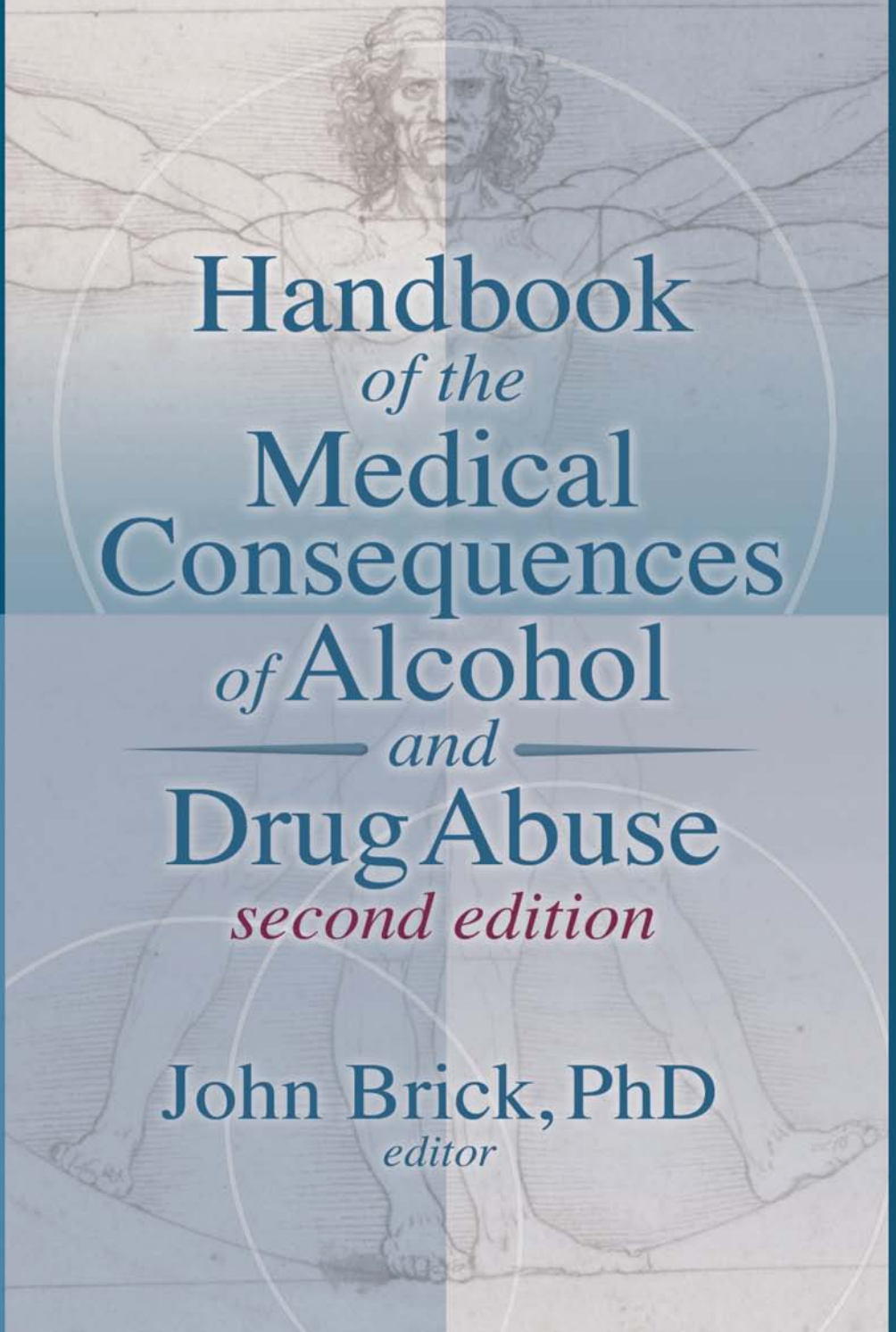

Handbook of the Medical Consequences of Alcohol and Drug Abuse

second edition

John Brick, PhD

editor

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Second Edition

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Second Edition

John Brick, PhD
Editor

Routledge
Taylor & Francis Group
New York London

Routledge is an imprint of the
Taylor & Francis Group, an informa business

Cover design by Jennifer Gaska.

Library of Congress Cataloging-in-Publication Data

Handbook of the medical consequences of alcohol and drug abuse / John Brick, editor.—2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-7890-3573-8 (hard : alk. paper)
ISBN 978-0-7890-3574-5 (soft : alk. paper)
1. Substance abuse—Pathophysiology—Handbooks, manuals, etc. I. Brick, John, 1950-
[DNLM: 1. Substance-Related Disorders—physiopathology. WM 270 H2365 2007]

RC564.H3585 2007
616.86—dc22

2007026488

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ABOUT THE EDITOR

John Brick, PhD, MA, FAPA, a scientist and educator specializing in alcohol and drug studies for more than twenty-five years, is Executive Director of Intoxikon International, a company that provides multidisciplinary education, training and consulting in alcohol and drug studies to governmental and other agencies. As a member of the research faculty of the Rutgers University Center of Alcohol studies for fourteen years, he held positions as Chief of Research at the Rutgers Center of Alcohol Studies, Education and Training Division, Chairman of the Graduate Curriculum on the Biology of Alcohol, Lab Director of the Alcohol Behavior Research Laboratory, and Associate Director of both the Rutgers Summer School of Alcohol Studies and the Advanced School of Alcohol and Drug Studies. He taught courses in neuropharmacology and related courses at Rutgers and elsewhere for twenty years.

Dr. Brick is the author of over 100 scientific treatises, including the *President's Commission of Model State Drug Laws–Socioeconomic Evaluation of Addictions Treatment; Drugs and the Brain; Drugs, the Brain and Behavior: The Pharmacology of Alcohol and Drug Abuse* (Haworth) and is co-editor of *Stress and Alcohol Use and Alcohol and Aggression* and has authored numerous book chapters and original research on the biobehavioral effects of alcohol and other drugs.

In 1990, Dr. Brick was one of six Americans invited to address the Soviet National Academy of Medicine on their centenary anniversary and the only American alcohol research scientist to receive this distinct honor. In 1992, he co-organized and chaired the International Conference of Alcohol and Aggression and was promoted to Fellow of the American Psychological Association for his outstanding contributions to the science of psychology. In 2002, Dr. Brick was a visiting faculty member at Peking University Institute of Mental Health/International Center of Health Concerns in Beijing, China. Dr. Brick taught Medical Consequences of Alcohol Abuse and addiction-related topics to physicians as part of the first WHO medical educa-

tion initiative in China. He is currently Senior Editor for the Haworth Medical Press Neuropharmacology Book Program and has an appointment as a consultant in Biological Psychology and Psychopharmacology for the Rockland County Medical Examiner's Office in New York. Dr. Brick has been in private practice in Yardley, Pennsylvania, since 1985.

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Foreword

When I wrote the foreword to the first edition of the *Medical Consequences of Alcohol and Drug Abuse,* I stated that the information in the book would remain current "for many years to come." Not satisfied with such currency, Dr. John Brick, editor, has chosen to update and expand upon the topics presented earlier, plus add a number of new and unique chapters. Thus, this edition has almost twice as many chapters as the first edition, with eight new ones and updated versions of the previous topics. To the editor's credit, most of the original authors agreed to update and expand their chapters and he has recruited a number of additional expert scientists to write on specific critical issues of the day regarding medical issues associated with drug use and overuse.

In addition to the original chapters on alcohol pharmacology and toxicology, neuropsychological consequences of alcohol and drug abuse, and alcohol effects on the brain neurochemistry, a new chapter on the consequences of chronic alcohol consumption on brain structure and function has been added. This chapter, written by experienced researchers in the field, provides the latest information on the microstructure and macrostructure of the brain after chronic alcohol use, magnetic resonance imaging (MRI) studies, how brain function changes are related to what is seen in MRIs, and longitudinal studies relating to recovery of function with abstinence.

Updated chapters from the first edition include important topics such as consequences of prenatal alcohol and other drug exposure (two chapters), health consequences of marijuana use, medical consequences of acute and chronic alcohol use, medical consequences of cocaine and other stimulant use and abuse, and consequences of inhalant abuse. These chapters have all been updated and remain significant sources of established and new information on topics mentioned previously. Of special importance, of course, is the information on stimulants, including cocaine, methamphetamine, and other stimulants that always seem to be in the news and are of interest because of their great dependence potential. I still find the chapter on mari-

juana to be very important because of its fair and balanced discussions on current topics and the medical aspects of marijuana use.

The remaining seven chapters of the *Handbook of the Medical Consequences of Alcohol and Drug Abuse* are perhaps even more unique and exciting, mainly because they are brand new. It is difficult to find synthesized easy-to-read reviews of contemporary drug problems involving steroids, over-the-counter (OTC) medications, and street drugs such as Ecstasy, LSD, PCP, and mescaline. However, this book has them. Although steroids are not generally considered to be "addicting," medical consequences associated with their use are significant. Furthermore, steroids are always in the news, yet few athletes or others on steroid-enhancing drugs realize or they apparently ignore the enormous risks associated with the use of these chemicals: effects on the endocrine system, the gastrointestinal system, the liver, the circulatory and musculoskeletal systems, and of course the central nervous system. The chapter on steroids clearly lays out all these medical risks and concludes with a discussion of problems associated with routes of supply and methods of administration.

The chapter on problems with the use of OTC medications is unexpectedly comprehensive, given the wide array of OTC medications that can be abused. Medications covered include antihistamines, "cold remedies," caffeine, cough medicines, decongestants, and nicotine replacement products. In this chapter, one can find answers to questions such as "What are the side effects of dextromethorphan on the liver, heart, and skin?" and "What are the medical consequences of caffeine?" This is a unique chapter on an important topic that readers will find fascinating.

Ecstasy and other "hallucinogens" are dealt with in another comprehensive chapter, and of course include "street" and "club" drugs that are so dangerous to adolescents and others who do not recognize their medical dangers. The psychological and physiological effects of these drugs are significant and are outlined with great clarity in this chapter. The coverage includes a history of the use of these drugs, drug interactions and pharmacokinetics of some of the drugs, and complete listings of the effects of these drugs on the major organ systems of the body.

Always contemporary and significant are the health effects of tobacco, nicotine, and exposure to tobacco smoke pollution, dealt with in another of the new chapters. I think this must have been a difficult chapter to write, since there is so much scientific literature on nicotine and smoking. However, the authors have done a fine job sorting out contemporary articles and mixing them with classic information. For example, the nature and history of tobacco use leads to a discussion of diseases caused by tobacco. The health effects of "light" (quotation marks intended) versus regular cigarettes

and noncigarette tobacco products (cigars, pipe smoking, and smokeless tobacco) are all included. Where else would you find a scientific discussion of beedis and kreteks, two other forms of noncigarette tobacco products? I was especially impressed with the topics having to do with the benefits of smoking cessation, the effects of smoking on the fetus and early child development, and exposure to tobacco smoke pollution, including secondhand smoke.

Nearing the end of Dr. Brick's book, one finds a highly significant chapter on the interaction of alcohol with medications and other drugs. Does alcohol interact with anticonvulsant medications? With antibiotics? With antidepressants? Of course, and the reasons are spelled out in this chapter. Two general types of interactions, pharmacodynamic and pharmacokinetic, are explained, along with the classical descriptions of additive, synergistic, potentiation, and antagonism types of interactions that are so common with many drugs, but especially with alcohol. As my favorite pharmacist would say, "Where was this information when I was going to school?" This is a wonderful listing of drugs that interact with alcohol that every medical professional should be aware of, along with explanations of the pharmacological mechanisms of those interactions.

The chapter on the little-considered adverse effects of alcohol and drug abuse in the oral cavity is very interesting. Many of us have heard of "meth mouth," but how many of us think about the oral effects of cannabis, Ecstasy, or even alcohol? What is the dental management of the patient who abuses alcohol or other drugs? This chapter, written by dental specialists, is an unusual and welcome addition to this second edition.

