218: Wilson's Disease
Stephen Kaler
Editor: Schafer, Andrew

219: Iron Overload (Hemochromatosis)
Bruce R Bacon
Editor: Schafer, Andrew

PART 17:NUTRITIONAL DISEASES

220: Nutrition's Interface with Health and Disease
Douglas Heimburger
Editor: Schafer, Andrew

221: Nutritional Assessment
Bruce Bistrian

Editor: Schafer, Andrew

222: Protein-Energy Malnutrition
Samuel Klein
Editor: Schafer, Andrew

223: Enteral Nutrition
Stephen McClave
Editor: Schafer, Andrew

224: Parenteral Nutrition
Greet Van den Berghe;Alexander Wilmer
Editor: Schafer, Andrew

225: Vitamins, Trace Minerals, and Other Micronutrients
Joel B. Mason
Editor: Schafer, Andrew

226: Eating Disorders
Marsha Marcus
Editor: Schafer, Andrew

227: Obesity
Michael Jensen
Editor: Schafer, Andrew

PART 18: ENDOCRINE DISEASES

228: Approach to the Patient with Endocrine Disease
David R. Clemmons
Editor: Schafer, Andrew

229: Principles of Endocrinology
David R. Clemmons
Editor: Schafer, Andrew

230: Neuroendocrinology and the Neuroendocrine System
Mark E. Molitch
Editor: Schafer, Andrew

231: Anterior Pituitary
Mark E. Molitch
Editor: Schafer, Andrew

232: Posterior Pituitary
Joseph G. Verbalis

Editor: Schafer, Andrew

233: Thyroid
Paul Ladenson;Matthew Kim
Editor: Schafer, Andrew

234: Adrenal Cortex
Lynnette Nieman
Editor: Schafer, Andrew

235: The Adrenal Medulla, Catecholamines, and Pheochromocytoma
William F. Young
Editor: Schafer, Andrew

236: Type I Diabetes Mellitus
Robert Sherwin;Silvio Inzucchi
Editor: Schafer, Andrew

237: Type II Diabetes Mellitus
Robert Sherwin;Silvio Inzucchi
Editor: Schafer, Andrew

238: Hypoglycemia/Pancreatic Islet Cell Disorders
Stephen N. Davis
Editor: Schafer, Andrew

239: Polyglandular Disorders
Henry Kronenberg
Editor: Schafer, Andrew

240: Multiple-Organ Syndromes: Carcinoid Syndrome
Kenneth Hande
Editor: Schafer, Andrew

241: Disorders of Sexual Differentiation
Perrin C. White
Editor: Schafer, Andrew

242: The Testis and Male Sexual Function
Ronald Swerdloff
Editor: Schafer, Andrew

243: Ovaries, Development and Menstrual Cycle
Robert W Rebar
Editor: Schafer, Andrew

244: Reproductive Endocrinology/Infertility

Robert W Rebar
Editor: Schafer, Andrew

PART 19: WOMEN'S HEALTH

245: Approach to Women's Health
Karen Freund
Editor: Schafer, Andrew

246: Contraception
Daniel Mishell Jr.
Editor: Schafer, Andrew

247: Common Medical Problems in Pregnancy
Karen Rosene Montella
Editor: Schafer, Andrew

248: Menopause
Deborah Grady;Elizabeth Barrett-Connor
Editor: Schafer, Andrew

249: Interpersonal Violence
Harriet MacMillan;Gene Feder
Editor: Schafer, Andrew

PART 20: DISEASES OF BONE AND MINERAL METABOLISM

250: Mineral and Bone Homeostasis
Murray Favus
Editor: Schafer, Andrew

251: Osteoporosis
Cliff Rosen
Editor: Schafer, Andrew

252: Osteomalacia and Rickets
Robert Weinstein
Editor: Schafer, Andrew

253: The Parathyroid Glands, Hypercalcemia, and Hypocalcemia
John Wysolmerski;Karl Insogna
Editor: Schafer, Andrew

254: Medullary Thyroid Carcinoma and Calcitonin
Samuel Wells Jr.

Editor: Schafer, Andrew

255: Paget's Disease of Bone
David Roodman
Editor: Schafer, Andrew

256: Osteonecrosis, Osteosclerosis/Hyperostosis and Other Disorders of Bone
Michael P. Whyte
Editor: Schafer, Andrew

PART 21: DISEASES OF ALLERGY AND CLINICAL IMMUNOLOGY

257: Approach to the Patient with Allergic or Immunologic Disease
Stephen I Wasserman
Editor: Schafer, Andrew

258: Primary Immunodeficiency Diseases
Mark Ballow
Editor: Schafer, Andrew

259: Allergic Rhinitis and Sinusitis
Larry Borish
Editor: Schafer, Andrew

260: Urticaria and Angioedema
Stephen Dreskin
Editor: Schafer, Andrew

261: Systemic Anaphylaxis, Food Allergy, and Insect Sting Allergy
Lawrence Schwartz
Editor: Schafer, Andrew

262: Drug Allergy
Leslie Grammer
Editor: Schafer, Andrew

263: Mastocytosis
Cem Akin
Editor: Schafer, Andrew

PART 22: RHEUMATIC DISEASES

264: Approach to the Patient with Rheumatic Disease
William Arend;George Lawry

Editor: Schafer, Andrew

265: Laboratory Testing in the Rheumatic Diseases
David Pisetsky
Editor: Schafer, Andrew

266: Imaging Studies in the Rheumatic Diseases
Lynne Steinbach
Editor: Schafer, Andrew

267: Connective Tissue Structure and Function
Richard Loeser
Editor: Schafer, Andrew

268: Inherited Diseases of Connective Tissues
Reed Edwin Pyeritz
Editor: Schafer, Andrew

269: The Systemic Autoinflammatory Diseases
Daniel Kastner
Editor: Schafer, Andrew

270: Osteoarthritis
Nancy Lane;Thomas J. Schnitzer
Editor: Schafer, Andrew

271: Bursitis, Tendonitis, and Other Periarticular Disorders, and Sports Medicine
Josephn J. Biundo
Editor: Schafer, Andrew

272: Rheumatoid Arthritis
James O'Dell
Editor: Schafer, Andrew

273: The Spondyloarthropathies
Robert Inman
Editor: Schafer, Andrew

274: Systemic Lupus Erythematosus
Mary Crow
Editor: Schafer, Andrew

275: Scleroderma (Systemic Sclerosis)
John Varga
Editor: Schafer, Andrew

276: Sjogren's Syndrome

PART 23: INFECTIOUS DISEASES

George M. Eliopoulos
Editor: Schafer, Andrew

288: Approach to Fever or Suspected Infection in the Normal Host
James Leggett
Editor: Schafer, Andrew

289: Approach to Fever and Suspected Infection in the Compromised Host
Kieren Marr
Editor: Schafer, Andrew

290: Approach to the Patient with Healthcare-associated Infections
Neil Fishman
Editor: Schafer, Andrew

291: Approach to the Patient with Suspected Enteric Infection
Herbert DuPont
Editor: Schafer, Andrew

292: Approach to the Patient with Urinary Tract Infection
Ragnar Norrby
Editor: Schafer, Andrew

293: Approach to the Patient with a Sexually Transmitted Disease
Myron S. Cohen
Editor: Schafer, Andrew

294: Approach to the Patient Before and After Travel
Paul, M. Arguin
Editor: Schafer, Andrew

295: Antibacterial Therapy
George Drusano
Editor: Schafer, Andrew

296: Staphylococcal Infections
Henry Chambers
Editor: Schafer, Andrew

297: Streptococcus Pneumoniae Infections
Lionel Mandell
Editor: Schafer, Andrew

298: Non-Pneumococcal Streptococcal Infections, Rheumatic Fever
Donald Low
Editor: Schafer, Andrew

299: Enterococcal Infections
Trish Perl;Eli N. Perencevich
Editor: Schafer, Andrew

300: Diphtheria and Other Corynebacteria Infections
Roland Sutter
Editor: Schafer, Andrew

301: Listeriosis
Bennett Lorber
Editor: Schafer, Andrew

302: Anthrax
Daniel Lucey
Editor: Schafer, Andrew

303: Erysipelothrix Infections
Annette C. Reboli
Editor: Schafer, Andrew

304: Clostridial Infections
Dale Gerding
Editor: Schafer, Andrew

305: Diseases Caused by Non-spore-forming Anaerobic Bacteria
Itzhak Brook
Editor: Schafer, Andrew

306: Neisseria Meningitidis Infections
David Stephens
Editor: Schafer, Andrew

307: Neisseria Gonorhoeaea Infections
Matthew Golden
Editor: Schafer, Andrew

308: Haemophilus and Moraxella Infections
Michael Simberkoff
Editor: Schafer, Andrew

309: Chancroid
Stanley Spinola
Editor: Schafer, Andrew

310: Cholera and Other Vibrio Infections
Carlos Seas
Editor: Schafer, Andrew

311: Campylobacter Infections
Ban Mishu Allos
Editor: Schafer, Andrew

312: Escherichia Enteric Infections
Richard Guerrant;Ted Steiner
Editor: Schafer, Andrew

313: Infections due to other Members of the Enterobacteriaceae, including Management of Multi-Drug Resistant Strains
David Paterson
Editor: Schafer, Andrew

314: Pseudomonas and Related Gram-Negative Bacillary Infections
Gerald Pier
Editor: Schafer, Andrew

315: Other Non-Fermenting Gram-Negatives: Acinetobacter and Stenotrophomonas sp
Robert Bonomo
Editor: Schafer, Andrew

316: Salmonella Infections (Including Typhoid Fever)
John A. Crump
Editor: Schafer, Andrew

317: Shigellosis
Gerald T. Keusch
Editor: Schafer, Andrew

318: Brucellosis
Eduardo Gotuzzo
Editor: Schafer, Andrew

319: Tularemia and Other Francisella Infections
William Schaffner
Editor: Schafer, Andrew

320: Plague and Other Yersinia Infections
Kenneth Gage
Editor: Schafer, Andrew

321: Whooping Cough and Other Bordetella Infections
Erik L. Hewlett
Editor: Schafer, Andrew

322: Legionella Infections

Thomas Marrie
Editor: Schafer, Andrew

323: Disease Caused by Bartonella Species
Didier Raoult;Jean-Marc Rolain
Editor: Schafer, Andrew

324: Granuloma Inguinale (Donovanosis)
Edward W. Hook III
Editor: Schafer, Andrew

325: Mycoplasma Infections
Stephen G. Baum
Editor: Schafer, Andrew

326: Diseases Caused by Chlamydiae
William, M. Geisler
Editor: Schafer, Andrew

327: Treponema Infection (Syphillis)
Edward W. Hook III
Editor: Schafer, Andrew

328: Nonsyphilitic Treponematoses
Edward W. Hook III
Editor: Schafer, Andrew

329: Lyme Disease
Gary Wormser
Editor: Schafer, Andrew

330: Relapsing Fever and Other Borrelia Infections
William Petri
Editor: Schafer, Andrew

331: Leptospirosis
Albert Ko
Editor: Schafer, Andrew

332: Tuberculosis
Jerrold Ellner
Editor: Schafer, Andrew

333: The Nontuberculous Mycobacteria
Steven Holland
Editor: Schafer, Andrew

334: Leprosy (Hansen's Disease)
Joel Ernst
Editor: Schafer, Andrew

335: Rickettsia Infections
Didier Raoult
Editor: Schafer, Andrew

336: Zoonoses
Stuart Levin
Editor: Schafer, Andrew

337: Actinomycosis
Itzhak Brook
Editor: Schafer, Andrew

338: Nocardiosis
Frederick Southwick
Editor: Schafer, Andrew

339: Systemic Antifungal Agents
David A. Stevens
Editor: Schafer, Andrew

340: Histoplasmosis
Carol Kauffman
Editor: Schafer, Andrew

341: Coccidioidomycosis
John N. Galgiani
Editor: Schafer, Andrew

342: Blastomycosis
Carol Kauffman
Editor: Schafer, Andrew

343: Paracoccidioidomycosis
Carol Kauffman
Editor: Schafer, Andrew

344: Cryptococcoisis
Carol Kauffman
Editor: Schafer, Andrew

345: Sporotrichosis
Carol Kauffman
Editor: Schafer, Andrew

346: Candidiasis
Carol Kauffman
Editor: Schafer, Andrew

347: Aspergillosis
Thomas Walsh
Editor: Schafer, Andrew

348: Mucormycosis
Dimitrios Kontoyiannis
Editor: Schafer, Andrew

349: Pneumocystis Penumonia
Joseph A. Kovacs
Editor: Schafer, Andrew

350: Mycetoma
Dimitrios Kontoyiannis
Editor: Schafer, Andrew

351: Dematiaceous Fungal Infections
Peter Pappas
Editor: Schafer, Andrew

352: Antiparasitic Therapy
Richard Pearson
Editor: Schafer, Andrew

353: Malaria
Philip Rosenthal;Moses R. Kamya
Editor: Schafer, Andrew

354: African Trypanosomiasis (Sleeping Sickness)
William Petri
Editor: Schafer, Andrew

355: American Trypanosomiasis (Chagas' Disease)
Louis V. Kirchhoff
Editor: Schafer, Andrew

356: Leishmaniasis
Simon Croft
Editor: Schafer, Andrew

357: Toxoplasmosis
Jose, G Montoya

Editor: Schafer, Andrew

358: Crytosporidiosis
Richard Guerrant;Aldo A. M. Lima
Editor: Schafer, Andrew

359: Giardiasis
Theodore E. Nash
Editor: Schafer, Andrew

360: Amebiasis
William Petri
Editor: Schafer, Andrew

361: Babesiosis and Other Protozoan Diseases
Sam Telford III
Editor: Schafer, Andrew

362: Cestode Infections
A. Clinton White;Enrico Brunetti
Editor: Schafer, Andrew

363: Schistosomiasis (Bilharziasis)
Aldo A. M. Lima;Edgar Carvalho
Editor: Schafer, Andrew

364: Liver, Intestinal, and Lung Fluke Infections
Eduardo Gotuzzo
Editor: Schafer, Andrew

365: Intestinal Nematodes
David Diemert
Editor: Schafer, Andrew

366: Tissue Nematodes
David Diemert
Editor: Schafer, Andrew

367: Arthropods and Leeches
Dirk Elston
Editor: Schafer, Andrew

368: Antiviral Therapy (Non-HIV)
John Beigel
Editor: Goldman, Lee

369: The Common Cold

381: Papillomavirus
John M. Douglas Jr.
Editor: Goldman, Lee

382: Herpes Simplex Virus Infections
Richard J. Whitley
Editor: Goldman, Lee

383: Varicella (Chickenpox, Shingles)
Jeffrey Cohen
Editor: Goldman, Lee

384: Cytomegalovirus
W. Lawrence Drew
Editor: Goldman, Lee

385: Epstein-Barr Virus Infection
Robert Schooley
Editor: Goldman, Lee

386: Human T-Cell Lymphotropic Viruses Type I and II
William Blattner
Editor: Goldman, Lee

387: Enteroviruses
José R Romero
Editor: Goldman, Lee

388: Rotaviruses, Noroviruses, and Other GI Viruses
Harry Greenberg;Manuel Franco
Editor: Goldman, Lee

389: Viral Hemorrhagic Fevers
Daniel G. Bausch
Editor: Goldman, Lee

390: Arthropod-borne Viruses Causing Fever and Rash
Stanley Naides
Editor: Goldman, Lee

391: Anthropod-borne Viruses Affecting the CNS
Thomas Bleck
Editor: Goldman, Lee

PART 24: HIV AND THE ACQUIRED IMMUNODEFICIENCY SYNDROME

392: Epidemiology of HIV Infection and AIDS
Thomas Quinn
Editor: Schafer, Andrew

393: Immunopathogenesis of HIV Infection
Robert Siliciano
Editor: Schafer, Andrew

