New Treatments for Addiction: Behavioral, Ethical, Legal, and Social Questions

Henrick J. Harwood and Tracy G. Myers, Editors, Committee on Immunotherapies and Sustained-Release Formulations for Treating Drug Addiction, National Research Council

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NEW TREATMENTS FOR ADDICTION

Behavioral, Ethical, Legal, and Social Questions

Committee on Immunotherapies and
Sustained-Release Formulations for Treating Drug Addiction
Henrick J. Harwood and Tracy G. Myers, *Editors*

Board on Behavioral, Cognitive, and Sensory Sciences
Division of Behavioral and Social Sciences and Education
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COMMITTEE ON IMMUNOTHERAPIES AND SUSTAINED-RELEASE FORMULATIONS FOR TREATING DRUG ADDICTION

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Preface

This report is the work of the Committee on Immunotherapies and Sustained-Release Formulations for Treating Drug Addiction. The committee was established in 2002 by the National Academies in response to a request from the National Institute on Drug Abuse (NIDA). NIDA is funding the development of new types of medications to treat drug addiction and sought the advice of the National Research Council and Institute of Medicine about the behavioral, ethical, legal, and social issues likely to arise as a result of the unique characteristics of these medications, if and when they become available.

The charge to the committee was to identify issues that will be raised in determining who should be given these medications and under what circumstances, given the fundamental issue of therapeutic safety. This study was not intended to be a safety review of immunotherapies and sustained-release formulations, which are still under development. However, safety formed a necessary backdrop for all of the issues the committee considered.

The availability of these medications will raise a host of issues, and this report only represents an initial effort identifying the most important ones. Some of these issues will marry traditional vaccine concerns (e.g., establishing and monitoring safety, ensuring efficacy, etc.) with traditional drug abuse treatment issues (e.g., ensuring patient adherence to treatment, use in a variety of settings). The committee was not expected to achieve consensus about how all of the issues should be addressed. Rather, it was expected to achieve consensus about what the issues are likely to be, why they are important, and which are likely to be the most pressing.

The committee's membership reflected wide-ranging areas of expertise, including bioethics, epidemiology and prevention, federal drug approval processes, federal drug policy, genetic aspects of drug addiction, legal issues related to substance use and abuse, risk analysis, state policy issues, financing, treatment delivery in medical and specialty addiction settings, and immunotherapy development.

The work of the committee was immeasurably advanced because several members had direct experience in the development and testing of the types of medications being studied. Two members of the committee have worked to develop active and passive immunotherapies for treating drug dependence; another member has been part of a research group developing depot formulations to treat drug dependence. In forming this committee, the National Research Council (NRC) and the Institute of Medicine (IOM) did not view this work as a conflict of interest but as essential to the accomplishment of the charge from NIDA: to identify and define the behavioral, ethical, legal, and social questions that will be raised in determining who should be given vaccines or depot medications, and under what circumstances.

The committee was not asked to recommend, approve, or disapprove support for the development of immunotherapies and sustained-release formulations for treating drug addiction. Nor was it asked to examine the safety or efficacy of these medications. These therapies are still early in development, and drug approval process of the Food and Drug Administration is ultimately responsible for such determinations.

The committee was aided substantially in its work by a set of commissioned papers, included in this volume, which helped us complete the report. Drafts of these papers were presented at a public workshop in April 2003. We thank the paper authors: Martin Iguchi, Kaley Klanica, Mark Kleiman, Thomas Kosten, Henry Kranzler, Robert MacCoun, Dennis McCarty, Frances Miller, Thomas Murray, Cindy Parks Thomas, Paul Pentel, M. Susan Ridgeley, and George Woody.

The committee's review of the papers presented at the workshop was aided by several individuals who volunteered their time and expertise. We gratefully acknowledge the contributions of these individuals to the committee's work: Jack Henningfield, Pinney Associates; Walter Ling, University of California at Los Angeles; David Smith, California Department of Alcohol and Drug Programs; Penny Ziegler, William J. Farley Center; Rick Sampson, American Institutes for Research; and Matthew Myers, Campaign for Tobacco-Free Kids.

The committee is also grateful for assistance provided by NIDA staff. Timothy Condon, Jamie Biswas, and Cindy Miner briefed the committee early on about the agency's goals for this project. They also very patiently

answered committee members' many questions. We are also thankful to Susan Weiss, who ably served as the NIDA project officer for this study.

At the National Research Council, Christine Hartel was instrumental in guiding and supporting the committee throughout its work. Wendy Keenan served as the skilled, professional, and always helpful senior project assistant, making invaluable contributions to the committee's work.

Finally, we thank the individual committee members. They volunteered their time and expertise working efficiently and cordially. They provided an exemplar of how an interdisciplinary process should work: debating ideas on their merit, sharing insights from various viewpoints, and being consistently respectful of each others' expertise.

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following individuals for their review of this report: Warren K. Bickel, Department of Psychiatry, Ira Allen School, University of Vermont; Peter J. Cohen, Georgetown University Law Center and Physician Health Committee, Medical Society of the District of Columbia; Dorothy K. Hatsukami, Department of Psychiatry, University of Minnesota; Steven Hyman, Office of the Provost, Harvard University; Walter Ling, Department of Psychiatry and Integrated Substance Abuse Programs, University of California at Los Angeles; Eric Nestler, Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas; Charles P. O'Brien, Department of Psychiatry, School of Medicine, University of Pennsylvania; Harold Pollack, Department of Health Management and Policy, University of Michigan School of Public Health; and David J. Rothman, Center for the Study of Society and Medicine, Columbia University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Herbert D. Kleber, Department of Psychiatry and Division on Substance Abuse, Columbia University, and Bernard Lo, Program in Medical Ethics, University of California at San Francisco. Appointed by the National Research Council, they were responsible for making certain that an independent

examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Henrick J. Harwood, *Chair*
Tracy G. Myers, *Study Director*

Executive Summary

New, improved therapies to treat and protect against drug dependence and abuse are urgently needed. In the United States alone, about 50 million people regularly smoke tobacco and another 5 million are addicted to other drugs. In a given year, millions of these individuals attempt—with or without medical assistance—to quit using drugs, though relapse remains the norm. Furthermore, each year several million teenagers start smoking, and nearly as many take illicit drugs for the first time.

Research is advancing on promising new means of treating drug addiction using immunotherapies and sustained-release (depot) medications. The aim of this research is to develop medications that can block or significantly attenuate the psychoactive effects of such drugs as cocaine, nicotine, heroin, phencyclidine, and methamphetamine for weeks or months at a time. The promise of the new medications rests not only on their longer action, but also on differences in the way they operate. Unlike most existing treatments, which are active in the brain itself, immunotherapies act by binding the drug in the bloodstream and preventing it from reaching the brain. This represents a fundamentally new therapeutic approach that shows promise for treating drug addiction problems that were difficult to treat in the past. Despite their potential benefits, however, several characteristics of these new methods pose distinctive behavioral, ethical, legal, and social challenges that require careful scrutiny.

At the request of and with support from the National Institute on Drug Abuse (NIDA), the National Research Council and Institute of Medicine established the Committee on Immunotherapies and Sustained-Release Formulations for Treating Drug Addiction to develop recommen-

dations for research in this emerging field. Specifically, the committee was charged with identifying and defining distinctive behavioral, ethical, legal, and social issues that are likely to arise if and when these medications become available for treating drug addiction. Such issues can be considered unique aspects of safety and efficacy that are fundamentally related to the distinct nature and properties of these new types of medications. The committee was not charged with determining whether or not immunotherapies and sustained-release formulations represented an efficacious approach for treating drug addiction. Nor was it asked to determine whether or not NIDA should continue to fund research on these types of therapies. Rather, the committee was charged with identifying and defining issues that are likely to arise if and when these medications become available. Essentially, the committee was charged with formulating a research agenda. The result of that work is presented herein. This research agenda has been informed by a series of commissioned papers, comments when these papers were presented at a public workshop, and the expertise and judgment of the committee.

BASIC IMMUNOLOGY

The committee examined three different types of therapeutic agents: active immunotherapies, passive immunotherapies, and depot formulations of opioid antagonists. Active immunotherapies use periodic injections to stimulate the body's own protective immune system to generate antidrug antibodies, which then bind drugs of abuse in the bloodstream before they can reach the brain. Passive immunotherapies use preformed antidrug monoclonal antibodies that are produced through advanced biotechnology techniques; they also bind drugs of abuse in the bloodstream and can be infused for immediate treatment for drug overdose. Depot medications are long-acting formulations of existing drugs that are slowly released over time, typically administered as injections.

To date, the new medications have been studied primarily for their efficacy in the treatment of drug dependence, chronic drug use, and drug overdose. It is plausible that they will prove efficacious in protecting against initiation and escalation of drug use. However, the immunotherapies are still quite new, and there is very limited research. The research to date suggests that the concept might work, but that limited research does not constitute evidence that this therapeutic approach or any particular new molecular entity is safe or efficacious. Although there is much more research on depot medications against opiate addiction, the committee was also not charged with a review of the safety or efficacy of depot medications.

Immunotherapy and depot medications can block or significantly

attenuate the psychoactive effects of drugs of abuse by either reducing the amount of drug in the brain (immunotherapies) or by blocking drug effects at their site of action in the brain (sustained-release medications). Research in both human and animal subjects demonstrates that consumption of a blocked drug can fall dramatically or even cease. Another important characteristic of these medications is that they have long durations of action—a month or even longer per administration—which should reduce the problem of nonadherence found with medications that must be taken daily.

Recommendation 1 The National Institute on Drug Abuse should support basic immunology studies on increasing the stability and longevity of antibody blood levels and on developing combination therapies to simultaneously treat a variety of abused drugs.

OFF-LABEL USE

Clinical trials for Food and Drug Administration (FDA) approval of these medications will likely be performed in limited populations—such as adult males and nonpregnant females being treated for drug dependence or drug overdose—because the companies sponsoring such trials seek the least costly way to obtain FDA approval. Once a pharmaceutical is approved, however, the FDA has little effective control over the way it is used in the practice of medicine. However, it is foreseeable that parents and physicians will be interested in using immunotherapies "protectively" with children and adolescents—before they have ever used tobacco or illicit drugs or when use is still at subclinical levels of severity—even if these medications have not been approved for such purposes. Likewise, addiction programs with pregnant patients will be inclined to use these new medications despite the lack of testing in that population. The perception of potential benefits from protective use of immunotherapies for adolescents and pregnant women may be quite high, because the consequences of drug use or addiction can be long-lasting and severe in these populations, and they pose unique challenges. Moreover, the general record of safety of immunotherapies when established for some populations might lead health professionals to expect such safety for these therapies with populations not yet tested.

The potential unwanted behavioral responses from off-label uses of these new medications point to a need to consider expanding the criteria for evaluating pharmaceutical products by the FDA. The means now used by the FDA to measure safety and efficacy in clinical trials may not provide an accurate picture of the costs to society or benefits that these medications will produce in actual use.

Recommendation 2 Recognizing that immunotherapy and sustained-release medications will be used in off-label situations that have not been specifically approved by the Food and Drug Administration, the National Institute on Drug Abuse should support preclinical studies addressing the potential safety and efficacy of these medications when given to vulnerable populations (e.g., pregnant women and their fetuses, adolescents, etc.). Long-term studies should be done with laboratory animals of different ages, as well as their offspring, before trials with vulnerable human populations are undertaken.

Recommendation 3 The National Institute on Drug Abuse should support studies of the likely extent and nature of off-label drug use, including factors and incentives that would promote or retard such use, and the opportunities for policy makers to intervene should the patterns of off-label use depart from what is in the best interest of the society.

TREATMENT

Immunotherapy medications present unique and far-reaching challenges for our current system of medical and addiction treatment. The development of these therapies highlights the need to view addiction as a chronic medical condition requiring long-term management. As such, they will require the historically separate systems of medical care and addiction treatment to forge new partnerships to ensure that both medication and integrated psychosocial services are available to those in need. Offering these treatments in primary care settings should reduce the stigma of substance abuse treatment, but the potential for long-term markers of these treatments or false-positive markers of drug use may discourage treatment participation.

Recommendation 4 The National Institute on Drug Abuse should support studies of whether the potential for discrimination due to long-lasting markers in the blood or urine deters people with drug dependence from accepting immunotherapies. The effects of immunotherapies on false-positive and false-negative drug testing results should also be studied.

Recommendation 5 The National Institute on Drug Abuse should support clinical effectiveness studies and financing models that integrate the new pharmacotherapies with psychosocial services in specialty addiction and primary medical care settings.

BEHAVIORAL EFFECTS

The great potential of immunotherapy will prove problematic if these new medications are incorrectly viewed as "magic bullets." The failure of these medications to meet expectations when used outside research settings could undermine their acceptance and the willingness of government agencies and private firms to finance the research needed to develop them. First, like any medications, these new therapies will not be completely effective for all patients. Second, some individuals may be unwilling to even accept the first dose if they fear making a commitment to sustained abstinence from their drug of addiction for a variety of reasons, including fear that they cannot easily reverse the medication or return to their drug use to relieve protracted withdrawal symptoms or for other needs. Third, for a variety of reasons, some patients will not remain in treatment but will relapse to smoking or drug use. Fourth, some individuals may refuse treatment because the therapies may leave long-lasting markers in their systems, thus subjecting them to possible adverse effects, such as denial for health insurance.

Fifth, some patients who receive these medications—even completely willingly—could behave in ways that would undermine their effectiveness, for example, by switching to drugs that are not targeted by the medication and by attempting to test or override the blocking effect of the medication by taking larger amounts of the drug. Moreover, the existence of what are seen as safe and effective treatments for addiction could make experimenting with drugs seem less risky and hence increase drug use. Conversely, if treatment programs using these new medications succeed in substantially reducing the number of existing addicts, dealers may aggressively attempt to interest new customer bases, as well as engage in violent "turf wars" to maintain profits in their existing markets.

Recommendation 6 The National Institute on Drug Abuse should support studies of behavioral consequences, such as the increased potential for accidental overdose and changes in drug use patterns, which may include switching drugs, increasing drug dosage or overall consumption, changing the route of administration (e.g. nasal to intravenous for greater bioavailability) or, conversely, avoiding use of other addictive substances.

Recommendation 7 The National Institute on Drug Abuse should support studies that examine the extent to which the availability of immunotherapy medications might reduce the perceived risk of drug use and the effects of such changes on drug use behavior in various populations.

Recommendation 8 The National Institute on Drug Abuse should support studies of the potential effect of immunotherapy medications on illicit drug markets and market-related behaviors.

CONSENT AND COERCED TREATMENT

Enthusiasm for the new medications should not obscure the fact that fully informed and voluntary consent is necessary under any and all circumstances. These medications can produce long-lasting biological markers (raising issues of confidentiality and potential for discrimination) and might interfere with drug-testing methods. The free and informed nature of consent is of special concern if the medications are used in settings and circumstances that are inherently coercive. These therapies may offer great benefit, even when used in such settings. However, any such benefit needs to be balanced against the rights to privacy and liberty that have long been recognized in the provision of medical care. Particular complications may arise in obtaining consent from persons in the criminal justice system, from pregnant women, from women who are already parents and involved with the child welfare system, and from adolescents and children whose parents or guardians seek to administer these medications for "protective" use.

Recommendation 9 The National Institute on Drug Abuse should support studies to determine the standards to be applied when immunotherapy medications are considered for use in the criminal justice and child welfare systems including due process protections when there is a government-imposed treatment requirement.

Recommendation 10 The National Institute on Drug Abuse should support studies to carefully articulate the behavioral, ethical, and social risks associated with treatment of pregnant women and their fetuses and protective therapy in minors and to develop clinical practice guidelines for such use or discouragement of such use.

1

Introduction and Background

Drug use is one of the nation's most expensive health problems, costing $109.8 billion in 1995 alone (Harwood, Fountain, and Livermore, 1998). In addition to the financial costs, drug use also exacts a human cost with thousands of lives being damaged and forever changed by drug use and addiction. Prevention and treatment research, as well as clinical experience, have shown that it is often possible to intervene successfully in addiction. However, such interventions must be grounded solidly in research and must also provide long-term behavioral and sometimes pharmacological support to ultimately achieve abstinence.

As part of these research-based interventions, the National Institute on Drug Abuse (NIDA) is funding the development of new classes of medications to treat drug addiction. These medications include immunotherapies and sustained-release formulations. Immunotherapies involve products that are introduced into the body to stimulate an immune response either through active immunization (e.g., vaccines) or passive immunization (monoclonal antibodies). This immune response counteracts the effects of the target drug. Currently, immunotherapies are being developed to counteract the effects of cocaine (see Carerra et al., 2001; Fox et al., 1996; Kantak et al., 2001), methamphetamine (see Aoki, Hirose, and Kuroiwa, 1990); phencyclidine ("angel dust" or PCP) (see Proksch, Gentry, and Owens, 2000), and nicotine (Hieda et al., 1997; Pentel et al., 2000; Tuncok et al., 2001). Sustained-release formulations, also known as depot medications, involve a slow, timed release of medications that counteract the effects of illicit drugs. Sustained-release preparations of naltrexone (Kranzler, Modesto-Lowe, and Nuwayser, 1998) for opioid addiction and

lofexidine (Rawson et al., 2000) to treat nicotine addiction are currently being developed. All three therapies—vaccines, monoclonal antibodies, and sustained-release formulations—are long acting, but time limited, with durations from weeks to months.

The availability of these medications will raise a host of issues. Some of these issues will marry traditional vaccine concerns, such as establishing and monitoring safety, ensuring efficacy, and financing and distributing the medications, with traditional drug abuse treatment issues, such as ensuring patient adherence to treatment, using these therapies in a variety of settings, and dealing with coercive legal methods that are sometimes used to "motivate" treatment initiation. In addition, less traditional issues may also be raised, such as who should be immunized or treated with a depot medication and when, and who will decide.

COMMITTEE CHARGE AND REPORT

NIDA requested the advice of the National Research Council and the Institute of Medicine of the National Academies about behavioral, ethical, legal, and social issues likely to arise as a result of research they are funding to develop immunotherapies and sustained-release formulations. The Committee on Immunotherapies and Sustained-Release Formulations for Treating Drug Addiction was formed to identify and define the behavioral, ethical, legal, and social questions that will be raised in determining who should be given these medications and under what circumstances, given the major issue of therapeutic safety. This study was not intended to be a safety review of immunotherapies and sustained-release formulations, which are still under development, but safety forms a necessary backdrop for all of the issues the committee considered. Morover, the committee was not asked to evaluate the actual or potential efficacy of immunotherapies and depot medications for treating drug addiction. These therapies are still under development, and none has even been submitted to the Food and Drug Administration (FDA) for approval.

The committee was not expected to achieve consensus about how all of the issues should be resolved. Rather, the committee was expected to achieve consensus about what the issues are likely to be and which are likely to be the most pressing Indeed, the committee was charged with anticipating issues that may or may not bear upon the assessment of safety and efficacy of these medications. The committee has attempted to forecast issues that may arise in the therapeutic use of these medications if and when they are approved by the FDA for use. The committee believes that the nature and importance of many of these issues are such that NIDA may wish to encourage research into these issues in parallel with—if not integrated into—clinical trials that are done in order to test and demon-

strate the safety and efficacy of medications. The committee suggests that some or all of these issues be examined during the FDA approval process.

This report reviews the behavioral, ethical, legal, and social issues likely to arise if, and when, immunotherapies and sustained-release formulations become available for treating drug addiction. It identifies the relevant issues and lays out a research agenda for NIDA. Because these therapies are still early in development, no literature exists that the committee could analyze or synthesize as a way of identifying and defining the behavioral, ethical, legal, and social issues. Rather, the committee reviewed similar, but related, literatures to better understand the potential implications of these new medications. This process required some creative thinking and use of judgment and members' expertise about what the issues are likely to be and which of them are most pressing.

The rest of this chapter provides a basic description of both immunotherapies and sustained-release formulations. In Chapter 2 the committee lays out considerations for clinical trials, focusing in particular on issues that are generally considered outside the usual FDA process.

Chapter 3 then considers a range of treatment issues, including the organization and delivery of care in alternative treatment settings, privacy, financing, and costs. Finally, in Chapter 4 the committee looks at potential adverse behavioral responses to the use of immunotherapies and at the difficult practical, ethical, and legal issues of consent, particularly for vulnerable populations.

MEDICAL BASIS OF IMMUNOTHERAPY

Vaccination (active immunization) for the prevention and treatment of human disease has a long and distinguished medical history dating back at least to the pioneering work of Jenner nearly 200 years ago. The World Health Organization (2003) suggests that clean water and vaccines have been the two greatest contributions to worldwide public health. Indeed, vaccines prevent illness or death in millions of individuals each year.

Vaccines work by stimulating an immune response to a disease-related organism or subunit(s). Over a period of weeks to months, immunization(s) lead(s) to the generation of protective antibodies in body fluids, which act as an early surveillance system to block or reduce the effects of an invading organism or substance, such as a toxin.

The next advance in immunotherapy came in the early 20th century. Before the advent of antibiotics, polyclonal antibodies in the form of a specific immune serum were used to treat infectious diseases. Although these antisera were highly effective in treating diseases, such as pneumococcal pneumonia and tetanus, they sometimes produce a serious adverse

side effect called serum sickness (Devi et al., 2002). This allergic reaction resulted from the administration of animal antisera to humans, so animal antisera could only be used as a last treatment option. Later, the technique of plasmapheresis and the development of specific vaccines provided the possibility of immunizing human donors and then collecting human immune globulin for the purpose of treatment (Mallat and Ismail, 2002). Indeed, human immune globulins are still used under certain situations to treat hepatitis B, tetanus, and Varicella zoster (which causes chickenpox) (Terada et al., 2002).

Advances in biotechnology and genetic engineering over the last 30 years have made it possible to generate the newest form of immunological medication, monoclonal antibodies. These antibodies are of uniform composition, well-characterized chemical properties (in terms of specificity, affinity, and amino acid composition) and can be produced by large-scale manufacturing techniques without the use of animals or animal proteins (Smith, 1996; Demain, 2000). Because monoclonal antibodies are not produced from human blood, they do not carry the risk of transmission of human infectious agents, such as HIV and hepatitis B and C viruses, and so represent an intrinsically safer product in that regard.

The medical rational for using immunotherapies for treating or preventing drug abuse is similar in concept to more traditional immunological applications. However, the primary action of an antidrug antibody in the serum is to reduce drug levels in the brain by binding the drug before it enters the brain (Pentel and Keyler, 2004). Because the drug binds with high affinity to the antibody, the rewarding as well as the medically harmful effects of the drug are reduced or blocked. And because these therapies target only the drug, they are potentially safer than treatment with small molecule drug agonists, which bind directly to important receptor systems in the brain and other organs (Pentel, this volume).

Current immunotherapies for drug abuse are of two types, active and passive. Although both treatments require highly specific, high-affinity antibodies, the medical use and the mechanisms of the therapies differ somewhat. In active immunizations, drug vaccines are used to stimulate the body to makes its own antibodies and to create a long-term immunological memory for a more rapid future response to the vaccine (Kosten et al., 2002a, 2002b) In passive immunotherapy, laboratory-generated antibodies (e.g., monoclonal antibodies) are injected: more antibody can be administered and the protection can be immediate, but it only lasts until the antibody is cleared, and there is no immunological memory against the drug (Owens et al., 1988). Depot medications are variations of currently available medications that are designed to release a drug slowly, over a long period of time. They act by binding to the drug receptor (in

the brain or elsewhere in the body), "locking out" the drug from the site of action.