The final chapter concerns a very difficult topic, special issues in patients with comorbid psychiatric and chemical dependency disorders. Most clinicians knowingly or unknowingly deal with such patients every day, yet know very little about how to help them. It takes special skills, not only to diagnose individuals with comorbid (co-occurring) disorders, but also to find ways to reduce their suffering. Complex issues such as whether chemical dependency leads to psychiatric illness or whether psychiatric symptoms lead to drug abuse or dependency are considered in some detail. Other questions about which symptoms relate to "true" comorbid disorders and which symptoms are less serious and temporary are dealt with head-on in this chapter. Included are assessment tools, treatment models of comorbid disorder, post–acute withdrawal syndrome, comorbid disorders and suicide, and alcoholism treatment medications and comorbid disorders. Clinicians who read this chapter will not only begin to understand the enormity of the problem but also will find some answers to the difficult question "How do I deal with such patients?" There is hope!

One person could never have written such a comprehensive book. The editor and the authors have done an outstanding job of updating previous chapters and covering some topics that are hard to find anywhere else. I still believe, as I said in my previous foreword, that this book is worth taking the time to read in its entirety. On the other hand, with today's busy professionals, cherry-picking the chapters of greatest importance to the reader is also very easy in such a well-organized book. Either way, John Brick's *Handbook of the Medical Consequences of Alcohol and Drug Abuse* is an excellent addition to anyone's resource library.

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Preface

In formulating the second edition of this book, I was again reminded of the magnitude of alcohol and drug abuse in everyday lives. The addition of many new chapters will hopefully expand the appreciation of this problem. As previously noted, the philosopher Thomas Hobbes (1588-1679) described the condition of humanity as "nasty, brutish and short." Interestingly, he was among the first proponents to write about the biological basis of behavior. In the ensuing 250 years or so, the great human condition and the quality of life have improved in most societies. Life is less nasty, less brutish, and far longer than it has ever been. With few exceptions, life as Hobbes knew it has changed dramatically, although then, as now, alcohol and other drugs were available and abused. Today, highly sophisticated neuroscientific research techniques enable scientists to study the neurophysiological and molecular changes that produce acute intoxication, and the increased longevity provided by advances in medical science allows the long-term consequences of alcohol and drug abuse to be more fully appreciated. Centuries ago, one was more likely to die from infectious diseases, other ailments, or occupational injuries before the pernicious medical consequences of alcohol or drug abuse presented themselves. This assumption is no longer true.

Handbook of the Medical Consequences of Alcohol and Drug Abuse is part of The Haworth Medical Press series in neuropharmacology and is written with the goal of bringing the most recent findings to scientists, physicians, other clinicians, and advanced students of this fascinating and important topic. Alcohol scientists know more about the long-term consequences of alcohol and other drugs than at any other time in our history. Basic and clinical research in this area must continue, as must the efforts to educate physicians and other health care professionals, and increase public education and awareness of this problem. Included in this book are those drugs that generate the most interest and greatest consequences. In the sec-

ond edition of this book, I am pleased to include eight new and important additional chapters that offer cutting-edge insights into the medical consequences of alcohol and other drugs, as well as updates in a field that is constantly evolving. No special significance should be given to the use of the phrase "alcohol and other drugs," which appears throughout this book. Alcohol is a drug and the use of the phrase is for heuristic convenience only.

Acknowledgments

The contributors have made this a pleasant and worthwhile endeavor and I thank them for taking time from their busy schedules to share their perspectives on this complicated problem. Several others, whose names do not appear in the list of contributors, have nonetheless been influential in this endeavor. Thanks to my first mentor, Dr. Mary E. Reuder, who instilled in me the value of academic excellence and encouraged my pursuit of knowledge; to colleagues Drs. Zelig Dolinsky and Carlton Erickson for their thoughtful comments throughout various stages of this book; and to Drs. Larissa Pohorecky and David Lester for stimulating my interest in alcohol studies. Special appreciation and thanks go to my secretary, Jacquelyn Kaizar. Her steadfast navigation through the seas of revisions made for clear sailing through both editions and was invaluable.

I have been extremely fortunate to have always the encouragement, understanding, and fresh perspective of my wife, Laurie Stockton, and my daughters, Stephanie and Kyla, who remind me every day what life is all about. Thank you. And last but not least, my thanks to Violet Holmes, without whom none of this would be possible. Thank you for providing a lifetime of optimism and hard work and for encouraging me to think with my head, not with my feet.

Chapter 1

Characteristics of Alcohol: Definitions, Chemistry, Measurement, Use, and Abuse

John Brick

We begin this textbook with an overview of alcohol, one of the oldest and most widely used psychoactive drugs on earth. In an effort to provide a foundation for the interpretation of terms related to alcohol and its use throughout this text and elsewhere, this introductory chapter will define alcohol both as a chemical and as a drug, explain the scientific notation for reporting alcohol in blood or serum, and present an overview of the use of alcohol: how we currently define alcohol use, abuse, and dependence in American society.

WHAT IS ALCOHOL?

The term "alcohol" is used to define several types of alcohol, including the three most common: ethyl alcohol (ethanol), methyl alcohol (methanol), and isopropyl alcohol (isopropanol). All alcohols have a similar chemical structure and contain a hydroxyl group, OH, attached to a saturated carbon molecule. Methyl alcohol, also known as methanol or wood alcohol, is so highly toxic that even small amounts (less than an ounce) may cause retinal damage. Methanol's toxicity is the result of its metabolism to formaldehyde and then to formic acid, a cellular toxin that is about six times more poisonous than methanol. The accumulation of formic acid produces severe metabolic acidosis and more than 6 to 7 ounces of methanol are lethal for most adults.

Isopropyl alcohol, also known as isopropanol or common rubbing alcohol, is also highly toxic. Small amounts, as little as a few ounces, can cause permanent damage to the visual system, and 8 ounces is considered a lethal dose. Some alcoholics may consume methanol or isopropanol, intentionally or unknowingly, and of the three alcohols with potentially lethal consequences discussed here, methanol and isopropanol are the most dangerous.

The alcohol that is the subject of this review and the alcohol consumed as a beverage by most people, is ethanol, a clear, relatively odorless chemical. The lethal dose (LD:50) of acute ethanol is estimated to be a blood alcohol concentration of about 0.40 percent, although death may occur at higher or lower concentrations depending upon factors such as tolerance or the presence of other drugs. Given reasonable alcohol pharmacokinetics, a 150-pound male would reach LD:50 after consuming about four to five drinks per hour over a four-hour period. Sublethal doses are more insidious and are the primary focus of this review. Throughout this chapter and throughout this book, the term alcohol will be synonymous with ethanol.

Whether we are discussing alcohol as a chemical or psychoactive drug, alcohol is a relatively simple molecule, CH_3–CH_2–OH, formed during a process of fermentation that occurs when yeast combines with water and sugar. The yeast recombines carbon, hydrogen, oxygen, and water to form alcohol and carbon dioxide. Different types of alcoholic beverages are derived from the use of different fermenting ingredients. Wine manufacturing, for example, may utilize grapes, apricots, berries, and other fruits that are rich in sugars and provide the necessary oxygen for fermentation. Fermentation continues until a maximum alcohol concentration of about 15 percent is reached, at which point, the concentration of alcohol is so high the yeast dies. Beers are manufactured with a *different* source of sugar, namely, the starch found in cereal grains, which is enzymatically converted to sugar through a malting process. This process involves sprouting cereal, such as barley, in water. The dried sprouts are then mixed with water. The enzymes formed during sprouting convert starch to sugar, which allows fermentation to proceed. For beers, the process of fermentation is stopped when the alcohol concentration reaches about 3 to 6 percent by volume, although some specialty beers may contain significantly more alcohol. For wines, the process is stopped, or found to be self-limiting, at higher concentrations (typically 11-13 percent by volume). Distillation of fermented beverages allows exceptionally high alcohol concentrations (typically 50-60 percent by volume in some beverages and up to nearly 100 percent in other products) to be obtained.

The range of alcohol concentration in alcoholic beverages is determined by biological processes, manufacturing design, or some combination of the two. Alcoholic beverage contents are usually expressed as a percentage of

alcohol by volume, as in the case of beers and wines, or as "proof," an archaic term that is twice the alcohol concentration by volume. From a scientific perspective, the total amount of alcohol in a measured drink should be standardized so that for all practical purposes it is the same from drink to drink. However, the differences in alcohol concentrations among beverages may have medical consequences because of the direct action of alcohol on the tissues with which it comes in contact. The concentration of alcohol in beverages varies widely from about 3 percent in the case of light beers to about 50 percent or more in some liquors. Outside the laboratory, the amount of alcohol in a serving varies due to many factors (e.g., container or serving size, drink formulation, etc.). As alcohol absorption to maximum concentration in blood takes from about 30 to 90 minutes in most social-drinking cases, and total absorption takes even longer; beverage type and beverage concentration may be a factor in determining some of the medical consequences of alcohol use (Brick, 2006). Therefore, studies regarding the acute effects of alcohol should be conducted, and the results interpreted with this fact in mind.

SCIENTIFIC NOTATION FOR ALCOHOL CONCENTRATIONS

Throughout this book, alcohol concentrations are expressed using various scientific notations. When comparing the results within these chapters with other references, it may be necessary to convert from one scientific notation to another. The concentration of alcohol in blood, serum, water, or any other liquid is the quantity of absolute alcohol by weight in a fixed volume of fluid. When alcohol is measured in breath, most breath-testing instruments are calibrated to take a fixed breath sample size. Instruments are designed on the basis of certain physiological assumptions and calibrated so that the results are reported as whole blood equivalents (e.g., 0.10 percent). In some literature, alcohol concentrations are reported as grams/2,100 cc air, and in blood or other tissues or fluids, they are more commonly reported in milligrams per deciliter (mg/dl). In molecular biological studies of how alcohol affects tissues, alcohol is sometimes reported in millimolar concentrations (mM). In those studies, mg/dl alcohol = mM alcohol × 4.6 provides a good conversion to a more identifiable concentration. This will be helpful for interpreting some of the data presented in Chapter 5, for example, ethanol concentrations of more than 50 mM (about 230 mg/dl) affect certain brain receptors but in some neurons, concentrations of more than

100 mM (about 460 mg/dl) were necessary to inhibit certain neuronal actions. These are relatively high doses.

When alcohol is measured in blood, the reported blood alcohol concentration (BAC) is the amount of alcohol by weight in a fixed volume of blood, which is usually 100 ml in the United States. BAC is usually expressed in g/100 ml or mg/100 ml of whole blood or serum. The following BAC notations are identical with regard to the amount of alcohol expressed: 0.10 percent, 0.10 g percent, 0.10 g/100 ml, 0.10 g/dl, 100 mg/dl, 100 mg percent, 100 mg/100 cc or ml.

Clinical Measurement of Alcohol

Most hospital clinical laboratories measure alcohol in serum, rather than in whole blood. As alcohol is distributed throughout the water-containing compartments of the body including the blood, serum alcohol is not the equivalent of a blood alcohol concentration because serum contains more water than the whole blood from which it is derived. Therefore, the concentration of alcohol in whole blood is less than that of the serum in proportion to their respective water contents. This may have important implications for scientists comparing test results. Early studies reported that the plasma: whole blood ethanol ratio ranged from 1.10 to 1.35 with an average of 1.18 (Payne, Hill, and Wood, 1968). Payne's average value of 1.18 has found acceptance in the literature (Baselt, 2000) and corresponds as well as our observations comparing serum alcohol measured by the alcohol dehydrogenase (ADH) method with gas chromatography analyses of the same sample (unpublished observations). Other studies suggest the ratio of serum: whole blood alcohol ranges from about 1.1 to 1.18 (Winek and Carfagna, 1987) to 1.25 (Hodgson and Shajani, 1985). Individual differences between subjects or within the same subject after some medical interventions, for example, may alter the water content of blood. Various mathematical models have been proposed when interpreting BACs particularly in patients with hemodilution or hemoconcentration (Brick, 2006; Brick and Erickson, 1999).

DEFINING ALCOHOL USE

Alcohol has been consumed for thousands of years, but the medical consequences of alcohol abuse have come to the attention of the medical/scientific community only in the last 150 years or so. Alcohol consumption and related problems have been well documented (Dufour, 1999). In the United States, for example, nearly half the adult population consumes

alcohol, and alcohol-related medical problems account for a disproportionate number of hospital admissions. Data from the National Longitudinal Epidemiologic Survey indicate that nearly 9 percent of adults in the United States consume, on average, more than two drinks per day (Dawson et al., 1995), and the results of an ongoing national survey of high school students recently reported that among twelfth graders, about 3 percent consume alcohol daily and about half of them had consumed alcohol within the last month of the survey (Johnston, O'Malley, and Bachman, 1999). The use of alcohol and other drugs also has a profound economic impact. Estimates place the cost of addiction at more than $200 billion per year from the effect of alcohol on families and society through lost wages, absent or ineffectual parental models, and shared exposure to high risks and resulting injuries associated with intoxication.