394: Biology of Human Immunodeficiency Viruses
George Shaw
Editor: Schafer, Andrew

395: Prevention of HIV Infection
Carlos Del Rio
Editor: Schafer, Andrew

396: Treatment of HIV Infection and AIDS
Henry Masur
Editor: Schafer, Andrew

397: Gastrointestinal Manifestions of HIV and AIDS
Christine Wanke;Tamsin Knox
Editor: Schafer, Andrew

398: Pulmonary Manifestations of HIV and AIDS
Laurence Huang
Editor: Schafer, Andrew

399: Skin Manifestations in Patients with HIV Infection
Toby Maurer
Editor: Schafer, Andrew

400: Hematology/Oncology in Patients with HIV Infection
Paul A. Volberding
Editor: Schafer, Andrew

401: Neurologic Complications of HIV Infection
Avindra Nath
Editor: Schafer, Andrew

402: Immune reconstitution Inflammatory Syndrome in HIV/AIDS
Robert Colebunders;Martyn French
Editor: Schafer, Andrew

PART 25: NEUROLOGY

403: Approach to the Patient with Neurological Disease
Ralph Jozefowicz;Michael Aminoff
Editor: Goldman, Lee

404: Psychiatric Disorders in Medical Practice
Jeffrey M. Lyness
Editor: Goldman, Lee

405: Headaches and Other Head Pain
Kathleen Digre
Editor: Goldman, Lee

406: Head and Spinal Cord Injury
Geoffrey Ling
Editor: Goldman, Lee

407: Spine, Disc, Spinal Cord and Spinal Root Disease
Richard, L Barbano
Editor: Goldman, Lee

408: Regional Cerebral Dysfunction
David Knopman
Editor: Goldman, Lee

409: Alzheimer's Disease and Other Dementias
David Knopman
Editor: Goldman, Lee

410: The Epilepsies
Samuel Wiebe
Editor: Goldman, Lee

411: Coma, Persistent Vegetative State and Brain Death
James L. Bernat
Editor: Goldman, Lee

412: Disorders of Sleep
Mark W. Mahowald
Editor: Goldman, Lee

413: Approach to Cerebrovascular Diseases
Justin Zivin
Editor: Goldman, Lee

414: Ischemic Cerebrovascular Disease
Justin Zivin
Editor: Goldman, Lee

415: Hemorrhagic Cerebrovascular Disease
Justin Zivin
Editor: Goldman, Lee

416: Parkinsonism
Anthony E Lang
Editor: Goldman, Lee

417: Other Movement Disorders
Anthony Lang
Editor: Goldman, Lee

418: ALS and Other Motor Neuron Diseases
Pamela J Shaw
Editor: Goldman, Lee

419: Multiple Sclerosis and Demyelinating Conditions of the CNS
Peter Calabresi
Editor: Goldman, Lee

420: Meningitis: Bacterial, Viral, and Other
Avindra Nath
Editor: Goldman, Lee

421: Brain Abscess and Parameningeal Infections
Avindra Nath;Joseph, R Berger
Editor: Goldman, Lee

422: Acute Viral Encephalitis
Allen Aksamit Jr.
Editor: Goldman, Lee

423: Poliomyelitis
Allen Aksamit Jr.
Editor: Goldman, Lee

424: Prion Diseases
Patrick J. Bosque
Editor: Goldman, Lee

425: Nutritional and Alcohol-Related Neurologic Diseases
Barbara Koppel
Editor: Goldman, Lee

426: Congenital, Developmental and Neurocutaneous Disorders
Jonathan W. Mink

PART 26: EYE, EAR, NOSE, AND THROAT DISEASES

Editor: Goldman, Lee

PART 27: MEDICAL CONSULTATION

438: Principles of Preoperative Consultation and Co-Management
Gerald Smetana
Editor: Goldman, Lee

439: Preoperative Evaluation
Steven Cohn
Editor: Goldman, Lee

440: Overview of Anesthesia
Jeanine Wiener-Kronish;Lee Fleisher
Editor: Goldman, Lee

441: Postoperative Care and Complications
Don Redelmeier
Editor: Goldman, Lee

442: Medical Consultation in Psychiatry
Peter Manu
Editor: Goldman, Lee

PART 28: SKIN DISEASES

443: Structure and Function of Skin
David Norris
Editor: Goldman, Lee

444: Examination of the Skin and an Approach to Diagnosing Skin Diseases
Cheryl Armstrong
Editor: Goldman, Lee

445: Principles of Therapy
Victoria Werth
Editor: Goldman, Lee

446: Eczema, Photosensitivity, and papulosquamous (including fungal) Diseases and Figurate Erythemas
Henry Lim
Editor: Goldman, Lee

447: Macular, Vesiculobullous, and Pustular Diseases
Neil Korman

Editor: Goldman, Lee

448: Urticaria, Drug Hypersensitivity Rashes, Nodules and Tumors, and Atrophic Diseases
Madeleine Duvic
Editor: Goldman, Lee

449: Infections, Hyper-and Hypopigmentation, Regional Dermatology, and Distinctive Lesions in Black Skin
Jean Bolognia
Editor: Goldman, Lee

450: Diseases of Hair and Nails
Antonella Tosti
Editor: Goldman, Lee

APPENDIX: LABORATORY REFERENCE INTERVALS AND VALUES

Appendix: Reference Intervals and Laboratory Values
Ronald J. Elin
Editor: Goldman, Lee

1

APPROACH TO MEDICINE, THE PATIENT, AND THE MEDICAL PROFESSION: MEDICINE AS A LEARNED AND HUMANE PROFESSION

LEE GOLDMAN AND ANDREW I. SCHAFER

APPROACH TO MEDICINE

Medicine is a profession that incorporates science and the scientific method with the art of being a physician. The art of tending to the sick is as old as humanity itself. Even in modern times, the art of caring and comforting, guided by millennia of common sense as well as a more recent, systematic approach to medical ethics (Chapter 2), remains the cornerstone of medicine. Without these humanistic qualities, the application of the modern science of medicine is suboptimal, ineffective, or even detrimental.

The caregivers of ancient times and premodern cultures tried a variety of interventions to help the afflicted. Some of their potions contained what are now known to be active ingredients that form the basis for proven medications (Chapter 28). Others (Chapter 38) have persisted into the present era despite a lack of convincing evidence. Modern medicine should not dismiss the possibility that these unproven approaches may be helpful; instead, it should adopt a guiding principle that all interventions, whether traditional or newly developed, can be tested vigorously, with the expectation that any beneficial effects can be explored further to determine their scientific basis.

When compared with its long and generally distinguished history of caring and comforting, the scientific basis of medicine is remarkably recent. Other than an understanding of human anatomy and the later description, albeit widely contested at this time, of the normal physiology of the circulatory system, almost all of modern medicine is based on discoveries made within the past 150 years. Until the late 19th century, the paucity of medical knowledge was perhaps exemplified best by hospitals and hospital care. Although hospitals provided caring that all but well-to-do people might not be able to obtain elsewhere, there is little if any evidence that hospitals improved health outcomes. The term *hospitalism* referred not to expertise in hospital care but rather to the aggregate of iatrogenic afflictions that were induced by the hospital stay itself.

The essential humanistic qualities of caring and comforting can achieve full benefit only if they are coupled with an understanding of how medical science can and should be applied to patients with known or suspected diseases. Without this knowledge, comforting may be inappropriate or misleading, and caring may be ineffective or counterproductive if it inhibits a sick person from obtaining appropriate, scientific medical care. *Goldman's Cecil Textbook of Medicine* focuses on the discipline of *internal medicine,* from which neurology and dermatology, which are also covered in substantial detail in this text, are relatively recent evolutionary branches. The term *internal medicine,* which is often misunderstood by the lay public, was developed in 19th century Germany. *Inneren medizin* was to be distinguished from clinical medicine because it emphasized the physiology and chemistry of disease, not just the patterns or progression of clinical manifestations. *Goldman's Cecil Textbook of Medicine* follows this tradition by showing how pathophysiologic abnormalities cause symptoms and signs and by emphasizing how therapies can modify the underlying pathophysiology and improve the patient's well-being.

Modern medicine has moved rapidly past organ physiology to an increasingly detailed understanding of cellular, subcellular, and genetic mechanisms. For example, the understanding of microbial pathogenesis and many inflammatory diseases (Chapter 264) is now guided by a detailed understanding of the human immune system and its response to foreign antigens (Chapters 44 to 48).

Health, disease, and an individual's interaction with the environment are also substantially determined by genetics. In addition to many conditions that may be determined by a single gene (Chapter 40), medical science increasingly understands the complex interactions that underlie multigenic traits (Chapter 41). In the not-so-distant future, the decoding of the human genome holds the promise that personalized health care can be targeted according to an individual's genetic profile, in terms of screening and presymptomatic disease management, as well as in terms of specific medications and their adjusted dosing schedules. Currently, knowledge of the structure and physical forms of proteins helps explain abnormalities as diverse as sickle cell anemia (Chapter 166) and prion-related diseases (Chapter 424). Proteomics, which is the normal and abnormal protein expression of genes, also holds extraordinary promise for developing drug targets for more specific and effective therapies.

Concurrent with these advances in fundamental human biology has been a dramatic shift in methods for evaluating the application of scientific advances to the individual patient and to populations. The randomized controlled trial, sometimes with thousands of patients at multiple institutions, has replaced anecdote as the preferred method for measuring the benefits and optimal uses of diagnostic and therapeutic interventions (Chapter 9). As studies progress from those that show biologic effect, to those that elucidate dosing schedules and toxicity, and finally to those that assess true clinical benefit, the metrics of measuring outcome has also improved from subjective impressions of physicians or patients to reliable and valid measures of morbidity, quality of life, functional status, and other patient-oriented outcomes (Chapter 10). These marked improvements in the scientific methodology of clinical investigation have expedited extraordinary changes in clinical practice, such as recanalization therapy for acute myocardial infarction (Chapter 73), and have shown that reliance on intermediate outcomes, such as a reduction in asymptomatic ventricular arrhythmias with certain drugs, may unexpectedly increase rather than decrease mortality. Just as physicians in the 21st century must understand advances in fundamental biology, similar understanding of the fundamentals of clinical study design as it applies to diagnostic and therapeutic interventions is needed. An understanding of human genetics will also help stratify and refine the approach to clinical trials by helping researchers select fewer patients with a more homogeneous disease pattern to study the efficacy of an intervention.

This explosion in medical knowledge has led to increasing specialization and subspecialization, defined initially by organ system and more recently by locus of principal activity (inpatient vs. outpatient), reliance on manual skills (proceduralist vs. nonproceduralist), or participation in research. Nevertheless, it is becoming increasingly clear that the same fundamental molecular and genetic mechanisms are broadly applicable across all organ systems and that the scientific methodologies of randomized trials and careful clinical observation span all aspects of medicine.

The advent of modern approaches to managing data now provides the rationale for the use of health information technology. Computerized health records, oftentimes shared with patients in a portable format, can avoid duplication of tests and assure that care is coordinated among the patient's various health care providers.

APPROACH TO THE PATIENT

Patients commonly have complaints (symptoms). These symptoms may or may not be accompanied by abnormalities on examination (signs) or on laboratory testing. Conversely, asymptomatic patients may have signs or laboratory abnormalities, and laboratory abnormalities can occur in the absence of symptoms or signs.

Symptoms and signs commonly define *syndromes,* which may be the common final pathway of a wide range of pathophysiologic alterations. The fundamental basis of internal medicine is that diagnosis should elucidate the pathophysiologic explanation for symptoms and signs so that therapy may improve the underlying abnormality, not just attempt to suppress the abnormal symptoms or signs.

When patients seek care from physicians, they may have manifestations or exacerbations of known conditions, or they may have symptoms and signs that suggest malfunction of a particular organ system. Sometimes the pattern of symptoms and signs is highly suggestive or even pathognomonic for a particular disease process. In these situations, in which the physician is focusing on a particular disease, *Goldman's Cecil Textbook of Medicine* provides scholarly yet practical approaches to the epidemiology, pathobiology, clinical manifestations, diagnosis, treatment, prevention, and prognosis of entities such as acute myocardial infarction (Chapter 73), chronic obstructive lung disease (Chapter 88), obstructive uropathy (Chapter 125), inflammatory bowel disease (Chapter 143), gallstones (Chapter 158), rheumatoid arthritis (Chapter 272), hypothyroidism (Chapter 233), tuberculosis (Chapter 332), and virtually any known medical condition in adults.

Many patients, however, have undiagnosed symptoms, signs, or laboratory abnormalities that cannot be immediately ascribed to a particular disease or cause. Whether the initial manifestation is chest pain (Chapter 50), diarrhea (Chapter 142), neck or back pain (Chapter 407), or a variety of more than 100 common symptoms, signs, or laboratory abnormalities, *Goldman's Cecil Textbook of Medicine* provides tables, figures, and entire chapters to guide the approach to diagnosis and therapy (see E-Table 1-1 or table on inside back cover). By virtue of this dual approach to known disease as well as to undiagnosed abnormalities, this textbook, similar to the modern practice of medicine, applies directly to patients regardless of their mode of manifestation or degree of previous evaluation.

The patient-physician interaction proceeds through many phases of clinical reasoning and decision making. The interaction begins with an elucidation of complaints or concerns, followed by inquiries or evaluations to address these concerns in increasingly precise ways. The process commonly requires a careful history or physical examination, ordering of diagnostic tests, integration of clinical findings with test results, understanding of the risks and benefits of the possible courses of action, and careful consultation with the patient and family to develop future plans. Physicians can increasingly call on a growing literature of evidence-based medicine to guide the process so that benefit is maximized while respecting individual variations in different patients. Throughout *Goldman's Cecil Textbook of Medicine,* the best current evidence is highlighted with specific grade A references that can be accessed directly in the electronic version.

The increasing availability of evidence from randomized trials to guide the approach to diagnosis and therapy should not be equated with "cookbook" medicine. Evidence and the guidelines that are derived from it emphasize proven approaches for patients with specific characteristics. Substantial clinical judgment is required to determine whether the evidence and guidelines apply to individual patients and to recognize the occasional exceptions. Even more judgment is required in the many situations in which evidence is absent or inconclusive. Evidence must also be tempered by patients' preferences, although it is a physician's responsibility to emphasize evidence when presenting alternative options to the patient. The adherence of a patient to a specific regimen is likely to be enhanced if the patient also understands the rationale and evidence behind the recommended option.

To care for a patient as an individual, the physician must understand the patient as a person. This fundamental precept of doctoring includes an understanding of the patient's social situation, family issues, financial concerns, and preferences for different types of care and outcomes, ranging from maximum prolongation of life to the relief of pain and suffering (Chapters 2 and 3). If the physician does not appreciate and address these issues, the science of medicine cannot be applied appropriately, and even the most knowledgeable physician will fail to achieve the desired outcomes.

Even as physicians become increasingly aware of new discoveries, patients can obtain their own information from a variety of sources, some of which are of questionable reliability. The increasing use of alternative and complementary therapies (Chapter 38) is an example of patients' frequent dissatisfaction with prescribed medical therapy. Physicians should keep an open mind regarding unproven options but must advise their patients carefully if such options may carry any degree of potential risk, including the risk that they may be relied on to substitute for proven approaches. It is crucial for the physician to have an open dialogue with the patient and family regarding the full range of options that either may consider.

The physician does not exist in a vacuum, but rather as part of a complicated and extensive system of medical care and public health. In premodern times and even today in some developing countries, basic hygiene, clean water, and adequate nutrition have been the most important ways to promote health and reduce disease. In developed countries, adoption of healthy lifestyles, including better diet (Chapter 220) and appropriate exercise (Chapter 15), is the cornerstone to reducing the epidemics of obesity (Chapter 227), coronary disease (Chapter 70), and diabetes (Chapter 237). Public health interventions to provide immunizations (Chapter 17) and reduce injuries (Chapter 16) and the use of tobacco (Chapter 31), illicit drugs (Chapter 33), and excess alcohol (Chapter 32) can collectively produce more health benefits than nearly any other imaginable health intervention.