In all cases, however, these medications only target the pharmacological effect of particular licit and illicit drugs. They do nothing to counteract the effects of craving and overlearned drug-seeking behavioral responses that frequently lead to relapse (Robinson and Berridge, 2000; Berke and Hyman, 2000; O'Brien et al., 1998). Consequently, their use is expected to require the concomitant availability of psychosocial and behavioral treatment programs to maximize their effectiveness. We discuss these issues in more detail in Chapter 3.

Active Immunotherapy

In active immunotherapy, a chemical derivative of the drug of abuse (called a hapten) is coupled to an antigenic protein carrier, which is then used as a vaccine (with or without an immune enhancing adjuvant) for immunization. Because stimulation of an immune response requires multiple interactions on the surface of an antibody-forming B lymphocyte, a single, small drug molecule (like cocaine or nicotine) cannot produce cross-linking of cell surface antibodies on a B cell to activate it to produce more antibodies. Consequently, drug haptens must be irreversibly bound to their large protein carriers for use as vaccines.

The molecular orientation and spacing of the drug haptens on the protein surface are critical factors that scientists must control for an optimal immune response. The antibody response will not increase if a vaccinated individual uses the small drug molecule itself; only the circulating antibody at the time of drug use will be protective. Because cross-linking of surface antibody on B cells is required to stimulate antibody production, the same drug hapten-protein vaccine must be used for boosting the immune response on later occasions. Periodic boosting with the vaccine is required to keep serum antibody levels high (Pentel, this volume).

The actual serum level of an antibody is affected by the quality of the drug-protein vaccine, the dose of the vaccine, the frequency of vaccinations, the time interval between immunizations, and poorly understood genetic variations among individuals (Pentel, this volume). On the basis of results from prior vaccine regimens, it is anticipated that the immune response will not be adequate for at least 3-6 weeks after the start of vaccination, and booster immunizations will be required every 1-6 months to maintain a sufficient level of drug-specific antibodies (Cerny et al., 2002; Hieda et al., 2000; Byrnes-Blake et al., 2001; Kantak et al., 2001). Improper timing of vaccinations could result in a poor response or a significant reduction in the amount of circulating antibody. Thus, the timing and dura-

tion of vaccinations will need to be carefully coordinated with patient needs and other medical interventions, such as counseling or behavioral modification programs.

Passive Immunotherapy

In passive immunotherapy, rather than vaccinating an individual to stimulate his or her antibody response, preformed antidrug antibody medications are administered directly. Although this antibody medication could be a polyclonal serum or a purified immunoglobulin fraction from the serum of an individual who has been vaccinated against a drug of abuse, a monoclonal antibody is more likely to be used. Given today's technology for making and selecting monoclonal antibodies, it should be possible to make high-affinity antibodies to most drugs.

The monoclonal antibodies that have been safely used in humans are chimeric monoclonal antibodies (comprised of 34 percent mouse protein and 66 percent human protein), humanized monoclonal antibodies (comprised of more than 90 percent human protein), and fully human antibodies (Villamor, 2003). All of these types of antibodies are currently made by advanced biotechnological techniques called antibody engineering. As of mid 2003 there are 10 FDA-approved therapeutic monoclonal antibodies and one FDA-approved monoclonal antibody approved. Of relevance to the therapeutic strategies for using immunotherapies for drugs of abuse is Synagis® (Simoes and Groothuis, 2002). This monoclonal antibody is approved for the prevention of serious lower respiratory disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of the disease. This antibody is administered before and then monthly throughout the RSV season to maintain protective circulating antibody levels (Simoes and Groothuis, 2002).

For treating drug abuse, monoclonal antibodies could be used in three clinical scenarios: to treat drug overdose, to prevent drug use relapse, or to protect certain at-risk populations who have not yet become drug dependent (e.g., adolescent children who have begun using cocaine). Other special populations, such as fetuses of drug-abusing mothers, might also warrant protective immunotherapy of the mother to prevent fetal exposure to the abused drug. Active vaccination could be used to prevent drug-use relapse or to protect at-risk individuals, though not for drug overdose. Depending on the particular situation, active vaccination or monoclonal antibody therapy (or a combination of the two) could be administered. For example, antibody fragments (of a size that would be cleared by the kidney) could be used to treat overdose so that not only would the antibody bind the drug and lower the amount in the brain, but also so the drug-antibody complexes would be cleared quickly from the

body. In a drug abuse protection or relapse setting, where it would be desirable to have significant antibody present over a long period of time, one could envision administering a loading dose of an antibody medication with carefully timed periodic repeat doses to maintain the desired serum antibody concentrations. An example of a current successful medical therapy is Remicade® for the treatment of rheumatoid arthritis (Vizcarra, 2003). This chimeric monoclonal antibody is given at 0, 2, and 6 weeks as a loading dose and then every 8 weeks thereafter. Vaccinations with an antinicotine vaccine might be appropriate in patients who are attempting to stop cigarette smoking.

Advantages and Potential Disadvantages of the Therapies

Both active and passive immunotherapy require high-affinity antibody binding to be medically effective, and both have potential strengths and weaknesses.

Advantages

- Antibodies target the drug, not the drug's sites of action in the brain.
- The binding of drug to antibody inactivates the drug.
- An antibody can be highly specific for a drug or drug class.
- Immunotherapies can complement conventional therapies (such as behavioral modification) for a more comprehensive medical approach.
- The use of immunotherapy would not necessarily preclude the use of chemical agonist or antagonist, but an important exception is the combined use of a nicotine agonist therapy and antinicotine antibodies.
- Immunotherapy has a different pattern of side effects (in theory, fewer) than treatment with chemical agonist or antagonist.
- Antibodies are not addictive, as are some chemical agonists.

Potential Disadvantages

- Monoclonal antibodies are time consuming and expensive to produce.
- The production of a high-affinity antidrug antibody is sometimes difficult.
- Vaccinations may lead to an inadequate response in some individuals.

- Vaccinations may not produce antibodies in a timely fashion for proper integration with other medical interventions (e.g., drug overdose).
- The beneficial effects of the therapy could be overcome by large amounts of drug.
- The immunotherapy could lead to allergic reactions.

There are other potential problems with the use of antidrug antibodies for the treatment of drug abuse. Because in some cases the drugs of abuse are closely related in structure to either neurochemicals or approved medications (e.g., nicotine replacement therapy for cigarette smoking), it is possible that the therapies could lead to unexpected adverse reactions or reduced effectiveness of other medications. Some of these possible outcomes can be avoided or anticipated by careful screening of the antibodies for cross reactivity against known drugs and neurochemicals before they are used in humans. It is also possible that immunological responses against an antidrug of abuse antibody binding site (called an anti-paratype response) could lead to a second generation of antibodies, which are complementary to the antibody binding site and are capable of being druglike, thus, able to activate receptor systems just like the drug of abuse. It is known that monoclonal antibodies and other protein therapeutics do stimulate an immune response to the product in some individuals; therefore, they may not be suitable for life-long or even extended use in all individuals. Vaccines comprised of the drug-protein conjugate might also lead to entirely unexpected allergic reactions. However, it is expected that most of these potential problems would be anticipated, tested for, and dealt with during the clinical trails of new medications and the FDA approval process.

Finally, there are ethical considerations, however remote, for the use of vaccines. Active vaccination can stimulate long-lasting immunologic memory that could serve as a marker of past immunization and could stigmatize an individual for extended periods of time, or even over their entire life if tests were available for detecting memory immune cells. Monoclonal antibodies, however, have a finite life span, and after some period of time following treatment would no longer be detectable. Depot medications would similarly be undetectable following treatment because of their finite life span.

Depot therapies for opioid addiction pose a different set of advantages and challenges. A great deal is already known about the therapeutic agent (naltrexone) that is being developed for depot use because it has been used in non-depot form for more than 20 years. Naltrexone is known to be very effective as well as safe when patients adhere to the medication. For the depot versions, extensive work has been done by companies seek-

ing to develop and obtain FDA approval for their products. Their primary advantage is expected to be in greater adherence, since dosing will only be about once every 30 days, instead of daily. One noteworthy issue is that patients on depot therapies who need treatment for acute pain (e.g., due to trauma) will present problems because naltrexone blocks opioid analgesics as well as illicit opioids. Special protocols (medications, dosing) will be required to treat pain for patients on naltrexone.

This consideration of the medical basis for immunotherapy and sustained-release formulations for treating drug addiction has led to one major recommendation by the committee, but several recommendations in subsequent sections are also related to the medical basis for these therapies.

Recommendation 1 The National Institute on Drug Abuse should support basic immunology studies on increasing the stability and longevity of antibody blood levels and on developing combination therapies to simultaneously treat a variety of abused drugs.

2

Clinical Trials

The medications that currently are available for human trials or use include vaccines for active immunizations against cocaine and nicotine and long-acting depot formulations of naltrexone, an opiate antagonist for alcoholism and opiate dependence. Monoclonal antibodies for passive immunotherapy are still in animal testing, but one for phencyclidine will be ready for human testing within the next few years. The clinical trials to test these medications may involve three kinds of testing: (1) for individuals who overdose, (2) for drug-dependent individuals who either volunteer for the medication or are encouraged/coerced to use the medication by another agent to prevent relapse, and (3) for nondependent individuals who either volunteer or are induced to receive the medication as a protection against initiating or increasing substance use (i.e., primary or secondary prevention, respectively) (Blaine et al., 1994; Klein, 1998). In all three kinds of tests, clinical trials subjects are likely to be adult males and nonpregnant adult females.

FDA PROCESS

The FDA clinical trials process is designed to assess safety and efficacy of new medications through four phases of testing (Blaine et al., 1994). Phase I is designed to establish the safety of new medications, in escalating doses, typically in a population of healthy adults. With active immunization, subjects are likely to require a series of doses in order to produce an optimal level of circulating antibody. Since repeated booster immunization could increase the risk for unexpected side effects, this type of study

should be conducted in abstinent former users. In contrast, with both passive immunization and sustained-release formulations, initial safety can be tested with a single dose in healthy non-users or abstinent former users (Kosten and Kranzler, this volume).

Phase II testing seeks to determine the optimum dosage of a medication and may also include comparison of the effects of new medications with those of a placebo treatment. Potential indications for use become important with phase II testing. FDA requirements may be different for depot medications than they would be for other kinds of new drugs. Because, in most cases, efficacy of the oral medication will already be established for sustained-release formulations, placebo-controlled testing may not be required as part of phase III (or phase II) testing (Kirchmayer, Davoli, and Verster, 2002). However, the efficacy of depot formulations will need to be tested against placebos.

Phase III testing is designed to establish safety and efficacy with large-scale, placebo-controlled studies. The specific outcomes of the studies and their designs may differ on the basis of the indications that are being considered. These indications will also affect the population from which subjects are recruited. For instance, if relapse prevention is the outcome of interest, former drug users who are currently abstinent would be the population of interest. The committee believes that a diverse group of patients who need relapse prevention ought to be examined during the phase III testing process, before moving to protection protocols or special populations, such as pregnant women.

Phase IV testing is used to monitor the use of a medication once it has been approved and is available for clinical practice. Populations that were not originally studied might be assessed, and relatively rare side effects might be detected. This standard stage-wise strategy for completing clinical trials is very unlikely to provide any information about the use of these interventions for a variety of important clinical applications. In particular, the committee believes that significant ethical issues in phase IV testing will arise with immunotherapies and sustained-release formulations.

PHASE IV CONSIDERATIONS

The surveillance that is an intrinsic part of the postmarketing experience will be critical, particularly for monitoring off-label uses in which premature applications may place certain populations at unacceptable risk. There is likely to be pressure to use these therapies in populations for which insufficient safety or efficacy data are available from the clinical trials, such as adolescents, pregnant women, polydrug abusers, criminal justice populations, or even military personnel. In these untested populations, as well as in those initially included in the clinical trials to support

FDA approval, postmarketing surveillance may provide data on relapse rates, drug substitution, and increased sensitivity to the abused drug after sustained treatment, events that may increase the potential for accidental drug overdoses (Kosten and Kranzler, this volume). Overall, these surveillance activities, as well as NIDA-funded health services studies, may offer substantially better data than the traditional clinical trials on the use of these immunotherapy and sustained-release medications in real-world situations. These studies could be conducted in the NIDA Clinical Trials Network.

In view of the strengths and limitations of data from clinical trials to support approval by the FDA for a specific indication, several issues will be particularly important during testing and postmarketing surveillance: NIDA's working collaboratively with the FDA to test and monitor the immunotherapy medications; NIDA's role to ensure commercial development of these immunotherapies; uses with a variety of special populations; prevention studies; and potential off-label uses after FDA approval.

NIDA and FDA Cooperation

It will be important for NIDA and the FDA to work together to establish guidelines for testing and monitoring immunotherapy and depot medications in the general medical community, where off-label use is quite likely. Mechanisms for achieving this cooperation might include reconstituting the FDA Drug Abuse Advisory Committee and conducting joint workshops that involve consultants from outside NIDA and the FDA.

Commercial Development

A second key issue involves NIDA support for clinical trials and commercial development through established mechanisms. This is particularly important in light of the barriers to the development of pharmacotherapies for drug abuse, as well articulated in a recent report on addictions medications development (Institute of Medicine, 1998). Established mechanisms to support these efforts include at lest four funding programs: Cooperative Research and Development Agreements, Small Business Innovation Research, Small Business Technology Transfer, and Strategic Program for Innovative Research on Cocaine (and Other Psychomotor Stimulants) Addiction Program. These grant programs have facilitated very productive partnerships among small businesses, such as biotechnology companies, academia, and the federal government. Products have included active vaccines, monoclonal antibodies, and depot medications.

Special Populations

A number of issues may arise with respect to special populations, a group that is likely to include pregnant women and adolescents, as well as people with particular indications, such as overdoses and for prevention of addiction in drug-naïve users. The committee does not believe that studies with these populations should run in parallel with the initial studies to establish safety and efficacy in competent adults. For example, testing in pregnant women is likely to raise a number of potential ethical issues in the absence of any preclinical data.

Vaccination raises a specific concern about the effect of these medications on fetal development, which undergirds the committee's cautions with respect to pregnant women. Immunotherapies would allow for the transfer of drug-specific antibodies to a fetus, with unknown effects. It is not known if this could even lead to greater fetal exposure to a targeted drug, possibly by pregnant women attempting to override medications or by switching their drugs of choice. If there is increased fetal exposure, it is likely to have negative effects on fetal development, as many of the drugs of abuse for which immunotherapies are currently being developed have either suspected or established adverse effects on fetal development (Plessinger, 1998; Ernst, 1999; Addis et al., 2001).

Of course, there is the hope and expectation that vaccination would reduce the amount of drug to which a fetus is exposed, as it reduces the distribution of drugs to the mother's brain and other organs. However, maternal antibodies are also transferred across the placenta (Simister and Story, 1997), and they could expose the fetus to the drug that is bound to antibodies. The antibodies might actually prolong the amount of time during which a fetus is exposed to a drug bound to antibodies because the antibody-bound drug is generally eliminated more slowly from the body (Keyler et al., 1999; Proksch et al., 2000). It is unknown how elimination by a fetus will be affected.

There are limited data to assess which of these outcomes is most likely. To date, only one preliminary study has sought to assess whether vaccination with immunotherapies would lead to greater or lesser amounts of drug exposure for a developing fetus (Shoeman, Keyler, and Pentel, 2002). Consequently, the committee believes that preclinical studies of these medications for use in pregnant women would provide the necessary safety data for use in all women, should the outcomes show acceptable safety profiles. This group may be especially important as most drug-dependent women are of childbearing age. Furthermore, long-term follow-up of children born to women who have received these medications during pregnancy is also likely to provide useful information on potential effects for a developing fetus.

Similarly, testing in adolescents should also await preclinical data . In addition, data might also be useful to address legal and social implications for the child and child-parent relationship. For example, what are the implications of having a parent decide on treatment for a minor who does not want to be treated or who may not feel free to decline treatment? Although adolescent populations are likely to be candidates for protection, rather than for relapse prevention, the committee believes that even testing for protection in adults would benefit from first having safety and efficacy data in relapse-prevention trials with competent adults.

The committee urges caution in testing these medications in children and adolescents for several reasons. First, these medications have yet to demonstrate efficacy in adults, and more toxicity testing would need to be done to ensure the level of safety required for administering these medications to adolescents or even young adults. Second, the biological focus of any blocking medication would not affect the some of the reasons that adolescents use drugs. The incentive to use licit and illicit drugs by children and adolescents is often not related to their pharmacological effects. Rather, peer pressure, demonstrating rebelliousness to parents, signaling membership in a clique or subculture, and asserting a social message are highly likely to be reasons for use of alcohol, tobacco, and other drugs by children and adolescents (von Sydow et al., 2002; Griesler et al., 2002; McCuller et al., 2001; Hofle et al., 1999; Farrelly et al., 1999; Sobeck et al., 2000; Flannery et al., 1999). A treatment that targets the pharmacological effects of licit and illicit drugs is unlikely to affect these motivations, and it may be substantially less cost effective than other prevention strategies.

The committee also believes that initial testing of these medications for overdose treatment would also be best with competent adults. Testing for treatment of overdose with patient-subjects who are not capable of providing informed consent would benefit from demonstration of safety and efficacy in trials with competent adults or, when this is not possible, trials for other uses (relapse-prevention or protection). If a trial involves the use of "emergency research" provisions in order to include patient-subjects who are not capable of providing informed consent, then advance approval by "community consultation" should include persons who are at risk of overdose and not simply community leaders who do not have any drug addiction problems.

The FDA has established procedures for gaining community consent through a consultative process for emergency research (see Center for Drug Evaluation and Research, 2003). Emergency research involves "subjects who are experiencing immediately life-threatening conditions for which available treatments are unproven or unsatisfactory." Informed consent is not able to be obtained because of the person's medical condi-

tion and a legally authorized representative or guardian is also not available to provide the informed consent. In this circumstance, FDA regulations allow for a community consultation process whereby researchers solicit opinions and input from representatives of the community in which the research will be done and from which subjects will be drawn. This consultative process can serve as a form of community consent for procedures being tested to treat emergency conditions when neither the subjects or their legally authorized representative is available to give individual, informed consent.

Prevention Studies

None of the phase III studies is likely to address issues relevant to the prophylaxis of addiction in nonabusers (primary prevention) because of the substantial cost and long duration of this type of clinical trial to establish safety and efficacy. Nevertheless, subjects with sustained abstinence, who are at high risk for relapse, might be approached for secondary prevention studies during phase IV monitoring. Four issues will be important for these prevention studies: the nature of the study population, the range of agents tested, the targeting of multiple therapeutic targets or integration with existing treatments, and the use of a variety of settings where testing and treatment are provided. The issue of where to conduct treatment may be a particular challenge, because many substance abuse treatment programs lack the medical infrastructure to deliver pharmacotherapies. In the past, coordination between substance abuse treatment programs and medical settings has not been very successful, as we describe in Chapter 3.

Off-Label Uses

As noted above, many ethical issues will arise as off-label uses of these immunotherapies or depot medications proliferate in the postapproval period. New populations may be studied, including adolescents, prisoners, and pregnant women, and new treatment settings, such as primary-care medical clinics, may be examined. The FDA testing process will provide only limited help in generalizing to off-label uses, and the extent to which the process will help will vary across the specific abused substances.

Off-label uses in medical settings are likely to be provided most effectively for nicotine products but much more poorly for cocaine, amphetamines, and PCP. The difficulties with services for the latter drugs include limited information on their use from the pivotal trials (e.g., the reversal of overdose using monoclonal antibodies for PCP), need for close coordination with substance abuse treatment settings that have limited

medical backgrounds, and social pressure to make any effective treatment available. Use of depot medications, such as naltrexone, for treating alcoholism are likely to be well informed by the FDA approval process, but other uses of depot naltrexone, such as treatment of heroin dependence, may not have been carefully studied.

Recommendation 2 Recognizing that immunotherapy medications will be used in off-label situations that have not been specifically approved by the Federal Drug Administration, the National Institute of Drug Abuse should support preclinical studies addressing the potential safety and efficacy of these medications when given to vulnerable populations (e.g., pregnant women and their fetus, adolescents, etc.). Long-term studies should be done with laboratory animals of different ages, as well as their offspring, before trials with vulnerable human populations are undertaken.

Recommendation 3 The National Institute on Drug Abuse should support studies of the likely extent and nature of off-label drug use, including factors and incentives that would promote or retard such use, and the opportunities for policy makers to intervene should the patterns of off-label use depart from what is in the best interest of the society.

3

Treatment, Financing, and Costs

The development of pharmacotherapies for drug addiction treatment provides an opportunity to substantially expand and improve the treatment of addiction. However, for these treatments to be successful, they must be integrated both into specialty addiction treatment programs and primary care medical practices. Historically, the development of distinct organizational and financial structures for treating drug and alcohol problems separately from other medical disorders has generated obstacles to this integration (Thomas and McCarty, this volume). The committee believes that new pharmacotherapies will only be effective to the extent that clinicians accept them in either specialty or primary care settings and their use is facilitated through adequate financing, organizational structures, and community support.

While the historical pattern in the United States has been of relatively rapid adoption of new pharmacotherapies, the adoption of medications to treat drug and alcohol dependence has been quite limited (Thomas and McCarty, this volume). No medication has been used by more than 25 percent of the affected population, and some have been used by less than 5 percent . The underuse of medications for addiction treatment has many root causes: societal ambivalence about whether addiction is a moral failure or a medical disorder (Lowinson et al., 1992); the general perception that medications for addiction treatment either do not work or represent substitution of one addiction for another (Woody and McNicholas, this volume); the weak efficacy or lack of patient acceptability of some medications (Krystal et al., 2001); and the perception that addiction is an acute, rather than a chronic, relapsing disorder that requires extended treatment

aimed at preventing relapse and reducing the severity of complications (McLellan et al., 2000). Underdosing of individuals with currently available medications has also been a problem (D'Aunno and Pollack, 2002).

These perceptions and attitudes are reflected in the separation between addiction treatment programs and regular medical care, a separation that perpetuates multiple barriers to the use of medication treatment for addictions. The clinical challenge of creating treatment programs tailored to the unique needs of the individual patient, as well as to the specific drugs to which he or she is addicted, is made more complicated by the existence of separate medical and addiction treatment systems. Moreover, the use of immunotherapies and sustained-release formulations will require complementary interventions with behavioral therapies, representing a major challenge to current practitioner and provider structures.

This chapter first reviews potential barriers to the integration of immunotherapies and sustained-release formulations in specialty addiction treatment programs and primary care medical settings. In the specialty setting, medical expertise and infrastructure must be developed or coordinated with behavioral interventions; in the primary care setting, behavioral interventions must be made available or developed for coordinated delivery with the medication treatments. The chapter then reviews the currently available medications for treating substance abuse disorders, identifying some lessons learned by the adoption of (or failure to adopt) these medications in substance abuse treatment. Lastly, we briefly consider some cost and related economic issues.

SPECIALTY ADDICTION TREATMENT SETTINGS

Current specialty addiction treatment programs do not routinely provide extensive medical services, and when medical services are provided, they are ancillary to the central role of psychosocial behavioral treatment (Substance Abuse and Mental Health Services Administration, 2002). The absence of medical services reflects organizational structures and staffing patterns in addiction treatment programs (D'Aunno, Vaughn, and McElroy, 1999; Nohria and Gulati, 1995), the philosophical resistance of staff to using medications for addictive disorders (Woody, 2003), and financing limitations that arise from the way that specialty addiction treatment is provided (Coffey et al., 2001; Mark et al., 2000).

Organization

Most specialty addiction care is provided in small, outpatient clinics that have little overlap with the larger general medical system, and they

have organizational structures, staffing patterns and other resources that are neither physician centered nor involve physician delivery or oversight (Substance Abuse and Mental Health Services Administration, 2002). Even the opioid treatment programs that use methadone or levo-alpha acetyl methadol (LAAM) generally have minimal medical oversight, and most lack even rudimentary medical diagnostic or primary care delivery capability (D'Aunno et al., 1999). The absence of medical staff poses a barrier to the adoption of new medications in specialty addiction treatment settings.