Alcohol use is not always associated with deleterious medical consequences. In fact, some research suggests that alcohol use under some conditions is beneficial to health. How alcohol exerts such biphasic effects has been the subject of considerable research and debate. However, we can define alcohol use in two ways: first, through current definitions of use, abuse, and dependence and, second, by defining what constitutes "a drink." The social use of alcohol is now generally described as a cold beer after a ball game, a glass of wine with meals, or a glass of champagne at festive occasions. Alcohol consumption is often defined as drug abuse (or misuse) whenever it places the drinker or others affected by the drinker's behavior at increased risk for injury. The term "moderate" drinking is sometimes used by clinicians, and often used by laypersons, to describe consumption that is neither abusive nor very infrequent, or that describes a constellation of behavioral or other factors that *differentiate* it from "light" or "heavy." However, these terms are relative. For example, a "moderate" drinker may drink heavily (e.g., more than six drinks a day on some days) but not be classified as a "heavy" drinker. On the other hand, the U.S. Department of Agriculture (USDA) and the U.S. Department of Health and Human Services in the *Dietary Guidelines for Americans* defines moderate drinking as one drink per day or less for women and two or fewer drinks per day for men (USDA, 1995). In addition, the National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2000) further recommends that people aged 65 and older limit their consumption of alcohol to one drink per day. The terms light, moderate, and heavy should be interpreted carefully based on the operational definition of the study as the definitions of these terms vary. Similarly, there is considerable variation in terms of defining "a drink" (Case, Destefano, and Logan, 2000; Kerr et al., 2005).

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 1994) defines two types of problem drinkers: (1) abusers, who intentionally drink too much, too often, and make wrong choices about their use of alcohol, and (2) dependent users (i.e., alcoholics), who lack control over their use of alcohol in lifestyle situations in which abusers would generally stop drinking. Voluntary alcohol abuse is a significant problem that contributes to accidents, medical expenses, lost productivity, family problems, and, of course, a host of direct and indirect medical consequences. Drug dependence, whether the drug is alcohol or some other psychoactive substance, is a brain disease caused by a neurochemical imbalance. The addict has no control of his or her alcohol or other drug use (see Erickson and Wilcox, 2001, for a review). Both types of drinkers are overly represented as inpatients and as patients in hospital emergency rooms.

What Constitutes a Drink?

We can also define what is meant by a drink by standardizing this definition across beverage types so that the interpretation is meaningful and useful. Many epidemiological and empirical research studies define alcohol consumption in terms of the number of drinks consumed or the number of grams of absolute alcohol. Often the precise definition of what constitutes a drink is not included in studies or the range of definitions makes it difficult to compare results across studies. Equating commonly consumed beverages, a drink can be defined as 1.5 ounces of 80-proof alcohol, 5 ounces of 12 percent wine, or a 12-ounce standard beer (~4.8 percent v/v) (Brick, 2006). Each of these contains approximately 14 grams of alcohol, 0.6 ounces of absolute alcohol, and about 100 kilocalories. Outside of the laboratory, a mixed drink may contain more or less than 1.5 ounces of 80-proof alcohol (or the equivalent) and wine may be served in volumes larger or smaller than 5 ounces. Similarly, the concentration of alcohol in beers varies from an average of about 3.8 percent (v/v) for "light" beers to about 5 percent (v/v) for most beers. Imported or specialty beers may contain significantly more alcohol by volume (Case et al., 2000).

Regardless of the type of alcoholic beverage consumed, it is the psychoactive drug ethanol that produces the effects on the brain, virtually all cells within the body, and behavior. The degree of those effects is determined by the concentration, amount, and time of consumption, bioavailability due to factors such as absorption and biotransformation of alcohol, and drinking experience. All of these factors ultimately result in the exposure and response of various cells to concentrations of alcohol.

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Chapter 2

Medical Consequences of Acute and Chronic Alcohol Abuse

John Brick

INTRODUCTION AND OVERVIEW

More has been written about alcohol and its diverse effects than any other drug. Alcohol is one of the oldest drugs known and it affects virtually every organ system in the body. The number of physiological systems affected by alcohol is staggering both in the scope of medical consequences and in terms of the economics of medical treatment of alcohol-related disorders. Alcohol damages the heart and can elevate blood pressure, increasing the risk of heart failure and stroke. Excessive alcohol consumption can injure various tissues, produce diverse physiological changes, and impair and interfere with the hormonal and biochemical regulation of a variety of cellular and metabolic functions. Chronic alcohol exposure increases the risk for certain forms of cancer, and both acute and chronic alcohol use significantly increase the risk for accidental injuries and impairs the recovery from those injuries. However, not all of the medical consequences of alcohol use are deleterious. Substantial research indicates the beneficial effects of this drug. Nonetheless, the economic and psychosocial costs of alcohol use in American society alone are estimated at more than $200 billion per year. This chapter will review the most significant and well-known medical consequences of alcohol use and abuse in four basic areas: accidental injuries, the skeletal system, the gastrointestinal system, the hepatic system, and the cardiovascular system.

ALCOHOL AND ACCIDENTAL INJURIES

Accidental injuries are a direct medical consequence of alcohol intoxication and it is well known that alcohol increases the risk of injuries through impairment of cognitive and psychomotor functioning while performing or engaging in a variety of behavioral activities. Among these, the effects of alcohol on automobile, bicycle, motorcycle, boating, aquatic, and pedestrian injuries, as well as homicide, suicide, and death from fire have been examined.

Impaired Driving

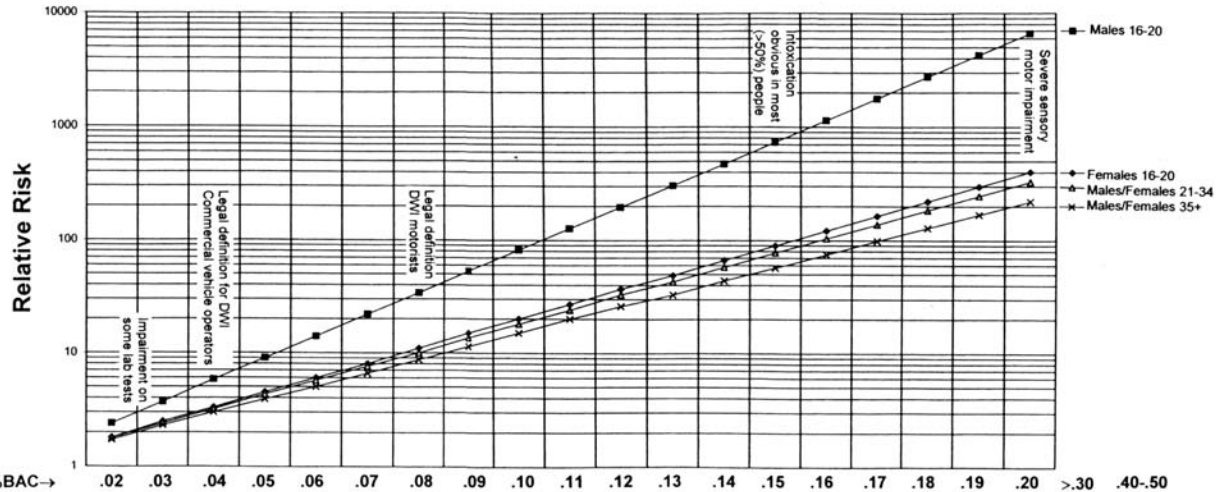
Driving while intoxicated is probably the most well-studied injurious consequence of drinking. Whereas the older scientific literature on drinking and driving focused on the effects of high blood alcohol levels on simple reaction time, on the visual system, and on gross impairment, it is now known that the effects of alcohol are much broader and occur at relatively low blood alcohol levels. For example, alcohol use is coupled with increased risk taking and impulsivity, at least among young males (Cherpitel, 1993), and decreased seat belt use (Centers for Disease Control [CDC], 1991), which invariably places drinkers at increased risk of injury. It is now known that very low levels of alcohol (0.02-0.03 percent) impair the performance of complex divided attention tasks, at least in laboratory studies. Divided attention is believed to be a critical factor in a variety of tasks outside the laboratory, and divided attention failure is the most likely cause of motor vehicle collisions at blood alcohol levels above 0.05 percent, for it is at this level that impairment translates into actual highway statistics (in which the intoxicated driver is the cause of the accident). At higher blood alcohol levels (e.g., 0.15 percent or more), impairment in proprioception, visual perception, and lengthened simple reaction time are additional significant contributing factors to motor vehicle accidents. Most people who present obvious symptoms of intoxication are driving impaired and at increased risk for a fatal crash. Unfortunately, the lack of obvious intoxication does not mean lack of impairment. Most subjects do not appear visibly intoxicated, even though they are intoxicated according to law in regard to motor vehicle operation (Brick and Carpenter, 2001; Brick et al., 1992; Wells et al., 1997; Langenbucher and Nathan, 1983). When most people appear obviously intoxicated, their blood alcohol concentration (BAC) is probably well in excess of any legal definition of intoxication (Hobbs, Rall, and Verdoorn, 1996).

Regardless of which functions are affected by alcohol, impaired drivers clearly present a public health risk because of the increased number of accidental injuries due to intoxication. About 16,000 people are killed each year as a result of drunken driving (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2000), and about 10 percent of all personal injury accidents and at least 180,000 to 200,000 property and personal injury crashes, respectively, are caused by alcohol intoxication per year (Wieczorek, 1995). The risk of injury as well as the responsibility for causing a collision when driving while intoxicated is proportional to the blood alcohol level. With the current legal definition of driving while intoxicated (0.08 percent), the relative risk for a crash is conservatively estimated to be about six to seven times greater than driving while sober (see Table 2.1). When the interaction between blood alcohol level, gender, and single versus multiple vehicle collisions is considered, the relative risk is many times greater than previously believed. For example, one recent study suggests that the relative risk of a single car collision for a 16- to 20-year-old male with a blood alcohol level of about 0.10 to 0.15 percent is about 82 to 735 times greater when compared with controls. Older subjects (21- to 34-year-olds) have less risk than younger less experienced drinkers, but it is still significantly high—about 18 to 58 times greater compared with controls (Zador, Krawchuk, and Voas, 2000).

Pedestrian and Fall-Down Injuries

The relationship between alcohol intoxication and automobile accidents is by far the most well-studied of alcohol-caused injuries, the investigation of the role of alcohol intoxication in other types of injuries is growing. Earlier studies estimated that about one-third of all fatally injured pedestrians had a BAC of 0.10 percent or more at the time of their death. As driving and pedestrian activity rely on divided attention and visual motor processes, it is reasonable to infer that they share similar alcohol-induced changes in relative risk, although, driving is obviously a more challenging task than walking. Blomberg et al. (1979) reported that the relative risk of involvement in a fatal pedestrian injury did not begin to rise significantly until the pedestrians reached a BAC of 0.15 percent or higher. More research is needed, particularly on the relative risk of nonfatal injuries in intoxicated pedestrians. Driving is a more complex task than pedestrian activity but both behaviors require divided attention, vigilance, and other cognitive skills that are sensitive to the impairment produced by alcohol, often at very low BACs (*Alcohol World,* 1990; NIAAA, 1988; Surgeon General's Workshop on Drunk Driving, 1988).