APPROACH TO THE MEDICAL PROFESSION

In a profession, practitioners put the welfare of clients or patients above their own welfare. Professionals have a duty that may be thought of as a contract with society. The American Board of Internal Medicine and the European Federation of Internal Medicine have jointly proposed that medical professionalism should emphasize three fundamental principles: the primacy of patient welfare, patient autonomy, and social justice. As modern medicine brings a plethora of diagnostic and therapeutic options, the interactions of the physician with the patient and society become more complex and potentially fraught with ethical dilemmas (Chapter 2). To help provide a moral compass that is not only grounded in tradition but also adaptable to modern times, the primacy of patient welfare emphasizes the fundamental principle of a profession. The physician's altruism, which begets the patient's trust, must be impervious to the economic, bureaucratic, and political challenges that are faced by the physician and the patient (Chapter 5).

TABLE 1-1 PROFESSIONAL RESPONSIBILITIES

Commitment to:
Professional competence
Honesty with patients
Patient confidentiality
Maintaining appropriate relations with patients
Improving the quality of care
Improving access to care
Just distribution of finite resources
Scientific knowledge
Maintaining trust by managing conflicts of nterest
Professional responsibilities

From Brennan T, Blank L, Cohen J, et al. Medical professionalism in the new millennium: a physician charter. *Ann Intern Med.* 2002;1136:243-246.

The principle of patient autonomy asserts that physicians make recommendations but patients make the final decisions. The physician is an expert advisor who must inform and empower the patient to base decisions on scientific data and how these data can and should be integrated with a patient's preferences.

The importance of social justice symbolizes that the patient-physician interaction does not exist in a vacuum. The physician has a responsibility to the individual patient and to broader society to promote access and to eliminate disparities in health and health care.

To promote these fundamental principles, a series of professional responsibilities has been suggested (Table 1-1). These specific responsibilities represent practical, daily traits that benefit the physician's own patients and society as a whole. Physicians who use these and other attributes to improve their patients' satisfaction with care are not only promoting professionalism but also reducing their own risk for liability and malpractice.

An interesting new aspect of professionalism is the increasing reliance on team approaches to medical care, as exemplified by physicians whose roles are defined by the location of their practice—historically in the intensive care unit or emergency department and more recently on the inpatient general hospital floor. Quality care requires coordination and effective communication across inpatient and outpatient sites among physicians who themselves now typically work defined hours. This transition from reliance on a single, always available physician to a team, ideally with a designated coordinator, places new challenges on physicians, the medical care system, and the medical profession.

The changing medical care environment is placing increasing emphasis on standards, outcomes, and accountability. As purchasers of insurance become more cognizant of value rather than just cost (Chapter 11), outcomes ranging from rates of screening mammography (Chapter 204) to mortality rates with coronary artery bypass graft surgery (Chapter 74) become metrics by which rational choices can be made. Clinical guidelines and critical pathways derived from randomized controlled trials and evidence-based medicine can potentially lead to more cost-effective care and better outcomes.

These major changes in many Western health care systems bring with them many major risks and concerns. If the concept of limited choice among physicians and health care providers is based on objective measures of quality and outcome, channeling of patients to better providers is one reasonable definition of better selection and enlightened competition. If the limiting of options is based overwhelmingly on cost rather than measures of quality, outcomes, and patient satisfaction, it is likely that the historic relationship between the patient and the truly professional physician will be fundamentally compromised.

Another risk is that the same genetic information that could lead to more effective, personalized medicine will be used against the very people whom it is supposed to benefit—by creating a stigma, raising health insurance costs,

or even making someone uninsurable. The ethical approach to medicine (Chapter 2), genetics, and genetic counseling (Chapter 39) provides means to protect against this adverse effect of scientific progress.

In this new environment, the physician often has a dual responsibility: to the health care system as an expert who helps create standards, measures of outcome, clinical guidelines, and mechanisms to ensure high-quality, cost-effective care and to individual patients who entrust their well-being to that physician to promote their best interests within the reasonable limits of the system. A health insurance system that emphasizes cost-effective care, that gives physicians and health care providers responsibility for the health of a population and the resources required to achieve these goals, that must exist in a competitive environment in which patients can choose alternatives if they are not satisfied with their care, and that places increasing emphasis on health education and prevention can have many positive effects. In this environment, however, physicians must beware of overt and subtle pressures that could entice them to underserve patients and abrogate their professional responsibilities by putting personal financial reward ahead of their patients' welfare. The physician's responsibility to represent the patient's best interests and avoid financial conflicts by doing too little in the newer systems of capitated care provides different specific challenges but an analogous moral dilemma to the historical American system in which the physician could be rewarded financially for doing too much.

In the current health care environment, all physicians and trainees must redouble their commitment to professionalism. At the same time, the challenge to the individual physician to retain and expand the scientific knowledge base and process the vast array of new information is daunting. In this spirit of a profession based on science and caring, *Goldman's Cecil Textbook of Medicine* seeks to be a comprehensive approach to modern internal medicine.

SUGGESTED READINGS

Ioannidis JP. Expectations, validity, and reality in omics. *J Clin Epidemiol*. 2010;63:945-949. *Perspectives on how modern biologic measurements and assays may individual ze health care if appropriately validated*.

Qaseem A, Snow V, Gosfield A, et al: Pay for performance through the lens of medical professionalism. *Ann Intern Med*. 2010;152:366-369. *Explores how these two ideas can coexist successfully*.

Rogers W, Ballantyne A. Towards a practical definition of professional behavior. *J Med Ethics*. 2010;36:250-254. *Emphas zes the importance of responsibility; relationships with and respect for patients; probity and honesty; self awareness, and capacity for reflection*.

Access the complete reference list online at http://www.expertconsult.com

E-TABLE 1-1 GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, AND LABORATORY ABNORMALITIES

	CHAPTER	SPECIFIC TABLES OR FIGURES
SYMPTOMS		
Constitutional		
Fever	302	Tables 302-1 to 302-8
Fatigue	293	Table 293-3
Poor appetite	134	Table 134-1
Weight loss	134, 233, 238	Figure 134-3; Table 134-4
Obesity	233	Figure 233-2
Snoring, sleep disturbances	101, 429	Table 429-3
Head, Eyes, Ears, Nose, Throat		
Headache	421	Table 421-1
Visual loss, transient	449	Tables 449-2, 450-1
Ear pain	452	Table 452-1
Hearing loss	454	Figure 454-1
Ringing in ears (tinnitus)	454	Figure 454-2
Vertigo	454	Figure 454-3
Nasal congestion	452	Figure 452-1
Rhinitis or sneezing	272	Figure 272-2
Loss of smell or taste	453	Table 453-1
Dry mouth	451	Table 451-7
Sore throat	455	Figure 455-2; Table 455-1
Hoarseness	455	
Cardiopulmonary		
Chest pain	48	Table 48-2
Bronchitis	96	
Shortness of breath	48, 83	Figures 48-1, 83-1
Palpitations	48, 61	Figure 61-1; Tables 48-3, 61-1
Dizziness	48, 61, 427	Figure 61-1; Table 427-1
Syncope	61, 427	Figures 61-1, 427-1 Tables 61-1, 427-1, 427-2
Cardiac arrest	62	Figures 62-2, 62-3
Cough	83	Figure 83-1; Tables 83-1, 83-2
Hemoptysis	83	Tables 83-5, 83-6
Gastrointestinal		
Nausea and vomiting	134	Table 134-3
Dysphagia, odynophagia	134, 140	Table 134-1
Hematemesis	137, 157	Figure 137-3; Table 137-1
Heartburn/dyspepsia	139, 140	Figures 139-2, 140-3
Abdominal pain:		
Acute	134, 145	Figure 134-1; Table 134-2
Chronic	134, 139	Figure 134-2; Table 134-2
Diarrhea	139, 143	Figures 139-1, 143-2, 143-3, 143-8 to 143-10
Melena	137	Figure 137-4; Table 137-4
Constipation	138, 139	Figures 138-4, 139-1; Table 138-2
Fecal incontinence	148	Figure 148-4
Anal pain	148	Table 148-2
Genitourinary		
Dysuria	306, 307	
Frequency	130, 306	
Incontinence	24	Figure 24-1; Table 24-3
Urinary obstruction	124	Tables 124-1 to 124-3
Renal colic	127	Figure 127-3
Vaginal discharge	307	
Menstrual irregularities	256	Figure 256-9; Tables 256-3 to 256-5
Female infertility	256	Table 256-6
Hot flushes	262	Table 262-1
Erectile dysfunction	253	
Male infertility	253	Figures 253-11, 253-12

E-TABLE 1-1 GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, AND LABORATORY ABNORMALITIES

	CHAPTER	SPECIFIC TABLES OR FIGURES
Musculoskeletal		
Neck or back pain	423	Figure 423-3; Tables 423-1 to 423-4
Pa nful joints	277	Table 277-2
Extremities		
Swollen feet, ankles, or legs		
Bilateral	48	Figure 48-8
Unilateral	81	Figure 81-2; Table 81-2
Claudication	79	Figure 79-2
Neurologic		
Weakness	418, 446, 447, 448	Tables 418-1, 446-2
Sensory loss	418, 446	Tables 446-1, 446-4 to 446-7
Memory loss	425	Figures 425-1, 425-2; Tables 425-1 to 425-6
Abnormal gait	418	Table 418-2
Seizures	426	Tables 426-1 to 426-4
Integumentary		
Abnormal bleeding	178	Table 178-1
Rash	462	Figure 462-1; Tables 462-1 to 462-4
Hives	273, 466	Figure 273-2; Tables 273-1, 466-1
Abnormal pigmentation	467	Table 467-2
Hirsutism and alopecia	261, 467	Tables 261-1, 467-5
SIGNS		
Vital Signs		
Fever	302, 303	Tables 302-1 to 302-8
Hypothermia	7, 110	Table 110-4
Tachycardia/bradycardia	7, 52, 61, 65	Figures 61-2, 61-3
Hypertension	66	Table 66-4
Hypotension/shock	7, 107	Figure 107-1
Altered respiration	7, 86, 105	Tables 86-1, 105-2
Head, Eyes, Ears, Nose, Throat		
Red eye	449	Table 449-4
Dilated pupil	450	Figure 450-4
Nystagmus	450	Table 450-5
Papilledema	450	Table 450-2
Strabismus	450	Figure 450-6
Jaundice	150	Figure 150-3; Tables 150-1 to 150-3
Otitis	452	Figure 452-1
Sinusitis	272, 452	Figure 452-1
Oral ulcer	451	Tables 451-1, 451-3, 451-4
Salivary gland enlargement	451	Table 451-6
Neck		
Neck mass	200	Figure 200-3
Lymphadenopathy	174	Tables 174-1, 174-2, 174-5
Thyroid nodule	244	Figure 244-4
Thyromegaly/goiter	244	Figures 244-1, 244-3
Breast		
Breast mass	208	
Lungs		
Wheezes	83	Table 83-3
Cardiac		
Heart murmur or extra sounds	48	Figure 48-4; Tables 48-6, 48-7
Jugular venous distention	48	Table 48-5
Carotid pulse abnormalities	48	Figure 48-5
Abdomen		
Hepatomegaly	149	Figure 149-4
Splenomegaly	174	Tables 174-6, 174-8
Acute abdomen	145	Tables 145-1 to 145-3

E-TABLE 1-1 GUIDE TO THE APPROACH TO COMMON SYMPTOMS, SIGNS, AND LABORATORY ABNORMALITIES

	CHAPTER	SPECIFIC TABLES OR FIGURES
Abdom nal swelling/ascites	146, 157	Table 157-3
Rectal bleeding/positive stool	137, 203	Figures 137-4, 137-5; Table 137-5
Hemorrhoids	148	Table 148-1
Genitourinary		
Scrotal mass	210	Figure 210-1
Vaginal discharge	307	
Genital ulcers or warts	307	
Musculoskeletal/Extremities		
Arthritis	277	
Edema	48	Figure 48-8
Cyanosis	48	
Clubbing	48	
Neurologic		
Delirium	26	Figure 26-1; Tables 26-1, 26-2
Psychiatric disturbances	420	Tables 420-1, 420-3 to 420-5, 420-7 to 420-9
Coma	428	Table 428-1
Stroke	431	Figure 431-4
Movement disorders	434	Tables 434-1 to 434-7
Neuropathy	446	Figure 446-1
Skin and Nails		
Suspicious mole	214	Table 214-1
Nail diseases	467	Table 467-4
COMMON LABORATORY ABNORMALITIES		
Hematology/Urinalysis		
Anemia	162	Figure 162-2; Tables 162-4 to 162-6
Polycythemia	172	Figure 172-3; Table 172-2
Leukocytosis	173	Figure 173-7; Table 173-4
Lymphocytosis	173	Table 173-7
Monocytosis	173	Table 173-6
Eosinophilia	176	Figure 176-2; Table 176-1
Neutropenia	173	Figures 173-2, 173-5; Table 173-1
With fever	303	Figures 303-1, 303-2
Thrombocytosis	177	Figure 177-1; Table 177-2
Thrombocytopenia	179	Table 179-1
Prolonged PT or PTT	178	Figures 178-3, 178-4
Urinalysis	115	Table 115-1
Chemistries		
Abnormal liver enzymes	150	Figures 150-3 to 150-5
Elevated BUN/creatinine		
Acute	121	Figure 121-1; Tables 121-1 to 121-5
Chronic	131	Table 131-1
Hyperglycemia	247, 248	Table 248-2
Hypoglycemia	249	Table 249-1
Electrolyte abnormalities	117, 118	Tables 117-3, 117-4, 117-6, 118-2, 118-3
Acid-base disturbances	119	Tables 119-1 to 119-5
Hypercalcemia	266	Table 266-1
Hypocalcemia	266	Table 266-4
Hypo- and hyperphosphatemia	120	Tables 120-2, 120-3
Elevated Pco_2	86	Figure 86-3
Chest Radiograph/ECG		
Solitary pulmonary nodule	201	Figure 201-5
Pleural effusion	100	Table 100-5
Suspected lung cancer	201	Figure 201-4
ECG abnormalities	52	Tables 52-2 to 52-5

BUN = blood urea nitrogen; ECG = electrocardiogram; PT = prothrombin time; PTT = partial thromboplastin time.

ADDITIONAL SUGGESTED READINGS

Bowen JL. Educational strategies to promote clinical diagnostic reasoning. *N Engl J Med*. 2006;355:2217-2225. *An educational review*.

Hafferty FW. Professionalism—the next wave. *N Engl J Med*. 2006;355:2151-2152. *Redefining professionalism in medical education*.

Snyderman R, Yoediono Z. Prospective care: a personalized, preventative approach to medicine. *Pharmacogenomics*. 2006;7:5-9. *How genetic information may allow targeting of preventive and therapeutic interventions*.

Stelfox HT, Gandhi TK, Orav EJ, et al. The relation of patient satisfaction with complaints against physicians and malpractice lawsuits. *Am J Med*. 2005;118:1126-1133. *More satisfied patients are less likely to sue*.

Stern DT, Papadakis M. The developing physician—becoming a professional. *N Engl J Med*. 2006; 355:1794-1799. *Standards of professional behavior in new physicians*.

50

APPROACH TO THE PATIENT WITH POSSIBLE CARDIOVASCULAR DISEASE

LEE GOLDMAN

Patients with cardiovascular disease may present with a wide range of symptoms and signs, each of which may be caused by noncardiovascular conditions. Conversely, patients with substantial cardiovascular disease may be asymptomatic. Because cardiovascular disease is a leading cause of death in the United States and other developed countries, it is crucial that patients be evaluated carefully to detect early cardiovascular disease, that symptoms or signs of cardiovascular disease be evaluated in detail, and that appropriate therapy be instituted. Improvements in diagnosis, therapy, and prevention has contributed to a 70% or so decline in age-adjusted cardiovascular death rates in the United States since the 1960s. However, the absolute number of deaths from cardiovascular disease in the United States has not declined proportionately because of the increase in the population older than 40 years as well as the aging of the population in general.