In order to provide immunotherapies and sustained-release formulations in specialty addiction treatment settings, substantial additional resources would be required to integrate medical services and medical personnel in these settings. Moreover, immunotherapies, particularly monoclonal antibodies, will need to be administered in a medical setting where emergency medical treatment is available.

Philosophy

Specialty treatment settings may also be limited in their ability or interest in adopting new pharmacotherapies due to philosophical resistance. Most addiction treatment staff have been trained in one or more psychosocial treatment approaches (e.g., 12 steps; cognitive behavioral therapy, relapse prevention). They understand these approaches, know they work with many patients, and have little motivation to use medication. Lack of training and understanding of the effects and side effects of addiction medications, and discomfort with the research supporting the use of medications, are additional barriers (Mark et al., 2000; Owen, 2002; Thomas, 2000; Thomas et al., 2003). Although the potential value of medications may be acknowledged, there may also be deep skepticism.

This philosophical difference emerges partly from a particular interpretation of the 12-step approach of Alcoholics Anonymous (AA). Although AA founder, Bill Wilson (1955), emphasized collaboration between 12-step programs and the medical profession, many 12-step programs developed a drug-free philosophy that extended even to psychoactive medications for major depression or other serious, nonsubstance related mental disorders, and many patients were pressured to stop all medications (Woody and McNicholas, this volume). The strong personal experiences of staff with recovery without the use of medications may have promoted opposition to the use of medication even when combined with psychosocial treatment. These antimedication biases have diminished, especially concerning patients with dual addiction and mental health diagnoses, but they are often still strong in the case of antiaddictive medications.

Financing

The financing and structure of specialty services for addiction treatment have developed idiosyncratically and relatively autonomously from the nation's system for medical care (Coffey et al., 2001; Mark et al., 2000). This isolation also poses a barrier to the integration of new immunotherapies. The presence of a large and autonomous system of specialty dependency treatment for chemical addictions reflects a legacy of poor service for alcohol and drug use disorders in health care and mental health care settings, limited coverage in health plans, and the resulting divergence in payer sources and regulatory mechanisms.

These financing problems have been further exacerbated by efforts to reduce health care costs. Medication costs seem high because their use requires medical personnel, who are the most expensive staff that can be hired in substance abuse treatment programs (Woody and McNicholas, this volume). Poor reimbursement for addiction treatment discourages treatment programs from adding these services, and medical personnel can usually earn more in other work (Thomas and McCarty, this volume). Addiction treatment often is disproportionately affected by cost-cutting efforts, and medical and other more highly paid staff become prime targets for elimination.

The availability of immunotherapies and sustained-release formulations will raise a host of questions for specialty addiction treatment settings. Research will need to explore the most effective clinical models for integrating medical services with psychosocial and behavioral treatment in specialty addiction settings. How medical personnel can be made available to administer medications and the effect of those personnel on nonmedical addiction treatment providers will need to be determined. In addition, models of public and private insurance that cover both medical and psychosocial treatment services will need to be developed and evaluated. At all levels, research should explore barriers to the use of immunotherapies and sustained-release formulations in specialty addiction treatment settings.

PRIMARY CARE SETTINGS

Medical settings offer the possibility of engaging patients with substance abuse diagnoses earlier in the course of their addictions and providing services to those who cannot or will not seek specialty care (Stein and Friedman, 2001; O'Connor and Samet, 2002). Despite these potential benefits, primary care settings have yet to routinely provide substance abuse treatment. There are a number of organizational, financing, and privacy-related considerations that have hindered such treatment

(Thomas and McCarty, this volume). These factors need to be taken into consideration as immunotherapies and sustained-release formulations are used for patients in medical settings.

Organization

Primary medical care settings are typically organized around procedural services and medications as the focus of treatment. While a portion of primary care has always been devoted to management of conditions that require ongoing psychosocial therapy, the linkages with psychosocial support systems have been largely secondary to medical therapy. Primary care providers often lack specific training or skills for substance abuse screening or treatment, have limited time to address problems of substance abuse, and have limited referral resources for specialized addiction counseling (Ferguson, Ries, and Russo, 2003; O'Toole et al., 2002; Friedmann, Alexander, and D'Aunno, 1999). The stigma associated with addiction problems also impedes efforts to provide appropriate services (Weissman, 2001).

Problems of addiction and its treatment share many features of other chronic medical disorders, such as diabetes or heart disease, which also require combined medication and behavioral treatment. To the extent that medical practices can incorporate chronic disease management strategies—including patient education, behavioral counseling for adherence and life-style change, and collaboration between physicians and other health care providers (nurses, pharmacists, counselors)—they will be successful in providing immunotherapies and sustained-release formulations for addiction treatment.

Financing

Differences in financing between general medical care and mental health and substance abuse treatment also will challenge the adoption of new therapies. The lack of insurance coverage parity between medical and addiction treatment complicates their integration, as many medical insurance programs limit funding for counseling and recovery support. Insurance benefits often require separate providers for medical and addiction services and deny reimbursement to medical providers who bill for addiction services. The financial incentives for delivery of screening and treatment for addictions in primary care are very limited, partly because there are no standard billing codes for reimbursement of these services. When providers are paid a monthly fee for all services (capitation), there is an incentive to limit new or expensive medications unless they save provider groups money in the short term.

Privacy

A special challenge for the promotion of linkages between primary care medical and specialty addiction services is the complexity of communicating across settings in the context of federal confidentiality regulations for drug and alcohol treatment records. Medical practices that want to provide these treatments need to comply not only with the Health Insurance Portability and Protection Act (HIPPA), but also the more stringent requirements of 42 CFR, which requires that addiction treatment records be segregated for the purposes of disclosure to various entities. These requirements present a greater barrier for primary care providers, who will be treating both addiction and other medical problems, than for addiction specialists, who do not function as a patient's primary care physician. In the primary care setting, practitioners may need to maintain two separate records for patients receiving general medical care and substance abuse treatment.

Discrimination

Treatment with immunotherapies, especially by active vaccination, has the potential to lead to long-term detectability because of markers in a person's blood or urine. The ability to detect these markers—in the absence of a universal vaccination program—may lead to discrimination in a number of settings, including employment and health insurance. The potential of determining that someone was treated with a medication that is designed to block the effects of licit or illicit drugs may dissuade people from receiving the medication because of the potential for discriminatory treatment. This, too, is an issue that should be a focus of future research by NIDA.

There are some laws that bar discrimination because of past alcohol or drug use. For instance, the Americans with Disabilities Act of 1990 (ADA) prohibits employers from discriminating against employees who are in recovery from drug and alcohol problems. This protection afforded by the ADA does not cover employees and applicants who currently use illegal drugs, with testing for current illegal drug use not restricted. It is unclear, however, whether an employer can refuse to rehire an employee who was initially fired for an alcohol or drug problem but who is now clean and sober. In fact, the U.S. Supreme Court is considering this specific issue at the time of this writing, with a decision expected within the next year (see *Raytheon v. Hernandez*, 2003). This blanket no-rehire policy, if allowed to stand, is likely to have some effect on the willingness of individuals to be treated with immunotherapies that can leave a long-term biological marker, which carries the potential for detectability.

Research Issues

The use of immunotherapies and sustained-release formulations for addiction treatment in primary care medical settings raises important research questions. They include determination of the most effective models for integrating behavioral therapies into primary medical settings; developing empirical support for strategies to educate physicians and primary care practices in optimal addiction management strategies; developing standards to facilitate appropriate management of privacy issues; and the development and evaluation of mechanisms to finance integrated medical and psychosocial and behavioral services.

Given the substantial barriers to implementation of these treatments, special consideration should be given to supporting research on the most effective ways to facilitate dissemination of immunotherapies and sustained-release formulations to medical and addiction treatment systems. In addition, health services research evaluating the effects of various organizational and financial models for delivering these new therapies will be necessary to understand how structural factors influence treatment access, cost, and outcomes. We believe that these finance issues, in particular, will be extremely important for making these medications available, should they be proven to be safe and effective. The absence of sufficient financing can mitigate the effects of any improvements in the other philosophical and organizational issues we noted above.

PREVIOUS PHARMACOTHERAPIES LESSONS LEARNED

In addition to the issues discussed above, some of the medications that are currently available for treating substance use disorders have also faced impediments to their use. Here we review impediments to some medications that are currently available.

Weak efficacy (Krystal et al., 2001) or poor patient acceptance (Greenstein et al., 1981)—or both—have been a serious limitation for some of the medications currently available to treat substance use disorders. Examples of weak efficacy include naltrexone for alcohol dependence. While 15 well-designed studies have shown a naltrexone effect in reducing alcohol relapse, the largest study, which was a multisite study done in the Veterans Healthcare Administration (VHA) system, showed no effect in comparison with a placebo (Krystal et al., 2001). As there are many VHA providers who are physicians and might prescribe naltrexone, this study was particularly damning for its use within the largest physician-based substance abuse treatment setting. Naltrexone for opioid dependence also perhaps best exemplifies poor patient acceptance. Less than 15 percent of heroin addicts will agree to use this phar-

macologically highly effective medication that blocks heroin completely, with minimal side effects or other drug interactions. Similar issues of weak efficacy have diminished the use of nicotine replacement therapies and buproprion for smoking cessation. The availability of these medications, which counteract the pharmacologic effects of opioids, has not obviated the need for concomitant psychosocial and behavioral treatment to help users manage the craving and drug-seeking behavior that can also serve as cues for relapse.

Impediments to Opioid Pharmacotherapy

Specific factors also have influenced the success and failure for pharmacotherapy of different abused substances. Loitering and drug dealing in the vicinity of methadone clinics has resulted in strong community opposition to new opiate agonist programs (Genevie et al., 1988). Federal and state regulations have limited treatment access by restricting methadone dispensing to certain locations and applying criminal penalties for failure to comply with the regulations. The wording of these regulations has made many health care providers hesitant to get involved. Political opposition has also been quite explicit. The statements made by former New York City Mayor Rudolph Giuliani when he wanted to close all the methadone programs in New York City in 1998 clearly illustrate such opposition: "I think methadone is an enslaver. It's a chemical that's used to enslave people" (Swarns, 1998).

The wording of the Addiction Free Treatment Act of 1999 also reflected an ideological bias against substitution therapy and, apparently, misunderstanding of the background, rationale, and substantial efficacy of long-term methadone and LAAM substitution treatment. Wording in the act noted that "heroin addicts and methadone addicts are unable to function as self-sufficient, productive members of society . . . " and concluded that the Congress needed to "work . . . to develop an effective drug control policy that . . . is based on detoxification and the comprehensive treatment of the pathology of drug addiction." These assertions failed to recognize that patients who are on methadone are often able to function and to be productive members of society and able to take care of themselves. The act also failed to recognize that drug treatment usually results in reductions in drug use and criminal behavior, as well as increases in employment and other prosocial activities, such as paying taxes.

The opiate antagonist naltrexone has different reasons for its very modest success in treating opioid dependence. Because it has no agonist properties, it is not well liked by patients (Mark et al., 2000). Environmental factors also may play a role. Current studies in Russia have demonstrated much higher levels of interest by patients in naltrexone treatment than

has been seen in U.S. trials. The environmental factors at play in Russia appear to be the unavailability of agonist treatments, such as methadone, and the relatively young age of heroin addicts (about 22 years old on average) with strong family ties to their parents. These parents, particularly mothers, are willing to apply strict behavioral limits to these predominantly young men in order to ensure adherence with naltrexone ingestion. Substantial success with naltrexone has also been described in similarly structured family programs in the United States (Kosten et al., 1983). As long as naltrexone is taken, it is pharmacologically effective: thus, success with these medications may depend as much on behavioral intervention as it does on the medication itself. The key to success appears to be an appropriate match between the medication and the behavioral intervention.

Impediments to Alcohol Pharmacotherapies

Naltrexone for alcohol dependence has different reasons for poor success, including many of the reasons detailed above for pharmacotherapy failure in general, including staff reliance on psychosocial treatment rather than medications, lack of medical personnel to prescribe the medication, and ideology. The common ideology is that using naltrexone will undermine a drug-free life style. Cost is also a major issue, because naltrexone medication costs about $150 per month and is often not covered by insurance or public assistance programs. Initially it was also not covered by the VHA, although coverage is now provided. Thus, a person has to have a significant commitment to abstinence, and the available resources, in order to buy the medication.

Successes of Nicotine Pharmacotherapies

Nicotine replacement therapies and buproprion have been successful when adhered to, and in their financial returns to the manufacturers. Smoking, like most addictions, is a chronic relapsing disease, and individuals typically make many attempts to stop smoking. With each attempt, these medications can be obtained either by prescription from a primary care physician or simply purchased over the counter. This easy availability has led to good patient acceptance of these medications, relatively widespread use, and substantial financial returns to providers and manufacturers.

However, the movement to over-the-counter sales using a relatively low dose and shorter-acting version of the anti-nicotine patch has been associated with less success than the higher-dose medications that are prescribed by physicians (Thorndike, Biener, and Rigotti, 2002). This reduced

success may also reflect the greater likelihood of getting a physician's advice to quit and concurrent behavioral interventions when nicotine replacement therapy is given by prescription.

The successful dissemination of these anti-addiction treatments was probably due to a variety of factors, including direct-to-consumer advertisements, substantial drug detailing by pharmaceutical representatives, good general publicity about their safety and utility, and aggressive education campaigns and tobacco control measures (e.g., smoking bans). We suspect that another potentially important factor, particularly in the marketing of nicotine replacement therapy, has been keeping the target population as adults with serious dependence on nicotine and not attempting to target adolescents who may be early in their tobacco smoking career. There are few data documenting the prevalence of nicotine replacement therapy among adolescents. One study involving more than 4,000 high school students found that only 5 percent had ever used either nicotine gum or patches (Klesges et al., 2003). Other studies have similarly documented low rates of nicotine replacement therapy by adolescents (Price et al., 2003; Lawrance 2001). Although it might be argued that adolescents would be more responsive to this treatment because they have less strongly ingrained habits (U.S. Department of Health and Human Services, 2000), the risks of these medications have generally been viewed as greater than these potential benefits. This "lesson" of not targeting adolescents may also be relevant to the new immunotherapies, where the goal might be to "protect" them from nicotine or other drug dependences even before they have any exposure. As we noted above regarding adolescents' use of illegal drugs, adolescents do not appear to smoke because of the pharmacologic effects of nicotine. As some researchers have noted (Pierce, Farkas, and Evans, 1993; Sargent, Mott, and Stevens, 1998), adolescent smoking seems to be more opportunistic, with the continuous delivery of nicotine transdermally potentially serving to increase dependence in some cases.

The example of anti-nicotine therapies provides an interesting case for study (Lagrue, 1999). Whether a similar confluence of helpful factors can be brought to bear on other addictions and the newly developing immunotherapies and sustained-release medications remains to be examined, particularly since nicotine addiction is difficult to treat and even though it has quite modest success rates at continuous abstinence.

The application of new medications for addiction treatment must address the current clinical, organizational, and financial barriers that separate primary medical care and addiction treatment services. Research will have to address a number of questions and their policy implications related to adequate financing of the medications and associated psychosocial and behavioral services; improved linkages between primary care

and specialty treatment, perhaps as one of a number of ways of allowing for the provision of medication and adjunct services and identifying best practices; and the appropriate education of providers, professional organizations, and the public to challenge some of the philosophical and other biases that may limit the usefulness of these therapies. The overall outcome of this research may be to identify what package of psychosocial and behavioral services (e.g., composition, approach, duration, amount, and practitioner type) needs to be linked with the different types of medications to achieve good patient outcomes.

The financing of these medications also needs further research. Again, we emphasize how centrally important these issues are to making immunotherapies and depot medications available. Financing is especially important because immunotherapies, in particular, are likely to have substantial initial costs. Consequently, it may be useful for NIDA to support health services research on how various public and private organizational and financing models for addiction medication delivery affect treatment access, cost, and outcomes.

Recommendation 4 The National Institute on Drug Abuse should support studies of whether the potential for discrimination due to long-lasting markers in the blood or urine deters people with drug dependence from accepting immunotherapies. The effects of immunotherapies on false-positive and false-negative drug testing results should also be studied.

Recommendation 5 The National Institute on Drug Abuse should support clinical effectiveness studies and financing models that integrate the new pharmacotherapies with psychosocial services in specialty and primary medical care settings.

COST AND ECONOMIC ISSUES

One of the primary reasons for looking at the introduction of new immunotherapies from an economic perspective is their high prospective cost and the belief by many experts that substance abuse treatment is already underfunded. There are other economic issues—issues that can be informed by economic theory and analysis—in considering the therapies and how they might interact with patients' behavior. This section considers three such issues, but we note that it is only suggestive of the types and complexities of economic issues for immunotherapies:

- the cost of these new therapies;
- the sensitivity of clients to the degree of effectiveness of the therapy; and

- the cost effectiveness of immunotherapies and sustained-release formulations.

Costs

After safety and efficacy have been established with immunotherapies and sustained-release formulations, the cost of these new therapies will have to be examined. Cost information will be essential for determining the prospective expense of making immunotherapies available, and it is highly likely to affect whether and how individuals use these therapies. Studies have shown that consumers are sensitive to the cost and cost-sharing of behavioral health services (Sturm, Goldman, and McCulloch, 1998), while public and private payers are equally attuned to, and resistant to, the costs associated with delivering these services. As discussed by Thomas and McCarty (this volume) new substance abuse treatment medications in the past decade have been slow to be accepted for reimbursement by public treatment systems or private insurance carriers.

There are only a very few monoclonal antibody immunotherapy products now on the market that are analogous to the proposed therapies; they appear to cost in the range of $1,500 to $2,000 per administration or infusion (Kosten and Kranzler, this volume). It is expected that a single administration of monoclonal antibodies will be effective for up to several months (Pentel, this volume). Moreover, patients are likely to need or want to have several courses of therapy due to the ongoing risk of relapse. It is unknown how costs might be affected if monoclonal antibodies for two or more drugs (e.g., methamphetamine and PCP) are infused simultaneously.

In contrast, vaccines and depot preparations currently under development tend to cost an order of magnitude less per administration (an injection delivered under medical supervision), and it seems likely that a patient will need to have injections every several months to maintain adequate levels of effectiveness. Because the field of immunotherapy is working to develop lower-cost methods of producing monoclonal antibodies, it may be important to examine and monitor cost trends for these classes of therapies.

Sensitivity of Clients to Effectiveness

While it is expected that complete effectiveness of these therapies (defined as blocking any psychoactive effects) will rapidly bring a compliant patient to near or complete cessation of the use of the targeted substance, current research indicates that the immunotherapies will only be partially effective (see Pentel, this volume). Patients that take the

"blocked" substances may get different degrees of (attenuated) psychoactive effects. Consequently, variations in effectiveness across patients—and why, as well as how, this can be optimized—and different patient's responses to different levels of effectiveness may be important to examine (National Research Council, 2001). As noted above, it is known that the effectiveness of immunotherapies to block psychoactive effects decreases over time.

In an economic sense, a therapy with low to modest ability to attenuate psychoactive effects could be modeled and thought of as a price increase for the drug in question (see Kleiman, this volume). Absent psychosocial or other interventions (such as testing and sanctions) the effectiveness of the immunotherapy or sustained-release formulation might be comparable in magnitude to an increase in the retail (or street) price of the drug.

Cigarette smokers who use low nicotine products have been observed to increase their consumption (use more cigarettes per day or inhale more deeply) to maintain their dosage of nicotine (and as an unintended consequence, quite possibly their intake of tar and other cigarette byproducts) (Kozlowski et al., 1996). Users of illicit drugs are known to be highly sensitive to the "quality" (e.g., purity or concentration of the active ingredient) of the drug consumed and adjust their consumption of the drug in a manner that regulates the dosage received. Thus, it is quite possible that a low efficacy medication may see continued use and even increased use by some patients, with possible adverse consequences for the individual (e.g., from harms such as HIV/HCV infection that are associated with administration not intoxication) and for society (e.g., from increased demand that stimulates increases in drug-related crime) (Kleiman, this volume).

Cost Effectiveness

The central economic fact of all health care is that resources are scarce and potential demands are virtually unlimited. Consumers, society, and the health system confront the fundamental economic question of how to optimize well-being in the face of scarce resources (Gold et al., 1996). The publicly subsidized substance abuse treatment system is well known to face limited financing, leading to waiting lists for clients and competition between providers and different types of care for resources (Center for Substance Abuse Treatment, 2000). Private and public insurance plans generally have limited coverage for substance abuse treatment therapies and medications. Cost effectiveness analysis can offer insights on the relative value of alternative health interventions.

Public and private purchasers of treatment will need to carefully consider how the benefits and costs of immunotherapies and depot medica-

tions compare with alternative, existing treatment approaches, as well as with other health services. Cost effectiveness analysis might be useful, as part of the clinical trial process, to provide potential purchasers and consumers with information that can be used in making financing decisions. To date, such analysis has had few applications in treatment for tobacco and drug abuse. Particular challenges are posed by substance abusers and the nature of the disorder that will need to be addressed, which include the fact that illicit drug and tobacco use often occurs over a number of years, with some effects occurring during the use period, while others may be delayed by many years. In addition, individuals are at risk of relapse (and, perhaps, reinitiated treatment) for a number of years. Another issue is that many of the consequences of drug use of most concern to communities are "externalities"—that is, the affects on the families of smokers and drug users, victims of crimes committed by drug users, and victims of disease transmitted by drug users.

Nonetheless, application of this decision methodology has spread rapidly throughout the general health field. Those responsible for making funding and purchasing decisions in health plans and those developing clinical practice guidelines will have an increasing need for cost effectiveness data.

4

Behavioral Responses and Consent

UNINTENDED BEHAVIORAL CONSEQUENCES

The "law of unintended consequences" demonstrates that promising innovations advanced with the noblest of intent can play out differently than anticipated, and possibly much less well than hoped for (Merton, 1936). Consequently, it can be useful early in the development of an innovation to think about how things might turn out badly. MacCoun (this volume) undertakes such an exercise for immunotherapies and sustained-release formulations for treating drug addiction. He finds that for those inclined to worry, it is not hard to envision a number of potentially negative scenarios.

These potentially negative scenarios can be divided into four types: (1) users' attempting to swamp or override the therapy with larger doses; (2) substitution of one drug whose effects have been blocked with another drug whose effects have not been blocked; (3) increased incidence or prevalence of drug use because of a perception that there is less risk involved; and (4) aggressive actions of drug sellers who are losing sales to try to move into new markets. This section reviews some of the considerations associated with each of these scenarios.

Users' Trying to Swamp or Override Treatment

It would be a major boon to treatment if an intervention such as immunotherapy or depot medication made a user completely uninterested in using a drug. Unfortunately, users who are offered these thera-

pies may still have some desire to use drugs for at least five reasons. First, as Pentel (this volume) has described, immunotherapies only partially block the transport of drug molecules into the brain. Second, effectiveness will vary over time, so that a treatment that is completely effective at one time may be ineffective at another time. Third, adherence rates for a wide range of treatment regimens have been far from perfect (not necessarily through any fault of the providers) (McLellan et al., 2000), Fourth, it is not completely clear how immunotherapies and sustained-release formulations affect drug craving (Pentel, this volume). Fifth, psychopharmacologic effects are not the sole motive for drug use (Kosten and Kranzler, this volume).