TABLE 2.1 Alcohol Intoxication, Behavior, and Relative Risk for a Single Vehicle Fatal Crash



%BAC→	.02	.03	.04	.05	.06	.07	.08	.09	.10	.11	.12	.13	.14	.15	.16	.17	.18	.19	.20	>.30	.40-.50
Age 16-20 females*	1.8	2.5	3.3	4.5	6	8	11	15	20	27	37	49	67	90	122	164	221	299	403	Comatose	~LD:50
Age 16-20 Males	2.4	3.7	5.8	9.0	14	22	34	53	82	127	196	305	473	735	1141	1772	2752	4273	6634		
Age 21-34 females/males	1.8	2.4	3.2	4.3	6	8	10	14	18	24	33	43	58	78	104	138	185	247	330		
Age 35+ females/males	1.7	2.3	3.0	3.9	5	7	9	11	15	20	26	33	44	57	75	99	129	169	221		

Note: Line graph shows relative risk (log) as a function of BAC, age, and gender. Data derived from stepwise logistic regression coefficients for relative risk is presented in tabularized form below graph. Coefficients are rounded to nearest tenth or whole number. These coefficients apply to single vehicle fatalities. Note that for women age 16-20, a coefficient of 0.03 (range 0.044-0.014) was used. *Source:* Based on Zador et al., 2000, *J Stud Alc* 61(3): 387-395, Zador et al., 2000, USDOT. NHTSA DOT HW 809 051. Also included are biobehavioral descriptors from Brick and Erickson, 1999.

With regard to pedestrian activity, the person must divide their attention between many different tasks. When sober, many of these tasks are performed without difficulty or conscious effort. However, alcohol intoxication may interfere with the ability to walk, in which it is necessary to lift the leg, flex the foot, step forward, rotate the hip, redistribute the weight to the load bearing leg, and repeat this sequence while also allowing for changes in the road surface, and so on. When an intoxicated individual must attend to the many components involved in walking and attend simultaneously to highway, roadway, or structural challenges, that person is at increased risk for an accident, much like the motor vehicle operator.

Injuries related to falls are the second leading cause of accidents in the United States, and account for about 13,000 deaths per year. Most studies suggest that alcohol increases the risk for injuries due to falls, but one study in particular included a control group that allowed researchers to analyze increases in relative risk for a fall due to alcohol intoxication. Honkanen et al. evaluated 313 emergency room patients, more than half of whom had blood alcohol levels greater than 0.20 percent, and compared them with pedestrians who were at the same location of the accident one week later at the same time of day (Honkanen et al., 1983). The comparison revealed the relative risk for a fall was three times greater for patients with blood alcohol levels between 0.05 and 0.10 percent, ten times greater for patients with blood alcohol levels between 0.10 and 0.15 percent, and 60 times greater for patients with BACs 0.16 percent or higher (Honkanen et al., 1983). More than two-thirds of drivers, pedestrians, and bicyclists (see the following) who are killed each year are intoxicated (National Highway Traffic Safety Administration [NHTSA], 1994).

Bicycling

Intoxication is believed to be a factor in nonmotorized vehicle injuries as well. According to NHTSA, there are about 200 fatalities and 7,000 injuries from alcohol-related bicycle crashes each year, and that bicyclists who died at the scene were four times as likely as those who died at hospitals to be legally intoxicated which may be due to the effects of alcohol on injury outcome (discussed later in this chapter). Olkkonen and Honkanen (1994) used a case-control study method, to estimate the relative risk of an alcohol-related bicycle crash. The study involved 200 bicycle victims who were injured fatally in road traffic accidents during the years 1982-1988, and 700 cyclists who were used as unmatched controls for these cases. The study found that alcohol was involved in 25 percent of the collision accidents and in 63 percent of the single accidents involving cyclists aged 15 to 64 years and whose

blood alcohol was measured. Only 4 percent of the controls were under the influence of alcohol. A relative risk was of the order of 3 overall, and 58 for the collisions related to alcohol use. Li et al. reported that fatally injured bicyclists were about twice as likely to be intoxicated as cyclists treated for nonfatal injuries (Li et al., 1996).

Fires and Burns

Alcohol intoxication is a contributing factor in injuries from fires and burns, which account for an estimated 5,000 fatalities and about 1.4 million injuries a year, and is a leading cause of accidents and deaths in the United States (Baker, O'Neill, and Karpf, 1992). Howland and Hingson (1987) reviewed studies on alcohol and burn injuries published between 1947 and 1986 and reported on the percentage of the victims who were intoxicated from alcohol. In the overwhelming majority of studies, it was concluded that alcohol exposure was more likely among those who died in fires ignited by cigarettes than from other causes. Although the evidence is not definitive, it strongly suggests that alcohol plays a role in the cause of fires and of subsequent burn injuries and is overly represented in burn victims. It is noteworthy that in a study of deaths due to fire, Hingson and Howland found that one-third to two-thirds of these victims had blood alcohol levels greater than 0.10 percent, which at the time of the study, represented the blood alcohol level that defined intoxicated driving in most states. The authors concluded from these data that alcohol intoxication is a risk factor for fire deaths (Hingson and Howland, 1993). Later studies further revealed that alcohol was a factor in about 22 percent (Cherpitel, 1989) to 26 percent (Jones et al., 1991) of burn injuries. Overall, intoxicated patients have a significantly higher fatality rate in severe burn cases. These data are more thoroughly reviewed in the Ninth Special Report to the U.S. Congress on Alcohol and Health (NIAAA, 1997).

Impairment from alcohol is one of several risk factors found in a substantial percentage of burn victims. For example, Brezel and Kassenbrock (1988) examined drug and alcohol abusers, psychiatric patients, and those with neurological dysfunction to determine whether this group had more complications, more surgical procedures, and longer hospital stays than burn patients without these disorders. However, alcohol abuse (defined as six or more cans of beer or the equivalent, per day) was the most common form of impairment. Although impaired patients had more complications and required a longer period of hospitalization, alcohol intoxication was only one of several contributory factors.

In a study of 1,074 patients admitted to a medical center burn unit, McGill et al. (1995) found that the 40 percent who were positive for alcohol were more likely to have a greater proportion of bodily burns and greater incidence of smoke inhalation than controls. Chronic alcoholics also seem to have a higher fatality rate than do patients without a history of chronic alcohol abuse (Haum et al., 1995). Interestingly, the authors found no significant differences between sober and acutely intoxicated alcoholics suggesting that neurological or other long-lasting consequences of alcohol abuse and acute intoxication produce risk. The authors conclude that alcohol intake prior to burn injury is an independent risk factor in this population.

In a review on the epidemiology and toxicological complications of burn cases involving alcohol and other drugs, Brick (2006a) concluded that there is a clear relationship between alcohol or drug intoxication and the risk for thermal injury. For example, alcohol-intoxicated persons may be at increased risk for accidental injury because of impaired judgment or psychomotor coordination while engaging in normal fire-starting activities (e.g., cooking), but psychomotor impairment is one part of the problem. Neuropsychological status while intoxicated may impair various domains of cognitive functioning decreasing the ability to anticipate problems, lower inhibitions, and increase risky behaviors. Once a fire has started, mental confusion and failure to recognize risk or danger may lead to an inability to anticipate or respond to danger, particularly at high levels of intoxication. This evolving literature shows that the interaction between burn injuries and intoxication is often complex and includes many variables in addition to intoxication.

Water Sports

The relationship between alcohol intoxication and leisure activities, such as swimming and boating, has been a subject of scientific interest for some time. For example, it can be reasonably predicted that because alcohol impairment causes errors in judgment, disorientation, hypothermia, impaired psychomotor skills, and a decrease in the ability to hold one's breath, it would increase drowning accidents. However, studies published prior to 1985 did not establish a causal relationship between these effects of alcohol intoxication and drowning. Hoxie et al. reported that 45 percent of drowning victims had some alcohol in their system and 22 percent were intoxicated with blood alcohol levels of 0.10 percent or more at the time of death (Hoxie et al., 1988). More recent studies suggest that alcohol consumption significantly increases risk for boating fatalities. In a review of the Boating Accident Report Files in Ohio from 1983 to 1986, Molberg et al. found that

alcohol consumption was a factor in up to 21 percent of reported boating accidents (Molberg et al., 1993). As alcohol deleteriously impairs balance, motor function, and judgment, intoxicated passengers, as well as vessel operators, are probably at risk for injury (Hingson and Howland, 1993).

In another water sport activity, diving, alcohol intoxication contributes to and aggravates spinal cord injuries that frequently follow diving accidents. In this context, Perrine et al. examined the effects of alcohol on the ability to perform shallow-water entry dives under experimental conditions (Perrine, Mundt, and Winer, 1994). The data revealed a progressive and significant impairment of specific aspects of diving performance at blood alcohol levels of 0.04 percent and higher. Interestingly, this study also correlated diving performance with psychomotor performance using the same standardized field sobriety tests used by many police to detect drunk drivers. Impaired diving correlated well with subjects who failed the validated scoring criteria for the detection of drivers with a blood alcohol level of more than 0.10 percent (Perrine, Mundt, and Winer, 1994).

Aircraft Operation

One of the more complex divided attention tasks to challenge persons outside of the laboratory is flying an aircraft. Pilots must attend to an array of instrumentation and make perceptual and cognitive decisions based on a large amount of information in an environment that changes in more than one plane. Although there have been few cases of fatal airline crashes due to pilot intoxication, sufficient data is available to raise concern about this issue of airline safety. For example, it is known from research in other fields that alcohol impairs skills such as divided attention that are believed necessary for safe motor vehicle operation. It is also known that alcohol deleteriously influences the ability of pilots to evaluate their performance (Morrow et al., 1991) and that low levels of alcohol (0.025-0.04 percent) impair performance of trained pilots in flight simulators (Billings et al., 1991; Ross, Yeazel, and Chau, 1992).

The effects of alcohol on piloting skills may exceed the direct pharmacological action of alcohol. It has also been suggested that alcohol can impair performance on flight simulators many hours after blood alcohol levels have returned to zero (Yesavage, Dolhert, and Taylor, 1994). Although these studies are based on known biobehavioral effects or on flight simulator results, rather than epidemiological data, it is clear more research is needed to understand this important relationship.

Suicide

Suicide or attempted suicide is an often undiagnosed medical consequence of alcohol use. Yet suicide is the eleventh leading cause of death, and for those aged 15-34, the third leading cause of death in the United States (National Center for Health Statistics, 2003).

In a recent review of 16 studies of acute intoxication and suicide attempts, Cherpitel et al. (2004) found that that the mean percentage of alcohol use was 40 percent but the range varied from 10 to 73 percent for attempted suicide and 10 to 69 percent for completed suicides. Although it is generally accepted that there is a relationship between alcohol use and suicide, existing data are often incomplete. For example, Cherpitel et al., in their excellent review, point out that definitions of intoxication in suicide reports included both subjective or objective alcohol data. Nevertheless, the relationship between intoxication and suicide is not difficult to understand. Acute intoxication reduces inhibitions, narrows attention, impairs the ability to appreciate the consequences of behavior, and may promote depressive thoughts and hopelessness, whereas chronic alcohol abuse is often complicated by mental illness, including depression (Cheng, 1995; Conner, Beautrais, and Conwell, 2003; see Waller and Lomer, this volume). In both acute and chronic intoxication, impaired psychomotor and cognitive skill, enhanced aggression including self-aggression, or the use of alcohol in combination with medications may be other biopsychological pathways mediating this behavior (Cherpital, Borges, and Wilcox, 2004). Although, it is unlikely that normally adjusted people commit or attempt to commit suicide simply because they are intoxicated, premorbid suicidal ideology is more likely to be acted upon while under the influence of alcohol. However, there is some evidence that acute intoxication is a greater risk factor for suicide than the previous drinking history (Borges and Rosovsky, 1996) but the causal mechanism for the relationship between alcohol and suicide is simply not known (Hufford, 2001). For more information, see Chiapella and Conner (2004).

Miscellaneous Injuries

In a recent case-control study, Dawson examined the relationship between intoxication and the risk of death from external causes (e.g., suicide, homicide, and accidental injuries) and found that relative to lifetime abstainers and infrequent drinkers, the risk of death from external causes increased logarithmically among infrequent binge drinkers (Dawson, 2001). There was no evidence of reduced risk of death among light or moderate drinkers. The group at highest risk of death from external causes were

drinkers who drank less than once a month, but when they did drink, consumed five or more drinks. Within this group, older subjects (defined as 65-plus years) were at the highest risk, but younger drinkers (defined as 18 to 24 years of age) were also at high risk of death. Middle-aged drinkers (25 to 64 years of age) did not show the same increased mortality risk, which the author suggested was related to tolerance and experience. Although these data suggest that infrequent binge drinking, as defined, increases risk as a function of age, possible tolerance, and age-related experience, the blood alcohol level that would result from five drinks would be relatively low, allowing the other variables to have a measurable impact.