In evaluating a patient with known or suspected heart disease, the physician must determine quickly whether a potentially life-threatening condition exists. In these situations, the evaluation must focus on the specific issue at hand and be accompanied by the rapid performance of appropriately directed additional tests. Examples of potentially life-threatening conditions include acute myocardial infarction (Chapter 73), unstable angina (Chapter 72), suspected aortic dissection (Chapter 78), pulmonary edema (Chapter 59), and pulmonary embolism (Chapter 98).

USING THE HISTORY TO DETECT CARDIOVASCULAR SYMPTOMS

Patients may complain spontaneously of a variety of cardiovascular symptoms (Table 50-1), but sometimes these symptoms are elicited only by obtaining a careful, complete medical history. In patients with known or suspected cardiovascular disease, questions about cardiovascular symptoms are key components of the history of present illness; in other patients, these issues are a fundamental part of the review of systems.

Chest Pain

Chest discomfort or pain is the cardinal manifestation of myocardial ischemia resulting from coronary artery disease or any condition that causes myocardial ischemia by an imbalance of myocardial oxygen demand compared with myocardial oxygen supply (Chapter 71). New, acute, often ongoing pain may indicate an acute myocardial infarction, unstable angina, or aortic dissection; a pulmonary cause, such as acute pulmonary embolism or pleural irritation; a musculoskeletal condition of the chest wall, thorax, or shoulder; or a gastrointestinal abnormality, such as esophageal reflux or spasm, peptic ulcer disease, or cholecystitis (Table 50-2). The chest discomfort of myocardial infarction commonly occurs without an immediate or obvious precipitating clinical cause and builds in intensity for at least several minutes; the sensation can range from annoying discomfort to severe pain (Chapter 73). Although a variety of adjectives may be used by patients to describe the sensation, physicians must be suspicious of any discomfort, especially if it radiates to the neck, shoulder, or arms. The probability of an acute myocardial infarction can be estimated by integrating information from the history, physical examination, and electrocardiogram (Fig. 50-1).

The chest discomfort of unstable angina is clinically indistinguishable from that of myocardial infarction except that the former may be precipitated more clearly by activity and may be more rapidly responsive to antianginal therapy (Chapter 72). Aortic dissection (Chapter 78) classically presents with the sudden onset of severe pain in the chest and radiating to the back; the location of the pain often provides clues to the location of the dissection. Ascending aortic dissections commonly present with chest discomfort radiating to the back, whereas dissections of the descending aorta commonly present with back pain radiating to the abdomen. The presence of back pain or a history of hypertension or other predisposing factors, such as Marfan syndrome, should prompt a careful assessment of peripheral pulses to determine whether the great vessels are affected by the dissection and of the chest radiograph to evaluate the size of the aorta. If this initial evaluation is suggestive, further testing with transesophageal echocardiography, computed tomography (CT), or magnetic resonance imaging (MRI) is indicated. The pain of pericarditis (Chapter 77) may simulate that of an acute myocardial infarction, may be primarily pleuritic, or may be continuous; a key physical finding is a pericardial rub. The pain of pulmonary embolism (Chapter 98) is commonly pleuritic in nature and is associated with dyspnea; hemoptysis also may be present. Pulmonary hypertension (Chapter 68) of any cause may be associated with chest discomfort with exertion; it commonly is associated with severe dyspnea and often is associated with cyanosis.

Recurrent, episodic chest discomfort may be noted with angina pectoris and with many cardiac and noncardiac causes (Chapter 71). A variety of stress tests (Table 50-3) can be used to provoke reversible myocardial ischemia in susceptible individuals and to help determine whether ischemia is the pathophysiologic explanation for the chest discomfort (Chapter 71).

Dyspnea

Dyspnea, which is an uncomfortable awareness of breathing, is commonly due to cardiovascular or pulmonary disease. A systematic approach (see Fig. 83-3 in Chapter 83) with selected tests nearly always reveals the cause. Acute dyspnea can be caused by myocardial ischemia, heart failure, severe hypertension, pericardial tamponade, pulmonary embolism, pneumothorax, upper airway obstruction, acute bronchitis or pneumonia, or some drug overdoses (e.g., salicylates). Subacute or chronic dyspnea is also a common presenting or accompanying symptom in patients with pulmonary disease (Chapter 83). Dyspnea also can be caused by severe anemia (Chapter 161) and can be confused with the fatigue that often is noted in patients with systemic and neurologic diseases (Chapters 264 and 403).

In heart failure, dyspnea typically is noted as a hunger for air and a need or an urge to breathe. The feeling that breathing requires increased work or effort is more typical of airway obstruction or neuromuscular disease. A feeling of chest tightness or constriction during breathing is typical of bronchoconstriction, which is commonly caused by obstructive airway disease (Chapters 87 and 88) but also may be seen in pulmonary edema. A feeling of heavy breathing, a feeling of rapid breathing, or a need to breathe more is classically associated with deconditioning.

In cardiovascular conditions, chronic dyspnea usually is caused by increases in pulmonary venous pressure as a result of left ventricular failure (Chapters 58 and 59) or valvular heart disease (Chapter 75). Orthopnea, which is an exacerbation of dyspnea when the patient is recumbent, is due to increased work of breathing because of either increased venous return to the pulmonary vasculature or loss of gravitational assistance in diaphragmatic effort. Paroxysmal nocturnal dyspnea is severe dyspnea that awakens a patient at night and forces the assumption of a sitting or standing position to achieve gravitational redistribution of fluid.

Palpitations

Palpitations (Chapter 62) describe a subjective sensation of an irregular or abnormal heartbeat. Palpitations may be caused by any arrhythmia (Chapters 64 and 65) with or without important underlying structural heart disease. Palpitations should be defined in terms of the duration and frequency of the episodes; the precipitating and related factors; and any associated symptoms of chest pain, dyspnea, lightheadedness, or syncope. It is crucial to use the history to determine whether the palpitations are caused by an irregular or a regular heartbeat. The feeling associated with a premature atrial or ventricular contraction, often described as a "skipped beat" or a "flip-flopping of the heart," must be distinguished from the irregularly irregular rhythm of atrial fibrillation and the rapid but regular rhythm of supraventricular tachycardia. Associated symptoms of chest pain, dyspnea, lightheadedness, dizziness, or diaphoresis suggest an important effect on cardiac output and mandate further evaluation. In general, evaluation begins with ambulatory electrocardiography (ECG) (Table 50-4), which is indicated in patients who have palpitations in the presence of structural heart disease or substantial accompanying symptoms. Depending on the series, 9 to 43% of patients have important underlying heart disease. In such patients, more detailed evaluation is warranted (See Fig. 62-1).

Lightheadedness or *syncope* (Chapter 62) can be caused by any condition that decreases cardiac output (e.g., bradyarrhythmia, tachyarrhythmia, obstruction of the left ventricular or right ventricular inflow or outflow, cardiac tamponade, aortic dissection, or severe pump failure), by

TABLE 50-1 CARDINAL SYMPTOMS OF CARDIOVASCULAR DISEASE

Chest pain or discomfort
Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, wheezing
Palpitations, dizziness, syncope
Cough, hemoptysis
Fatigue, weakness
Pain n extremities with exertion (claudication)

reflex-mediated vasomotor instability (e.g., vasovagal, situational, or carotid sinus syncope), or by orthostatic hypotension (see Table 62-1 in Chapter 62). Neurologic diseases (e.g., migraine headaches, transient ischemic attacks, or seizures) also can cause transient loss of consciousness. The history, physical examination, and ECG are often diagnostic of the cause of syncope (see Table 62-2 in Chapter 62). Syncope caused by a cardiac arrhythmia usually occurs with little warning. Syncope with exertion or just after conclusion of exertion is typical of aortic stenosis and hypertrophic obstructive cardiomyopathy. In many patients, additional testing is required to document central nervous system disease, the cause of reduced cardiac output, or carotid sinus

TABLE 50-2 CAUSES OF CHEST PAIN

CONDITION	LOCATION	QUALITY	DURATION	AGGRAVATING OR RELIEVING FACTORS	ASSOCIATED SYMPTOMS OR SIGNS
CARDIOVASCULAR CAUSES					
Angina	Retrosternal region; radiates to or occasionally isolated to neck, jaw, epigastrium, shoulder, or arms (left common)	Pressure, burning, squeezing, heaviness, indigestion	<2-10 min	Precipitated by exercise, cold weather, or emotional stress; relieved by rest or nitroglycerin; atypical (Prinzmetal's) angina may be unrelated to activity, often early morning	S_3 or murmur of papillary muscle dysfunction during pain
Rest or unstable angina	Same as angina	Same as angina but may be more severe	Usually <20 min	Same as angina, with decreasing tolerance for exertion or at rest	Similar to stable angina but may be pronounced; transient heart failure can occur
Myocardial infarction	Substernal and may radiate like angina	Heaviness, pressure, burning, constriction	≥30 min but variable	Unrelieved by rest or nitroglycerin	Shortness of breath, sweating, weakness, nausea, vomiting
Pericarditis	Usually begins over sternum or toward cardiac apex and may radiate to neck or left shoulder; often more localized than the pain of myocardial ischemia	Sharp, stabbing, knifelike	Lasts many hours to days; may wax and wane	Aggravated by deep breathing, rotating chest, or supine position; relieved by sitting up and leaning forward	Pericardial friction rub
Aortic dissection	Anterior chest; may radiate to back	Excruciating, tearing, knifelike	Sudden onset, unrelenting	Usually occurs in setting of hypertension or predisposition, such as Marfan syndrome	Murmur of aortic insufficiency, pulse or blood pressure asymmetry; neurologic deficit
Pulmonary embolism (chest pain often not present)	Substernal or over region of pulmonary infarction	Pleuritic (with pulmonary infarction) or angina-like	Sudden onset; minutes to <1 hr	May be aggravated by breathing	Dyspnea, tachypnea, tachycardia; hypotension, signs of acute right ventricular failure, and pulmonary hypertension with large emboli; rales, pleural rub, hemoptysis with pulmonary infarction
Pulmonary hypertension	Substernal	Pressure; oppressive	Similar to angina	Aggravated by effort	Pain usually associated with dyspnea; signs of pulmonary hypertension
NONCARDIAC CAUSES					
Pneumonia with pleurisy	Localized over involved area	Pleuritic, localized	Brief or prolonged	Painful breathing	Dyspnea, cough, fever, dull to percussion, bronchial breath sounds, rales, occasional pleural rub
Spontaneous pneumothorax	Unilateral	Sharp, well localized	Sudden onset, lasts many hours	Painful breathing	Dyspnea; hyperresonance and decreased breath and voice sounds over involved lung
Musculoskeletal disorders	Variable	Aching	Short or long duration	Aggravated by movement; history of muscle exertion or injury	Tender to pressure or movement
Herpes zoster	Dermatomal in distribution	Burning, itching	Prolonged	None	Vesicular rash appears in area of discomfort
Esophageal reflux	Substernal, epigastric	Burning, visceral discomfort	10-60 min	Aggravated by large meal, postprandial recumbency; relief with antacid	Water brash
Peptic ulcer	Epigastric, substernal	Visceral burning, aching	Prolonged	Relief with food, antacid	
Gallbladder disease	Epigastric, right upper quadrant	Visceral	Prolonged	May be unprovoked or follow meals	Right upper quadrant tenderness may be present
Anxiety states	Often localized over precordium	Variable; location often moves from place to place	Varies; often fleeting	Situational	Sighing respirations, often chest wall tenderness

Modified from Andreoli TE, Carpenter CCJ, Griggs RC, et al. Evaluation of the patient with cardiovascular disease. In: *Cecil Essentials of Medicine*. 6th ed. Philadelphia: WB Saunders; 2004:34-35.

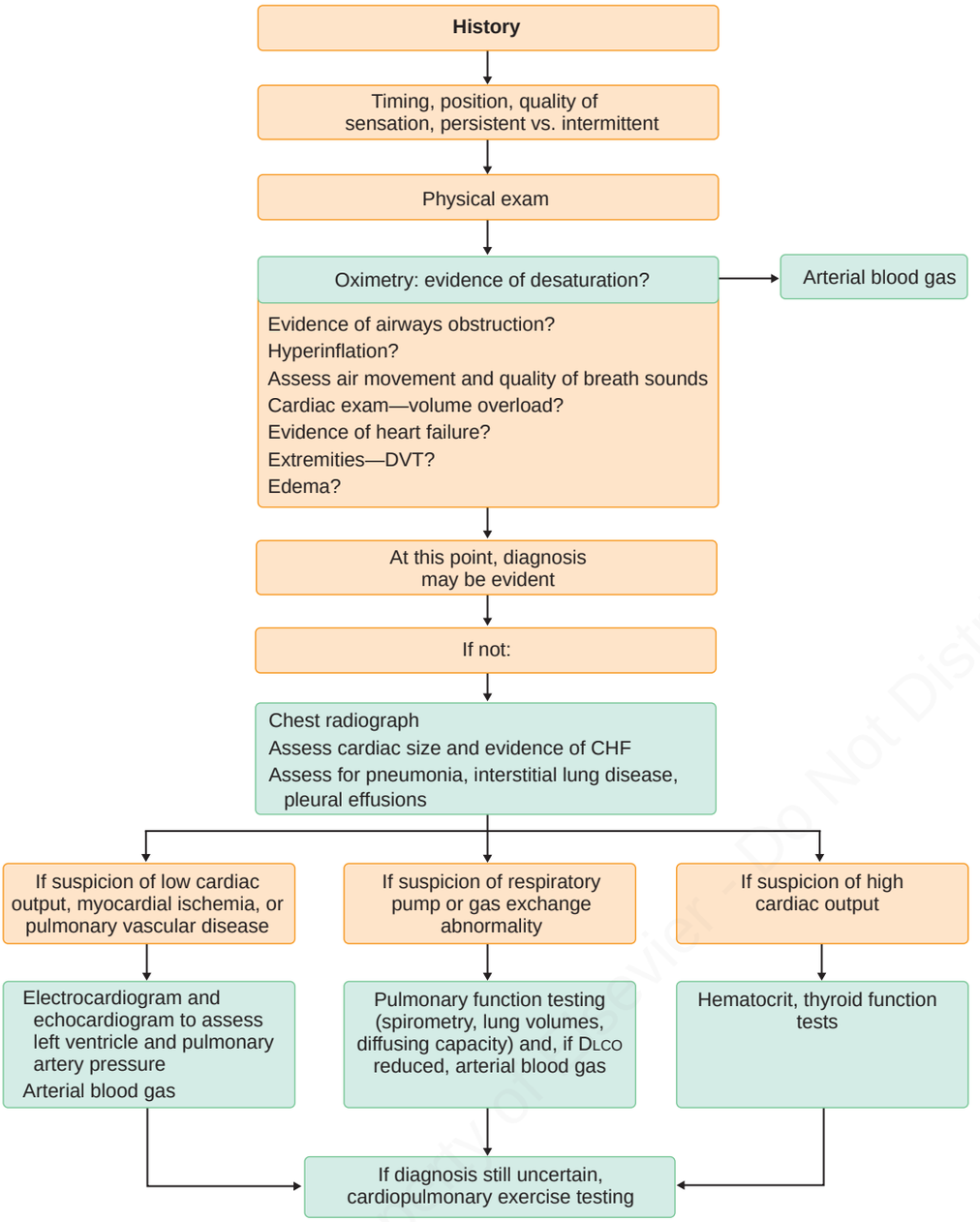

FIGURE 50-1. Flow diagram to estimate the risk for acute myocardial infarction in emergency departments in patients with acute chest pain. For each clinical subset, the numerator is the number of patients with the set of presenting characteristics who had a myocardial infarction; the denominator is the total number of patients presenting with that characteristic or set of characteristics. CHF = congestive heart failure; DVT = deep vein thrombosis. ***(Modified from Pearson SD, Goldman L, Garcia TB, et al. Physician response to a prediction rule for the triage of emergency department patients with chest pain.*** **J Gen Intern Med.** ***1994;9:241-247.)***

TABLE 50-3 COMMON EXERCISE TEST PROTOCOLS*

PROTOCOL	STAGE	DURATION (min)	GRADE (%)	RATE (mph)	METABOLIC EQUIVALENTS AT COMPLETION	FUNCTIONAL CLASS
Modified Bruce protocol†	1	3	0	1.7	2.5	III
	2	3	10	1.7	5	II
	3	3	12	2.5	7	I
	4	3	14	3.4	10	I
	5	3	16	4.2	13	I
Naughton protocol‡	0	2	0	2	2	III
	1	2	3.5	2	3	III
	2	2	7	2	4	III
	3	2	10.5	2	5	II
	4	2	14	2	6	II
	5	2	17.5	2	7	I

*Ramp protocols in which the workload is gradually increased on the basis of the patient's estimated functional capacity to achieve maximal effort in approximately 10 minutes are also useful.
†Commonly used in ambulatory patients.
‡Commonly used in patients with recent myocardial infarction, unstable angina, or other conditions that are expected to limit exercise.
Modified from Braunwald E, Goldman L, eds. *Primary Cardiology*. 2nd ed. Philadelphia: WB Saunders; 2003.