It is likely that some or even many people given immunotherapies or sustained-release formulations of opioid blockers will continue to have some desire or craving to take drugs. Moreover, for some individuals, drug-taking may still have some effect on their brain (including cognition, reward pathways, and other effects). These individuals can be thought of as having received some fraction of the benefits of a 100 percent effective blocking of the drug, yet partial effects may be better than no effects at all. Individuals might continue to ingest some of the drug, but less than they otherwise would have and, hence, they and society generally would benefit. Another possibility, however, is that these individuals will try to swamp or override the partial blockade of the drug by ingesting larger doses than they would have in the absence of the immunotherapy or depot medication, resulting in greater total use than before treatment.

This perverse outcome is not implausible. To caricature, if using an immunotherapy meant that twice as much of the drug had to be ingested to get the same effect, from a drug consumer's point of view that may be equivalent to a doubling of the price of a drug. In either event (a 50 percent effective immunotherapy or a price doubling), the user would have to spend twice as much to get the "same" brain reward. The critical question is how clients in treatment who receive these medications respond to different degrees of effectiveness, individually and on average. It is quite likely that some users will periodically attempt to swamp or override the medications at any level of effectiveness.

From an economic perspective, the responsiveness of consumers to price changes (or in this case, to medication effectiveness) can be summarized as the price elasticity of demand (MacCoun, this volume). In general, when prices increase (medication effectiveness increases) the amount of a commodity purchased decreases. When the price increases, the total amount spent on the commodity may decline, remain the same, or actually increase, depending on the nature and degree of change in consumption. The total amount spent on a commodity increases if the proportional

reduction in amount consumed is less than the proportional increase in the price. This effect is known as price elasticity: the drug is a price inelastic commodity, and the reduction in total amount spent is price elastic. (In contrast, commodities that are price elastic show proportionally equal or larger reductions in consumption as prices rise.) In the context of immunotherapies, although there is little reason to think that attempts to swamp or override treatment will lead to increases in the amount of the drug reaching the brain—since it is only the effective price of getting drugs into the brain not the actual price paid by a user to the drug seller that increases—increased spending implies increased purchasing from the seller. That is, if demand for the drug behaves as if it were inelastic in response to immunotherapy-induced increases in the effective price, there would be increased demand for drug purchases. It is not now known which drugs have elastic or inelastic demand. Originally, it was presumed that demand was probably inelastic. More recent evidence suggests that for some substances demand may be elastic, although the evidence base for this assertion is thin (see Chaloupka and Pacula, 2000, for a review).

The potential problems from user's seeking to override or swamp immunotherapies and sustained-release formulations are varied. Future studies may find it productive to differentiate among use-driven harms related to the drug's reaching the brain (e.g., many behavioral effects) or reaching other body parts (e.g., the heart or placenta) and those associated with drug ingestion or administration itself (e.g., risks of injection). Traditional forms of treatment generally affect all three types of harms proportionally, but immunotherapies, in contrast, can be expected to influence each category to a different degree and, indeed, could reduce some while increasing others. It is not clear if these new therapies protect other body parts as well as, better than, or less well than they protect the brain. Indeed, the answer may be medication-, organ-, or drug-specific, or some combination of the three.

One major concern with attempts to override the blockade effects of immunotherapy and depot medications is the risk of accidental overdose, because the level of medication effect is expected to wane over time following administration. Because there is no obvious signal to the patient that the blocking effects of an immunotherapy or depot medication have diminished after weeks or months of sustained blockade, toward the end of the effective duration of a medication dose a patient may ingest a relatively large amount of drug that had produced no overdose while the medication was more effective (more proximal to medication administration), resulting in an overdose.

Some harm stems from behaviors associated with drug use itself. Those potential harms would be exacerbated if users sought to override immunotherapies' partial blocking by taking more of the drug. Two

obvious examples are the spread of infectious diseases, such as the ones caused by human immunodeficiency virus (HIV) and the hepatitis C virus (HCV) through shared injection equipment and the risk of lung cancer from cigarette smoke. (The nicotine vaccine intercepts nicotine in the bloodstream, but not the tars and other carcinogens in the esophagus and lungs.)

For illicit drugs, adverse consequences of swamping could extend beyond the drug user to other people. If immunotherapies reduced the amount of an illicit drug reaching users' brains but increased demand from drug dealers, it could affect the black markets for those drugs (MacCoun and Reuter, 2001). For example, it is common to divide drug-related crime into three categories: psychopharmacological crime (that driven directly by drug intoxication or withdrawal), economic-compulsive crime (crime committed by users to get money to buy drugs), and systemic crime (conflict related to drug transactions, such as disputes among dealers over drug money). Very roughly these three components seem to account for about one-sixth, one-third, and one-half of drug-related crime, respectively (Caulkins et al., 1997). The first is driven by drug use, but the latter two categories are more directly related to drug market spending and revenues. If immunotherapies and sustained-release formulations reduced the amount of the drug reaching the brain but increased market demand, they could yield a net increase in drug-related crime and violence. The nature and magnitude of such an increase would depend on many market factors, including the elasticity of supply.

Drug Substitution

Immunotherapies and sustained-release medications are generally drug specific. Most are highly drug specific, while others (opioid blockers) target a class of related drugs. However, an immunotherapy that binds with cocaine, for instance, will not bind with heroin or PCP. None of these medications can bind or block alcohol. One possible behavioral response to immunotherapy or sustained-release medications for illicit drugs could be for users to substitute one (or more) substance for a blocked drug. This concern is not novel to immunotherapies, as patients in methadone maintenance programs sometimes test positive for cocaine, benzodiazepines, or other drugs and alcohol. However, it is a significant concern inasmuch as polydrug use is the norm, not the exception, among dependent substance abusers. Thus, administration of a medication specific to one drug leaves users susceptible to the use or abuse of other drugs. Still, the mere fact of drug substitution does not necessarily imply that the intervention was not helpful. For instance, the intervention might still bring benefits if the substituted drug is less dangerous than the original, but it could be counterproductive if the substituted drug is more dangerous.

Risk Calculations

As MacCoun describes (this volume), technologies that reduce the riskiness of an activity sometimes increase the prevalence of that activity. For example, there is evidence that people in cars with seat belts and air bags drive less safely (Sagberg, Fosser, and Saetermo, 1997) and that smokers may smoke more filtered or low-tar cigarettes than regular cigarettes (Kabat, 2003). If there were such a behavioral response to immunotherapy medications it could undermine some of the hoped-for benefits. Major surveys of public attitudes (such as Monitoring the Future) carefully track the perceived danger or risk of using illicit drugs and find that, over time, increases and decreases in perception are inversely and strongly correlated with use of particular drugs (Johnson, Rosenblum, and Kleber, 2003). The question arises as to whether the availability of efficacious immunotherapies and depot medications might make the risk of addiction seem to be less dangerous and possibly invite increased use of drugs (and tobacco products). A separate mechanism that might promote initiation is the possibility that successful treatment would remove "negative role models" whose presence, and problems of dependence, serve as a caution that increases youths' perceptions of the risks of drug use and, hence, reduces their initiation.

This issue of the perception of how dangerous an addictive product appears to be is at the base of recent suits against tobacco companies related to their introduction of "light," "mild," and low tar and nicotine cigarettes. It is asserted by plaintiffs in these cases that their decision to smoke or continue smoking was affected by the perception that they could reduce their potential health risks by smoking these products (Kozlowski et al., 1998). Terry Pechacek, a scientist at the Centers for Disease Control and Prevention, has speculated in interviews with the news media that an effective immunotherapy for nicotine could send kids the wrong message—that as long as you don't get addicted, it is OK to smoke . For HIV, one of the recent phenomena being studied is how the availability of increasingly effective medications affects risk-taking behavior (Blower, Schwartz, and Mills, 2003). There is a concern that HIV risk-taking behavior has increased as the perceived risk is believed to have decreased because of new medications. Thus, an unfortunate scenario might be that increases in perceived effectiveness of immunotherapies will lead to decreases in perceived risks associated with initiation and use.

MacCoun (this volume) observes that there is little evidence that risk compensation completely undermines the benefits of the intervention to users. However, drug use, particularly use of illicit drugs, generates considerable negative externalities (i.e., harms to people other than the user), and the presence of such externalities increases the risk that risk compensation could turn an intervention into a net negative for society, even if it

continues to bring benefits for the target population in question. Specifically, illicit drug users on such a medication might buy and use more of the drug (in order to occasionally override the block), but experience fewer health consequences because of the medication. However, in order to finance the increased drug use and purchases, they may have to commit more crimes (e.g., theft, drug dealing), resulting in increased harms (externalities) to the community. Thus, to the extent that individual patients on these medications increase their total drug purchases and use in order to override the medication, there is likely to be a net negative benefit to society from that individual's taking the medication.

Sellers

Illicit drug markets are not well understood, so it is difficult to predict how drug dealers would respond to demand changes induced by immunotherapies or sustained-release formulations. It is possible, however, to project some negative outcomes (see MacCoun, this volume). If the medications materially suppressed market demand, drug dealers might respond by seeking to expand into new markets or they may get more aggressive (e.g., more violent) about defending their remaining markets. Behavioral responses by sellers need not be confined to sellers of illicit drugs. Cigarette manufacturers could respond in somewhat parallel ways, for example, by increasing marketing or targeting new customer bases. At present such possibilities are highly speculative, but their possibility underscores the need for research.

An entirely different set of issues is raised by the possible behavior of the sellers of the immunotherapies and sustained-release formulations and the actions they might take in order to maximize their profits. With the very conspicuous exception of nicotine, the market revenue potential for addiction treatment may be modest. The medications developed for treatment of addictions (except nicotine) have to date realized extremely limited sales, compared with medications for other disorders such as high cholesterol, diabetes, high blood pressure, and depression. Public agencies have been unwilling or unable to fund medications for drug treatment. Furthermore, many people who are dependent on illicit drugs lack health insurance or the income to pay for expensive medications.

The populations that could benefit from new immunotherapies or sustained-release medications are significantly smaller than for many other health problems, and it appears that much less than a third of these populations actually get any care in a given year. On the basis of household surveys, the Substance Abuse and Mental Health Services Administration (2002) estimates that there are about 3.5 million individuals that could benefit from treatment for marijuana, and about 1 million that need

care for cocaine. However, when the Office of National Drug Control Policy (2001) includes the criminal justice population, they estimate that there are about 2.7 million "chronic" cocaine abusers. Studies estimate that there are somewhat fewer than 1 million heroin- or opioid-dependent individuals (Office of National Drug Control Policy, 2001). There appear to be no rigorous published estimates of the size of the population in need of treatment due to methamphetamines, although in arrestee and treatment populations they are less than one third the size of the heroin population (thus, fewer than 300,000). The PCP user population is a small fraction of the methamphetamine user population.

The potential market for use of immunotherapies to treat overdoses can be crudely gauged from data on emergency room visits involving various illicit drugs (Substance Abuse and Mental Health Services Administration, 2003). In 2001 there were 638,000 emergency room episodes involving illicit drugs, of which 193,000 involved cocaine (any form), 15,000 involved methamphetamines, and 6,000 involved PCP. Unfortunately it is difficult to estimate demand for a medication from this data because not every visit that involves a particular drug type may require treatment for overdose. However, some patients with potential symptoms of overdose may be given an immunotherapy as a precaution before it is ascertained that they actually ingested any, or a particular, drug.

As discussed in other sections of this report, there is concern that there may be interest in off-label use of these medications for "protective" purposes with certain vulnerable populations. For illicit drugs, the potential market in drug use prevention or "protection" is numerically far larger than the potential market for addiction or overdose treatment, even if one considers only juveniles: there are about 4 million youth per birth cohort, or about 16 million youths between the ages of 14 and 17, inclusive. Consequently, companies that develop these medications may want to see them used for protection.

FDA regulations restrict marketing of pharmaceutical products for indications or uses that have not been researched and approved. However, this regulation provides little assurance that the companies will either perform the necessary and costly research and go through the approval process for protective use in vulnerable populations or actively educate physicians about the lack or research for and potential risks with such use. If these medications are approved for treatment or for overdose, it would be important to track the behavior of pharmaceutical firms with respect to their off-label "protective" use.

We believe that it is worth repeating that this committee strongly recommends that NIDA support appropriate research at an early date on vulnerable populations, particularly because of the strong and well-intentioned motives there may be to administer immunotherapy medica-

tions for protective purposes, and the unfortunately negligible—or even financially perverse—incentives for pharmaceutical companies to do the needed research and educate physicians.

This quick summary of some of the possible unintended behavioral consequences of developing immunotherapies shows that many of them lie entirely outside the usual FDA review process. That is, even if a therapy were correctly judged to be safe and efficacious, many if not most of these potential adverse scenarios would remain concerns. This, again, strongly suggests that the research agenda associated with immunotherapies ought to extend well beyond those that are customarily considered in pharmacotherapy development.

Recommendation 6 The National Institute on Drug Abuse should support studies of behavioral consequences, such as the increased potential for accidental overdose and changes in drug use patterns which may include switching drugs, increasing drug dosage or overall consumption, changing the route of administration (e.g. nasal to intravenous for greater bioavailability) or, conversely, avoiding use of other addictive substances.

Recommendation 7 The National Institute on Drug Abuse should support studies that examine the extent to which the availability of immunotherapy medications might reduce the perceived risk of drug use and the effects of such perceptions on drug use behavior in various populations.

Recommendation 8 The National Institute on Drug Abuse should support studies of the potential effect of immunotherapy medications on illicit drug markets and market-related behaviors.

CONSENT AND VULNERABLE POPULATIONS

As noted early in this report, the committee has particular concerns around behavioral, ethical, legal and social issues for vulnerable populations. Such populations include adolescents, pregnant women, and those involved with the criminal justice and child welfare systems. These populations are vulnerable in several different respects. First, such populations are often excluded from clinical trials of new medications; thus, less is known about the safety and efficacy of new treatments with them. Second, the range and degree of behavioral responses to immunotherapies and sustained-release medications for adolescents and pregnant women and their fetuses may be different from those of adult males and nonpregnant females, who are likely to be the participants in initial clinical trials. Finally, people in these populations may be susceptible to being coerced to accept therapies that they would reject if free to make their own decisions.

The committee fully expects that in the vast majority of cases, immunotherapies and sustained-release medications will be used appropriately with such vulnerable individuals: individuals will be given the opportunity to voluntarily consent to this treatment modality after being informed of the risks and benefits of the treatment and informed of other treatment options. However, even infrequent, well-intentioned misuses and abuses of these therapies with vulnerable individuals might receive significant public attention and might have an adverse effect on the acceptance and use of these potentially important advances in treatment for addictions. Therefore, the committee recommends (above) early, preclinical research on the use of these therapies in vulnerable populations, the outcome of which may be useful for determining whether and when clinical trials involving these groups should be undertaken.

The challenge in prescribing these medications for vulnerable populations is inextricably linked with individuals' rights to consent to or refuse medical care, after receiving complete information. While medical consent is a nearly unqualified principle in the U.S. health system, adherence to this principle may be compromised in the zeal to address tobacco and drug addiction among individuals whose drug dependence places them in coercive settings. Adherence to informed consent may consequently require constant monitoring.

This section reviews three issues related to providing immunotherapies and sustained-release formulations to these vulnerable populations: standards related to an individual's right to determine care; providing these medications to minors; and providing these medications to adults who are mandated or coerced to receive them.

The Individual Right to Determine Care

Legal Considerations

Competent adults have the right to make their own decisions about whether to accept or reject medical treatment, including life-sustaining treatment, free from interference by anyone, including the state (Ridgely, Iguchi, and Chiesa, this volume). This right is based on the constitutional rights to liberty and privacy grounded in the Fifth and Fourteenth Amendments and the common law right of bodily integrity and self-determination. The right to make medical decisions is maintained through the doctrine of informed consent, which prohibits a physician from performing any medical procedure without first explaining all relevant information and obtaining the individual's knowing and voluntary agreement (see *Kaimowitz v. Department of Mental Health for the State of Michigan,* 1973).

Individuals who are not deemed competent to provide consent as a result of age, mental condition, or mental capacity grant consent to medical care through a guardian. Even individuals who have been institutionalized because of a mental illness are presumed competent to make their own medical decisions, unless they are adjudicated incompetent (under standards established by state statutes).

The voluntary nature of consent is not necessarily suspect if rendered in a coercive setting (e.g., prison) or under coercive circumstances (e.g., facing the prospect of civil commitment). To the extent that a state-based coercive setting exists, the provision of procedural due process protections (e.g., advice of counsel or independent review by a judge or administrative hearing officer) and other protections (e.g., nonexperimental treatment and "good faith" dealing) have been found to adequately protect the voluntariness of the coercive decision-making process (*Rogers v. Commissioner of the Department of Mental Health,* 1983). Studies with psychiatric populations also demonstrate that courts are more likely to view "coercive" acts and processes of the state as legitimate if moral norms of fairness, good faith dealing, respect, and consideration of patient views are provided (Appelbaum and Grisso, 1995).

In the drug treatment context, drug-dependent individuals who might benefit from immunotherapies or sustained-release formulations (approved by the FDA for treatment purposes) have the right to be informed of the risks and benefits associated with the treatment and to provide or withhold their consent for its use. The fact that an individual's decision-making ability may be affected by the use of a psychoactive substance (either temporarily or for an indefinite time) does not affect his or her right to consent, unless an independent determination of incompetence has been made. The voluntariness of the consent must be evaluated in the particular context in which it is rendered and the establishment of due process protections tailored to the particular context. An institutional review process to assure good faith dealing and full disclosure of medical information would likely satisfy existing legal standards. These protections would also be fundamental to decision making in a situation in which the long-term health effects of the therapy are not known and the potential for identification of a drug use history—and therefore the potential for discrimination—exists.

Ethical Considerations

In addition to legal considerations, there are ethical issues that affect the right of individuals to determine the kind of care they receive. Three core ethical principles in medical treatment and research are respect, beneficence, and justice (Dresser, 1996; Sieber, 1994). These principles

were outlined in the "Belmont Report" (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978), which governs the conduct of research on human subjects. These principles also have implications for the consent process and offering treatments to patients.

Respect, as enunciated in the Belmont principles, requires that researchers and clinicians view patients and study subjects as autonomous agents who are able to make decisions about what they will and will not do, as long as those decisions and resulting actions do not cause harm to others. Respect also means that patients who are not capable of exercising autonomy are protected from actions that would be harmful to them. For patients who are not able to exercise autonomy or who have a diminished capacity to make these decisions, a balancing act is required that considers the potential risks and benefits of the proposed action or treatment.

Beneficence is also defined in terms of two general rules. Beneficence requires that clinicians not take actions that may potentially harm their patients. It also requires that any potential benefits be maximized, while any prospective harm is minimized. The benefits can be for the patient or for the larger society.

The principle of justice focuses on the recipients of benefits and the burdens of medical procedures. Justice, in this context, focuses on fairness in the distribution of the benefits or the unjust application of the burdens.

The National Advisory Council on Alcohol Abuse and Alcoholism (1988) and the National Advisory Council on Drug Abuse (NACDA) (1997) have applied these principles to working with individuals who have substance use disorders. The NACDA guidelines, for example, suggest that individuals be given the opportunity to choose what does and does not happen to them and also speaks to the importance of providing protections for persons with diminished autonomy or capacity. Beneficence requires that researchers not only seek to minimize any potential harms, but also work to maximize the potential benefits to the individual and to society. Justice requires a fair and equal distribution of benefits and burdens of research involving human subjects. In terms of consent issues, the NACDA guidelines require that researchers: assure that an informed consent process is in place that gives individuals all the information needed to make decisions; give adequate consideration to the mental and physical condition of participants to ensure that they fully understand the "context of consent;" conduct an independent evaluation if there is a question about a person's ability to comprehend the consent process; and update the informed consent process when new data about safety and efficacy are available.

Even with this guidance, some people have questioned the capacity of individuals with substance use disorder diagnoses to consent to par-

ticipation in research or to clinical care (McCrady and Bux, 1999). These questions have focused on whether a person can understand the procedures (DeRenzo, 1994), whether the person's decision-making capacity is impaired because of substance use (Dresser, 1996; Cohen, 2002), and the nature of the informed consent process itself (Shimm and Speece, 1992). Despite these concerns, however, the literature that examines these issues is limited (McCrady and Bux, 1999). The NACDA guidelines were developed with an awareness of these issues. Adherence to the ethical principles discussed above and use of guidelines has served to help researchers and clinicians appropriately include individuals with substance use diagnoses in their research, woth their giving consent to treatment, barring any indication of diminished autonomy or capacity.

The Belmont principles and NACDA guidelines support the considerations noted above, in terms of the ability of drug-dependent individuals to make their own decisions about receiving immunotherapies or depot medications, with the full knowledge of the expected risks and benefits of treatment, as well as an understanding of alternative treatments that may be available. However, in terms of the vulnerable populations that we refer to throughout this report, these ethical principles require that basic knowledge be available to help inform those decisions. For instance, it is necessary to have information about the likely short-term and long-term effects on pregnant women and their fetuses and how immunotherapies and depot medications might affect the behavioral and physiological development of children and adolescents. Absent any data that might answer these questions for these populations, the committee recommends preclinical studies to elucidate these issues prior to clinical studies with these populations.

Minors

If and when immunotherapies for tobacco or illicit drugs receive FDA approval, some parents may seek to have their children immunized to attempt to "protect" them against addiction. There are a number of issues that should be examined in anticipation of this use, some of which have been described above. Certainly, the primary consideration concerns the safety and efficacy of the therapies in adolescents, which may be somewhat different from the safety and efficacy for adults because of developmental and behavioral differences. A second key consideration involves who makes the decision about treatment and whose decision prevails if an adolescent is unwilling to undergo treatment. Moreover, if parents or guardians overrule an unwilling adolescent, there may be effects on the parent-child relationship, which should be examined.

In most cases, the law recognizes the rights of parents or guardians to

make medical decisions for their children, absent other state standards. This recognition is captured by a statement made by the U.S. Supreme Court in the case of *Prince v. Massachusetts* (321 U.S. 158, 1944), "It is cardinal with us that the custody, care and nurture of the child reside first in the parents, whose primary function and freedom include preparations for obligations the state can neither supply nor hinder." The law recognizes, however, that there are situations in which legal intervention may take place to overturn parental decisions; ". . . if it appears that parental decisions will jeopardize the health and safety of the child" (see *Wisconsin v. Yoder,* 1971). Under these situations, the state may step in to seek permission from the judicial system to assume guardianship status for a specific life-threatening or life-altering medical situation (e.g., when a child requires blood transfusions or chemotherapy or for a child with massive facial disfiguration). These legal parameters suggest that for minors, parents and, in well-defined circumstances, the state (often through the courts), have a major say in medical decision making.

The law presumes that children under the age of 14 lack the capacity to give meaningful consent to their own medical treatment because they lack the maturity and the ability to judge both short- and long-term implications of illness and treatment. For adolescents between the ages of 14 and 18, although constraints remain, the law supports the need for their assent to treatment as their cooperation for treatment is well recognized. In addition, statutes in some states permit adolescents to make particular medical decisions without parental review. Indeed, the laws in many states already give adolescents the right of consent to alcohol and drug treatment. Thus, medical decision making for children and adolescents is affected by the minor's age and the particular type of medical care at issue.

In general, parents (or guardians) make three kinds of medical decisions for their children: (1) routine preventive or protective measures, such as standard childhood immunizations; (2) therapies for previously diagnosed medical problems, such as ongoing urinary tract infections or broken limbs; and (3) improvement of physical, intellectual or emotional well-being such as use of growth hormones where no diagnosed medical condition exists (Miller and Klanica, this volume). This third category of medical decisions is the most controversial and would presumably apply if parents wanted to use immunotherapy to protect an adolescent against the potential use of tobacco or drugs.