Intoxication and Injury Outcome

Not only does alcohol intoxication produce direct medical consequences as a result of injuries (e.g., fractures, traumatic amputations, etc.) sustained in a motor vehicle crash, for example, it may also affect injury outcome, particularly head injuries. This is highly significant as up to half of traumatic brain-injured patients have BACs of 0.10 percent or more at the time of injury (Zink et al., 2001). For example, motorcycle riders with head injuries are about twice as likely to have fatal head injuries if they are intoxicated than similarly injured riders who are sober (Luna et al., 1984), and contrary to popular misconception, drunk drivers are more likely to be seriously or fatally injured than sober drivers (Waller et al., 1986). Alcohol-intoxicated accident victims with central nervous system injuries were more than twice as likely to die sooner than anatomically matched controls (Zink, Maoi, and Chen, 1996).

The mechanisms of the exacerbating effects of alcohol on central nervous system injuries are intriguing, but not well understood. Animal studies suggest that the mechanism may be due to the inhibition of free radical scavengers such as dimethyl sulfoxide (Albin and Bunegin, 1986), alcohol-induced cerebral edema as a result of lipid peroxidation (DeCrescito et al., 1974), or increases in plasma osmolality (Elmer, Goransson, and Zoucas, 1984; Steinbok and Thompson, 1978). However, Ward, Flynn, and Miller (1982) found that hospitalized major trauma victims with average blood alcohol levels of about 0.15 percent were significantly less likely to die from injuries than victims in the sober control group. Similarly, Kraus et al. (1989) found that contrary to expectations, injury severity and mortality were inversely related to blood alcohol levels. This may imply that the mechanisms through which alcohol exacerbates some injuries may be related to metabolic by-products as well as the direct pharmacological actions of alcohol itself. In any case, these older study results support the commonly

held belief that being intoxicated somehow protects against injuries. However, such a belief is not supported by the majority of more current research on this topic (e.g., Fell and Hertz, 1993). Recent studies suggest that the severity of hemorrhagic shock is greater when intoxicated and results in a higher mortality rate compared with sober controls (Molina et al., 2002). Hemorrhagic shock also induces acidosis with marked hypercarbia. In such cases, alcohol-induced acidosis would likely increase morbidity and mortality (Chen et al., 2000; Kinkaid et al., 1998; Molina et al., 2002) possibly because of the effects of acidosis on ventilatory responses. Although the literature is complex, some evidence suggests that the effects of alcohol on respiration are mediated through an opioid system. Zink et al. (and others) found that the opiate antagonist naloxone can improve hemodynamics and cerebral infusion following traumatic brain injury and hemorrhagic shock but not in alcohol-treated animals. However, alcohol-induced depression of hypercapnic (carbon monoxide) ventilatory drive was reversed by naltrexone (Zink et al., 2001). As previously discussed, alcohol abuse also increases risk for death in burn patients (Brick, 2006a).

ALCOHOL AND THE SKELETAL SYSTEM

Although it is not difficult to appreciate the positive and causal relationship between alcohol intoxication and skeletal fractures—one need only look at the large number of motor vehicle and slip-and-fall injuries involving alcohol intoxication—this relationship is more complex and certainly did not start with current epidemiological studies. In fact, the relationship between alcohol abuse and increased risks for skeletal fractures was observed by the ancient Egyptians (Conn, 1985; Mathew, 1992; Seller, 1985). This relationship has since been confirmed by research that suggests alcoholics suffer from a generalized skeletal fragility and are prone to fracture.

Alcohol-Induced Fractures

Much of the current scientific research on the prevalence of fractures in alcoholic subjects is based on epidemiological studies. Those results are complex and are often generally inconsistent. Even so, there is some evidence of a positive association between alcohol intake and fracture occurrence. For example, men hospitalized for alcohol-related problems are four times more likely to have rib fractures than nondrinking patients (Lindsell, Wilson, and Maxwell, 1982) and up to 14 times more likely to have spinal-crush fractures (Crilly et al., 1988; Israel et al., 1980).

Women

In a prospective study, Tuppurainen et al. (1995) found alcohol intake higher among 3,140 perimenopausal women who experienced fractures than among those without fractures. Women who drank alcohol had a risk of a fracture that was about 50 percent higher than among women who did not drink. In another study, increased weekly alcohol intake was associated with greater risks for osteoporotic fractures in postmenopausal women (Paganini-Hill, Ross, and Gerkins, 1981). In the Paganini-Hill study, osteoporotic fractures in women who consumed more than eight drinks per week were almost twice as likely as in nondrinkers. Similarly, a survey of 84,500 U.S. women (ages 34 to 59) who consumed 25 grams of alcohol per day was associated with a 133 percent increase in risk for hip fractures and a 38 percent increase in risk for wrist fractures (Hernandez-Avila et al., 1991). This effect is less common in other populations where the consumption of seven or more standard drinks per week was associated with a twofold increased risk of hip fractures in Japanese women (Fujiwara et al., 1997) and a 4.6-fold increased risk of fractures in a study of black women (Grisso et al., 1994).

In the studies described previously, investigators often compare the relationship between drinking quantity and frequency (e.g., drinks per day) with some medical outcome. The definition of what constitutes "a drink" varies between studies, or in some cases, is not well defined. Therefore, the results from such studies should be viewed in relative rather than absolute terms (Brick, 2006b; Miller, Heather, and Hall, 1991).

Men

Alcohol also increases the risk for fractures in men. In men under the age of 65, two to six drinks per week significantly increased the risk of fractures compared with the same injuries in subjects who consumed less than two drinks per week. For male heavy drinkers younger than age 65, there was almost ten times the risk of hip fractures as men in the same age group who drank lightly (Felson et al., 1988). As sobering as the results for men may be, other investigators have not identified any significant association between alcohol intake and risks for various fractures in women (Cumming and Klineberg, 1994; Diaz, O'Neill, and Silman, 1997; Huang et al., 1996; Johnell et al., 1995; O'Neill et al., 1996). Thus, evidence suggests that excessive alcohol intake increases the risk of fracture but the results are not unanimous. Further, the consequences of low levels of alcohol consumption on skeletal integrity are not well understood.

Age

Studies involving older or intoxicated patients, two groups at high risk for fractures, have methodological limitations including but not limited to defining and quantifying alcohol use due to memory impairment. Despite these problems, including a host of confounding environmental factors such as diet, exercise, and general health, a thorough scientific investigation of the relationship between (moderate) alcohol intake and fracture risks would still have enormous public health implications.

Alcohol-Induced Osteoporosis

In addition to the risk of falls and related injuries previously reviewed, some evidence suggests that alcoholics may also suffer from a generalized skeletal fragility. Bone density is a predictor of fractures and the term "osteoporosis" is synonymous with low bone density or osteopenia (NIAAA, 2000). Saville was the first to demonstrate the association of osteopenia with alcohol abuse (Saville, 1965). Studying the bone mass of cadavers, Saville found marked reductions in the bone mass of persons with a history of alcoholism and further noted that the bone mass of young alcoholic males were comparable to elderly, postmenopausal females. Since those initial observations, numerous studies have confirmed this effect (Peris et al., 1995; Spencer et al., 1986). In a prospective case-control analysis of risk factors for the development of osteoporosis, Blaauw et al. found that average alcohol consumption was two to three times higher in both osteoporotic men and women than in age-matched controls (Blaauw et al., 1994). A similar finding was made in an earlier study in which premenopausal women who consumed more than two standard drinks per day exhibited 13 percent lower bone density of the hip, compared with women who consumed less than one standard drink per week (Gonzalez-Calvin et al., 1993).

Alcohol-reduced bone density is not universally reported within or between studies. Some studies have suggested that increasing alcohol consumption was positively, but anatomically and selectively correlated with bone density (Holbrook and Barrett-Connor, 1993; Lairinen, Valimaki, and Keto, 1991; Lairinen et al., 1993). The Study of Osteoporotic Fractures (7,963 ambulatory, nonblack women ages 65 and older) revealed that modest alcohol intake, less than one drink per day in about 85 percent of the subjects, was associated with higher bone density (Orwoll et al., 1996).

Alcohol's contribution to osteopenia in the overall population is not known, although it is tempting to speculate that lower levels of consumption are less likely to be associated with low bone density and may even be associ-

ated with higher bone density. However, the evidence for a protective effect of moderate alcohol consumption is not entirely compelling and should be interpreted with caution as many confounding factors exist in and between studies.

Microscopic Changes in Bone

Microscopic examination of bone (bone histomorphometry) from alcoholics has been helpful in understanding the etiology of skeletal disorders induced by alcohol. Bone mass is controlled by a remodeling cycle that begins with bone breakdown by cells called osteoclasts. This initial period of resorption is coupled with an equal amount of new bone formation by cells called osteoblasts. Bone mass remodeling is an ongoing process throughout most of the life cycle, but one that can be disrupted by alcohol. Alcoholics generally show a reduction in new bone formation with varying reports of increases (Schnitzler and Soloman, 1984) or no changes in bone resorption (Diamond et al., 1989). Overall, these studies suggest that alcoholic bone disease is characterized by considerable suppression of bone formation.

Although alcohol can disrupt the modeling cycle, these changes are reversible. Rapid recovery of osteoblast function occurs within two weeks of abstinence (Diamond et al., 1989; Feitelberg et al., 1987; Lairinen et al., 1992). Evidence also suggests that lost bone tissue is recovered following abstinence (Peris et al., 1994).

Potential Mechanisms of Alcohol-Induced Bone Disease

The normal growth of bone cells depends upon a variety of orchestrated factors, including adequate nutrition and the function and interaction of various hormones and intercellular regulating factors. Research in this area suggests that, although the exact mechanism through which alcohol affects the integrity of the skeleton is not known, much has been learned. Even so, likely candidates have not been clearly identified.

Chronic consumption of relatively low amounts of alcohol (one to two drinks per day for women; three to four drinks per day for men) can interfere with the normal metabolism of nutrients. As a result of poor diets, impaired nutrient absorption, or increased renal excretion, alcoholics often have deficiencies in minerals such as calcium, phosphate, and magnesium (Bikle et al., 1985; Kalbfleisch et al., 1963; Lairinen et al., 1992; Tetrito and Tanaka, 1974), as well as low levels of vitamin D, which is necessary for the absorption of calcium from the intestinal system (Lalor et al., 1986; Mobarhan et al., 1984). However, there is little histomorphometric evidence that nutritional defi-

ciencies related to alcohol use are a major cause of alcohol-induced bone disease.

Another agent that may contribute to alcohol-induced bone disease is calcitonin, a peptide produced by the thyroid gland. Calcitonin inhibits bone resorption, in effect protecting bone. Some evidence suggests that the acute administration of alcohol (equal to about four drinks in a 150-pound male) increases calcitonin levels by about 38 percent three hours after consumption by nonalcoholic males (Williams et al., 1978). Such hypercalcitoninemia might explain why moderate intake of alcohol is associated with higher bone density. However, little is known about repeated alcohol use or how chronic alcohol affects calcitonin.

Blood calcium levels are regulated primarily through parathyroid hormone (PTH). When blood calcium levels drop, PTH induces the release of calcium from bone and reduces renal excretion of calcium. In nonalcoholic subjects, acute alcohol consumption decreased PTH levels three hours after drinking, but prolonged drinking for three weeks increased PTH levels as well as serum calcium (Lairinen, Valimaki, and Keto, 1991). It is still unclear how alcohol might affect PTH and calcium in a clinical population where decreases in bone density are typically observed.

Gonadal hormones may also play a role in alcohol-induced bone disease since impaired gonadal function is a well-known risk factor for osteoporosis. Moreover, alcohol abuse has long been associated with impotence, sterility, testicular atrophy (Valimaki, Salaspuro, and Ylikahri, 1982), and low testosterone (Van Thiel, Lester, and Sherins, 1974) in men, and menstrual disturbances, spontaneous abortions and miscarriages, impaired fertility, sexual function, and premature menopause in women (Gavaler, 1991; Hugues et al., 1980; Mello, Mendelson, and Teoh, 1993; Valimaki et al., 1984). Studies in women have yielded inconsistent results. Alcohol increases estradiol, a potent form of estrogen, but this effect has only been reported in postmenopausal women who are undergoing hormone replacement therapy. Nonetheless, if moderate alcohol consumption increases estrogen, it could explain the positive relationship between alcohol use and increased bone density in women (Holbrook and Barrett-Connor, 1993; Orwoll et al., 1996).