TABLE 50-4 AMERICAN HEART ASSOCIATION/AMERICAN COLLEGE OF CARDIOLOGY GUIDELINES FOR USE OF DIAGNOSTIC TESTS IN PATIENTS WITH PALPITATIONS*

AMBULATORY ELECTROCARDIOGRAPHY	
Class I	Palpitations, syncope, dizziness
Class II	Shortness of breath, chest pain, or fatigue (not otherwise explained, episodic, and strongly suggestive of an arrhythmia as the cause because of a relation of the symptom with palpitation)
Class III	Symptoms not reasonably expected to be due to arrhythmia
ELECTROPHYSIOLOGIC STUDY	
Class I	1. Patients with palpitations who have a pulse rate documented by medical personnel as inappropriately rapid and in whom electrocardiographic recordings fail to document the cause of the palpitations 2. Patients with palpitations preceding a syncopal episode
Class II	Patients with clinically significant palpitations, suspected to be of cardiac origin, in whom symptoms are sporadic and cannot be documented; studies are performed to determine the mechanisms of arrhythmias, to direct or provide therapy, or to assess prognosis
Class III	Patients with palpitations documented to be due to extracardiac causes (e.g., hyperthyroidism)
ECHOCARDIOGRAPHY	
Class I	Arrhythmias with evidence of heart disease Family history of genetic disorder associated with arrhythmias
Class II	Arrhythmias commonly associated with, but without evidence of, heart disease Atrial fibrillation or flutter
Class III	Palpitations without evidence of arrhythmias Minor arrhythmias without evidence of heart disease

*Class I, general agreement the test is useful and indicated; class II, frequently used, but there is a divergence of opinion with respect to its utility; class III, general agreement the test is not useful.
From Braunwald E, Goldman L, eds. *Primary Cardiology*. 2nd ed. Philadelphia: WB Saunders; 2003:132.

TABLE 50-5 A COMPARISON OF THREE METHODS OF ASSESSING CARDIOVASCULAR DISABILITY

CLASS	NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION	CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION	SPECIFIC ACTIVITY SCALE
I	Patients with cardiac disease but without resulting limitations of physical activity Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation	Patients can perform to completion any activity requiring ≥7 metabolic equivalents, e.g., can carry 24 lb up 8 steps; carry objects that weigh 80 lb; do outdoor work (shovel snow, spade soil); do recreational activities (skiing, basketball, squash, handball, jog or walk 5 mph)
II	Patients with cardiac disease resulting in slight limitation of physical activity They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.	Slight limitation of ordinary activity Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening Walking >2 blocks on the level and climbing >1 flight of ordinary stairs at a normal pace and in normal conditions	Patient can perform to completion any activity requiring ≥5 metabolic equivalents but cannot and does not perform to completion activities requiring ≥7 metabolic equivalents, e.g., have sexual intercourse without stopping, garden, rake, weed, roller skate, dance fox trot, walk at 4 mph on level ground
III	Patients with cardiac disease resulting in marked limitation of physical activity They are comfortable at rest. Less than ord nary physical activity causes fatigue, palpitations, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity Walking 1 or 2 blocks on the level and climbing >1 flight in normal conditions	Patient can perform to completion any activity requiring ≥2 metabolic equivalents but cannot and does not perform to completion any activities requiring ≥5 metabolic equivalents, e.g., shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, dress without stopping
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort—anginal syndrome may be present at rest	Patient cannot or does not perform to completion activities requiring ≥2 metabolic equivalents; cannot carry out activities listed above (Specific Activity Scale, class III)

From Goldman L, Hashimoto B, Cook EF, et al. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation.* 1981;64:1227-1234. Reproduced by permission of the American Heart Association.

syncope. When the history, physical examination, and ECG do not provide helpful diagnostic information that points toward a specific cause of syncope, it is imperative that patients with heart disease or an abnormal ECG be tested with continuous ambulatory ECG monitoring to diagnose a possible arrhythmia (see Fig. 62-1 in Chapter 62); in selected patients, formal electrophysiologic testing may be indicated (Chapter 62). In patients with no evident heart disease, tilt testing (Chapter 62) can help detect reflex-mediated vasomotor instability.

Other Symptoms

Nonproductive *cough* (Chapter 83), especially a persistent cough (see Fig. 83-1 in Chapter 83), can be an early manifestation of elevated pulmonary venous pressure and otherwise unsuspected heart failure. *Fatigue* and *weakness* are common accompaniments of advanced cardiac disease and reflect an inability to perform normal activities. A variety of approaches have been used to classify the severity of cardiac limitations, ranging from class I (little or no limitation) to class IV (severe limitation) (Table 50-5). *Hemoptysis*

(Chapter 83) is a classic presenting finding in patients with pulmonary embolism, but it is also common in patients with mitral stenosis, pulmonary edema, pulmonary infections, and malignant neoplasms (see Table 83-5 in Chapter 83). *Claudication,* which is pain in the extremities with exertion, should alert the physician to possible peripheral arterial disease (Chapters 79 and 80).

Complete Medical History

The complete medical history should include a thorough review of systems, family history, social history, and past medical history (Chapter 14). The review of systems may reveal other symptoms that suggest a systemic disease as the cause of any cardiovascular problems. The family history should focus on premature atherosclerosis or evidence of familial abnormalities, such as may be found with various causes of the long QT syndrome (Chapter 65) or hypertrophic cardiomyopathy (Chapter 60).

The social history should include specific questioning about cigarette smoking, alcohol intake, and use of illicit drugs. The past medical history may reveal prior conditions or medications that suggest systemic diseases, ranging from chronic obstructive pulmonary disease, which may explain a complaint of dyspnea, to hemochromatosis, which may be a cause of restrictive cardiomyopathy. A careful history to inquire about recent dental work or other procedures is crucial if bacterial endocarditis is part of the differential diagnosis.

PHYSICAL EXAMINATION FOR DETECTION OF SIGNS OF CARDIOVASCULAR DISEASE

The cardiovascular physical examination, which is a subset of the complete physical examination, provides important clues to the diagnosis of asymptomatic and symptomatic cardiac disease and may reveal cardiovascular manifestations of noncardiovascular diseases. The cardiovascular physical examination begins with careful measurement of the pulse and blood pressure (Chapter 7). If aortic dissection (Chapter 78) is a consideration, blood pressure should be measured in both arms and, preferably, in at least one leg. When coarctation of the aorta is suspected (Chapter 69), blood pressure must be measured in at least one leg and in the arms. Discrepancies in blood pressure between the two arms also can be caused by atherosclerotic disease of the great vessels. Pulsus paradoxus, which is more than the usual 10 mm Hg drop in systolic blood pressure during inspiration, is typical of pericardial tamponade (Chapter 77).

General Appearance

The respiratory rate may be increased in patients with heart failure. Patients with pulmonary edema are usually markedly tachypneic and may have labored breathing. Patients with advanced heart failure may have Cheyne-Stokes respirations.

Systemic diseases, such as hyperthyroidism (Chapter 233), hypothyroidism (Chapter 233), rheumatoid arthritis (Chapter 272), scleroderma (Chapter 275), and hemochromatosis (Chapter 219), may be suspected from the patient's general appearance. Marfan syndrome (Chapter 268), Turner's syndrome (Chapter 243), Down syndrome (Chapter 40), and a variety of congenital anomalies also may be readily apparent.

Ophthalmologic Examination

Examination of the fundi may show diabetic (see Fig. 431-15 in Chapter 431) or hypertensive retinopathy (see Fig. 67-11 in Chapter 67) or Roth's spots (see Fig. 431-17 in Chapter 431) typical of infectious endocarditis. Beading of the retinal arteries is typical of severe hypercholesterolemia. Osteogenesis imperfecta, which is associated with blue sclerae, also is associated with aortic dilation and mitral valve prolapse. Retinal artery occlusion (see Fig. 431-20 in Chapter 431) may be caused by an embolus from clot in the left atrium or left ventricle, a left atrial myxoma, or atherosclerotic debris from the great vessels. Hyperthyroidism may present with exophthalmos and typical stare (see Fig. 431-14 in Chapter 431), whereas myotonic dystrophy, which is associated with atrioventricular block and arrhythmia, often is associated with ptosis and an expressionless face (see Fig. 429-2 in Chapter 429).

Jugular Veins

The external jugular veins help in assessment of mean right atrial pressure, which normally varies between 5 and 10 cm H_2O; the height (in centimeters) of the central venous pressure is measured by adding 5 cm to the height of the observed jugular venous distention above the sternal angle of Louis

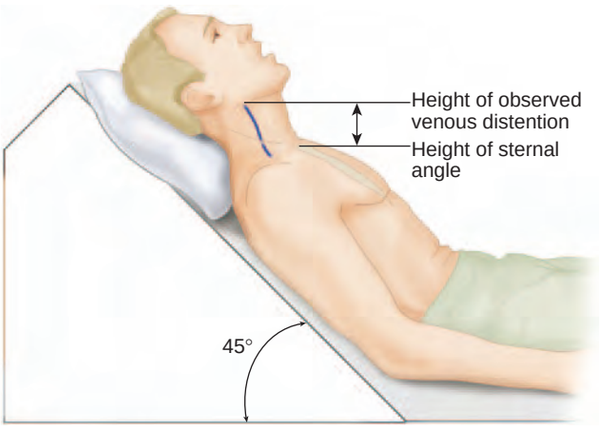

FIGURE 50-2. Jugular venous distention is defined by engorgement of the internal jugular vein more than 5 cm above the sternal angle at 45 degrees. The central venous pressure is the observed venous distention above the sternal angle plus 5 cm. ***(From American Academy of Family Physicians Online. <http://www.aafp.org/afp/20000301/1319.html.> Accessed 06.09.10.)***

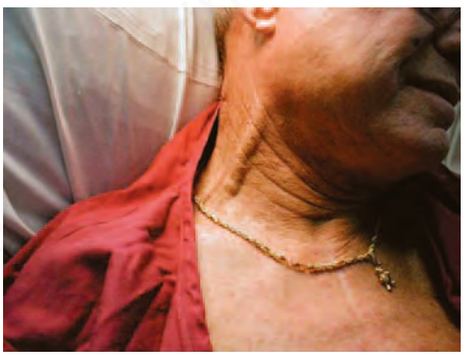

FIGURE 50-3. Typical distention of the internal jugular vein. ***(From <http://courses.cvcc.vccs.edu/WisemanD/jugular_vein_distention.htm.>)***

(Fig. 50-2). The normal jugular venous pulse, best seen in the internal jugular vein (and not seen in the external jugular vein unless insufficiency of the jugular venous valves is present), includes an *a* wave, caused by right atrial contraction; a *c* wave, reflecting carotid artery pulsation; an *x* descent; a *v* wave, which corresponds to isovolumetric right ventricular contraction and is more marked in the presence of tricuspid insufficiency; and a *y* descent, which occurs as the tricuspid valve opens and ventricular filling begins (Fig. 50-3). Abnormalities of the jugular venous pressure (Fig. 50-4) and arterial pulse are useful in detecting conditions such as heart failure, pericardial disease, tricuspid valve disease, and pulmonary hypertension (Table 50-6).

Carotid Pulse

The carotid pulse should be examined in terms of its volume and contour. The carotid pulse (Fig. 50-5) may be increased in frequency and may be more intense than normal in patients with a higher stroke volume secondary to aortic regurgitation, arteriovenous fistula, hyperthyroidism, fever, or anemia. In aortic regurgitation or arteriovenous fistula, the pulse may have a bisferious quality. The carotid upstroke is delayed in patients with valvular aortic stenosis (Chapter 75) and has a normal contour but diminished amplitude in any cause of reduced stroke volume.

Cardiac Inspection and Palpation

Inspection of the precordium may reveal the hyperinflation of obstructive lung disease or unilateral asymmetry of the left side of the chest because of right ventricular hypertrophy before puberty. Palpation may be performed with the patient either supine or in the left lateral decubitus position; the latter position moves the left ventricular apex closer to the chest wall and increases the ability to palpate the point of maximal impulse and other phenomena. Low-frequency phenomena, such as systolic heaves or lifts from the left ventricle (at the cardiac apex) or right ventricle (parasternal in the third

or fourth intercostal space), are felt best with the heel of the palm. With the patient in the left lateral decubitus position, this technique also may allow palpation of an S_3 gallop in cases of advanced heart failure or an S_4 gallop in cases of poor left ventricular distensibility during diastole. The left ventricular apex is more diffuse and sometimes may be frankly dyskinetic in patients with advanced heart disease. The distal palm is best for feeling thrills, which are the tactile equivalent of cardiac murmurs. By definition, a thrill denotes a murmur of grade 4/6 or louder. Higher-frequency events may be felt best with the fingertips; examples include the opening snap of mitral stenosis or the loud pulmonic second sound of pulmonary hypertension.

Auscultation

The first heart sound (Fig. 50-6), which is largely produced by closure of the mitral and—to a lesser extent—the tricuspid valves, may be louder in patients with mitral valve stenosis and intact valve leaflet movement and less audible in patients with poor closure due to mitral regurgitation (Chapter 75). The second heart sound is caused primarily by closure of the aortic valve, but closure of the pulmonic valve is also commonly audible. In normal individuals, the louder aortic closure sound occurs first, followed by pulmonic closure. With expiration, the two sounds are virtually superimposed. With inspiration, by comparison, the increased stroke volume of the right ventricle commonly leads to a discernible splitting of the second sound. This splitting may be fixed in patients with an atrial septal defect (Chapter 69) or a right bundle branch block. The split may be paradoxical in patients with left bundle branch block or other causes of delayed left ventricular emptying. The aortic component of the second sound is increased in intensity in the presence

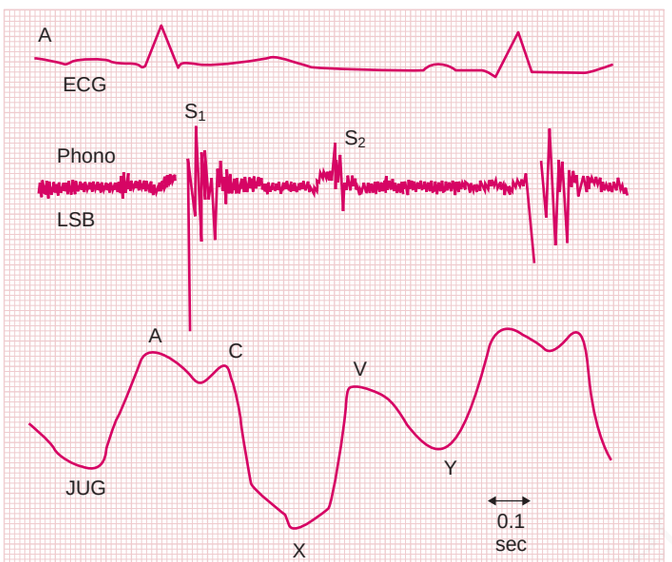

FIGURE 50-4. Normal jugular venous pulse. ECG = electrocardiogram; JUG = jugular vein; LSB = left sternal border; phono = phonocardiogram; S_1 = first heart sound; S_2 = second heart sound.