Under what circumstances are parents permitted to make medical decisions that fall in the third category, in which there is no medical necessity for the therapy? How would a court resolve a dispute between a parent and an unwilling adolescent? Guidance from the legal system is extremely limited (Miller and Klanica, this volume). Probably the most

extreme situation is whether the therapy administered to a minor has long-term implications for the child when she or he reaches maturity. The potential long-term effect of immunotherapies and sustained-release formulations highlights the need for data to address this concern and underlies the earlier recommendation that preclinical studies with minors be conducted before clinical trials are undertaken.

Coerced Treatment for Adults

The human and societal costs of drug dependence have compelled virtually all sectors—medical, criminal justice, education, child welfare, social services, and religious—to search for effective solutions to prevent and treat drug dependence. If, and when, the safety and efficacy of immunotherapies or sustained-release formulations is demonstrated, the severity of the drug problem together with the promise of these therapies may result in a push in some state agencies to mandate the use of these therapies for drug-dependent individuals in the civil or criminal systems.

Individuals with drug problems can already be required to undergo treatment as a condition of their criminal justice status (whether incarcerated, on probation or parole, or through diversion program), or to participate in the child welfare system, by virtue of their inability to care for themselves or reliance on public benefits (cash assistance, public housing or other disability benefits) (Ridgely, Iguchi, and Chiesa, this volume). In such cases, treatment is deemed to be mandated or coerced since the failure to participate in or comply with the proscribed treatment can result in the loss of freedom (incarceration or civil commitment), parental rights, or receipt of basic means for sustenance and health care.

The potential use of immunotherapies for overdose treatment, relapse prevention, or primary prevention adds a new wrinkle to mandated treatment. The key question here is whether individuals may be required to receive a *specific* type of pharmacotherapy, rather than *some kind* of treatment—behavioral, medication based, or some combination of the two. The statute and case law are not settled around this issue.

Unquestionably, mandated treatment for drug dependence is lawful in some circumstances. There is no clear answer, however, in the drug treatment setting, on whether the state could, acting under either its police power or *parens patriae* authority, require an adult who does not consent to treatment with immunotherapies or sustained-release formulations to participate in such treatment. Most of the legal standards that address the mandatory use of particular medications have been based on persons with mental illness who pose a danger to themselves or to other people and who refuse to take medications (Ridgely, Iguchi, and Chiesa, this volume). It will be necessary to extrapolate from these and other legal principles

and precedents when evaluating the legality of the potential mandatory use of the new therapies.

Some states have exercised their police and *parens patriae* powers to enact and (much less frequently) enforce civil commitment statutes (Ridgely, Iguchi, and Chiesa, this volume). These statutes permit the involuntary detention of individuals with alcohol and drug dependence who have been determined through some adjudicative process to be dangerous to themselves or others or, depending on the particular statute, to be incapacitated or unable to care for themselves. However, there are few legal standards that apply with immunotherapies and sustained-release formulations. States rarely use their civil commitment authority to deal with drug-dependent individuals who may require treatment. Moreover, only a small number of state statutes actually require the availability of treatment as a precondition for commitment.

To apply the forced medication standards that have evolved for mental illness in the context of civil commitment to these new therapies, a state would be required to obtain a separate finding of incompetence to medicate an individual against his or her will. Moreover, courts have required an examination of the medical appropriateness of the medication, the potential adverse side effects and the availability of less intrusive measures when determining whether to override the liberty and privacy interests of the individual who objects to forced medication (*Sell v. United States*, 2003).

States have used their police powers much more often to mandate treatment as a condition of an individual's criminal justice status, either in a correctional facility, for those seeking probation or parole, and for those who participate in diversion programs. Mandatory prison-based treatment requirements, which are established through either state statute or administrative practices, vary widely, and most efforts do not proscribe the type of treatment that must be provided. (The availability of *any* treatment is often the most significant problem).

Looking again to the mental illness context for guidance on whether an incarcerated individual can refuse to undergo a particular type of treatment, the Supreme Court has enunciated a qualified right of mentally ill individuals to refuse psychotropic medication. The government's interest to compel treatment has been held to outweigh an inmate's right to refuse psychotropic medication in one case when the inmate was found to be dangerous and treatment was deemed by professionals to be in his best interest. In a second case, the Supreme Court upheld a medication requirement when treatment was necessary to restore the individual to competency to stand trial for a serious crime, there was evidence that the medication was justified by safety considerations, and no less intrusive means existed to accomplish the same result. The Supreme Court clarified the

standard for permitting forced medication just recently in *Sell v. United States* (2003). The Court said that the government interest at stake must be important, forced medication must significantly further those state interests, there must be no less intrusive treatments likely to achieve substantially the same result, and the treatment must be medically appropriate. These same standards should guide an evaluation of whether a state could impose treatment with immunotherapies or sustained-release formulations in a prison context.

State and federal authorities also have wide latitude to impose treatment requirements as a condition of probation or parole, and courts have enforced those conditions. Individuals who accept but then violate those conditions, including the refusal to comply with treatment, may be punished through revocation of probation or parole and face renewed incarceration. Again, the imposition of a particular type of treatment on parolees or probationers appears to be less of an issue than the dearth of treatment for most of those who need it. Yet to the extent that community-based services are offered and rejected by an individual, he or she would be subject to revocation of probation or parole. The same standards would likely apply in drug court or diversion programs: refusal to comply with the treatment requirements could be the basis for a finding of noncompliance that triggers consequences in the criminal justice system.

Perhaps the most controversial area of coerced treatment relates to prenatal use of drugs. Some states have adopted public health as well as punitive policies to address maternal drug use, including the identification and referral to treatment of women who use drugs prenatally; monitoring and enforcement of civil child abuse and neglect statutes following the birth; and prosecution under existing state criminal laws for neglect or other drug delivery crimes during pregnancy and after birth. With the exception of South Carolina, no state has adopted the position that a fetus is a "person" for purposes of prosecuting civil and criminal abuse and neglect laws against a woman who use drugs during pregnancy. Importantly, the Supreme Court has held that pregnant women do not lose their constitutional right to be free from warrantless searches and seizures even if the state's goal is to detect drug use during pregnancy.

The imposition of a particular type of treatment on pregnant women has been less of an issue than the therapeutic value, need, and clinical capacity to impose *any* type of treatment given the severe shortage of services that are appropriate for and available to pregnant and parenting women. The mandatory use of immunotherapies for pregnant women who do not voluntarily consent raises the particular issue of whether safety data will be available to make the necessary determination of safety and efficacy of these therapies for pregnant women and fetuses, which would be required before being imposed.

There is little question that child protective services can mandate persons who have custody over children to seek evaluation and treatment for drug dependence and successfully complete treatment as a condition of retaining custody of children. Those who fail to comply with treatment requirements and who are found, after due process, to be negligent or abusive may have parental rights terminated. Nothing in the case law sets limits on the specific treatment modality that can be mandated, although basic fairness would require that an immunotherapy or sustained-release formulation be deemed safe and effective before being imposed.

Decisions about the coerced use of immunotherapies must also take into consideration the potential stigmatization of both the individuals who are required to participate in the treatment and the treatment itself. There is a risk that an individual who has been actively immunized can be identified through the use of a blood test for a long time. That information might then be used to adversely affect employment, insurance, and other necessities of life. While discrimination on the basis of a past drug history is currently prohibited under the Americans with Disabilities Act and some state disability discrimination statutes, the scope of those protections for persons with disabilities has been limited by the courts. Care must be taken in imposing a treatment that could result in potential negative consequences long after an individual has stopped drug use.

It is also important to ask whether the coerced use of immunotherapies could cast a shadow on this new therapy that, if found to be effective and safe, might significantly change the face of drug treatment. Such a stigma might deter individuals from accessing a potentially useful treatment and further inhibit the mainstreaming of drug dependence treatment into general medical practice.

Recommendation 9 The National Institute on Drug Abuse should support studies to determine the standards to be applied when immunotherapy medications are considered for use in the criminal justice and child welfare systems, including due process protections when there is a government-imposed treatment requirement.

Recommendation 10 The National Institute on Drug Abuse should support studies to carefully articulate the behavioral, ethical, and social risks associated with treatment of pregnant women and their fetuses and protective therapy in minors and to develop clinical practice guidelines for such use or discouragement of such use.

References

Addis, A., Moretti, M.E., Ahmed Syed, F., Einarson, T.R., and Koren, G. (2001). Fetal effects of cocaine: An updated meta-analysis. *Reproductive Toxicology, 15*(4), 341-369.

Aoki, K., Hirose, Y., and Kuroiwa, Y. (1990). Immunoassay for methamphetamine with a new antibody. *Forensic Science International, 44*, 245-255.

Appelbaum, P.S., and Grisso, T. (1995). The MacArthur Treatment Competence Study. I: Mental illness and competence to consent to treatment. *Law and Human Behavior, 19*(2), 105-126.

Berke, J., and Hyman, S. (2000). Addiction, dopamine, and the molecular mechanisms of memory [Review]. *Neuron, 25*(3), 515-532.

Blaine, J.D., Ling, W., Kosten, T.R., O'Brien, C.P., and Chiarello, R.J. (1994). Establishing the efficacy and safety of medications for the treatment of drug dependence and abuse: Methodological issues. In R. Prien and E. Robinson (Eds.), *Clinical evaluation of psychotropic drugs: Principles and guidelines.* New York: Raven Press.

Blower, S.M., Schwartz, E.J., and Mills, J. (2003). Forecasting the future of HIV epidemics: The impact of antiretroviral therapies and imperfect vaccines. *AIDS Reviews, 5*(2), 113-125.

Byrnes-Blake, K.A., Carroll, F.I., Abraham, P., and Owens, S.M. (2001). Generation of anti-(+)methamphetamine antibodies is not impeded by (+)methamphetamine administration during active immunization of rats. *International Immunopharmacology, 1*(2), 329-338.

Carrera, M.R., Ashley, J.A., Wirsching, P., Koob, G.F., and Janda, K.D. (2001). A second-generation vaccine protects against the psychoactive effects of cocaine. *Proceedings of the National Academy of Sciences, USA, 98*(4), 1988-1992.

Caulkins, J.P., Rydell, C.P., Schwabe, W., and Chiesa, J. (1997). *Mandatory minimum drug sentences: Throwing away the key or the taxpayers' money?* (MR-827-DPRC). Santa Monica, CA: RAND Corporation.

Center for Drug Evaluation and Research. (2003). *CDER manual of policies and procedures.* Available: http://www.fda.gov/cder/map.htm [November 6, 2003].

Center for Substance Abuse Treatment. (2000). *Changing the conversation: Improving substance abuse treatment—The National Treatment Plan Initiative*. Rockville, MD: U.S. Department of Health and Human Services.

Cerny, E.H., Levy, R., Mauel, J., Mpandi, M., Mutter, M., Henzelin-Nkubana, C., Patiny, L., Tuchscherer, G., and Cerny, T. (2002). Preclinical development of a vaccine against smoking. *Onkologie, 2*, 406-411.

Chaloupka, F., and Pacula, R. (2000). Economics and antihealth behavior: The economic analysis of substance use and misuse. In W. Bickel and R. Vuchinich (Eds.), *Reframing health behavior change with behavioural economics* (pp. 89-111). Mahwah, NJ: Lawrence Erlbaum.

Coffey, R.M., Mark, T., King, E., Harwood, H., McKusick, D., Genuardi, J., Dilonardo, J., and Chalk, M. (2001). *National estimates of expenditures for substance abuse treatment, 1997* (DHHS Publication No. SMA-01-3511). Rockville, MD: Center for Substance Abuse Treatment.

Cohen, P.H. (2002). Untreated addiction imposes an ethical bar to recruiting addicts for non-therapeutic studies of addictive drugs. *Journal of Law, Medicine and Ethics, 30*(1), 73-81.

D'Aunno, T., and Pollack, H.A. (2002). Changes in methadone treatment practices: Results from a national panel study, 1988-2000. *Journal of the American Medical Association, 288*(7), 850-856.

D'Aunno, T., Vaughn, M., and McElroy, P. (1999). An institutional analysis of HIV prevention efforts by the nation's outpatient drug abuse treatment units. *Journal of Health and Social Behavior, 40*, 175-192.

Demain, A.L. (2000). Small bugs, big business. The economic power of the microbe. *Biotechnology Advances, 18*(6), 499-514.

DeRenzo, E.G. (1994). The ethics of involving psychiatrically impaired persons in research. *IRB: A Review of Human Subjects Research, 16*(6), 7-9.

Devi, C.M., Bai, M.V., Lal, A.V., Umashankar, P.R., and Krishnan, L.K. (2002). An improved method for isolation of anti-viper venom antibodies from chicken egg yolk. *Journal of Biochemical and Biophysical Methods, 51*(2), 129-138.

Dresser, R. (1996). Mentally disabled research subjects: The enduring policy issues. *Journal of the American Medical Association, 276*(1), 67-72.

Ernst, E. (1999). Second thoughts about safety of St. John's wort [published erratum in *Lancet*, *355*, 580]. *Lancet, 354*(9195), 2014-2016.

Farrelly, M.C., Bray, J.W., Zarkin, G.A., Wendling, B.W., and Liccardo Pacula, R. (1999). *The effects of prices and policies on the demand for marijuana: Evidence from the National Household Surveys on Drug Abuse.* (Working Paper No. w6940). Cambridge, MA: National Bureau of Economic Research.

Ferguson, L., Ries, R., and Russo, J. (2003). Barriers to identification and treatment of hazardous drinkers as assessed by urban/rural primary care doctors. *Journal of Addictive Diseases, 22*(2), 79-90.

Flannery, D.J., Williams, L.L., and Vazsonyi, A.T. (1999). Who are they with and what are they doing? Delinquent behavior, substance use, and early adolescents' after-school time. *American Journal of Orthopsychiatry, 69*(2), 247-253.

Fox, B.S., Kantak, K.M., Edwards, M.A., Black, K.M., Bollinger, B.K., Botka, A.J., French, T.L., Thompson, T.L., Schad, V.C., Greenstein, J.L., Gefter, M.L., Exley, M.A., Swain, P.A., and Briner, T.J. (1996). Efficacy of a therapeutic cocaine vaccine in rodent models. *Nature Medicine, 2*(10), 1129-1132.

Friedmann, P.D., Alexander, J.A., and D'Aunno, T.A. (1999). Organizational correlates of access to primary care and mental health services in drug abuse treatment units. *Journal of Substance Abuse Treatment, 16*(1), 71-80.

Genevie, L., Struening, E.L., Kallos, J.E., Geiler, I., Muhlin, G.L., and Kalplan, S. (1988). Urban community reaction to health facilities in residential areas: Lessons from the placement of methadone facilities in New York City. *International Journal of the Addictions, 23*(6), 603-616.

Gold, M.R., Siegel, J.E., Russell, L.B., and Weinstein, M.C. (Eds.). (1996). *Cost-effectiveness in health and medicine*. New York: Oxford University Press.

Greenstein, R.A., O'Brien, C.P., Woody, G., Long, M., Coyle, G., Grabowski, J., and Vittor, A. (1981). Naltrexone: A short-term treatment alternative for opiate dependence. *American Journal of Drug and Alcohol Abuse, 8*(3), 291-300.

Griesler, P.C., Kandel, D.B., and Davies, M. (2002). Ethnic differences in predictors of initiation and persistence of adolescent cigarette smoking in the National Longitudinal Survey of Youth. *Nicotine and Tobacco Research, 4*(1), 79-93.

Harwood, H., Fountain, D., and Livermore, G. (1998). *The economic costs of alcohol and drug abuse in the United States, 1992-1998.* (NIH Pub. No. 98-4327). Washington, DC: National Institute on Drug Abuse.

Hieda, Y., Keyler, D.E., Vandevoort, J.T., Kane, J.K., Ross, C.A., Raphael, D.E., Niedbalas, R.S., and Pentel, P.R. (1997). Active immunization alters the plasma nicotine concentration in rats. *Journal of Pharmacology and Experimental Therapeutics, 283*(3), 1076-1081.

Hieda, Y., Keyler, D.E., Ennifar, S., Fattom, A., and Pentel, P.R. (2000). Vaccination against nicotine during continued nicotine administration in rats: Immunogenicity of the vaccine and effects on cocaine distribution to brain. *International Journal of Immunopharmacology, 22*(10), 809-819.

Institute of Medicine. (1998). *Bridging the gap between practice and research: Forging partnerships with community-based drug and alcohol treatment.* Committee on Community-Based Drug Treatment. S. Lamb, M.R. Greenlick, and D. McCarty (Eds.). Washington, DC: National Academy Press.

Johnson, B.D., Rosenblum, A., and Kleber, H. (2003). *A new opportunity to expand treatment for heroin users in New York City: Public policy challenges for bringing buprenorphine into drug treatment programs and general medical practice*. White Paper for New York City Department of Health and Mental Hygiene. Available: http://www.nyc.gov/html/doh/pdf/public/dmh/whitepaper.pdf [August 21, 2003].

Kabat, G.C. (2003). Fifty years' experience of reduced-tar cigarettes: What do we know about their health effects? *Inhalation Toxicology, 15*(11), 1059-1102.

Kantak, K.M., Collins, S.L., Bond, J., and Fox, B.S. (2001). Time course of changes in cocaine self-administration behavior in rats during immunization with the cocaine vaccine IPC-1010. *Psychopharmacology, 153*(3), 334-340.

Keyler, D.E., Hieda, Y., St. Peter, J., and Pentel, P.R. (1999). Altered disposition of repeated nicotine doses in rats immunized against nicotine. *Nicotine Tobacco Research, 1*, 241-249.

Kirchmayer, U., Davoli, M., and Verster, A. (2004). Naltrexone maintenance treatment for opioid dependence. In *The Cochrane Library* (Issue 1). Chichester, England: John Wiley & Sons.

Kleiman, M.A.R. (2004). Costs and benefits of immunotherapies or depot medications for the treatment of drug abuse. In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

Klein, M. (1998). Research issues related to development of medications for treatment of cocaine addiction. *Annals of the New York Academy of Sciences, 844*, 75-91.

Klesges, L.M., Johnson, K.C., Somes, G., Zbikowski, S., and Robinson, L. (2003). Use of nicotine replacement therapy in adolescent smokers and nonsmokers. *Archives of Pediatrics and Adolescent Medicine, 157*, 517-522.

Kosten, T.R., Jalali, B., Hogan, I., and Kleber, H.D. (1983). Family denial as a prognostic factor in opiate addict treatment outcome. *Journal of Nervous and Mental Disease, 171*(10), 611-616.

Kosten, T.R., and Kranzler, H.R. (2004). What will we learn from the FDA clinical trials process and what will we still want to know about immunotherapies and depot medications to treat drug dependence? In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

Kosten, T.R., Rosen, M., Bond, J., Settles, M., Roberts, J.S., Shields, J., Jack, L., and Fox, B. (2002a). Human therapeutic cocaine vaccine: Safety and immunogenecity. *Vaccine, 20*, 1196-1204.

Kosten, T.R., Gonsa, K., St. Clair Roberts, J., Jack, L., Bond, J., Mitchell, E., and Fox, B. (2002b). *Phase II human study of cocaine vaccine TA-CD*. Paper prepared for the College on Problems of Drug Dependence Annual Meeting, June 8-13, Quebec City.

Kozlowski, L.T., Goldberg, M.E., Yost, B.A., Ahern, F.M., Aronson, K.R., and Sweeney, C.T. (1996). Smokers are unaware of the filter vents now on most cigarettes: Results of a national survey. *Tobacco Control, 5*(4), 265-270.

Kozlowski, L.T., Goldberg, M.E., Yost, B.A., White, E.L., Sweeney, C.T., and Pillitteri, J.L. (1998). Smokers' misperceptions of light and ultra-light cigarettes may keep them smoking. *American Journal of Preventive Medicine, 15*(1), 9-16.

Kranzler, H.R., Modesto-Lowe, V., and Nuwayser, E.S. (1998) Sustained-release naltrexone for alcoholism treatment: A preliminary study. *Alcoholism, Clinical and Experimental Research, 22*, 1074-1079.

Krystal, J.H., Cramer, J.A., Krol, W.F., Kirk, G.S., and Rosenheck, R.A. (2001). Veterans Affairs Naltrexone Cooperative Study G. Naltrexone in the treatment of alcohol dependence. *New England Journal of Medicine, 345*(24), 1734-1739.

Lagrue, G. (1999). Nicotine replacement therapy and smoking cessation: What choice for its status? *Bulletin de l'Academie Nationale de Medecine, 183*(6), 1175-1182.

Lawrance, K.G. (2001). Adolescent smokers' preferred smoking cessation methods. *Canadian Journal of Public Health, 92*(6), 423-426.

Lowinson, J.H., Payte, J.T., Joseph, H., Marion, I.L., and Dole, V.P. (1992). Methadone maintenance. In J.H. Lowinson, P. Ruiz, R.B. Milman, and J.G. Langrod (Eds.), *Substance abuse: A comprehensive textbook* (pp. 405-414). Philadelphia: Williams and Wilkins.

MacCoun, R., and Reuter, P. (2001). *Drug war heresies: Learning from other vices, times, and places.* New York: Cambridge University Press.

MacCoun, R.J. (2004). Anticipating unintended consequences of vaccine-like immunotherapies for addictive drug use. In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

Mallat, S.G., and Ismail, N. (2002). Plasmapheresis and related techniques: What should we know. *Lebanese Medical Journal, 50*(1-2), 45-49.

Mark, T.L., Coffey, R.M., King, E., Harwood, H., McKusick, D., Genuardi, J., Dilondardo, J., and Buck, J.A. (2000). Spending on mental health and substance abuse treatment, 1987-1997. *Health Affairs, 19*(4), 108-120.

McCrady, B.S., and Bux, D.A. (1999). Ethical issues in informed consent with substance abusers. *Journal of Consulting and Clinical Psychology, 67*(2), 186-193.

McCuller, W.J., Sussman, S., Dent, C.W., and Teran, L. (2001). Concurrent prediction of drug use among high-risk youth. *Addictive Behaviors, 26*(1), 137-142.

McLellan, A.T., Lewis, D., O'Brien, C.P., and Kleber, H.D. (2000). Drug addiction as a chronic medical illness: Implications for treatment, insurance and evaluation. *Journal of the American Medical Association, 284*(13), 1689-1695.

Merton, R.K. (1936). The unanticipated consequences of purposive social action. *American Sociological Review, 1*, 894-904.

Miller, F.H., and Klanica, K. (2004). Vaccines and immunotherapies to control addiction in minors: The legal framework. In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

National Advisory Council on Alcohol Abuse and Alcoholism. (1988). *Recommended council guidelines on ethyl administration in human experimentation.* Washington, DC: National Institute on Alcohol Abuse and Alcoholism.

National Advisory Council on Drug Abuse. (1997). *Recommended guidelines for the administration of drugs to human subjects.* Washington, DC: National Institute on Drug Abuse.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research.* (Publication No. OS 78-0012). Washington, DC: U.S. Department of Health, Education, and Welfare.

National Research Council. (2001). *Informing America's policy on illegal drugs: What we don't know keeps hurting us.* Committee on Data and Research for Policy on Illegal Drugs. C.F. Mansiki, J.V. Pepper, and C.V. Petrie (Eds.). Committee on Law and Justice and Committee on National Statistics. Commission on Behavioral and Social Sciences and Education. Washington, DC: National Academy Press.

Nohria, N., and Gulati, R. (1995). Is slack good or bad for innovation? *Academy of Management Journal, 39*, 716-725.

O'Brien, C.P., Childress, A.R., Ehrman, R., and Robbins, S.J. (1998). Conditioning factors in drug use: Can they explain compulsion? *Journal of Psychopharmacology, 12*(1), 15-22.

O'Connor, P.G., and Samet, J.M. (2002). Substance abuse: The expanding role of general internal medicine. *Journal of General Internal Medicine, 17*, 398-399.