Chronic heavy drinking alters the growth and proliferation of many different cell types. In alcoholics, biochemical and histomorphometric studies reveal a significant impairment in osteoblastic, but not osteoclastic activity, suggesting that alcohol's primary adverse effects on bones is through osteoblasts. Since bone remodeling and mineralization both are dependent on osteoblasts, chronic heavy alcohol consumption will ultimately reduce bone mass and consequently lead to fractures.

Alcohol may decrease osteoblast proliferation through a direct toxic mechanism or by the inhibition of intracellular signaling processes that regulate cell replication. Preprogrammed cell death (apoptosis) of some cells is enhanced by alcohol (De et al., 1994; Ewald and Shao, 1993).

Alcohol reduces cell protein and deoxyribonucleic acid (DNA) synthesis in normal osteoblasts (Chavassieux et al., 1993; Friday and Howard, 1991) and impairs the induction of compounds called polyamines (Klein and Carlos, 1995), which regulate the synthesis of DNA. By disrupting the intracellular process that normally stimulates polyamine biosynthesis vital to osteoblast proliferation, alcohol even at low blood alcohol levels (0.04 percent range) may inhibit cell division. Exogenous polyamines antagonize the inhibitory effect of alcohol on cell proliferation (NIAAA, 2000). Osteocalcin is a small peptide synthesized by osteoblasts. When released into the circulation, osteocalcin levels are positively correlated with histomorphometric parameters of bone formation in healthy individuals (Garcia-Carrasco, Gruson, and De Vernejoul, 1988) and patients with metabolic bone disease (Delmas et al., 1985). Alcohol produces a dose-dependent decrease in osteocalcin levels and chronic alcoholic patients have significantly lower osteocalcin levels than controls (Labib et al., 1989).

CANCERS

Gastrointestinal Diseases

Not all of the effects of alcohol occur rapidly, as in the cases of motor vehicle crashes, pedestrian falls, subsequent skeletal injuries, or suicide. Some medical consequences of alcohol are more insidious, taking years to unfold before any significant medical consequence is detected. Among these are cell damage caused by the direct or indirect toxic effects of alcohol. The first tissue that alcohol comes into contact with is, in most instances, the upper gastrointestinal system.* With the exception of minute quantities of alcohol that are directly absorbed through membranes in the buccal cavity and esophagus, when swallowed, alcohol goes directly to the stomach in high concentrations. As the toxic effects of alcohol are directly related to dose and concentrations, one might reasonably predict that high concentrations of

* The author has received anecdotal reports from clinicians and recovering alcoholics about intravenous and rectal administration of alcohol, but it is believed that such experimental drug use is rare.

alcohol have potentially deleterious effects throughout the cells of the gastrointestinal system.

Alcohol inhibits smooth muscle contractions in the lower esophagus (Keshavarzian et al., 1994), which may cause chronic esophageal inflammation. Impaired contraction of the smooth muscles in the esophagus and in the stomach can also precipitate gastric acid reflux, resulting in a range of symptoms from the relatively benign but very uncomfortable heartburn, to severe esophagitis (inflammation of the esophagus). Prolonged gastric reflux may lead to permanent tissue alteration, or metaplasia, of the esophageal lining that may progress to esophageal adenocarcinoma (Gray, Donnelly, and Kingsnorth, 1993).

The relationship between alcohol consumption and various cancers of the gastrointestinal and other systems has been the subject of considerable research. For example several studies have demonstrated a positive relationship between alcohol and esophageal cancer. People who consume more than three drinks per day (21 drinks per week) have almost a tenfold higher risk of esophageal cancer than those who drink less than one drink per day (Vaughan et al., 1995). Esophageal cancers include adenocarcinomas as well as cancers that are derived from normal esophageal cells (i.e., squamous cell carcinomas). Both types of carcinomas are related by the local effects of alcohol metabolites or alcohol-metabolizing enzymes such as alcohol dehydrogenase (ADH) on esophageal cells (Yin et al., 1993). For example, acetaldehyde may alter normal DNA repair mechanisms in esophageal cells and lead to gene alterations and tumor formation (Wilson et al., 1994). Alcohol also increases levels of the CYP2E 1 isozyme in the esophageal mucosa, which can activate dietary carcinogens such as nitrosamines (Shimizu et al., 1990).

Even though high concentrations of alcohol reach the stomach from the esophagus, and in spite of the effects of alcohol consumption or alcohol metabolites on DNA, alcohol use is not clearly associated with a risk of stomach cancer (Franceschi and La Vecchia, 1994). Alcohol can cause gastritis, but other factors, such as bacterium, may be responsible for inflammation of the stomach. For example, gastritis and ulcer disease in nonalcoholics is often caused by *Helicobacter pylori*. Heavy drinkers have a higher incidence of *H. pylori* and gastritis, than do light drinkers (Paunio et al., 1994). As alcoholic gastritis is not readily cured by abstinence but is improved by treatment with antibiotics, it has been quite reasonably suggested that gastritis is caused by bacterium (Uppal et al., 1991).

The nexus between gastritis and increased risk for stomach cancer is not well established, and the mechanism that leads the progression from chronic gastritis to neoplasia probably involves many factors besides alcohol. For

example, nutritional factors, and in particular the deleterious effects of alcohol on the bioavailability of nutrients, probably play a role in alcohol-related colon cancer in humans. Alcohol in combination with diets low in essential nutrients such as methionine and folate, measurably increases the risk for colon cancer (Giovannucci and Willett, 1994; Giovannucci et al., 1995). Alcohol also induces the formation of benign hyperplastic polyps in the colon and rectum in humans (Kearney et al., 1995).

The association between alcohol and cancers of the colon and rectum is positive, but weak (Doll et al., 1993; Longnecker, 1992; Longnecker et al., 1990; Seitz and Pöschl, 1997). Again, although alcohol probably plays some role, other mechanisms are probably involved. Recent studies indicate that smoking tobacco coupled with drinking alcohol may serve as a triggering mechanism for colon cancer (Yamada et al., 1997). Acetaldehyde may also have a role as a cocarcinogen in cases of rectal cancer (Seitz and Pöschl, 1997). See NIAAA (2000) for further discussion on this topic.

Does Alcohol Increase the Risk for Breast Cancer?

Despite decades of research suggesting that alcohol increases the risk for breast cancer, reviews of this relationship suggest that the evidence for this relationship is not compelling (English et al., 1995; International Agency for Research on Cancer, 1988; Longnecker, 1992, 1994, 1995; McPherson, Engelsman, and Conning, 1993; Smith-Warner et al., 1998). For example, in a meta-analysis of epidemiological studies, alcohol sometimes showed a one- to twofold fold increase in risk for breast cancer (Longnecker, 1994). One factor may be that a complex alcohol-endocrine interaction exists that may be related to postmenopause hormone replacement therapy (Colditz, 1990; Gapstur et al., 1992; Schatzkin and Longnecker, 1994; Zumoff, 1997). As breast cancers are estrogen dependent and androgen and estrogen levels are both increased by alcohol, and in women with breast cancer, the weak relationship between alcohol and this form of cancer may be obscured by other risk factors (Beard, 1996).

ALCOHOL-INDUCED PANCREATIC INJURY

It is well known that alcohol abuse can lead to chronic pancreatic inflammation, atrophy, and fibrosis, although only a small proportion of alcoholics develop pancreatic injury. Specific risk and mechanisms that lead to alcoholic pancreatitis have been difficult to identify (Doll et al., 1993; Haber et al., 1995), but research from animal models suggests that acetaldehyde

may play some role in the development of alcoholic pancreatitis, as may diets high in polyunsaturated fat. Although alcohol is believed to be a cause of pancreatitis, a link between alcohol and pancreatic cancer has not been made (NIAAA, 2000).

ALCOHOL-INDUCED LIVER INJURY

As a major portion of the alcohol consumed leaves the gastrointestinal tract, it travels via the hepatic portal vein from the small intestines to the liver, the largest organ in the body and the primary site of alcohol metabolism. As some alcohol metabolites are toxic, and because the concentration of alcohol reaching the liver is so high, and the liver is the primary site of alcohol metabolism, liver damage may be among the most likely and most serious physiological consequences of alcohol abuse. This is particularly significant because of the central role the liver plays in so many physiological activities. Epidemiological data clearly reveals that alcohol abuse is by far the leading cause of liver-related mortality in the United States. Excessive alcohol consumption leads to three serious types of liver injuries: fatty liver, hepatic inflammation (alcoholic hepatitis), and progressive liver scarring (fibrosis or cirrhosis). Chronic heavy drinking can alter normal metabolism and lead to an accumulation of fat in the liver. As a result, the liver cells become infiltrated and the liver itself becomes enlarged. The bad news is that extensive lipid infiltration may damage cells. The good news is that fatty liver condition is reversible with abstinence.

Hepatitis is a more serious medical condition, characterized by prolific inflammation and tissue damage. Hepatitis is life threatening but there can be significant recovery following abstinence. The most serious form of liver damage is cirrhosis. This irreversible liver disease is characterized by scarring and cell death. Impaired liver functioning can cause primary hepatic encephalopathy, a brain disorder characterized by altered psychomotor, intellectual, and behavioral functioning.

Although chronic, heavy drinking may produce metabolic tolerance and unusually high rates of alcohol elimination, hepatitis and fibrosis will ultimately impair liver function and produce a reverse metabolic tolerance and impaired oxidation of alcohol. Underreporting of alcohol consumption makes the exact prevalence of alcoholic liver disease in the United States difficult to measure, but health statistics suggest that some form of alcoholic liver disease affects more than 2 million drinkers (Dufour, Stinson, and Caces, 1993). It is estimated that 900,000 Americans have cirrhosis, and

of the 26,000 who die each year, 40 to 90 percent have a history of alcohol abuse (Dufour, Stinson, and Caces, 1993).

It is clear that the development of alcoholic liver disease is due to a combination of factors, most notably, prolonged alcohol consumption. One commonly asked question by both scientists and concerned drinkers is "How much alcohol does one need to drink before liver damage occurs?" Epidemiological studies suggest that reliable signs of injury begin after a "threshold" dose of alcohol is reached. Although there are always individual exceptions, the evidence suggests that the threshold is equal to a cumulative dose of about 600 kilograms for men, and between 150 and 300 kilograms for women. To place this in perspective, at the high end (for men), this is roughly equivalent to the average consumption of 10 to 12 drinks a day for ten years, and at the low end (for women), about three drinks per day (see Chapter 1). Below these doses, it is difficult (but certainly not impossible) to reliably detect liver injury (Lelbach, 1975; Marbet et al., 1987; Mezey et al., 1988; Tuyns and Pequignot, 1984), or the damage is not significant enough to warrant medical attention. The differences in threshold doses between men and women cannot be accounted for by anthropometrics or pharmacokinetics. In addition, many individuals who consume these amounts of alcohol never develop liver disease and less than one-half of heavy drinkers develop alcoholic hepatitis or liver fibrosis (Lelbach, 1975). This suggests that alcohol does not produce its effects independently and that hereditary and/or environmental factors interact with alcohol to affect the natural history of liver injury (Marbet et al., 1987). Marbet et al. suggested that other factors contribute to the pathogenesis of liver disease in alcoholics because even though a substantial amount of alcohol is required to induce liver injury, alcohol dose alone is not a good predictor of the severity of liver injury (Marbet et al., 1987).

Numerous possible mechanisms may affect the susceptibility of certain people to alcohol-induced liver damage, but the exact mechanisms by which chronic alcohol abuse leads to liver disease are unknown. A number of mechanisms have been suggested which will be briefly reviewed in following text.

Mechanisms of Liver Injury

The metabolism of alcohol by hepatocytes requires oxygen, a process that produces free radicals, such as hydroxyl and 1-hydroxyethyl radicals and superoxide anions (Kukielka, Dicker, and Cederbaum, 1994; Rashba-Step, Turro, and Cederbaum, 1993; Reinke et al., 1994). These highly reactive compounds can interact with proteins, lipids, and DNA to cause damage or death to liver cells (Fromenty et al., 1995; Nordmann, Rjbiere, and Rouach,

1992). Chronic alcohol consumption also causes white blood cells (neutrophils) to migrate to the liver where they are activated by an inflammatory substance to release large amounts of superoxides, which may contribute to liver pathology (Bautista et al., 1992).