TABLE 50-6 ABNORMALITIES OF VENOUS PRESSURE AND PULSE AND THEIR CLINICAL SIGNIFICANCE

Positive hepatojugular reflux	Suspect heart failure, particularly left ventricular systolic dysfunction (echocardiography recommended)
Elevated systemic venous pressure without obvious *x* or *y* descent, quiet precordium, and pulsus paradoxus	Suspect cardiac tamponade (echocardiography recommended)
Elevated systemic venous pressure with sharp *y* descent, Kussmaul's sign, and quiet precordium	Suspect constrictive pericarditis (cardiac catheterization and MRI or CT recommended)
Elevated systemic venous pressure with a sharp brief *y* descent, Kussmaul's sign, and evidence of pulmonary hypertension and tricuspid regurgitation	Suspect restrictive cardiomyopathy (cardiac catheterization and MRI or CT recommended)
A prominent *a* wave with or without elevation of mean systemic venous pressure	Exclude tricuspid stenosis, right ventricular hypertrophy due to pulmonary stenosis, and pulmonary hypertension (echo-Doppler study recommended)
A prominent *v* wave with a sharp *y* descent	Suspect tricuspid regurgitation (echo-Doppler or cardiac catheterization to determine etiology)

CT = computed tomography; MRI = magnetic resonance imaging.
From Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine.* 5th ed. Philadelphia: WB Saunders; 1997.

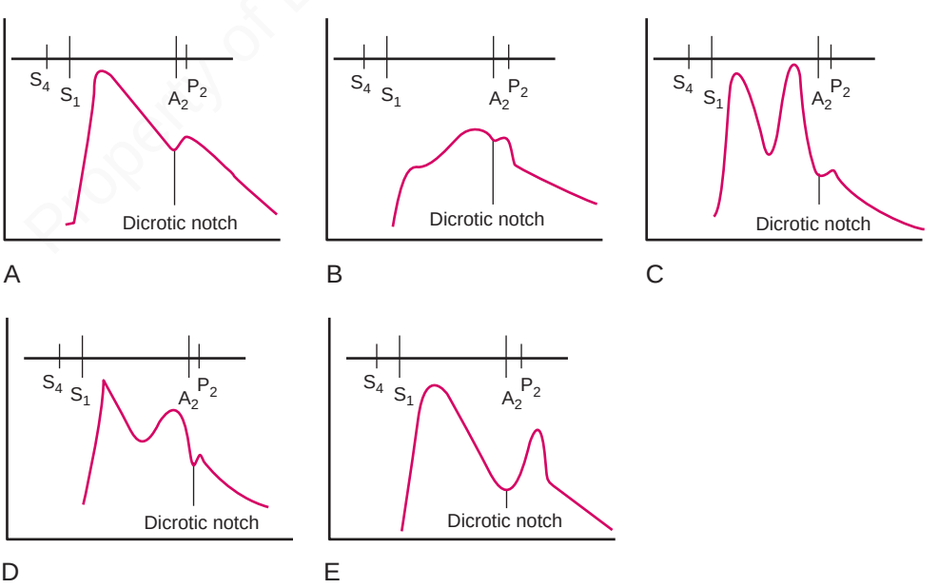

FIGURE 50-5. Schematic diagrams of the configurational changes in the carotid pulse and their differential diagnosis. Heart sounds also are illustrated. **A,** Normal. **B,** Anacrotic pulse with slow initial upstroke. The peak is close to the second heart sound. These features suggest fixed left ventricular outflow obstruction, such as valvular aortic stenosis. **C,** Pulsus bisferiens, with percussion and tidal waves occurring during systole. This type of carotid pulse contour is observed most frequently in patients with hemodynamically significant aortic regurgitation or combined aortic stenosis and regurgitation with dominant regurgitation. It rarely is observed in patients with mitral valve prolapse or in normal individuals. **D,** Pulsus bisferiens in hypertrophic obstructive cardiomyopathy. This finding rarely is appreciated at the bedside by palpation. **E,** Dicrotic pulse results from an accentuated dicrotic wave and tends to occur in sepsis, severe heart failure, hypovolemic shock, and cardiac tamponade and after aortic valve replacement. A_2 = aortic component of the second heart sound; P_2 = pulmonary component of the second heart sound); S_1 = first heart sound; S_4 = atrial sounds. ***(From Chatterjee K. Bedside evaluation of the heart: the physical examination. In: Chatterjee K, Chetlin MD, Karliner J, et al, eds.* Cardiology: An Illustrated Text/Reference. *Philadelphia: JB Lippincott; 1991:3.11-3.51.)***

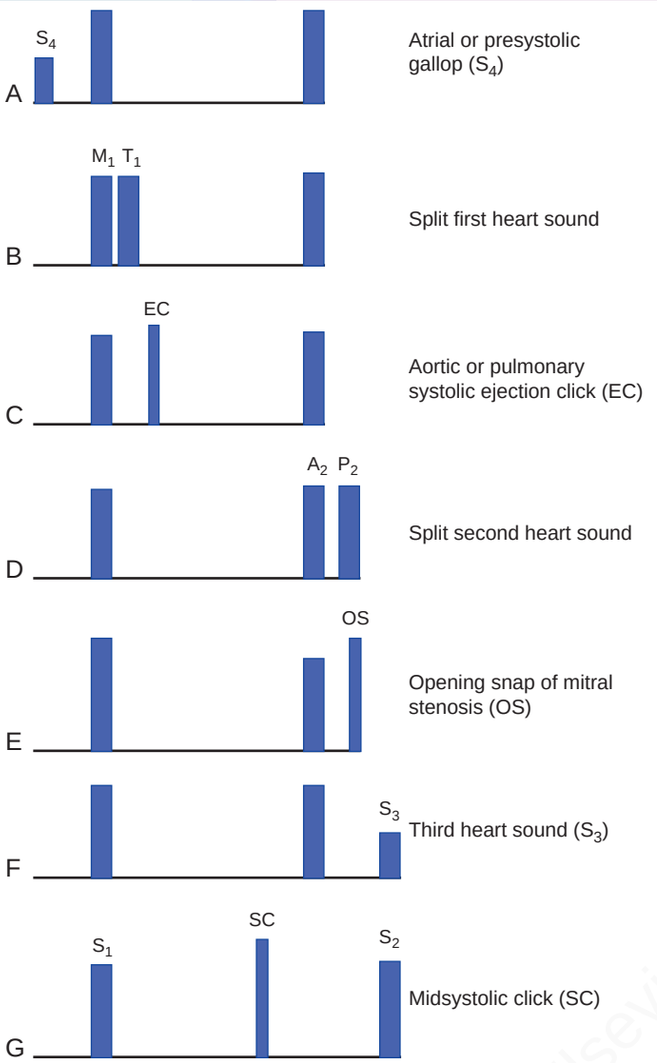

FIGURE 50-6. Timing of the different heart sounds and added sounds. *(Modified from Wood P.* Diseases of the Heart and Circulation. *3rd ed. Philadelphia: JB Lippincott; 1968.)*

of systemic hypertension and decreased in intensity in patients with aortic stenosis. The pulmonic second sound is increased in the presence of pulmonary hypertension.

Early systolic ejection sounds are related to forceful opening of the aortic or pulmonic valve. These sounds are common in congenital aortic stenosis, with a mobile valve; in hypertension, with forceful opening of the aortic valve; and in healthy young individuals, especially when cardiac output is increased. Midsystolic or late systolic clicks are caused most commonly by mitral valve prolapse (Chapter 75). Clicks are relatively high-frequency sounds that are heard best with the diaphragm of the stethoscope.

An S_3 corresponds to rapid ventricular filling during early diastole. It may occur in normal children and young adults, especially if stroke volume is increased. After about 40 years of age, however, an S_3 should be considered abnormal; it is caused by conditions that increase the volume of ventricular filling during early diastole (e.g., mitral regurgitation) or that increase pressure in early diastole (e.g., advanced heart failure). A left ventricular S_3 gallop is heard best at the apex, whereas the right ventricular S_3 gallop is heard best at the fourth intercostal space at the left parasternal border; both are heard best with the bell of the stethoscope. An S_4 is heard rarely in young individuals but is common in adults older than 40 or 50 years because of reduced ventricular compliance during atrial contraction; it is a nearly ubiquitous finding in patients with hypertension, heart failure, or ischemic heart disease.

The opening snap of mitral and, less commonly, tricuspid stenosis (Chapter 75) occurs at the beginning of mechanical diastole, before the onset of the rapid phase of ventricular filling. An opening snap is high pitched and is heard best with the diaphragm; this differential frequency should help distinguish an opening snap from an S_3 on physical examination. An opening snap commonly can be distinguished from a loud pulmonic component of the second heart sound by the differential location (mitral opening snap at the apex, tricuspid opening snap at the left third or fourth intercostal space, pulmonic second sound at the left second intercostal space) and by the longer interval between S_2 and the opening snap.

Heart murmurs may be classified as systolic, diastolic, or continuous (Table 50-7). Murmurs are graded by intensity on a scale of 1 to 6. Grade 1 is faint and appreciated only by careful auscultation; grade 2, readily audible; grade 3, moderately loud; grade 4, loud and associated with a palpable thrill; grade 5, loud and audible with the stethoscope only partially placed on the chest; and grade 6, loud enough to be heard without the stethoscope on the chest. Systolic ejection murmurs usually peak in early to mid systole when left ventricular ejection is maximal; examples include fixed valvular, supravalvular, or infravalvular aortic stenosis and pulmonic stenosis. The murmur of hypertrophic obstructive cardiomyopathy has a similar ejection quality, although its peak may be later in systole when dynamic obstruction is maximal (Chapter 60). Pansystolic murmurs are characteristic of mitral or tricuspid regurgitation or with a left-to-right shunt from conditions such as a ventricular septal defect (left ventricle to right ventricle). A late systolic murmur is characteristic of mitral valve prolapse (Chapter 75) or ischemic papillary muscle dysfunction. Ejection quality murmurs also may be heard in patients with normal valves but increased flow, such as occurs with marked anemia, fever, or bradycardia secondary to congenital complete heart block; they also may be heard across a valve that is downstream from increased flow because of an intracardiac shunt. Maneuvers such as inspiration, expiration, standing, squatting, and hand gripping can be especially useful in the differential diagnosis of a murmur; however, echocardiography commonly is required to make a definitive diagnosis of cause and severity (Table 50-8).

High-frequency, early diastolic murmurs are typical of aortic regurgitation and pulmonic regurgitation from a variety of causes. The murmurs of mitral and tricuspid stenosis begin in early to mid diastole and tend to diminish in intensity later in diastole in the absence of effective atrial contraction, but they tend to increase in intensity in later diastole if effective atrial contraction is present.

Continuous murmurs may be caused by any abnormality that is associated with a pressure gradient in systole and diastole. Examples include a patent ductus arteriosus, ruptured sinus of Valsalva aneurysm, arteriovenous fistula (of the coronary artery, pulmonary artery, or thoracic artery), and a mammary soufflé. In some situations, murmurs of two coexistent conditions (e.g., aortic stenosis and regurgitation; atrial septal defect with a large shunt and resulting flow murmurs of relative mitral and pulmonic stenosis) may mimic a continuous murmur.

Abdomen

The most common cause of hepatomegaly in patients with heart disease is hepatic engorgement from elevated right-sided pressures associated with right ventricular failure of any cause. Hepatojugular reflux is elicited by pressing on the liver and showing an increase in the jugular venous pressure; it indicates advanced right ventricular failure or obstruction to right ventricular filling. Evaluation of the abdomen also may reveal an enlarged liver caused by a systemic disease, such as hemochromatosis (Chapter 219) or sarcoidosis (Chapter 95), which also may affect the heart. In more severe cases, splenomegaly and ascites also may be noted. Large, palpable, polycystic kidneys (Chapter 129) commonly are associated with hypertension. A systolic bruit suggestive of renal artery stenosis (Chapter 127) or an enlarged abdominal aorta (Chapter 78) is a clue of atherosclerosis.

Extremities

Extremities should be evaluated for peripheral pulses, edema, cyanosis, and clubbing. Diminished peripheral pulses suggest peripheral arterial disease (Chapters 79 and 80). Delayed pulses in the legs are consistent with coarctation of the aorta and are seen after aortic dissection.

Edema (Fig. 50-7) is a cardinal manifestation of right-sided heart failure. When it is caused by heart failure, pericardial disease, or pulmonary hypertension, the edema is usually symmetrical and progresses upward from the ankles; each of these causes of cardiac edema commonly is associated with jugular venous distention and often with hepatic congestion. Unilateral edema suggests thrombophlebitis or proximal venous or lymphatic obstruction (Fig. 50-8). Edema in the absence of evidence of right-sided or left-sided heart failure suggests renal disease, hypoalbuminemia, myxedema, or other noncardiac causes. Among unselected patients with bilateral edema, about

TABLE 50-7 SOME COMMON CAUSES OF HEART MURMURS*

	USUAL LOCATION	COMMON ASSOCIATED FINDINGS
SYSTOLIC		
Holosystolic		
Mitral regurgitation	Apex → axilla	↑ with handgrip; S_3 if marked mitral regurgitation; left ventricular dilation common
Tricuspid regurgitation	LLSB	↑ with inspiration; right ventricular dilation common
Ventricular septal defect	LLSB → RLSB	Often with thrill
Early-mid systolic		
Aortic valvular stenosis	RUSB	
Fixed supravalvular or subvalvular	RUSB	Ejection click if mobile valve; soft or absent A_2 if valve immobile; later peak associated with more severe stenosis
Dynamic infravalvular	LLSB → apex + axilla	Hypertrophic obstructive cardiomyopathy; murmur louder if left ventricular volume lower or contractility increased, softer if left ventricular volume increased†; can be later in systole if obstruction delayed
Pulmonic valvular stenosis	LUSB	↑ with inspiration
Infravalvular (infundibular)	LUSB	↑ with inspiration
Supravalvular	LUSB	↑ with inspiration
"Flow murmurs"	LUSB	Anemia, fever, increased flow of any cause‡
Mid-late systolic		
Mitral valve prolapse	LLSB or apex → axilla	Preceded by click; murmur lengthens with maneuvers that decrease left ventricular volume†
Papillary muscle dysfunction	Apex → axilla	Ischemic heart disease
DIASTOLIC		
Early diastolic		
Aortic regurgitation	RUSB, LUSB	High-pitched, blowing quality; endocarditis, diseases of the aorta, associated aortic valvular stenosis; signs of low peripheral vascular resistance
Pulmonic valve regurgitation	LUSB	Pulmonary hypertension as a causative factor
Mid-late diastolic		
Mitral stenosis, tricuspid stenosis	Apex, LLSB	Low pitched; in rheumatic heart disease, opening snap commonly precedes murmur; can be due to increased flow across normal valve‡
Atrial myxomas	Apex (L), LLSB (R)	"Tumor plop"
Continuous		
Venous hum	Over jugular or hepatic vein or breast	Disappears with compression of ve n or pressure of stethoscope
Patent ductus arteriosus	LUSB	
Arteriovenous fistula		
Coronary	LUSB	
Pulmonary, bronchial, chest wall	Over fistula	
Ruptured sinus of Valsalva aneurysm	RUSB	Sudden onset

LLSB = left lower sternal border (4th intercostal space); LUSB = left upper sternal border (2nd-3rd intercostal spaces); RLSB = right lower sternal border (4th intercostal space); RUSB = right upper sternal border (2nd-3rd intercostal spaces).
*See also Chapters 69 and 75.
†Left ventricular volume is decreased by standing or during prolonged, forced expiration against a closed glottis (Valsalva maneuver); it is increased by squatting or by elevation of the legs; contractility is increased by adrenergic stimulation or in the beat after an extrasystolic beat.
‡Including a left-to-right shunt through an atrial septal defect for tricuspid or pulmonic flow murmurs, and a ventricular septal defect for pulmonic or mitral flow murmurs.