Office of National Drug Control Policy. (2001). *The economic costs of drug abuse in the United States, 1992-1998.* (Publication No. NCJ-190636). Washington, DC: Executive Office of the President. Available: http://www.whitehousedrugpolicy.gov/publications/pdf/economic_costs98.pdf [August 21, 2003].

O'Toole, T.P., Strain, E.C., Wand, G., McCaul, M.E., and Barnhart, M. (2002). Outpatient treatment entry and health care utilization after a combined medical/substance abuse intervention for hospitalized medical patients. *Journal of General Internal Medicine, 17*(5), 334-340.

Owen, P. (2002). The pros and cons of addiction medications. *Hazelden Voice, 7*, 3-12.

Owens, S.M., Zorbas, M., Lattin, D.L., Gunnell, M., and Polk, M. (1988). Antibodies against arylcyclohexylamines and their similarities in binding specificity with the phencyclidine receptor. *Journal of Pharmacology and Experimental Therapeutics, 246*, 472-478.

Pentel, P.R. (2004). Vaccines and depot medications for drug addiction: Rationale, mechanisms of action, and treatment implications. In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

Pentel, P.R., and Keyler, D.E. (2004). Vaccination as a treatment for drug abuse: Nicotine, cocaine, phencyclidine. In M.M. Levine (Ed.), *New generation vaccines*. New York: Marcel Dekker.

Pentel, P.R., Malin, D.H., Ennifar, S., Hieda, Y., Keyler, D.E., Lake, J.R., Milstein, J.R., Basham, L.E., Coy, R.T., Moon, J.W., Naso, R., and Fattom, A. (2000). A nicotine conjugate vaccine reduces nicotine distribution to brain and attenuates its behavioral and cardiovascular effects in rats. *Pharmacology, Biochemistry, and Behavior, 65*, 191-198.

Pierce, J., Farkas, A., and Evans, N. (1993). *Tobacco use in California 1992: A focus on preventing uptake in adolescents*. Sacramento: California Department of Human Services.

Plessinger, M.A. (1998). Prenatal exposure to amphetamines: Risks and adverse outcomes in pregnancy. *Obstetrics and Gynecology Clinics of North America, 25*, 119-138.

Price, J.H., Yingling, F., Dake, J.A., and Telljohann, S.K. (2003). Adolescent smoking cessation services of school-based health centers. *Health Education and Behavior, 30*(2), 196-208.

Proksch, J.W., Gentry, W.B., and Owens, S.M. (2000). Anti-phencyclidine monoclonal antibodies provide long-term reductions in brain phencyclidine concentrations during chronic phencyclidine administration in rats. *Journal of Pharmacology and Experimental Therapeutics, 292*(3), 831-837.

Rawson, R.A., McCann, M.J., Hasson, A.J., and Ling, W. (2000). Addiction pharmacotherapy 2000: New options, new challenges. *Journal of Psychoactive Drugs, 32*, 371-378.

Ridgely, M.S., Iguchi, M.Y., and Chiesa, J. (2004). The use of immunotherapies and sustained-release formulations in the treatment of drug addiction: Will current law support coercion? In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

Robinson, T.E., and Berridge, K.C. (2000). The psychology and neurobiology of addiction: An incentive-sensitization view. *Addiction, 95*(Suppl 2), S91-S118.

Sagberg, F., Fosser, S., and Saetermo, I.A. (1997). An investigation of behavioural adaptation to airbags and antilock brakes among taxi drivers. *Accident, Analysis and Prevention, 29*(3), 293-302.

Sargent, J.D., Mott, L.A., and Stevens, M. (1998). Predictors of smoking cessation in adolescents. *Archives of Pediatrics and Adolescent Medicine, 152*(4), 388-393.

Shimm, D.S., and Speece, R.G. (1992). Rate of refusal to participate in clinical trials. *IRB: A Review of Human Subjects Research, 14*, 7-9.

Shoeman D., Keyler, D.E., and Pentel, P. (2002). *Vaccination of female rats against nicotine reduces nicotine distribution to fetal brain* (abstract). Paper presented at the Society for Research on Nicotine and Tobacco Annual Meeting, Savannah, GA.

Sieber, J.E. (1994). Ethical considerations in planning and conducting research on human subjects. *Academic Medicine, 68*(Suppl 9), 9-13.

Simister, N.E., and Story, C.M. (1997). Human placental Fc receptors and the transmission of antibodies from mother to fetus. *Journal of Reproductive Immunology, 37*, 1-23.

Simoes, E.A., and Groothuis, J.R. (2002). Respiratory syncytial virus prophylaxis—the story so far. *Respiratory Medicine, 96*(Suppl B), S15-S24.

Smith, M.D. (1996). Antibody production in plants. *Biotechnology Advances, 14*(3), 267-281.

Sobeck, J., Abbey, A., Agius, E., Clinton, M., and Harrison, K. (2000). Predicting early adolescent substance use: Do risk factors differ depending on age of onset? *Journal of Substance Abuse, 11*(1), 89-102.

Stein, M.D., and Friedman, P.D. (2001). Generalist physicians and addiction care: From turfing to sharing the turf. *Journal of the American Medical Association, 286*, 1764-1765.

Sturm, R., Goldman, W., and McCulloch, J. (1998). Mental health and substance abuse parity: A study of Ohio's state employee program. *Journal of Mental Health Policy and Economics, 1*(3), 129-134.

Substance Abuse and Mental Health Services Administration. (2002). *National Survey of Substance Abuse Treatment Services (N-SSATS): 2000 data on substance abuse treatment facilities.* (Rep. No. DASIS Series: A-16; DHHS Publication No. SMA 02-3668). Rockville, MD: Author.

Substance Abuse and Mental Health Services Administration. (2003). *The DAWN report: Trends in drug-related emergency department visits, 1994-2001 at a glance*. Available: http://dawninfo.samhsa.gov/pubs_94_02/shortreports/files/TDR_EDvisits_glance_1994_2001.pdf [November 7, 2003].

Swarns, R.L. (1998) Giuliani orders 5 city hospitals to wean addicts off methadone. *New York Times*, August 15.

Terada, K., Niizuma, T., Ogita, S., and Kataoka, N. (2002). Responses of varicella zoster virus (VZV)-specific immunity in seropositive adults after inhalation of inactivated or live attenuated varicella vaccine. *Vaccine, 20*(31-32), 3638-3643.

Thomas, C.P. (2000). *No magic bullet: Adoption of naltrexone by clinical providers.* Dissertation, Brandeis University.

Thomas, C.P., and McCarty, D. (2004). Adoption of drug treatment technology in specialty and primary care settings. In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

Thomas, C.P., Walack, S., Lee, S.S., McCarty, D., and Swift, R. (2003). Research to practice: Factors affecting the adoption of naltrexone in alcoholism treatment. *Journal of Substance Abuse Treatment, 24*, 1-11.

Thorndike, A.N., Biener, L., and Rigotti, N.A. (2002). Effect on smoking cessation of switching nicotine replacement therapy to over-the-counter status. *American Journal of Public Health, 92*(3), 437-442.

Tuncok, Y., Hieda, Y., Keyler, D.E., Brown, S., Ennifar, S., Fattom, A., and Pentel, P.R. (2001). Inhibition of nicotine-induced seizures in rats by combining vaccination against nicotine with chronic nicotine infusion. *Experimental and Clinical Psychopharmacology, 9*(2), 228-234.

U.S. Department of Health and Human Services. (2000). *Treating tobacco use and dependence*. Washington, DC: U.S. Public Health Service.

Villamor, N. (2003). Mechanism of action and resistance to monoclonal antibody therapy. *Seminars in Oncology, 30*(4), 424-433.

Vizcarra, C. (2003). New perspectives and emerging therapies for immune-mediated inflammatory disorders. *Journal of Infusion Nursing, 26*(5), 319-325.

von Sydow, K., Lieb, R., Pfister, H., Hofler, M., and Wittchen, H.U. (2002). What predicts incident use of cannabis and progression to abuse and dependence? A 4-year prospective examination of risk factors in a community sample of adolescents and young adults. *Drug and Alcohol Dependence, 68*(1), 49-64.

Weissman, M. (2001). Stigma. *Journal of the American Medical Association, 285*, 261-262.

Wilson, B. (1955). *Alcoholics Anonymous: The story of how many thousands of men and women have recovered from alcoholism*. New York: Alcoholics Anonymous.

Woody, G.E. (2003). Treating dually diagnosed patients. *Psychiatric Times, 20*(1), 29-30.

Woody, G.E., and McNichols, L. (2004). Putting addiction treatment medications to use: Lessons learned. In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

World Health Organization. (2003). *The history of vaccination*. Available: http://www.who.int/vaccines-diseases/history/history.shtml [November 5, 2003].

Appendixes

A

Vaccines and Depot Medications for Drug Addiction: Rationale, Mechanisms of Action, and Treatment Implications

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OVERVIEW

Immunotherapies and depot medications (dosage forms designed to release a drug gradually over a prolonged period of time) are of particular interest as approaches to treating drug addictions because of their long duration of action. Clinical effects may persist for months, eliminating the need for daily medication and potentially improving patient compliance. At the same time, a long duration of action could help prevent patients from opting out of treatment prematurely and could prolong the duration of any side effects of treatment. These possibilities raise unique questions regarding the therapeutic role for such medications and their ethical implications. The purpose of this appendix is to present the scientific basis for vaccines and depot medications as a background for addressing these unusual and challenging issues.

IMMUNIZATION

The first study of immunotherapy as a treatment for drug dependence was a report in 1974 that a vaccine directed against heroin reduced heroin self-administration in monkeys (Bonese et al., 1974). This new treatment approach was not pursued because of concerns about whether heroin addicts might simply switch to a different opiate. This appendix considers more recent and ongoing efforts directed at cocaine, phencyclidine, nicotine, and methamphetamine dependence. Initial clinical trials have begun on immunotherapies against cocaine and nicotine, but only preliminary

safety data and no efficacy data are available so far. The discussion below is based primarily on data derived from animal studies.

Definitions

There are two general strategies for immunotherapy: active immunization with vaccines and passive immunization with monoclonal antibodies. A *vaccine* is a chemical that can elicit an immune response consisting of the production of antibodies. Antibodies are large protein molecules that circulate in the blood and that can bind the chemical used in the vaccine. There are other features to an immune response, but they are not important for the treatment of drug addiction and will not be considered here. *Vaccination* is the process of administering a vaccine repeatedly to elicit an immune response and is sometimes referred to as *active immunization*. Thus an experimental animal or a person might be vaccinated to elicit antibodies that would potentially be of use as a treatment for drug addiction. It is also possible to vaccinate an experimental animal, remove and purify the antibodies, and administer these to an experimental animal or a person. This is referred to as *passive immunization*. Antibodies can also be produced in cell cultures rather than whole animals. To accomplish this, a single antibody-producing cell from a mouse is cloned (replicated) in a manner that allows it to grow in a flask and continue to produce antibody. Such antibodies are called *monoclonal* because they are all identical, in contrast to the antibodies produced by a vaccinated animal, which may have a range of abilities to bind the drug in question. In addition, monoclonal antibodies can be engineered to improve their properties. Because of these potentially advantageous features, monoclonal antibodies are generally considered the most suitable form of antibody for passive immunization.

Vaccination has received the greatest attention as a potential treatment for drug addiction because it requires just a few doses and produces a long-lasting response. Vaccination is easy to perform, relatively inexpensive, is already widely used to prevent infectious diseases, and has an excellent safety record. However, the strength of the immune response varies among individuals and could be inadequate in some. In addition, vaccination requires a series of injections over several weeks to several months before it becomes effective. Passive immunization would likely be more expensive and require more frequent dosing than vaccination but would allow the antibody dose to be controlled and adjusted according to individual needs, and there is no lag time between administration and onset of action. However, clinical experience and safety data with the high antibody doses needed are limited. Both vaccination and passive

immunization may therefore prove to have their own advantages, limitations, and potential uses for the treatment of drug dependence.

For the purposes of this discussion, chemical compounds that produce addiction will be called *drugs*, and chemical compounds used to treat addiction will be called *medications*.

Scope of Discussion

The antibodies discussed in this appendix act by *binding* drug and altering its fate in the body. Immunization can also be used to produce catalytic antibodies, which act by *breaking down* the drug (Mets et al., 1998; Baird et al., 2000). This appendix considers only binding antibodies because this application is better studied and because the ethical issues raised by catalytic antibodies are analogous.

Rationale

Drugs of abuse produce their addictive effects by acting on specific neural pathways in the brain. Most medications that have been developed or studied as treatments for drug addiction also act in the brain to reduce the effects of addictive drugs or substitute for them in order to reduce withdrawal and cravings (Kreek, LaForge, and Butelman, 2002). While this approach has had substantial successes (nicotine replacement therapy, bupropion, and nortriptyline for tobacco dependence; opiate agonists and antagonists for opiate dependence; naltrexone for alcohol dependence), each of these medications has inherent limitations. The brain pathways targeted by these medications are involved in mediating many normal and essential functions apart from drug addiction, including cognition, emotions, memory, and movement. Medications used to target these pathways can therefore affect these normal functions as well, leading to adverse effects or limits on the usable medication dose.

Immunotherapies represent an attempt to exploit a very different treatment strategy in which the *therapeutic target is the drug rather than the brain* (Pentel and Keyler, 2004). Vaccines directed against drugs of abuse stimulate the immune system to produce drug-specific antibodies that circulate in the blood and are capable of binding the drug tightly. Antibodies themselves cannot enter the brain because of their large size. Thus any drug bound to antibody also cannot enter the brain. If a sufficient amount of antibody is present when a drug is administered, a substantial fraction of the dose will bind to antibody in the blood so that the fraction of the dose entering the brain is reduced (Figure A-1). Because addictive drugs act in the brain, limiting the amount of drug entering the brain should

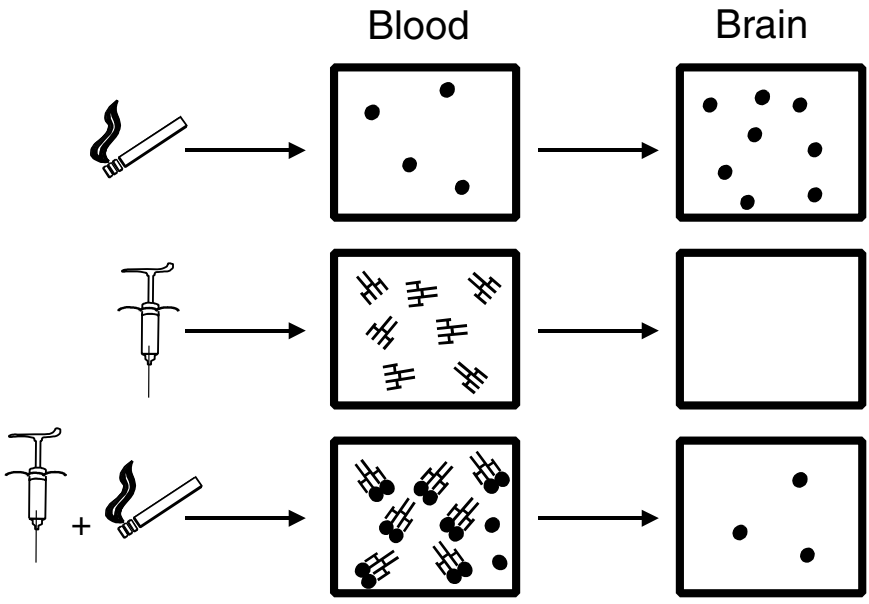

FIGURE A-1 Effects of vaccination on drug distribution to the brain, illustrated for nicotine derived from cigarettes. When nicotine is administered alone (top) it rapidly enters the blood and is delivered to the brain. Vaccination elicits the production of nicotine-specific antibodies in the blood (middle). Because antibodies are large molecules, they are excluded from the brain. If a vaccinated animal is given a dose of nicotine (bottom), a substantial fraction of that dose is bound and sequestered in the blood by the antibody and less nicotine enters brain.
SOURCE: Pentel and Keyler (2004).

also reduce the drug's effects. The hope in using this strategy is to reduce the rewarding effects of the drug that lead to and sustain addiction. For example, a cocaine addict who is vaccinated and then takes a puff of crack cocaine would feel little effect and therefore be less likely to continue using it.

Attractive Features of Immunotherapy as a Treatment for Drug Dependence

Vaccines or passive immunization have several potential advantages compared to other medications for drug addiction.

Long Duration of Action

Vaccination may elicit therapeutic concentrations (titers) of antibodies in the blood that persists for 3 to 6 months, perhaps longer (Cerny et al., 2002; Kosten et al., 2002a). If needed, satisfactory antibody concentrations could be maintained by periodic booster doses (e.g., every several months). A long duration of action could potentially improve treatment compliance by providing a measure of protection without the need for patients to return frequently to a clinic or remember to take daily medication.

Novel Mechanism of Action

The mechanism of action of vaccines as treatments for drug abuse is unique and distinct from that of currently used medications. Two treatments acting via different mechanisms often have additive effects such that the combination is more effective than either one alone. Vaccines may target different aspects of drug addiction than available medications. For example, nicotine replacement therapy reduces the severity of withdrawal symptoms, while vaccination (based on animal studies) may be more helpful for preventing the rewarding effects of a cigarette that can lead to relapse. Combining medications that have different types of effects may expand the spectrum of therapeutic actions that can be achieved and improve overall results.

Safety

Because the antibodies produced by vaccination do not appreciably enter the brain, vaccination should circumvent the central nervous system side effects that limit the use of other medications (Killian et al., 1978). Because the drug-specific antibodies elicited by vaccination bind to the addictive drug and nothing else, vaccination should also be relatively free of side effects outside of the central nervous system (Owens et al., 1988; Hieda et al., 1997). The generally excellent safety record of vaccines used to prevent infectious diseases supports this notion.

Immunology of Vaccination

Composition of a Vaccine

Small molecules such as drugs of abuse are not by themselves immunogenic and cannot stimulate the immune system to produce antibodies. A commonly used strategy for eliciting antibodies to small molecules such as these is to chemically link the drug to a larger protein molecule

(Figure A-2). The resulting molecule, consisting of drug linked to protein, is called an immunogen because it is now capable of eliciting an immune response. When used as a vaccine, this type of immunogen is referred to as a conjugate vaccine because it represents a small molecule conjugated (linked) to a protein.

Vaccination

Vaccination consists of injecting an immunogen, usually into the muscle of the upper arm, or less commonly administering it as a nasal spray or oral liquid. A single injection of vaccine generally does not stimulate significant immunity, and one or more booster injections at intervals of several weeks to months are needed to achieve a satisfactory response. This response consists of the production of antibody molecules by the cells of the immune system. An immune response may include other components in addition to antibody production, but they do not contribute to the effects of vaccines on drugs of abuse.

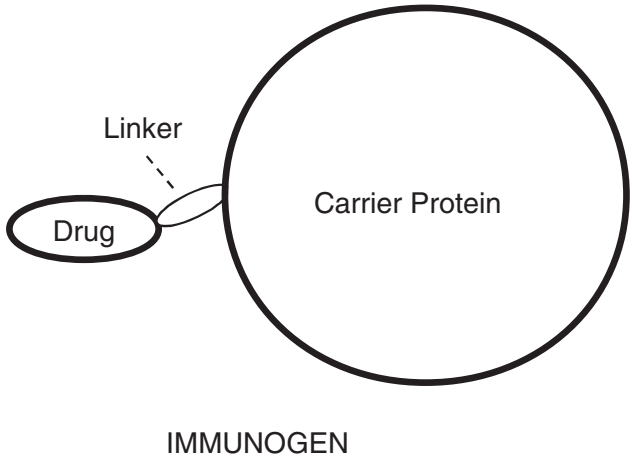

FIGURE A-2 Immunogen structure. Drugs are too small to be recognized by the immune system. To render them immunogenic, drugs must be linked to a large foreign protein. The resulting complex is the complete immunogen. A vaccine consists of the complete immunogen mixed with a chemical adjuvant that enhances the immune response. Because drugs of abuse by themselves are not complete immunogens, they do not elicit antibodies, nor can they boost an immune response in a vaccinated animal or individual. The complete immunogen is needed to boost the immune response.

Antibodies

Antibodies are protein molecules that have the ability to bind tightly to the portions of the immunogen used to stimulate their production. This is achieved through a binding pocket that is complementary in size, shape, and electrical charge to a part of the immunogen, such that the immunogen and antibody fit together in a lock-and-key fashion (Figure A-3). The antibody binding pocket is not large enough to bind the entire immunogen. Rather, immunization produces many antibodies that can bind many different parts of the immunogen. Some of these antibodies may bind the part of the immunogen that has drug linked to it, and these antibodies can also bind drug that is not linked to carrier protein. Thus a portion of the elicited antibodies will be capable of binding the free (unbound) drug.

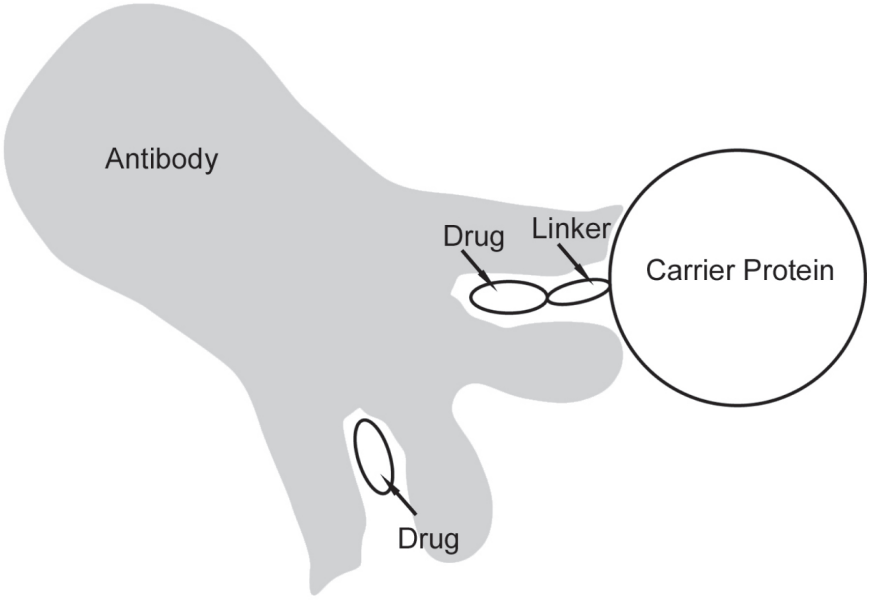

FIGURE A-3 Binding of drug to antibody. The binding site on the antibody consists of a pocket that is complementary to the drug in size, shape, and electrical charge, such that the drug fits into the binding pocket in a lock-and-key fashion. The result is tight (high-affinity) binding that is quite specific for that particular drug. Each antibody molecule has two identical binding sites. The upper site in the figure illustrates antibody binding to the complete immunogen that was used to stimulate antibody production. The lower site illustrates that the drug alone can also bind to this site.

The binding of drug to antibody is typically very tight (high affinity) and very specific. For example, antibodies to nicotine elicited by a vaccine bind only nicotine and do not bind nicotine metabolites (breakdown products), other molecules normally present in the body such as neurotransmitters or hormones, or other drugs or medications (Pentel et al., 2000). This exquisite degree of specificity suggests that the actions of these antibodies should also be quite specific.

Measuring the Response to Vaccination

The three antibody characteristics of greatest interest are the antibody *concentration* in blood, how tightly the antibodies bind the drug (*affinity*), and whether the antibodies bind anything other than the drug in question (*specificity*). All three are readily measured from small blood samples. Antibody concentration is often expressed as a titer, or dilution; higher titers indicate higher antibody concentrations. Measurements are typically obtained from serum or plasma, the liquid portion of blood exclusive of red blood cells.