Normal liver cells contain antioxidants that can neutralize free radicals. Chronic alcohol consumption decreases antioxidant levels in the liver resulting in a state of oxidative stress that makes liver cells more susceptible to free-radical-induced injury. One such antioxidant is glutathione, which is present at high concentrations in liver cytosol and mitochondria. Alcohol inhibits glutathione transport from the cytosol to the mitochondria of the cell, causing impaired mitochondrial functioning, which is believed to cause necrosis (Fernandez-Checa et al., 1991; Garcia-Ruiz et al., 1994).

Acetaldehyde is another highly reactive compound that may promote hepatic injury as high concentrations of this metabolite can become a substrate for aldehyde oxidase and other enzymes which produce free radicals as byproducts of this reaction (Kato et al., 1990; Shaw and Jayatilleke, 1990; Tsukamoto et al., 1995). Since earlier studies have demonstrated that alcoholics accumulate high levels of acetaldehyde (Baraona et al., 1987), acetaldehyde may be part of the process by which the production of free radicals increase and injure liver cells. Acetaldehyde also can react with specific amino acid residues on cellular proteins to form acetaldehyde-protein adducts (Holstege et al., 1994; Niemela, Juvonen, and Parkkila, 1991), which tend to be localized in sites of greatest liver injury. Acetaldehyde-protein adducts may also stimulate liver cells to produce collagen, which may result in fibrosis and, ultimately, cirrhosis (Bedossa et al., 1994; Casini et al., 1993). Eriksson (2001) recently pointed out that the most compelling evidence that acetaldehyde plays a role in alcoholic liver disease comes from a study of alcoholics who carry the ALDH2*2 and ADH2*2 alleles. In Asian, but not Caucasian alcoholics, there is an association between ADH2*2 alleles and cirrhosis. Interestingly, people with this allele drink less than those without it but are not protected from alcoholic liver disease. In fact, they may develop liver disease (i.e., cirrhosis) at lower levels of alcohol consumption (Eriksson, 2001).

Chronic alcohol use also depletes hepatic levels of vitamin A and E antioxidants (Hagen et al., 1989; Leo, Rosman, and Lieber, 1993), which enhance alcohol-induced lipid peroxidation and exacerbates liver injury in animals (Kawase, Kato, and Lieber, 1989; Sadrzadeh and Nanji, 1994). However, health-supplement drinkers should note that neither vitamin A nor E has been shown to have any significant preventative effects against alcoholic liver injury (Ahmed, Leo, and Lieber, 1994; Leo et al., 1992; Sadrzadeh et al., 1995).

Cytokines are a diverse group of substances with inflammatory, fibrogenic, and growth-promoting properties. Many cytokines associated with alcohol-related liver disease are also believed to be mediators of liver injury because patients with alcohol-related hepatitis frequently have high circulating levels of cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor–alpha (TNF-alpha) (Bird et al., 1990; Hill et al., 1992, 1993; Khoruts et al., 1991; Ohlinger et al., 1993; Sheron et al., 1993; Tilg et al., 1992). Cytokines IL-8 and TNF-alpha, in particular, correlate negatively with prognosis of liver disease (Felver et al., 1990; Hill et al., 1992, 1993; Sheron et al., 1993). Another cytokine transforming growth factor-beta (TGF-beta), which is found in the livers of alcoholics, is believed to be critical in the development of hepatic fibrosis.

Cirrhosis

Chronic alcohol consumption induces liver fibrosis (scarring) by stimulating the fat-storing cells of the liver to differentiate into collagen-producing stellate cells. It is believed this leads to irreversible cirrhosis. Alcoholic liver fibrosis may occur indirectly through acetaldehyde-protein adducts that can enhance collagen synthesis by stellate cells in vitro (Bedossa et al., 1994; Casini et al., 1993; Moshage, Casini, and Lieber, 1990). Products of lipid peroxidation also increase collagen synthesis which may lead to fibrosis (Maher, Tzagarakis, and Gimenez, 1994; Parola et al., 1993; Tsukamoto, 1993).

Though there are a variety of biomechanical mechanisms through which alcohol or alcohol metabolites may cause liver damage, the problem is more complex. Hereditary variations in enzymes may explain why only a small proportion of alcoholics develop serious liver disease. Although generic variants, polymorphisms in ADH, CYP2E1 isozyme, and aldehyde dehydrogenase (ALDH) result in various rates of alcohol metabolism among different ethnic groups, no single ADH allele has been causally linked to alcoholic liver injury (Chao et al., 1994; Day et al., 1991; Poupon et al., 1992).

ALDH polymorphisms may also play a role in the development of alcoholic liver injury. ALDHY, an allele which is present in about half of all Chinese and Japanese, encodes an enzyme that is completely nonreactive toward acetaldehyde. ALDHY homozygotic individuals (those who have two copies of this allele) generally have an aversion to alcohol because of the accumulation of acetaldehyde. However, chronic drinkers who are ALDHY heterozygotes (those who have one copy of the ALDHY allele) do not have an alcohol aversion and develop liver injury more frequently and at lower

cumulative doses than people with normal ALDH (Enomoto et al., 1991; see Eriksson, 2001).

Finally, gender may also play a role in the development of alcohol-induced liver damage. Some evidence indicates that women are more susceptible than men to the cumulative effects of alcohol on the liver, even though women drink less than men (Becker et al., 1996; Gavaler and Arria, 1995; Hisatomi et al., 1997; Naveau et al., 1997; NIAAA, 1997). Compared with men, women who have alcoholic liver injuries remain at higher risk of disease progression even with abstinence (Galambos, 1972; Pares et al., 1986). This curious gender difference suggests that gastric ADH may be a causative factor. ADH is present at high levels in the liver in both men and women, but differences in gastrointestinal ADH between men and women may affect its bioavailability. Women have lower levels of gastric ADH activity than men (Frezia et al., 1990; Seitz et al., 1992) so their livers receive more concentrated levels of alcohol from the gut, thereby placing women a greater risk for liver damage. Although this is an interesting concept, other investigators have found no such gender differences in gastric ADH activity (Thuluvath et al., 1994), and some researchers question the significance of the stomach in the first-pass metabolism of alcohol (Levitt and Levitt, 1994).

Gender differences in alcohol-induced liver injury may be related to gender differences in the metabolism of fatty acids rather than alcohol itself. The accumulation of nonmetabolized fatty acids in the liver through alcohol inhibition of the oxidation of fatty acids by hepatic mitochondria has long been known to be part of the alcoholic disease process (Lieber and DeCarli, 1970; Lieber, Jones, and DeCarli, 1965). It is believed the infiltration of fat impairs intracellular functioning and causes cell injury (NIAAA, 1997).

CARDIOVASCULAR DISEASES

Cardiovascular disease is the leading cause of death among Americans, followed by cancer and stroke (U.S. Department of Health and Human Services [USDHHS], 1995). The role of alcohol as both a risk factor and a potential protective factor for cardiovascular disease has been the focus of intense investigation for many years (see NIAAA, 1997; Zakhari and Wassef, 1996). The results are clear: alcohol has both deleterious and beneficial effects, but the conditions under which alcohol exerts these unusual behavior effects and the mechanisms involved are complex at best.

Alcohol and Heart Disease

It has been known for nearly 80 years that heavy drinking decreases longevity. Pearl noted that moderate drinkers lived longer than either abstainers or heavy drinkers (Pearl, 1926). Over the life span, total alcohol consumption is inversely associated with heart damage. The deterioration of heart muscle, a condition known as alcoholic cardiomyopathy, is one of the most serious consequences of chronic heavy drinking. As cardiac cells deteriorate, the unique ability of these cells to contract is impaired. This is particularly significant in the heart's left ventricle, which pumps freshly oxygenated blood throughout the body. Compensatory mechanisms result in an enlarged heart, but any benefit from such cardiac hypertrophy is temporary. Eventually the heart is unable to meet the body's demand for oxygen. Alcoholic cardiomyopathy is the most common cause of nonischemic cardiomyopathy in Western societies and is a major source of heart failure and death (NIAAA, 1997, 2000).

As with other diseases, women may also be more sensitive to the toxic effects of alcohol on the heart, even though women drink less, or report drinking less, than men (Fernandez-Sola et al., 1997; Urbano-Marquez et al., 1995).

Possible Beneficial Effects of Alcohol on Coronary Heart Disease (CHD)

Several prospective studies have reported a reduced risk of death from CHD across a wide range of alcohol consumption. These include studies among men in the United Kingdom (Doll et al., 1994), Germany (Keil et al., 1997), Japan (Kitamura et al., 1998), and the United States (Fuchs et al., 1995). The definitions of moderate drinking vary among studies; however, most, if not all, of the apparent protective effect against CHD was realized at low to moderate levels of alcohol consumption. For example, in the Fuchs study of more than 85,000 U.S. women, "light to moderate" drinking ranging from one to three drinks per week to one to two drinks per day was associated with a reduced risk of death from cardiovascular diseases.

A meta-analysis of data from 19 cohort studies and six case-control studies found that the risk of death from CHD was reduced at all levels of alcohol consumption, but the maximum reduction in risk occurred when alcohol consumption was low (English et al., 1995). Other studies have suggested that the protective effects of alcohol are greatest in people already at risk for cardiovascular diseases. For example, an analysis of data from a nine-year follow-up of 490,000 Americans in the Cancer Prevention Study II (Thun et al.,

1997) found that both men and women who consumed alcohol had a 30 to 40 percent lower risk of death from all cardiovascular diseases compared with those who abstained from drinking. This effect was greatest among people diagnosed as at risk and was not related to the amount of alcohol consumed.

Similarly, another large U.S. survey, the National Health and Nutrition Examination Survey I, found that the incidence of CHD in men who drank was lower across all levels of consumption than in nondrinkers (Rehm et al., 1997). CHD was also reduced among women, but only in those who consumed low to moderate levels of alcohol. In fact, an increased risk was observed in subjects who consumed more than 28 drinks per week, a finding that is not unique (see Hanna, Chou, and Grant, 1997).

An association between moderate drinking and lower risk for CHD does not necessarily mean that alcohol itself is the protective agent. For example, a review of population studies indicates that the higher mortality risk among abstainers may be attributable to shared traits—socioeconomic and employment status, mental health, overall health, and health habits such as smoking—rather than participants' nonuse of alcohol (Fillmore et al., 1998).

It is also important to note that the apparent benefits of moderate drinking on CHD mortality are offset at higher drinking levels by increased risk of death from other types of heart disease, cancer, liver cirrhosis, and trauma (USDHHS, 1999). For these and other reasons, the U.S. Department of Agriculture (USDA) and the USDHHS have defined moderate drinking as one drink per day or less for women and two or fewer drinks per day for men (USDA, 1995). In addition, the NIAAA further recommends that people aged 65 and older limit their consumption of alcohol to one drink per day (NIAAA, 2000). Definitions of what constitutes a standard drink vary considerably and should be taken into consideration in interpreting such data (Brick, 2006b).

Beverage Type and Medical Risks/Benefits

The National Longitudinal Alcohol Epidemiological Survey (NLAES) is a measure of the prevalence of alcohol use disorders and associated physical and psychological disorders. Chou, Grant, and Dawson (1998) reasoned that nonalcoholic components of beer, wine, or liquor might produce different effects on health and may explain the "French Paradox" (relatively low mortality despite high saturated fat diets among the French) and examined NLAES data to determine the relationship, if any, between a broad range of diseases associated with alcohol abuse and beverage preference. Compared with abstainers, beer and wine drinkers had reduced morbidity

rates from cardiovascular disease and hypertension. However, liquor drinkers were at increased risk for multiple disorders including diseases of the digestive track, coronary diseases, and arthritis (Chou, Grant, and Dawson, 1998). The authors note that since the nature of the observed effects are unclear and as there are many other factors including amount of alcohol consumed, and interactions with other medications and breast cancer, all of which are associated with moderate drinking, the results should be interpreted with extreme caution. Nevertheless, this study adds to the interesting but complex interrelationship between the protective effects of alcohol use in some people, under some conditions.