40% have an underlying cardiac disease, about 40% have an elevated pulmonary blood pressure, about 20% have bilateral venous disease, about 20% have renal disease, and about 25% have idiopathic edema.

Cyanosis (Fig. 50-9) is a bluish discoloration caused by reduced hemoglobin exceeding about 5 g/dL in the capillary bed. Central cyanosis is seen in patients with poor oxygen saturation resulting from a reduced inspired oxygen concentration or inability to oxygenate the blood in the lungs (e.g., as a result of advanced pulmonary disease, pulmonary edema, pulmonary arteriovenous fistula, or right-to-left shunting); it also may be seen in patients with marked erythrocytosis. Methemoglobinemia (Chapter 161) also can present with cyanosis. Peripheral cyanosis may be caused by reduced blood flow to the extremities secondary to vasoconstriction, heart failure, or shock. *Clubbing* (Fig. 50-10), which is loss of the normal concave configuration of the nail as it emerges from the distal phalanx, is seen in patients with pulmonary abnormalities such as lung cancer (Chapter 197) and in patients with cyanotic congenital heart disease (Chapter 69).

Examination of the Skin

Examination of the skin may reveal bronze pigmentation typical of hemochromatosis (Chapter 219); jaundice (see Fig. 149-2 in Chapter 149) characteristic of severe right-sided heart failure or hemochromatosis; or capillary hemangiomas typical of Osler-Weber-Rendu disease (see Fig. 176-2 in Chapter 176), which also is associated with pulmonary arteriovenous fistulas and cyanosis. Infectious endocarditis may be associated with Osler's nodes (see Fig. 76-2 in Chapter 76), Janeway's lesions, or splinter hemorrhages (Fig. 50-11) (Chapter 76). Xanthomas (Fig. 50-12) are subcutaneous deposits of cholesterol seen on the extensor surfaces of the extremities or on the palms and digital creases; they are found in patients with severe hypercholesterolemia.

Laboratory Studies

All patients with known or suspected cardiac disease should have an ECG and chest radiograph. The ECG (Chapter 54) helps identify rate, rhythm,

TABLE 50-8 SENSITIVITY AND SPECIFICITY OF BEDSIDE MANEUVERS IN THE IDENTIFICATION OF SYSTOLIC MURMURS

MANEUVER	RESPONSE	MURMUR	SENSITIVITY (%)	SPECIFICITY (%)
Insp ration	↑	RS	100	88
Expiration	↓	RS	100	88
Valsalva maneuver	↑	HC	65	96
Squat to stand	↑	HC	95	84
Stand to squat	↓	HC	95	85
Leg elevation	↓	HC	85	91
Handgrip	↓	HC	85	75
Handgrip	↑	MR and VSD	68	92
Transient arterial occlusion	↑	MR and VSD	78	100

HC = hypertrophic cardiomyopathy; MR = mitral regurgitation; RS = right sided; VSD = ventricular septal defect.

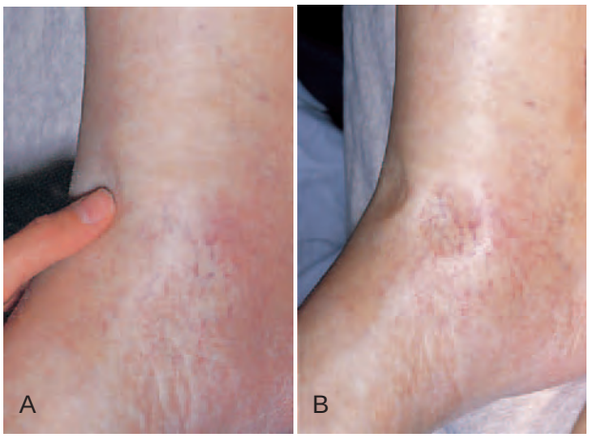

FIGURE 50-7. Pitting edema in a patient with cardiac failure. A depression ("pit") remains in the edema for some minutes after firm fingertip pressure is applied. ***(From Forbes CD, Jackson WD.* Color Atlas and Text of Clinical Medicine. *3rd ed. London: Mosby; 2003.)***

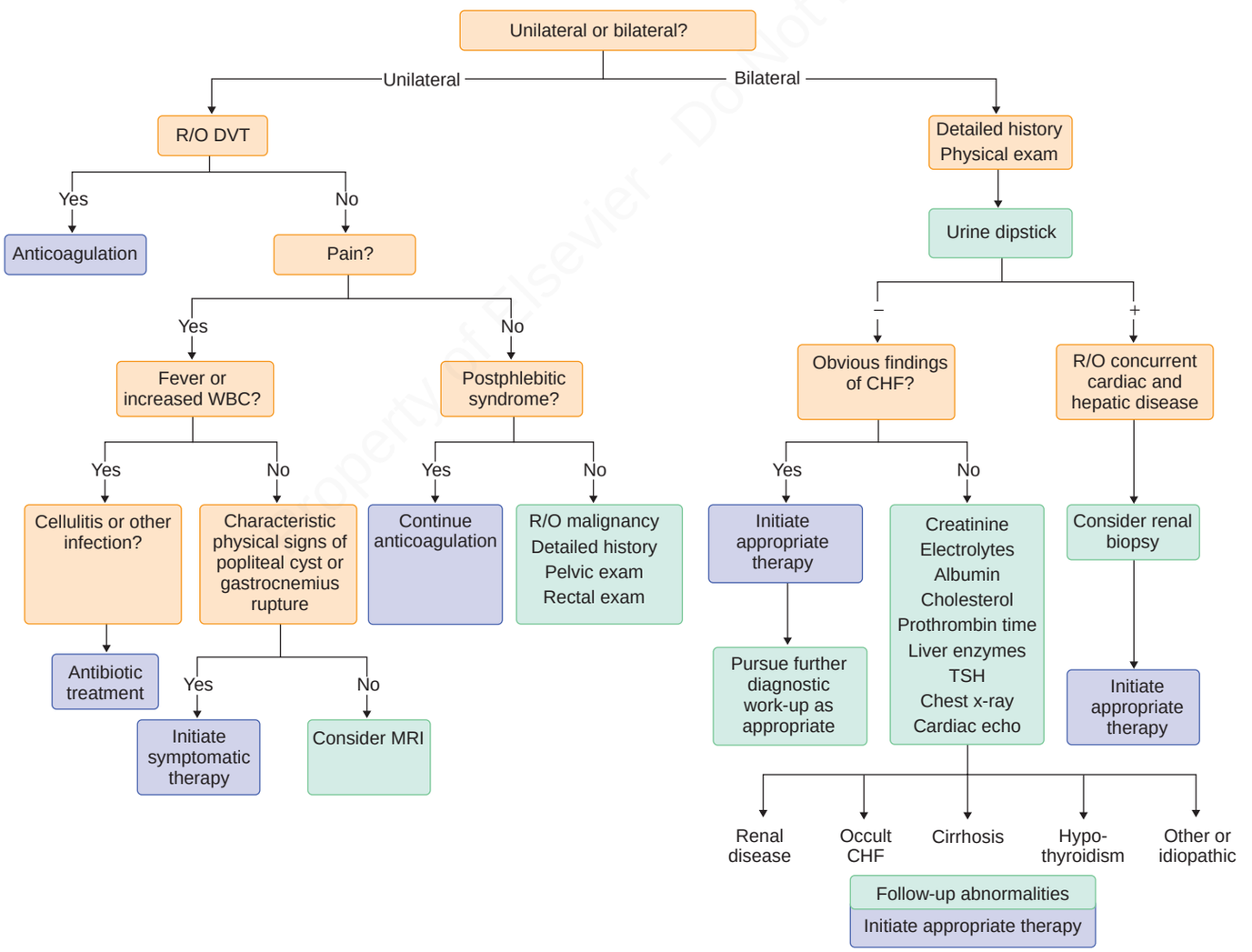

FIGURE 50-8. Diagnostic approach to patients with edema. CHF = congestive heart failure; DVT = deep venous thrombosis; MRI = magnetic resonance imaging; R/O = rule out; TSH = thyroid-stimulating hormone; WBC = white blood cell count. ***(From Chertow G. Approach to the patient with edema. In: Braunwald E, Goldman L, eds. Primary Cardiology. 2nd ed. Philadelphia: WB Saunders; 2003.)***

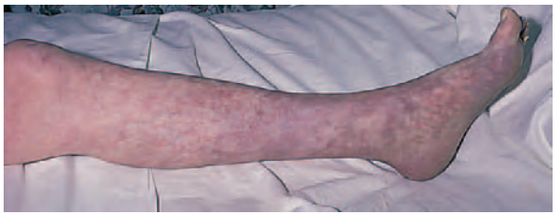

FIGURE 50-9. Arterial embolism causing acute ischemia and cyanosis of the leg. Initial pallor of the leg and foot was followed by cyanosis. *(From Forbes CD, Jackson WD.* Color Atlas and Text of Clinical Medicine. *3rd ed. London: Mosby; 2003.)*

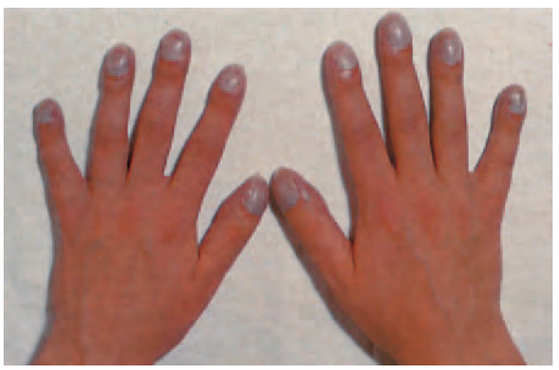

FIGURE 50-10. Severe finger clubbing in a patient with cyanotic congenital heart disease. *(From Forbes CD, Jackson WD.* Color Atlas and Text of Clinical Medicine. *3rd ed. London: Mosby; 2003.)*

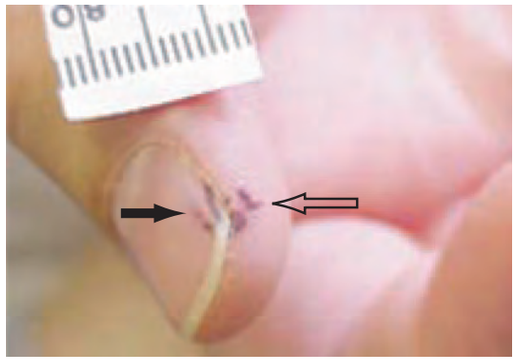

FIGURE 50-11. Splinter hemorrhage (*solid arrow*) and Janeway's lesions (*open arrow*). These findings should stimulate a work-up for endocarditis. *(From American Academy of Family Physicians Online. <http://www.aafp.org/afp/20040315/1417.html.> Accessed 06.09.10.)*

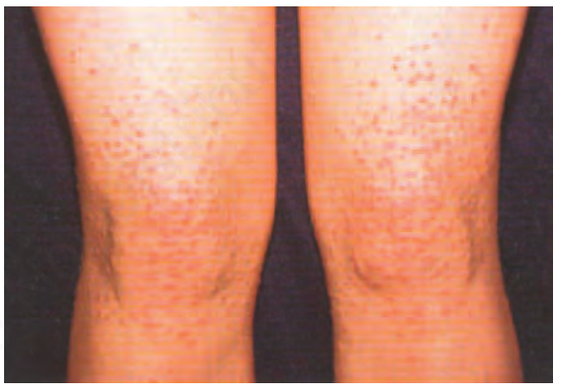

FIGURE 50-12 Eruptive xanthomas of the extensor surfaces of the lower extremities. This patient had marked hypertriglyceridemia. *(From Massengale WT, Nesbitt LT Jr. Xanthomas. In: Bolognia JL, Jorizzo JL, Rapini RP, eds.* Dermatology. *Philadelphia: Mosby; 2003:1449.)*

conduction abnormalities, and possible myocardial ischemia. The chest radiograph (Chapter 53) yields important information on chamber enlargement, pulmonary vasculature, and the great vessels.

Blood testing in patients with known or suspected cardiac disease should be targeted to the conditions in question. In general, a complete blood cell count, thyroid indices, and lipid levels are part of the standard evaluation.

Echocardiography (Chapter 55) is the most useful test to analyze valvular and ventricular function. By use of Doppler flow methods, stenotic and regurgitant lesions can be quantified. Hand-held ultrasonography performed by generalists can improve the assessment of left ventricular function, cardiomegaly, and pericardial effusion. Transesophageal echocardiography is the preferred method to evaluate possible aortic dissection and to identify clot in the cardiac chambers. Radionuclide studies (Chapter 56) can measure left ventricular function, assess myocardial ischemia, and determine whether ischemic myocardium is viable. CT can detect coronary calcium, which is a risk factor for symptomatic coronary disease (Chapter 56). In the setting of acute chest pain, multislice CT is effective in diagnosing coronary disease, but it currently cannot adequately determine the physiologic significance.[1]

Stress testing by exercise or pharmacologic stress is useful to precipitate myocardial ischemia that may be detected by ECG abnormalities, perfusion abnormalities on radionuclide studies, or transient wall motion abnormalities on echocardiography. These tests are often crucial in diagnosis of possible myocardial ischemia (Chapter 71) and in establishment of prognosis in patients with known ischemic heart disease.

Cardiac catheterization (Chapter 57) can measure precise gradients across stenotic cardiac valves, judge the severity of intracardiac shunts, and determine intracardiac pressures. Coronary angiography provides a definitive diagnosis of coronary disease and is a necessary prelude to coronary revascularization with a percutaneous coronary intervention (Chapter 74) or coronary artery bypass graft surgery (Chapter 74).

Continuous ambulatory ECG monitoring can help diagnose arrhythmias. A variety of newer technologies allow longer-term monitoring in patients with important but infrequently occurring symptoms (Chapter 62). Formal invasive electrophysiologic testing can be useful in the diagnosis of ventricular or supraventricular wide-complex tachycardia, and it is crucial for guiding a wide array of new invasive electrophysiologic therapies (Chapter 66).

SUMMARY

The history, physical examination, and laboratory evaluation should help the physician establish the cause of any cardiovascular problem; identify and quantify any anatomic abnormalities; determine the physiologic status of the valves, myocardium, and conduction system; determine functional capacity; estimate prognosis; and provide primary or secondary prevention. Key preventive strategies, including diet modification, recognition and treatment of hyperlipidemia, cessation of cigarette smoking, and adequate physical exercise, should be part of the approach to every patient, with or without heart disease.

Grade A

1. Goldstein JA, Gallagher MJ, O'Neill WW, et al. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol.* 2007;49:863-871.