Initiation of Vaccination

It is likely that a series of two to four injections over 1 to 2 months will be needed for vaccination to produce a satisfactory immune response (Hieda et al., 2000; Byrnes-Blake et al., 2001; Kantak et al., 2001; Kosten et al., 2002a). This 1- to 2-month interval is a potentially important disadvantage since the onset of therapeutic effect would be similarly delayed. However, vaccination can be accomplished even while drug use continues; the presence of drug does not diminish the immune response (Hieda et al., 2000; Byrnes-Blake et al., 2001). Thus individuals could be vaccinated in preparation for stopping drug use by starting 1 to 2 months in advance. When this is not possible, the use of counseling and, when available, other medications with more immediate effects could be used until the vaccine becomes effective.

Duration of Response to Vaccination

Because drugs of abuse by themselves cannot elicit an immune response, drug abusers do not normally have antibodies directed against these drugs. It is only after a series of vaccinations that antibodies are formed. Because the antibody response fades with time, the concentrations of antibodies in serum will fall over a period of months to years. To maintain satisfactory antibody concentrations in serum, it will be necessary to

administer booster doses of vaccine periodically. The frequency of boosting needed is not known, but an interval of approximately every 2 to 6 months is likely (Cerny et al., 2002; Kosten et al., 2002a). It is important to note that vaccines for drug addiction differ in this respect from vaccines for infectious diseases. Infectious microorganisms (bacteria or viruses) are complete immunogens, so exposure to the infectious agent automatically boosts the immune response. In contrast, a drug addict relapsing to drug use would not boost his or her immune response but would require additional vaccination.

Sustained-release vaccines have been studied in animals as a means of reducing the number or frequency of required vaccine injections (Gupta, Singh, and O'Hagan, 1998; Langer, Cleland, and Hanes, 1997). With this technology, one injection might substitute for several monthly injections. This technology has not yet been applied to humans.

The time course of the antibody response to vaccination is critical to determining its duration of action. At some point the concentration of antibody in blood will fall below that needed to have any effect on drug action (Carrera et al., 2000; Kantak et al., 2000; Proksch, Gentry, and Owens, 2000). Thus for practical purposes the effects of vaccination are not permanent. It is difficult at present to estimate the duration of action for any of the vaccines discussed in this chapter. In a Phase I study of a cocaine vaccine, antibody concentrations in serum declined to nearly the prevaccination level by 10 months after the last vaccine dose (Kosten et al., 2002b). It cannot categorically be said, at this point, that these minimal antibody concentrations would have no effect, but the likelihood is very high that this is so. As a result, vaccination can be viewed as a medication with a potentially long duration of action, most likely measured in months, rather than a permanent effect.

While very low levels of antibody persisting months to years after vaccination are unlikely to have any effect on drug use, they may still be detectable. If so, their detection could potentially identify a person as an addict (someone previously treated with vaccination). The length of time that antibodies could be reliably detected at a level sufficient to indicate previous vaccination is unknown.

It is important to note that having a long duration of action, with therapeutic and possible toxic effects that cannot be reversed for periods of weeks to months, is not confined to vaccines, passive immunization, or depot medications for drug addiction. Table A-1 lists several medications in common clinical use that have long durations of action and that have proven to be acceptable and valuable treatments for certain indications.

TABLE A-1 Medications with Long Durations of Action Used to Treat Disorders Other Than Drug Addiction

Drug	Indication	Persistence of Drug in the Body	Comment
Amiodarone	Cardiac arrhythmia	Several months	Side effects may persist for weeks to months after the last dose.
Isotretinoin	Acne	Days to weeks	Teratogenic risk requires use of contraception for 1 month after the last dose.
Depot fluphenazine	Schizophrenia	1-2 months	Therapeutic effect and side effects may persist for 1-2 months.
Depot medroxyprogesterone	Contraception	At least 3 months	Administered every 3 months. Delayed return of fertility may occur and last several additional months after the next scheduled dose.
Monoamine oxidase inhibitors	Depression	1-2 weeks	Therapeutic effect, adverse effects, and risk of adverse drug interactions may persist for 1-2 weeks after last dose.

NOTE: Several medications have long durations of action because they are eliminated from the body slowly, while others have been purposely formulated as depot medications.

Fate of Antibody After Vaccination

Antibodies are continually produced and broken down (metabolized and inactivated) in the body. The most common type of antibody (IgG) has a half-life in blood of about 3 weeks (Waldmann and Strober, 1969). That is, about half of the antibody produced on day 1 is eliminated by day 21. Blood levels of antibody after vaccination are maintained because new antibody is continually produced. After passive immunization with monoclonal antibodies, a steady decline in antibody level with a half-life of about 3 weeks is expected, so repeated antibody doses every few months would probably be needed to maintain antibody levels in blood.

Mechanisms of Action

Active immunization (vaccination) and passive immunization for drug addiction act in a similar manner and will be discussed together. Drugs of abuse produce their actions by rapidly entering the brain. When a drug is injected intravenously or smoked, it reaches the brain within 10 to 20 seconds and its rewarding or pleasant effects are equally rapid in onset (Henningfield, Miyasato, and Jasinski, 1985). When an experimental animal is vaccinated, the resulting drug-specific antibodies circulate in the blood and fluid surrounding tissues. When drug is administered, a fraction of that dose binds to the antibody and is prevented from entering the brain (Fox et al., 1996; Valentine and Owens, 1996; Pentel et al., 2000). In this manner the effects of the drug are diminished. If this reduction of effects is sufficiently large, it might lead to a reduction in drug use.

Binding of Drug by Antibody

The brain is protected by the blood-brain barrier, which separates blood in arteries and veins from brain cells. Many small molecules such as drugs of abuse (molecular weights of 200 to 300 Daltons) can readily cross the blood-brain barrier while larger molecules such as antibodies (molecular weights of about 150,000 Daltons) cannot (Bradbury and Lightman, 1990). Thus any drug that is bound to antibody also cannot cross the blood-brain barrier. When a drug is administered to a vaccinated animal, a fraction of the drug becomes bound to antibody while some remains free; the fraction that becomes bound depends on the amount of drug administered and the amount of antibody available to bind it. Only the free (unbound) drug can enter the brain.

Importance of the Amount of Antibody Available

Vaccination is most effective when the available amount of antibody is large compared to the drug dose (Fox et al., 1996; Valentine et al., 1996; Keyler et al., 1999). Surprisingly, vaccination remains effective in reducing drug distribution to the brain even when drug doses exceed the available binding capacity of antibody (Carrera et al., 2001; Tuncok et al., 2001). This is fortunate because the single and daily doses of most drugs of abuse exceed the amount of drug-specific antibody that can be elicited by vaccination. Nevertheless, the amount of antibody elicited by vaccination is very important, and greater amounts confer greater efficacy in altering drug distribution and reducing drug effects. Thus individuals with better responses to a vaccine (higher titers, implying greater total amounts of antibody elicited) would be expected to derive greater benefit from vaccination.

Although the amount of antibody elicited by vaccination has a limit, passive immunization allows the administration of as much antibody as desired. Passive immunization may prove to have advantages in settings where very high antibody doses are needed for clinical efficacy or for individuals who are vaccinated but fail to achieve a satisfactory antibody response.

Effects of Vaccination on Drug Concentrations in Blood and Tissue

When a drug is administered to a vaccinated animal, the drug is bound and retained in the blood by the high concentration of antibody present (Figure A-4). As a result, the total concentration of drug in the blood is *higher* in a vaccinated animal (Owens and Mayersohn, 1986; Fox et al., 1996). At the same time, the concentration of free (unbound) drug is reduced (Malin et al., 2001). Because only free drug can enter brain, the concentration of drug in the brain is also reduced. The very high total

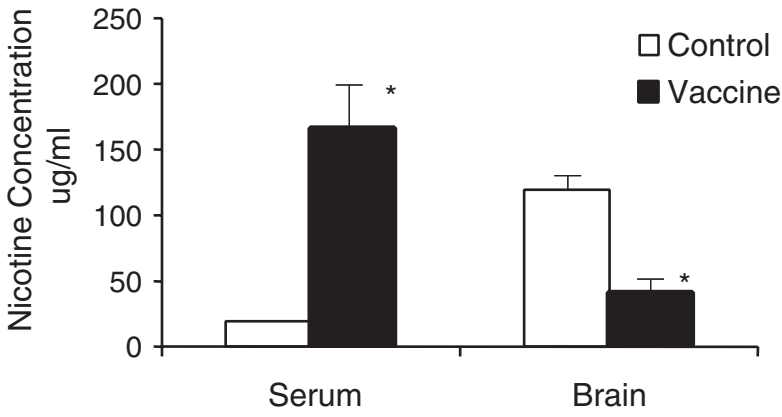

FIGURE A-4 Vaccination effects on nicotine concentration in the blood and brain of rats. Rats were vaccinated over a period of 6 weeks and then given a single dose of nicotine intravenously. Three minutes later the concentrations of nicotine in the blood were substantially higher in the vaccinated rats than in nonvaccinated controls owing to the binding and sequestration of nicotine in the blood. Brain nicotine concentration at the same time was reduced by 65 percent. This very prompt effect is important because the rewarding effects of drugs are also greatest in the first few minutes after a dose. *p <.01.
SOURCE: Adapted from Pentel et al. (2000).

drug concentration in blood is not toxic because the bound drug is unable to interact with tissues.

In animals, immunotherapy reduces drug distribution to the brain within the first few minutes after a single drug dose by up to 80 percent (Fox et al., 1996; Pentel et al., 2000). This is important because the rewarding effects of drugs are also greatest in the first few minutes after a dose. Vaccination is also effective when the drug is administered repeatedly or chronically. In a rat, the ability of vaccination to reduce nicotine distribution to the brain after a single dose equivalent (considering the rat's size) to two cigarettes is not impaired by the concurrent infusion of nicotine for several weeks at a rate equivalent to smoking three packs of cigarettes daily (Hieda et al., 2000; Cerny et al., 2002). Similarly, a single dose of phencyclidine-specific monoclonal antibody passively administered to rats reduced phencyclidine concentration in the brain despite the continuous infusion of phencyclidine over a period of 4 weeks (Proksch et al., 2000).

Drug-specific antibodies can also slow elimination of a drug from the body because the bound drug is less available for metabolism (conversion to an inactive form) or excretion in urine (Keyler et al., 1999; Proksch et al., 2000). Since bound drug and unbound drug exist in equilibrium, the unbound drug is also eliminated more slowly. The importance of slower drug elimination is not entirely clear. Slowed elimination could lead to drug accumulation and saturation of antibody with drug, rendering it less effective. On the other hand, slowed drug elimination could delay the onset of cravings after a dose by prolonging the drug's effects, leading to less frequent drug use (Sellers, Kaplan, and Tyndale, 2000).

Table A-2 lists the status of current research on immunotherapies in animals and humans.

Immunization Effects in Animals

Cocaine

Both vaccination and passive immunization have been shown to block or reduce cocaine self-administration in rats (Figure A-5) (Fox et al., 1996; Kantak et al., 2000, 2001). In this model, rats are fitted with a chronic intravenous cannula and can press a level in their cage to receive a dose of cocaine. Rats given access to cocaine in this manner readily learn to self-administer the drug (as well as the other drugs of abuse discussed below), demonstrating its potent reinforcing properties. If rats trained to self-administer cocaine are given single doses of cocaine-specific monoclonal antibody, cocaine self-administration over the next few days can be completely blocked (Fox et al., 1996). That is, lever pressing decreases to the

TABLE A-2 Status of Current Immunotherapy Studies in Animals and Humans

Type of Immunotherapy	Drug Effects Blocked or Reduced in Animals	Effects in Humans
Vaccination		
Cocaine	Self-administration: Maintenance Reacquisition Locomotor activation Conditioned place preference Distinguishing cocaine from saline	Phase I trial: Immunogenic No important adverse effects Phase II trial started
Nicotine	Self-administration: Acquisition Reinstatement Transfer of nicotine from mother to fetus Nicotine-induced seizures	Phase I trial: Vaccine immunogenic No important adverse effects
Methamphetamine	Distinguishing methamphetamine from saline	
Passive Immunization		
Cocaine	Self-administration: Maintenance Reinstatement Reacquisition Locomotor activation	
Nicotine	Development of dependence Relief of withdrawal by nicotine Locomotor activation Distinguishing nicotine from saline	
Phencyclidine	Locomotor activation	

NOTE: Most studies were performed using rats; see text.

same extent as if it delivered only saline. Vaccination also reduces cocaine self-administration. In this case, vaccination administered during continued daily access to cocaine became maximally effective only after the second booster dose was administered, as would be expected since it takes that long for the maximal antibody concentration in blood to be achieved (Kantak et al., 2001).

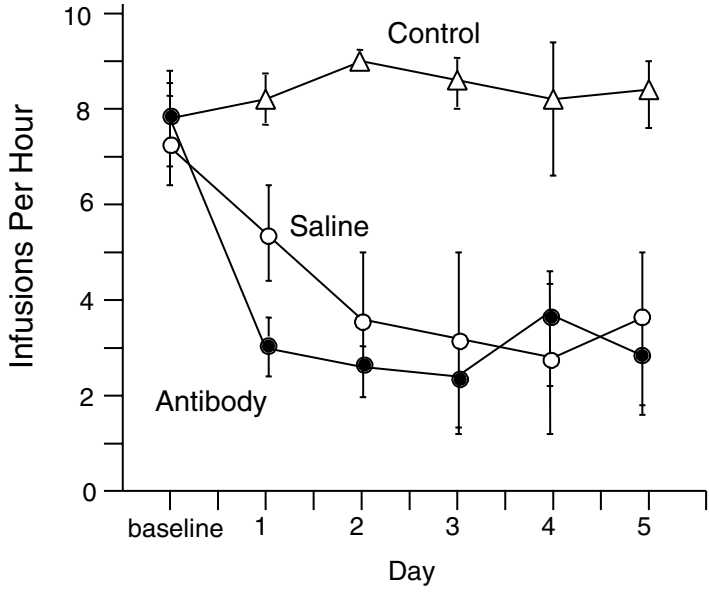

FIGURE A-5 Immunization effects on cocaine self-administration in rats. Rats were trained to self-administer intravenous doses of cocaine by pressing a lever. The top line (control) shows the number of lever presses each day in control rats. One group had saline substituted for cocaine, resulting in decreased lever pressing. A third group continued to have access to cocaine but received an injection of cocaine-specific monoclonal antibodies. Lever pressing in this group decreased to the same extent as the saline substitution group. This experiment illustrates the use of passive immunization. A similar decrease in lever pressing can be obtained with vaccination but requires 6 weeks to become evident because of the gradual rise in antibody levels in vaccinated rats.
SOURCE: Adapted from Fox et al. (1996).

Vaccination has also been shown to be effective in blocking the reacquisition of cocaine self-administration (Carrera et al., 2000; Kantak et al., 2000). Rats were first trained to self-administer cocaine; then their access to cocaine was terminated, and they underwent a 4- to 6-week period of vaccination. When cocaine was again made available, the vaccinated rats showed markedly reduced lever pressing compared to nonvaccinated controls. In a similar protocol, rats were trained to self-administer cocaine, then were vaccinated in the absence of access to cocaine, and then were reexposed to just a single scheduled dose of cocaine. This "reinstatement" procedure is meant to mimic the ability of a single drug exposure to act as

a cue for relapse. In control animals the single dose of cocaine resulted in a burst of lever pressing even though the lever pressing did not result in cocaine infusion. In the vaccinated rats this burst was greatly reduced. Insofar as reacquisition or reinstatement can be considered models of relapse to drug use, these findings suggest that vaccination may be useful in this regard.

The degree to which cocaine self-administration in rats is blocked by immunization depends on the concentration of antibody in the blood (Carrera et al., 2000; Kantak et al., 2000). Efficacy in blocking cocaine self-administration appears to require a certain threshold antibody concentration. Rats with lower antibody concentrations may show either no effect or a paradoxical increase in self-administration, presumably to compensate for the partial blockade of its effects. Whether compensation occurs likely depends on the concentration of antibody in blood and the cocaine dose. Whether compensation occurs may also depend on the immunogen used to elicit antibodies, as it has not been found in all studies (Kantak et al., 2000). These data suggest that the blockade of cocaine effects by vaccination is greatest when antibody concentrations in blood are high and that either loss of efficacy or compensation could occur with lesser antibody concentrations.

A number of other responses to cocaine can be blocked or attenuated in rats. Increases in locomotor activity resulting from very large cocaine doses are reduced by either prior vaccination or passive immunization (Carrera et al., 2001). These data suggest a potential role for passive immunization in the treatment of cocaine overdose, but less expensive therapies are available for this purpose. Vaccination also reduces the preference of rats for cocaine compared to saline, another model of the reinforcing properties of cocaine (Ettinger, Ettinger, and Harless, 1997), and the ability of rats to distinguish cocaine from saline (Johnson and Ettinger, 2000). Only limited studies have been done in other species. Vaccination of monkeys diminished the ability of cocaine to reduce food intake, demonstrating the ability of vaccination to elicit antibodies and affect a cocaine-related behavior in a primate (Koetzner et al., 2001).

Nicotine

Like cocaine, both vaccination and passive immunization have been shown to attenuate a variety of nicotine's behavioral effects in rats. A number of studies have focused on nicotine withdrawal because the discomfort of withdrawal is one important reason why some smokers who try to quit are unable to do so. If rats are given a continuous infusion of nicotine over a week, they become dependent, as evidenced by developing signs of withdrawal when the nicotine infusion is stopped (Malin, 2001). Rats

passively immunized at the same time they receive the week of nicotine infusion develop less severe withdrawal when the nicotine infusion is stopped (Malin, 2002). When rats develop withdrawal, it can be relieved by administering nicotine, just as smokers who quit and become uncomfortable because of withdrawal can relieve their discomfort by smoking a cigarette. If rats are passively immunized with nicotine-specific antibody given just prior to developing withdrawal, nicotine loses its ability to relieve withdrawal (Malin et al., 2001). Since relief of withdrawal from smoking a cigarette may lead to relapse, blockade of this effect could have a role in relapse prevention (Hughes et al., 1984). Passive immunization also reduces nicotine-induced increases in locomotor activity and the ability to discriminate nicotine from saline in rats (Pentel et al., 2000; Malin et al., 2002; Sanderson et al., 2003).

The effects of immunization on drug self-administration have not been studied as extensively with nicotine as with cocaine. Vaccination reduces the reinstatement of lever pressing in rats after administration of a single low dose of nicotine (Lindblom et al., 2002). A preliminary report suggests that prior vaccination attenuates the acquisition of nicotine self-administration in rats (LeSage et al., 2001). Aside from suggesting that vaccination reduces this important behavioral effect of nicotine, this study introduces the possibility of using vaccination for primary prevention (see below).

Phencyclidine

Studies of immunization against phencyclidine have focused on the use of passive immunization with high-affinity monoclonal antibodies or antibody fragments and on the treatment of phencyclidine toxicity (Valentine, Arnold, and Owens, 1994; Hardin et al., 1998). In contrast to cocaine toxicity, which can be readily managed, the treatment of phencyclidine toxicity is difficult, and better treatment for overdose is needed. Passive immunization of rats with phencyclidine-specific monoclonal antibodies has been shown to markedly reduce the entry of phencyclidine into the brain and to reduce its central nervous system toxicity (Proksch et al., 2000; Hardin et al., 2002). Of particular interest is that a single dose of phencyclidine-specific antibody can reduce phencyclidine toxicity for up to 2 weeks despite repeated phencyclidine challenges at doses that exceed the binding capacity of antibody for the drug (Figure A-6). These data support the feasibility of using passive immunization therapeutically as an alternative or supplement to vaccination. Apart from demonstrating efficacy, they have shown the safety of administering the required high doses of monoclonal antibody. While passive immunization is far more expensive than vaccination, the ability to administer a well-defined anti-

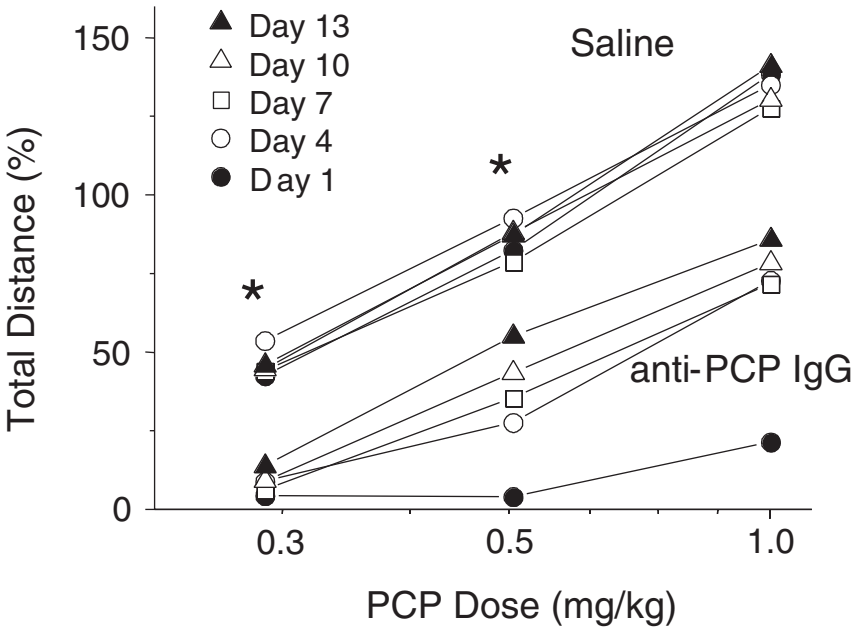

FIGURE A-6 Passive immunization produces long-lasting attenuation of the locomotor activating effects of phencyclidine. Rats received a single intravenous dose of phencyclidine-specific monoclonal IgG (the most common class of antibody) and were challenged with a phencyclidine injection at various times afterward. The top five lines represent control animals, which received saline treatment, showing locomotor activation at all phencyclidine doses. The bottom five lines represent immunized animals that received phencyclidine-specific IgG. Locomotor activity after each phencyclidine challenge dose was attenuated, even 2 weeks after the antibody was administered. *$p < .05$.
SOURCE: Adapted from Hardin et al. (2002).

body with suitable affinity and specificity and to titrate the antibody dose to produce the desired effect could prove helpful. The immediate onset of effect could also be helpful for facilitating the initiation of treatment for addiction or for the treatment of drug overdose.

Methamphetamine

The initiation of studies on immunization for methamphetamine is more recent, and only limited data are available. A monoclonal antibody directed against methamphetamine has been shown to reduce the ability

of rats or pigeons to discriminate methamphetamine from saline (Byrnes-Blake et al., 2001; McMillan et al., 2002).

Summary of Animal Data

In aggregate the available animal data provide strong proof of principle that both vaccination and passive immunization can block or attenuate a variety of drug effects in animals that are relevant to drug addiction in humans. Because this type of intervention is new and no clinical precedents exist, assessing the clinical potential of immunotherapy for drug abuse will only be possible through clinical trials. Both vaccination and passive immunization appear to be feasible. The success of vaccination will depend in part on whether sufficient blood concentrations of antibody can be elicited. Passive immunization appears to be feasible but is expensive. Both vaccination and passive immunization have advantages and disadvantages in terms of their potential clinical roles and practicality, and both could have a place in therapy.

Clinical Trials of Immunization

Cocaine

A Phase I study of a cocaine vaccine has been reported that demonstrates immunogenicity of the vaccine in humans and a lack of serious adverse effects (Kosten et al., 2002a). Efficacy was not studied in this initial clinical trial. Vaccine was administered at 0, 1, and 2 months intramuscularly and at three dose levels. Antibody titers in blood were detectable after the second injection, were maximal at 3 months (1 month after the final injection), and had returned to baseline by 1 year. Although antibody titers were not as high as in rats with this vaccine, titers were dose related, so higher vaccine doses or a greater number of injections might result in higher antibody titers. A Phase II clinical trial testing different immunization regimens and efficacy in suppressing cocaine use is under way (Kosten et al., 2002b).