How Does Alcohol Protect Against Heart Disease?

The mechanisms through which alcohol may protect against CHD are diverse. Animal studies suggest that alcohol may impede uptake of fatty acids into the heart (Brick, Pohorecky, and DeTurck, 1987), the accumulation of fatty deposits, or atherosclerotic plaques in coronary arteries (Dai, Miller, and Lin, 1997). Furthermore, alcohol consumption may increase links of high-density lipoproteins (HDL), or "good cholesterol," that is clinically associated with lower risk of CHD (Fumeron et al., 1995).

Other studies have indicated that alcohol consumption increases HDL cholesterol levels by decreasing the activity of cholesteryl ester transfer protein (CETP), which transfers cholesterol molecules from HDL particles to low density lipoproteins (LDL) or very low density lipoproteins (VLDL) density lipoprotein particles. High levels of LDL and VLDL are associated with increased risk of CHD (Fumeron et al., 1995). Drinking alcohol seems to alter the gene functioning to increase HDL cholesterol. Researchers have confirmed the association between alcohol consumption and increased HDL cholesterol in people through several large epidemiological studies (e.g., Huijbregts, Freskens, and Kromhout, 1995; Marques-Vidal et al., 1995; Sonnenberg et al., 1996). However, these changes in HDL cholesterol and LDL-cholesterol levels contribute only about half of the observed protection against CHD with alcohol consumption. This suggests that other mechanisms may be contributory to the protective effects of alcohol. For example, alcohol may have antithrombotic effects, and may reduce platelet activation and clotting factor activity (Rubin and Rand, 1994). Indeed, evidence suggests that drinking 30 grams of alcohol (just over two drinks) per day for four weeks causes a reduction of platelet aggregation and a decrease in blood levels of fibrinogen, which stimulates clot formation (Pellegrini et al., 1996). Moderate alcohol consumption may have other antithrombic effects by increasing blood levels of tissue plasminogen activator, an enzyme that breaks

down blood clots (Ridker et al., 1994), or it may suppress the production of substances that promote clotting (Booyse, Aiken, and Grenett, 1999).

Beverage Type and Pattern of Consumption

Wine may confer special protection against CHD (Goldberg, Hahn, and Parkes, 1995) or this protective effect may be due to the alcohol itself (Doll, 1997; Rimm et al., 1996). Reviews of lipid-reducing effects of wines are available (see Chadwick and Goode, 1998; Goldberg, Hahn, and Parkes, 1995) and at least one recent study of Chinese men revealed no additional reduction in overall mortality associated with drinking rice-fermented wine (Yuan et al., 1997). However, other factors besides wine may contribute to this effect. The pattern of drinking, rather than the type of alcohol consumed, may help explain how drinking wine might protect against CHD (Doll, 1997; Grønboek et al., 1995; Klatsky and Armstrong, 1993). For example, wine drinkers tend to consume small amounts of alcohol daily rather than consume larger amounts of alcohol on weekends. It has been suggested that the pattern of frequent drinking may confer some protection against CHD and that large amounts are not needed to achieve a beneficial effect (Bondy, 1996). Similarly, alcohol consumed with meals was found to reduce the postprandial elevations of blood lipids (Beenstra et al., 1990; Rubin and Rand, 1994). Other studies have reported a reduced risk of coronary death or acute myocardial infarction with moderate, regular drinking and an increased risk associated with binge drinking (Kauhanen et al., 1991, 1997; McElduff and Dobson, 1997).

Finally, because many of the epidemiological studies from which much of the evidence is derived have involved middle-aged or older persons in stable social situations, the findings may not necessarily apply to younger drinkers, whose risk of CHD is low to begin with, or to other social groups.

In summary, lowered CHD risk is most closely associated with a consistent pattern of drinking small amounts of alcohol. The apparent CHD benefit is largely, if not wholly, attributable to alcohol itself and not to specific beverages or to other constituents of particular beverages such as red wine. Future research should help bring clarity to this body of literature (Klatsky, Armstrong, and Friedman, 1997; Rimm et al., 1996).

Alcohol and Blood Pressure

There is a well-documented association between heavy alcohol consumption and hypertension (Ascherio et al., 1996; Campbell et al., 1999; Seppa, Laippala, and Sillanaukee, 1996; York and Hirsch, 1997). Heavy al-

cohol consumption elevates blood pressure and causes or exacerbates hypertension (Puddey et al., 1995; Ueshima et al., 1993). It is estimated that one drink per day can chronically increase blood pressure by one millimeter of mercury in aged individuals, and even more in the elderly and people with preexisting hypertension (Beilin, Puddey, and Burke, 1996). Controversy remains as to whether moderate alcohol consumption has any beneficial effects on blood pressure, but reducing alcohol intake may be one means of reducing blood pressure in people with hypertension (Lang et al., 1995; World Health Organization, 1996).

Despite the well-recognized association between alcohol and hypertension, the cellular mechanisms of alcohol's effect on blood pressure are not well understood and are made confusing by the fact that, initially, drinking alcohol dilates blood vessels, which lowers blood pressure. Studies looking to explain how long-term, heavy alcohol consumption reverses this effect and leads to elevated blood pressure have generally concluded that this effect is due to the action of alcohol on the autonomic nervous system. For example, heavy alcohol consumption has been associated with increased release of the stress hormones adrenaline and norepinephrine, which constrict the blood vessels, increase blood pressure, and decrease the sensitivity of baroreceptors. This may be one mechanism through which alcohol leads to hypertension.

Moderate alcohol consumption (about one to three drinks per day) is associated with a slight reduction in blood pressure and may protect against age-related development of hypertension (Gillman et al., 1995; Palmer et al., 1995). The significance of these findings may be offset by an increased risk of death from causes unrelated to cardiovascular disease (e.g., accidental injuries, liver disease, etc.). Heavy alcohol consumption also may alter peripheral regulation of blood pressure by affecting smooth muscle cells in the walls of blood vessels (see Altura and Altura, 1996).

Evidence indicates that the increased blood pressure associated with alcohol use is related to alcohol withdrawal rather than a direct effect of alcohol. Kawano et al. found that a single drink of alcohol depresses the blood pressure of patients with hypertension for several hours (Kawano et al., 1996). However, patients who consume one drink each evening for seven days have blood pressure that seesaws; it is low in the evening and increases in the morning, suggesting that regular consumption of alcohol can raise blood pressure during the hours that alcohol is not consumed (Abe et al., 1994). These findings are consistent with observations that sympathetic-nervous-system-induced increases in blood pressure occur during alcohol withdrawal (Denison et al., 1997).

Stroke Risk

There are two relevant forms of stroke: ischemic and hemorrhagic. Ischemic stroke occurs when a blood vessel in the brain is blocked. Hemorrhagic stroke occurs when a blood vessel in the brain ruptures. Alcohol-related hypertension, or high blood pressure, may increase the risk of both forms of stroke. Yet in people with normal blood pressure, the risk of ischemic stroke may be decreased due to the apparent ability of alcohol to lessen damage to blood vessels due to lipid deposits and to reduce blood clotting. However, whereas alcohol's anticlotting effects may decrease the risk of ischemic stroke, alcohol-induced hypertension may increase the risk of hemorrhagic stroke (Hillbom and Juvela, 1996).

Two relatively recent reviews of the relationship between alcohol consumption and stroke risk revealed no differences in the risk patterns for ischemic or hemorrhagic stroke. One study found clear evidence that heavy drinking was associated with increased stroke risk, particularly in women. This evidence was inconsistent regarding a protective effect of low doses of alcohol against stroke (English et al., 1995). In the second review, the author concluded that although moderate drinking (defined in this review as usual consumption of fewer than two drinks daily for men and less than one drink daily for women) does not appear to increase the risk of ischemic stroke, it is not clear whether moderate drinking protects against this type of stroke (Camargo, 1996). Other studies also fail to offer clear evidence that moderate drinking protects against stroke (Knuiman and Vu, 1996; Yuan et al., 1997) and there is evidence, albeit inconsistent, that moderate drinking may actually increase the risk of hemorrhagic stroke (Camargo, 1996).

In contrast, the Cancer Prevention Study II found that all levels of drinking were associated with a significant decrease in the risk of stroke death in men, but in women, the decreased risk was significant only among those who consumed one drink or less per day (Thun et al., 1997). The Physicians' Health Study reported that male physicians who consumed more than one drink per week had a reduced overall risk of stroke compared with participants who had less than one drink per week (Berger et al., 1999). The authors concluded that the benefit was apparent with as little as one drink per week.

Among young people, long-term heavy alcohol consumption has been identified as an important risk factor for stroke (You et al., 1997). Very recent alcohol intoxication has also been found to be associated with a significant increase in the risk of ischemic stroke, especially in both men and women aged 16 through 40 (Hillbom et al., 1995). For example, researchers in another study reported that recent consumption of alcohol was associated with the onset of stroke in young people during weekends and holidays,

possibly reflecting an association with heavy drinking (Haapaniemi, Hillbom, and Juvela, 1996).

In summary, heavy drinking appears to increase the risk of hypertension and, although the evidence is not entirely consistent, may also increase the risk of stroke. It remains uncertain whether lower levels of alcohol can help prevent ischemic stroke. In addition to examining how much alcohol is consumed, it may be important to consider drinking patterns in determining stroke risk.

Peripheral Vascular Disease

The possibility that alcohol may protect against CHD has led researchers to hypothesize that alcohol may also protect against peripheral vascular disease. In a 1985 analysis of data from the Framingham Heart Study, alcohol was not found to have a significant relationship, either harmful or protective, with regard to peripheral vascular disease (Kannel and McGee, 1985). Other studies have failed to find a significant relationship between alcohol consumption and the narrowing of blood vessels that define peripheral vascular disease as well. However, a recent study produced much more encouraging results. In an analysis of the 11-year follow-up data from more than 22,000 men enrolled in the Physicians' Health Study, researchers found that daily drinkers who consumed seven or more drinks per week had a 26 percent reduction in risk of peripheral vascular disease (Camargo et al., 1997). This study took into account the effects of smoking, exercise, diabetes, and parental history of myocardial infarction.

Two other studies found inconsistent results with regard to gender. One study of middle-aged and older men and women in Scotland showed that as alcohol consumption increased, the prevalence of peripheral vascular disease declined in men, but not in women (Jepson et al., 1995). In contrast, among people with non-insulin-dependent diabetes, alcohol was associated with a lower prevalence of peripheral vascular disease in women but not in men (Mingardi et al., 1997). Clearly, the relationship of alcohol consumption to peripheral vascular disease requires further study.

SUMMARY AND CONCLUSIONS

As a pharmacological agent, alcohol is a relatively simple compound. The ubiquitous nature of this drug on most, if not all major organ systems is consistent with its simple molecular structure and its widespread use. Alcohol affects the gastrointestinal, hepatic, cardiovascular, and skeletal sys-

tems included in this chapter, but these effects extend to the organism as a whole when accidental injuries due to intoxication are considered.

From the available alcohol research, several conclusions may be drawn regarding the medical consequences of alcohol use. Most notably and across physiological systems, alcohol's effects are multiphasic. Although the nature of the deleterious and possible protective effects of alcohol continue to emerge, the conditions under which these medical consequences present themselves is complex and will, in all probability, remain elusive for several years. Variables such as gender, diet, environment, lifestyle, genetics, dose and frequency of alcohol use, other drugs, and age interact in complex but sometimes visible ways. The majority of studies suggest that, overall, higher doses of alcohol are deleterious to many physiological systems and precipitate a range of psychosocial and biobehavioral problems. In some individuals and under some conditions, alcohol use seems to have a beneficial effect on health. Both experimental and clinical studies suggest that the protective effects of alcohol, when they do occur, are most often associated with low doses (the equivalent of about one to two drinks per day).

There are many other medical consequences beyond those selected for this chapter, some of which are presented elsewhere in this book. The exclusion of that body of literature was a function of the enormity of the topic and not the significance of that research. Also, while the research relied upon in this chapter focused on clinical studies, preclinical research has been helpful in testing and identifying many of the underlying mechanisms through which alcohol use and abuse causes pernicious as well as beneficial medical consequences. Finally, the importance of continued multidisciplinary research to identify the conditions under which, and the subjects in whom, alcohol produces medical consequences cannot be overstated.

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