SUGGESTED READINGS

Brown AF, Cullen L, Than M. Future developments in chest pain diagnosis and management. *Med Clin North Am.* 2010;94:375-400. *Review.*

Martin LD, Howell EE, Ziegelstein RC, et al. Hand-carried ultrasound performed by hospitalists: does it improve the cardiac physical examination? *Am J Med.* 2009;122:35-41. *It improves the accuracy of the assessment of left ventricular dysfunction, cardiomegaly, and pericardial effusion.*

Woo KM, Schneider JI. High-risk chief complaints I: chest pain—the big three. *Emerg Med Clin North Am.* 2009;27:685-712. *Review of key clues to myocardial infarction and ischemia, thoracic aortic dissection, and pulmonary embolism.*

Access the complete reference list online at http://www.expertconsult.com

ADDITIONAL SUGGESTED READINGS

Marcus GM, Vessey J, Jordan MV, et al. Relationship between accurate auscultation of a clinically useful third heart sound and level of experience. *Arch Intern Med*. 2006;166:617-622. *The S_3 auscultated by more experienced physicians demonstrated fair agreement with phonocardiographic findings.*

Shah MG, Cho S, Atwood JE, et al. Peripheral edema due to heart disease: diagnosis and outcome. *Clin Cardiol*. 2006;29:31-35. *A case series showing that cardiac causes are difficult to diagnose but associated with high mortality.*

Treadway K. Heart sounds. *N Engl J Med*. 2006;354:1112-1113. *Common heart sounds on audio.*

Vukanovic-Criley JM, Criley S, Warde CM, et al. Competency in cardiac examination skills in medical students, trainees, physicians, and faculty: A multicenter study. *Arch Intern Med*. 2006;166:610-616. *Emphasizes the limitations of physical examination of training and cardiology experience, except cardiologists.*

286

INTRODUCTION TO MICROBIAL DISEASE: HOST-PATHOGEN INTERACTIONS

W. MICHAEL SCHELD

Infectious diseases have profoundly influenced the course of human history. The "black death" (caused by *Yersinia pestis*) changed the social structure of medieval Europe, in the process eliminating approximately a third of the population. The outcomes of military campaigns have been altered by outbreaks of diseases such as dysentery and typhus. Examples include Napoleon's retreat from Russia, after typhus did more damage to his army than the opposition forces did; the decision by the French to sell the Louisiana Territory after French soldiers died from yellow fever in Cuba and the Gulf Coast; and the introduction of smallpox to the nonimmune population of the New World by Europeans, thus facilitating the "conquest" and the dawn of the colonial age. Malaria influenced the geographic and racial pattern and distribution of hemoglobins and erythrocyte antigens in Africa. The development of *Plasmodium falciparum* is inhibited by the presence of hemoglobin S, and Duffy blood group–negative erythrocytes are resistant to infection with *Plasmodium vivax.* Thus, populations with these erythrocyte factors are found in areas where malaria is common.

Infections are a major cause of morbidity and mortality in the world. Of the approximately 53 million deaths worldwide in 2009, at least a third were due to infectious diseases. In the United States, pneumonia is the fifth leading cause of death overall and the most common cause of death related to infection. In addition, invasive disease caused by *Streptococcus pneumoniae* and community-acquired pneumonia overall have increased in incidence over the past decade. Acquired immunodeficiency syndrome (AIDS) threatens to disrupt the social fabric in many countries of Africa and is severely distressing the health care system in the United States and other parts of the world. The year 2006 marked the 25th "anniversary" of the AIDS epidemic. Approximately 33 million people worldwide are currently infected with human immunodeficiency virus (HIV), and since 1981, approximately 25 million have died (≈ 600,000 in the United States alone). AIDS is now the leading cause of death in sub-Saharan Africa.

Infection can be defined as the multiplication of microbes (from viruses to multicellular parasites) in the tissues of the host. The host may or may not be symptomatic. For example, HIV infection may cause no overt signs or symptoms of illness for years. The definition of infection should also include the multiplication of microbes on the surface or in the lumen of the host that causes signs and symptoms of illness or disease. For example, toxin-producing strains of *Escherichia coli* may multiply in the gut and cause a diarrheal illness without invading tissues. Microbes can cause diseases without actually coming in contact with the host by virtue of toxin production. *Clostridium botulinum* may grow in certain improperly processed foods and produce a toxin that can be lethal on ingestion. A relatively trivial infection such as that caused by *Clostridium tetani* in a small puncture wound can cause devastating illness because of a toxin released from the organism growing in tissues. It has now become apparent that multiple virulence factors of microorganisms can be carried in tandem on so-called pathogenicity islands of the genome (the "virulome").

We live in a virtual sea of microorganisms, and all our body surfaces have indigenous bacterial flora. This normal flora actually protects us from infection. Reduction of gut colonization increases susceptibility to infection by pathogens such as *Salmonella enteritidis* serovar *typhimurium.* Bacteria that constitute the normal flora are thought to exert their protective effect by several mechanisms: (1) utilizing nutrients and occupying an ecologic niche, thus competing with pathogens; (2) producing antibacterial substances that inhibit the growth of pathogens; and (3) inducing host immunity that is cross-reactive and effective against pathogens. These conclusions appear to be oversimplistic, however. For example, colonization of the gastrointestinal tract with *Bacteroides fragilis* expressing an immunodominant bacterial polysaccharide, through dendritic cell activation and induction of a T_H1-mediated response, leads to a splenic response characterized by normal numbers of $CD4^+$ T cells, lymphoid architecture, and systemic lymphocytic expansion. Thus, a single bacterial molecule in our gut is necessary to make us "immunologically fit." In addition to the normal flora, transient colonization may be seen with known or potential pathogens. This may be a special problem in hospitalized patients because it can lead to nosocomial infection (Chapter 290).

Only a small proportion of microbial species can be considered primary or professional pathogens, and even among these species, a relatively small number of clones have been shown to cause disease. For example, epidemic meningococcal meningitis and meningococcemia are due to a small number of clones of *Neisseria meningitidis,* and the worldwide explosion of penicillin-resistant *S. pneumoniae* can be traced to a few clones originating in South Africa and Spain. This observation supports the concept that pathogenic organisms are highly adapted to the pathogenic state and have developed characteristics that enable them to be transmitted, attach to surfaces, invade tissue, avoid host defenses, and thus cause disease. In contrast, opportunistic pathogens cause disease principally in impaired hosts, and these organisms, which may be harmless members of normal flora in healthy persons, can act as virulent invaders in patients with severe defects in host defense mechanisms. Although opportunistic infection has traditionally been viewed as the exploitation of a weakened host through physiologic stress or immunocompromise (or both) by relatively "avirulent" pathogens, this is an oversimplification. For example, *Pseudomonas aeruginosa* recognizes host immune activation, specifically by binding interferon-γ to a cell surface protein OprF, which in turn, through a quorum-sensing signaling system, leads to the overexpression of virulence determinants such as PA-I (lecA) and pyocyanin. Thus, bacteria have developed a "contingency system" that recognizes immunologic perturbations in the host and counters this response by the expression of virulence factors.

Pathogenic organisms may be acquired by several routes. Direct contact has been implicated in the acquisition of staphylococcal disease. Airborne spread, usually by droplet nuclei, occurs in respiratory diseases such as influenza and in severe acute respiratory syndrome (SARS). Contaminated water is the usual vehicle in *Giardia* infection and typhoid fever. Food-borne toxic illnesses may be caused by extracellular toxins produced by *Clostridium perfringens* and *Staphylococcus aureus.* Blood and blood products may be vectors for transmitting hepatitis B and C viruses, as well as HIV. Sexual transmission is also important for these agents and for a variety of other pathogens, including *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae* (gonorrhea), and *Chlamydia trachomatis* (nonspecific urethritis). The fetus may be infected in utero, and the infection may be devastating if the agent is rubella virus or cytomegalovirus. Arthropod vectors may be important, as illustrated by mosquitoes for malaria and dengue, ticks for Lyme disease and ehrlichiosis, and lice for typhus.

Pathogens are able to cause disease because of a finely tuned array of adaptations, including the ability to attach to appropriate cells, often mediated by specialized structures such as the pili on gram-negative rods. Microbes such as *Shigella* species have the ability to invade cells and cause damage. Toxins may act at a distance or may intoxicate only infected cells. Pathogens have the ability to thwart host defenses by a variety of ingenious maneuvers. The antiphagocytic coat of the pneumococcus is an example. Organisms may change their surface antigen display at an astonishingly rapid rate to outmaneuver the host immune system. Examples include influenza virus and trypanosomes. Certain pathogens have the ability to inhibit the respiratory burst of phagocytes *(Toxoplasma gondii),* and others can destroy phagocytic cells that have engulfed them (e.g., *Streptococcus pyogenes*). The environment plays an important role in infection, both in transmission and in the host's ability to combat the invader. The humidity and temperature of air may affect the infectivity of airborne pathogens. The sanitary state of food and water, woefully lacking in many areas of the developing world, is an important factor in the acquisition of enteric pathogens, one of the major causes of mortality and morbidity, such as physical and mental developmental delay leading to poor performance in school and other consequences. The malaria associated with the "bad air" of swamps is, in fact, due to the mosquitoes there, but the environmental association was appropriate. The nutritional status of the host is clearly a significant factor in certain infectious diseases. It is likely that micronutrient deficiency contributes to the invasion and multiplication of certain pathogens. A new concept is the possibility that infectious diseases cause malnutrition through a vicious circle of diarrhea leading to dehydration and poor oral intake, resulting in secondary diarrhea with a propensity for "stunting" and delaying intellectual development. Establishment of infection is a complicated interplay of factors involving the microbe, the host, and the environment.

Host reaction to infection may result in illness. For example, previous infection with *Campylobacter jejuni* is responsible for about 40% of cases of Guillain-Barré syndrome. The mechanism is thought to be the production of antibodies against *C. jejuni* lipopolysaccharides that cross-react with gangliosides in peripheral nerves. Similarly, much of the damage resulting from meningitis is due to the host's response to invading bacterial pathogens.

With some exceptions, infectious diseases are often treatable and curable. Thus, it is important to make an accurate etiologic diagnosis and institute appropriate therapy promptly. In acute infections such as pneumonia, meningitis, or sepsis, rapid institution of therapy may be life-saving; thus, a presumptive etiologic diagnosis should be established before a definitive diagnosis. This presumptive diagnosis is based on the history, physical examination, epidemiology of illness in the community, and rapid techniques such as microscopic examination of appropriate Gram-stained specimens. Antimicrobial therapy can then be instituted for the presumptive etiologic agents, but it must be reevaluated as more definitive diagnostic information becomes available.

The study as well as the understanding of infectious diseases is a dynamic process. A number of factors or themes of current interest contribute to this conclusion, including the following:

EMERGING INFECTIONS. The most obvious is AIDS, but recent examples with a major impact on the public health in the United States include community-associated methicillin-resistant *S. aureus*, a hypervirulent strain of *Clostridium difficile*, and the 2009 H1N1 influenza. More than 300 new, emerging infectious diseases have been described in the last 70 years; approximately 60% are zoonoses associated with geographic "hotspots." Their emergence is driven largely by ecologic, socioeconomic, and environmental factors.

GENOMICS AND OTHER "OMICS". The exact sequence of the genome of more than 2000 microbes relevant to humans has been determined. This new information, in concert with genomic information from multicellular organisms such as the *Anopheles* mosquito, offers significant promise for the development of new therapies and vaccines. Careful analysis of the genomes of pathogens will continue to yield important information about the pathogenesis of infection. For example, genome sequencing of group A streptococci, collected over time with relevant robust clinical information, has detected the acquisition of new determinants (often by prophage) responsible for increased virulence and resulting in toxic shock syndrome, necrotizing fasciitis, or both. Proteomics, transcriptomics, metabolomics, and virulomics have transformed research on infectious diseases and promise significant improvements in diagnostics and therapeutics in the future.

GENETIC FACTORS ALTERING SUSCEPTIBILITY TO INFECTION AND THE RESPONSE TO INFECTIOUS DISEASES. This field promises new and significant information relevant to the wide variety of responses to infectious diseases in humans. For example, an overvigorous response, with generation of tumor necrosis factor-α, may accentuate the development of cerebral complications in falciparum malaria. Analysis of single-nucleotide polymorphisms of the human genome will lead to an enhanced understanding of two fundamental issues in infectious diseases: why invasive, overt disease develops in only a small fraction of individuals colonized with a given microbe, and why infections are more severe in some people than in others. Variants in genes that encode molecules that mediate attachment, pathogen recognition, inflammatory cytokine response, and innate and adaptive immunity are being identified at an astonishing rate.

INNATE IMMUNITY. This is the most active field in immunology. The identification of pattern recognition receptors (e.g., Toll-like receptors [TLRs] and NOD-like receptors) that recognize pathogen-associated molecular patterns, as well as endogenous substances reflecting tissue injury (e.g., alarmins), has revolutionized our understanding of the early host response to infection. Agonists or antagonists of TLRs have already entered clinical trials as adjuvant therapies (e.g., editoran for sepsis) or to improve the immunogenicity of vaccines. The other area that has exploded recently is the study of antimicrobial peptides (e.g., defensins, cathecidins, histatins, galectins) and their role in the early response to infectious disorders.

ANTIMICROBIAL RESISTANCE. The development of new antimicrobial agents has slowed despite the burgeoning problem of antimicrobial resistance. This disconnect has been the focus of meetings among the pharmaceutical industry, the Infectious Diseases Society of America, the Food and Drug Administration, and others. Multiresistant pneumococci, vancomycin resistance in *S. aureus,* vancomycin-resistant enterococci, and, perhaps most important, multidrug-resistant gram-negative bacilli (MDR-GNB) are just a few examples. Some MDR-GNB are susceptible to only a few agents of "last resort," such as colistin or tigecycline; others are truly untreatable (Chapter 313). Unfortunately, new agents active against these strains are years, if not decades, away from introduction.

THE ROLE OF INFECTIOUS AGENTS IN CHRONIC DISEASES. Many so-called idiopathic diseases may in fact have an infectious basis. Conditions for which there is some evidence (but not conclusive proof) of an infectious basis include diabetes, atherosclerosis, acute leukemia, collagen vascular diseases, and inflammatory bowel disease. Detection of "uncultivatable" microorganisms by newer techniques, such as 16S RNA analysis, may uncover agents responsible for "noninfectious" diseases or suggest a role in conditions that are considered infectious but in which the pathogen or pathogens are controversial (e.g., bacterial vaginosis). In addition, we know that hepatitis C virus, human papillomavirus, and *Helicobacter pylori* cause human cancers. In addition, changes in our own microbiome may lead to disease. Alterations in the gut microbiome are associated with obesity. Another recent example comes from experiments with mice lacking TLR5. These mice develop hyperphagia and hallmark features of the metabolic syndrome, including hyperlipidemia, hypertension, insulin resistance, and increased adiposity, associated with an altered gut microbiome. Further, transfer of this changed microbiota into germ-free wild-type mice induces most features of the metabolic syndrome in the recipients.

SUGGESTED READINGS

Gibson DG, Glass JI, Lartigue C, et al. Creation of a bacterial cell controlled by a chemically synthesized genome. *Science.* 2010;329:52-56. *Report of the design, synthesis, assembly, and transfer of a 1.08–megabase pair* Mycoplasma *genome, with retention of donor characteristics by the recipient.*

Jones KE, Patel NG, Levy MA, et al. Global trends in emerging infectious diseases. *Nature.* 2008;451:991-994. *Catalogs 335 infectious diseases emerging between 1940 and 2004; approximately 60% are zoonoses, and 54% are due to bacteria or rickettsia, reflecting a large number of drug-resistant microbes in the database.*

Sogaard OS, Lohse N, Harboe ZB, et al. Improving the immunogenicity of pneumococcal conjugate vaccine in HIV-infected adults with a Toll-like receptor 9 agonist adjuvant: A randomized controlled trial. *Clin Infect Dis.* 2010;51:42-50. *Example of the use of Toll-like receptor agonists as adjuvants to enhance vaccine immunogenicity.*

Turvey SE, Broide DH. Innate immunity. *J Allergy Clin Immunol.* 2010;125:S24-S32. *Excellent review of recent advances, and how innate immunity interacts with adaptive immunity.*

Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science.* 2010;328:228-231. *The salient findings of these experiments are discussed in the text.*