Nicotine

Preliminary data are available from Phase I trials of two distinct nicotine vaccines, both indicating immunogenicity of the vaccine and the absence of serious adverse effects (Lindmayer et al., 2002; St. Clair Roberts et al., 2002). Further clinical trials aimed at establishing suitable vaccination regimens are under way.

Safety: Adverse Effects and Unintended Consequences

Vaccination

Adverse effects Because the drug-specific antibodies elicited by vaccination bind only the drug in question and presumably nothing else in the body, unwanted side effects from the antibodies per se would not be expected. A favorable safety profile is in fact typical of vaccines for infectious diseases. The animal and human data available to date suggest that vaccines against drugs of abuse share this favorable safety profile; no substantial adverse effects have been found other than soreness or irritation at the injection site (Kosten et al., 2002a, 2002b; St. Clair Roberts et al., 2002). However, antibody per se is only one consideration with regard to vaccine safety because vaccines also change the distribution of the abused drug in the body and in some cases its metabolism as well. Vaccines are intended to reduce the amount of drug in the brain, and may reduce the amount of drug in other organs as well, by binding and sequestering it in the blood (Valentine and Owens, 1996). It is conceivable that increased drug in the blood could have adverse effects of its own—for example, by delivering more drug to certain organs. Data presented below argue that such adverse effects are unlikely and have not been observed, but it is important to consider this possibility as novel clinical situations (e.g., pregnancy) are encountered. In addition, a note of caution is appropriate simply because vaccination for drug abuse is a new approach that is without an analogous clinical precedent. Unexpected side effects, such as the binding of antibody to as yet unidentified endogenous compounds or structures, are possible and justify vigilance in looking for such effects in clinical trials.

Preventing or reducing drug effect In the context of this discussion, the ability of vaccination to block or reduce the addictive effects of drugs is the desired therapeutic outcome. However, if a cigarette smoker decided to abandon his or her attempt at cessation and wanted to resume smoking, vaccination could interfere with the ability to do so until antibody concentrations in the blood declined sufficiently. Although this effect would be temporary, patients getting vaccinated would need to be aware of this possibility.

In other circumstances, drugs of abuse may also be used for therapeutic purposes. For example, cocaine is sometimes used for local anesthesia, and nicotine is being studied as a cognitive enhancer in patients with certain cognitive disorders such as Alzheimer's disease (Lopez-Arrieta, Rodriguez, and Sanz, 2000). If such a therapeutic action were desired, vaccination could potentially block or counteract it. The extent of blocking

effect would depend on the concentration of antibody present in blood and would wane over time but could be present transiently.

Pharmaceutical nicotine is also widely used therapeutically as a treatment for smoking cessation (Fiore, Bailey, and Cohen, 2000). Vaccination could prevent nicotine replacement therapy from being effective, thus eliminating this important therapeutic option. However, rat studies suggest that vaccination and nicotine replacement therapy may in fact be compatible because vaccination has its greatest effect on blocking the early distribution of nicotine to the brain (first few minutes after a puff) but has less effect at later times (Hieda et al., 2000; Tuncok et al., 2001). Thus vaccination may reduce the early rewarding effects of smoking but still allow nicotine administered therapeutically to enter the brain and retain its typical effects of reducing withdrawal and cravings.

Compensation If immunotherapy partially blocks the effect of a drug, it is possible that this blocking effect could be overcome by simply increasing drug intake (the size of each dose or the total daily dose). Some but not all cocaine vaccine studies in rats demonstrate this kind of compensation, primarily in rats with the lowest antibody titers in blood (Carrera et al., 2000; Kantak et al., 2001). Whether compensation takes place in a patient will likely depend on the strength of the antibody response in that individual, the individual's motivation to remain abstinent, and the use of additional treatment measures, including counseling and other medications. In any event, compensation would remain important only so long as antibody concentrations in the blood remain high and would wane and presumably disappear over time.

One particular concern with compensation, even if transient, is that a drug user might escalate his or her drug use sufficiently to cause an inadvertent overdose. This possibility cannot be discounted and can probably be avoided only with attention to counseling and other adjunctive measures as well as education regarding the dangers of dose escalation in this setting.

Even if drug escalation does not result in overdose, it could increase exposure to other toxins present in the drug formulation. For example, a cigarette smoker could increase his or her rate of smoking to compensate for blockade of nicotine's effects by vaccination and thereby increase his or her exposure to carbon monoxide as well (Benowitz, Jacob, Kozlowski, and Yu, 1986). Again, this possibility underscores the importance of using vaccination in the context of a comprehensive treatment program with specific education about the risks of compensation.

Pregnancy While potential effects on the fetus are a concern with all new medications, immunotherapy poses specific additional issues. In addition

to the transfer of drug-specific antibodies to the fetus, immunotherapy may alter fetal exposure to the drug that is being targeted. This is particularly important because each of the drugs of abuse considered here have either established or suspected adverse effects on fetal development (Plessinger, 1998; Ernst, 1999; Addis et al., 2001). Women who are immunized in an effort to treat their drug dependence could inadvertently become pregnant. It is therefore important to understand the effects of immunization on fetal risk.

Vaccination could possibly reduce drug distribution to the fetus, just as it reduces drug distribution to the brain and other organs in the mother. On the other hand, maternal antibodies are transferred across the placenta (Simister and Story, 1997) and could act to escort even more drug into the fetus. Only limited data are available addressing this question from one preliminary study of immunization against nicotine (Shoeman, Keyler, and Pentel, 2002). Rats were vaccinated prior to pregnancy, and a single dose of nicotine was administered late in pregnancy. The overall distribution of nicotine to the fetus was not altered. However, nicotine levels in the fetal brain were lower than in controls, which could serve to protect against some of nicotine's adverse effects on neural development. While these data identify no risk to the fetus from immunization, they are very preliminary and further study is needed in order to assess the safety and acceptability of immunization as a treatment for drug dependence in women with childbearing potential.

Passive Immunization

As with vaccination, the specificity of passive immunization suggests a favorable safety profile. No important adverse effects have been noted to date in animal studies of either polyclonal or monoclonal antibodies to reverse or prevent drug effects. Passive immunization is used for many therapeutic purposes other than drug addiction, but the doses of antibody required are generally lower. Additional safety studies of the higher antibody doses required for treatment of drug addiction or drug overdose are needed. Antibodies considered for clinical use would almost certainly be monoclonal, rather than purified from immunized animals, because antibodies from another species can produce allergic reactions. Monoclonal antibodies can be "humanized" by altering their structure to resemble human antibodies, without compromising their ability to bind drug (Berger, Shankar, and Vafai, 2002). Humanized antibodies used (in smaller doses) for other purposes are generally well tolerated, but allergic reactions, although uncommon, can still occur, and the potential need to administer antibodies repeatedly over long periods of time for the treatment of drug abuse will require specific safety studies.

Each of the considerations mentioned above for vaccine safety apply to passive immunization as well. However, monoclonal antibody concentrations in blood will fall at a predictable rate after the last dose (decreasing by half approximately every 3 weeks), so the duration of action should be quite predictable (Waldmann and Strober, 1969). Moreover, the problem of long-term persistence of very low levels of antibody will not occur with passive immunization. For practical purposes, antibody concentrations in blood should be negligible within about 6 months of the last dose.

Anticipated Clinical Role of Immunization

Expectations

The experience of both health care professionals and the public with vaccines is with those used to prevent infectious diseases. When used for infectious diseases, vaccines often confer complete or nearly complete protection. It is important to realize that vaccination for drug dependence is conceptually different. Rather than supplementing the body's immune response to an infection, it is simply reducing the access of drug to the brain. Immunization for drug abuse is more likely to reduce than to completely block drug effects and is unlikely confer the complete protection afforded by vaccines for infectious diseases. Immunization is best considered as another medication option for drug dependence, with a range of effects that address some but not all of the features of drug dependence.

Uses

Because immunization for drug abuse has no clinical precedent, anticipating its clinical role is difficult. Immunization's principal action is to block those drug effects that require the presence of drug in the brain. Thus the pleasure associated with using a drug may be diminished or absent. Immunization would not be expected to directly block withdrawal or craving, since these occur when drug is no longer present. One potential clinical role for immunization is in relapse prevention. In this setting, if a period of abstinence is threatened by a "slip" consisting of just one or a few drug doses, immunization could block or reduce the rewarding effect of those doses and thereby make relapse less likely. Because relapse typically starts with just one or a few drug doses, the ratio of antibody to drug would be high and would maximize the efficacy of immunization. In a comprehensive treatment program, additional measures would be needed to address cravings, withdrawal, and the many psychosocial issues surrounding drug dependence.

Combining

Immunotherapy medications Because immunotherapy acts by a mechanism that is distinct from most other medications for the treatment of drug dependence, immunotherapy should be compatible with concurrent use of these medications. In this case, the combination could have greater efficacy or a broader range of effects. An additional possibility is the combination of vaccination and passive immunization. Vaccination is simpler and less expensive than passive immunization and may require less frequent dosing. However, some patients may not develop an adequate response to vaccination. In this event (which could be determined by a simple blood test to measure antibody concentration in blood), passive immunization with a modest dose of drug-specific monoclonal antibody might be used to supplement vaccination. Passive immunization might also be used to obtain an immediate effect during the 1 to 2 months required to complete vaccination. This strategy should be feasible because passive immunization would not be expected to interfere with the ability of vaccination to stimulate a satisfactory immune response.

Summary of Features of Immunotherapies Requiring Special Consideration

Immunotherapy as a treatment for drug dependence differs from most other medications, even those used for other purposes, because of its unusual mechanism and long duration of action. None of these features are entirely unique to immunization. Nevertheless, their impact in the setting of drug dependence raises issues that may require special consideration. Table A-3 lists some key features of immunotherapies for drug dependence that requires further consideration. Those issues are briefly reviewed below.

Commitment to Therapy

The duration of action of vaccination as a treatment for drug dependence in humans is not known. Animal studies and initial clinical data suggest a duration of at least several months after the last booster dose (Hieda et al., 2000; Kosten et al., 2002a). Antibodies may persist in blood for much longer, but their concentrations would likely be too low to sustain a therapeutic effect. During the several months after vaccination, patients would therefore be committed to this therapy. A similar commitment to therapy occurs with a number of other medications used for other purposes (Table A-1), and is not unique to vaccination. However, drug use (particularly cigarette smoking) is perceived by some as a "choice,"

TABLE A-3 Key Features of Immunotherapy for Drug Dependence That Require Special Consideration

Commitment to therapy	Long duration of action of immunization commits a patient to its effects until antibody levels in the blood decline sufficiently (up to several months for passive immunization, possibly longer for vaccination).
Blockade of therapeutic drug effect	When a drug of abuse is also used for therapeutic purposes (e.g., nicotine for replacement therapy), immunization may block those actions as well until antibody levels decline.
Compensation	Attempts to overcome the blockade-of-drug effect from immunization could lead to greater drug use, overdose, or toxicity from adulterants.
Pregnancy	Immunization could alter the amount or duration of fetal drug exposure. Insufficient data are available to adequately assess risk.
Primary prevention	The presumed safety and long duration of action of vaccination allow consideration of its use for this purpose.
Privacy	Detection of antibodies using simple blood tests could identify recipients of vaccination for months or longer after the last booster dose.

and the decision to resume drug use could be thwarted or made more difficult (requiring higher drug doses) until the effects of vaccination wane. In addition, the duration of persistence of antibody after vaccination is likely to vary among individuals and be difficult to estimate precisely.

The duration of action of passive immunization with monoclonal antibodies is also not known in humans but is likely to be several weeks to several months after the last dose, depending on the dose size (Hardin et al., 2002). Commitment to therapy would be analogous to that following vaccination.

Blockade of Therapeutic Drug Effects

In addition to the use of pharmaceutical nicotine as a treatment to aid smoking cessation, nicotine is being studied as a treatment for dementias and other neurological disorders (Lopez-Arrieta et al., 2000). If it proves to have a therapeutic role, vaccination could temporarily block the ability to gain therapeutic benefit from nicotine. Since the disorders in question

are chronic, their presence would likely be known at the time of vaccination rather than appearing abruptly and requiring immediate treatment.

Compensation

The blockade of drug effect provided by immunization may be incomplete. The concurrent use of counseling and perhaps other medications may be helpful in achieving a therapeutic benefit despite incomplete blockade. However, some patients may try to overcome the partial blockade by using higher or more frequent drug doses. Aside from thwarting the therapeutic intent, increased drug use could be harmful if it is sustained after antibody levels decline. Adverse effects could result if patients do not know how much drug is required to overcome immunization and inadvertently overdose. If a drug is mixed with an adulterant, immunization would reduce the effect of the drug but not the adulterant, and toxicity from the adulterant could result. Targeting immunization to motivated patients who are treated with concurrent counseling would seem the best approach to minimizing such occurrences.

Pregnancy

Vaccines or passive immunization per se are unlikely to harm a fetus, but they could alter the amount of abused drug transferred to a fetus. Limited data suggest, if anything, a protective effect with lesser drug transfer, but these data are very preliminary (Shoeman et al., 2002; Keyler et al., 2003). In addition, antibodies can potentially prolong exposure to a drug because the antibody-bound drug is more slowly eliminated from the body (Keyler et al., 1999; Proksch et al., 2000). Thus a pregnant woman who stops smoking will have unmeasurable nicotine levels in her blood (and presumably in her fetus) within several days, but a woman vaccinated against nicotine who stops smoking could have low levels of nicotine persisting in her blood for weeks. Whether this bound nicotine would be harmful to the fetus is not known. The main point with regard to fetal exposure to a drug is that current data are insufficient to judge whether vaccination or passive immunization will increase, decrease, or have no effect on exposure and harm.

The use of potentially fetotoxic or teratogenic medications during pregnancy is commonly dealt with by recommending that adequate contraceptives be used during the period of exposure. While this strategy could also be applied to immunization for drug dependence, compliance may be lower in drug-dependent women. Thus studying and understanding the potential risks (or benefits) of immunotherapy in women who could become pregnant will be very important.

Primary Prevention

The use of medications for primary prevention (preventing the initial acquisition) of drug dependence has received little consideration because most medications have potential adverse effects, the target population is predominantly young and still undergoing neural development, and the period of risk is protracted, so the duration of treatment and expense would be considerable. In contrast to many other candidate medications, vaccination so far appears free of adverse effects, the resulting antibodies do not enter the brain and therefore should not affect neural development, and the need for only infrequent dosing makes a prolonged period of treatment conceivable. This potential application is of course quite speculative, since efficacy has not yet been demonstrated in humans, and much more toxicity testing would be needed to assure the high level of safety required for administration to teenagers or young adults. However, vaccination could be targeted to high-risk groups—for example, teenagers who already smoke a few cigarettes weekly and who have a very high likelihood of becoming regular smokers over the next 1 to 2 years (Institute of Medicine, 1994). In addition to the issues raised above, this would involve vaccination of minors. While other vaccines are routinely administered to minors, the issue of "choice" discussed above could be raised.

Privacy

Patients who have been vaccinated could potentially be identified as drug abusers by virtue of detection of antibodies from a simple blood test. Because these tests are quite sensitive, antibody from previous vaccination might be detectable long after the therapeutic effect of the vaccination has subsided. This problem is no different from the ability to identify an opiate addict by detecting methadone in urine, or identifying someone as a cardiac patient by detecting the antiarrhythmic agent amiodarone in blood, except that the period during which this may be possible could be considerably longer. Passive immunization would also allow its recipients to be identified by a blood test, but antibody levels would decline in a more predictable manner and probably be undetectable within 6 months.

DEPOT MEDICATIONS

Formulations

Depot medications are formulations of standard medications designed to release a drug slowly and over a long period of time, typically days to weeks. Depot medications can be formulated as a liquid mixture or sus-

pension of small particles that can be injected under the skin (e.g., depot medroxyprogesterone; see Table A-1) (Gupta et al., 1998; Putney and Burke, 1998; Hatefi and Amsden, 2002; Mantripragada, 2002). Slow release of medication can also be achieved by impregnating a device such as a small plastic rod with a drug and placing the device under the skin (e.g., the previously marketed Norplant contraceptive). One important difference between these two technologies is that only the latter is retrievable. An implanted plastic rod can readily be removed to terminate its action, whereas a liquid injected under the skin cannot. In addition, the potential durations of action of these technologies differ. Liquid formulation may release drug for up to several months, while impregnated devices can have durations of years (5 years for Norplant). Thus a wide range of durations is potentially available through the use of depot formulations. Not all medications can be formulated in this manner. Depot formulations are best suited to high-potency medications where the required daily dose is low and only a modest amount of drug needs to be incorporated into the formulation or device. Low-potency medications, requiring higher amounts of drug to be incorporated, may prove too bulky to be practical.

Depot Naltrexone for Opiate or Alcohol Dependence

There are no depot medications currently in clinical use to treat drug dependence. One depot medication being studied for opiate dependence is the opiate antagonist naltrexone. Naltrexone is an effective oral therapy approved by the Food and Drug Administration for opiate dependence that acts by blocking the access of opiates to their brain receptors. It is possible to give a high enough dose of naltrexone orally to block the actions of typical heroin doses, but its duration of action is modest so daily dosing is required (Modesto-Lowe and Van Kirk, 2002). Compliance with naltrexone for the treatment of opiate dependence is lower than with methadone because naltrexone lacks the pleasant receptor-activating effects of methadone. Measures to improve long-term compliance with naltrexone are needed.

Naltrexone has been experimentally formulated as a slow-release suspension of microspheres administered by intramuscular injection that can deliver therapeutic doses over a period of up to 4 weeks after a single injection (Chiang et al., 1985; Comer et al., 2002). Its actions are identical to those of orally administered naltrexone, but daily dosing is not required and substantial blockade of heroin effects is achieved for up to 1 month (Figure A-7). Clinical trials of depot naltrexone for opiate dependence are ongoing (J. Cornish, personal communication, 2003). Once administered, the naltrexone dose cannot be retrieved, so recipients are obligated to its effects for that period of time. The implications of this prolonged effect

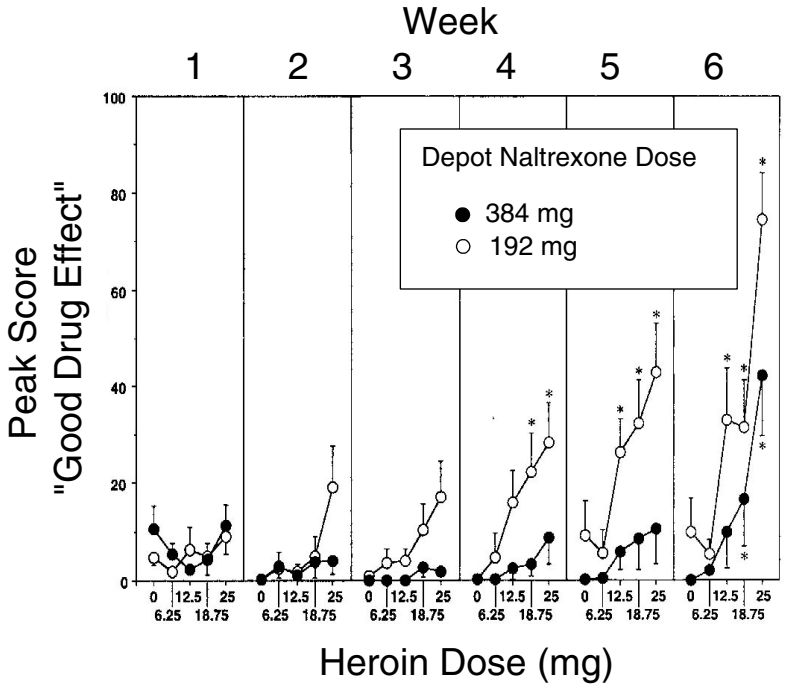

FIGURE A-7 Blockade of heroin effects by depot naltrexone. Subjects were given a single injection of depot naltrexone and were then given increasing doses of heroin at weekly intervals. The "good drug effect" associated with heroin was substantially blocked for a month, more so with the higher naltrexone dose. SOURCE: Adapted from Comer et al. (2002).

are analogous to those discussed above for immunization, in particular passive immunization, because the dose is controlled and the duration of action is uniform and predictable. The therapeutic effect of naltrexone cannot be readily reversed during the month after dosing (Comer et al., 2002). One difference between depot naltrexone and immunization for other drugs of abuse is that opiates do have an important therapeutic use in the treatment of pain. Naltrexone blocks the pain-relieving ability of all opiates, so the use of this entire class of drugs is difficult after naltrexone is administered. In a hospital setting, higher opiate doses could partially overcome the blockade. In the setting of drug abuse, attempts to overcome the blockade could result in increased drug use, overdose, or toxicity from adulterants.

Naltrexone is also effective in treating alcoholism, and daily doses of oral naltrexone are widely used for this purpose (Streeton and Whelan, 2001). As with its use for opiate dependence, compliance is an issue (Modesto-Lowe and Van Kirk, 2002). Depot naltrexone is therefore being studied for this indication (Alkermes, 2003; Drug Abuse Sciences, 2003).

Many other depot medications are in current clinical use. Depot formulations of several antipsychotic agents are available, with durations of action of several weeks (Adams et al., 2001). Like medications for drug dependence, depot antipsychotic medications are administered to a vulnerable population in order to improve compliance. Thus the clinical and ethical issues presented by depot naltrexone have a precedent in antipsychotic medications. Depot antipsychotic medications have proven to be acceptable to both patients and health care providers when used in select patients (Adams et al., 2001; Walburn et al., 2001).

CONCLUSIONS

The very long duration of action of immunotherapies and depot medications proposed for the treatment of drug dependence makes them attractive as potential treatments for drug dependence. A long duration of action could increase medication compliance and thereby facilitate a comprehensive treatment plan consisting of both medication and counseling. In addition, the unique mechanism of action of immunization may confer both safety and a distinct spectrum of therapeutic effects on this approach. However, a long duration of action raises issues that are not presented by other currently used medications. Patients receiving these long-acting treatments will be obligated to their therapeutic effects for weeks to months, so the decision to undergo treatment may not be readily reversed. Adverse effects could similarly persist for weeks to months. Insofar as some drugs of abuse also have therapeutic uses, these beneficial effects could be blocked during this period as well. The detection of drug-specific antibodies by simple blood tests after immunization, or of treatment medication after use of a depot formulation, could identify patients as drug abusers and compromise their privacy. Immunization may alter drug transfer to the fetus in a woman who subsequently becomes pregnant; present data are insufficient to asses any possible risk. With either immunization or depot antagonist medications, patients could try to overcome the blockade of drug effect by increasing their drug use, leading to overdose or toxicity due to adulterants. The potential use of vaccination for primary prevention of drug dependence is conceivable because of its safety but likely would involve minors. While these issues are new to the field of drug dependence, each has precedents in other areas of pharmacotherapy. The appropriate use of immunization and depot medications

to treat drug dependence will benefit from an understanding of their underlying mechanisms and consideration of approaches adapted for the use of long-acting medications for other purposes.

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REFERENCES

Adams, C.E., Fenton, M.K., Quraishi, S., and David, A.S. (2001). Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *British Journal of Psychiatry, 179*, 290-299.

Addis, A., Moretti, M.E., Ahmed, S.F., Einarson, T.R., and Koren, G. (2001). Fetal effects of cocaine: An updated meta-analysis. *Reproductive Toxicology, 15*(4), 341-369.

Alkermes Inc. (2003). *Vivitrex® background kit*. Available at http://www.alkermes.com/news/background_kits.asp [August 22, 2003].

Baird, T.J., Deng, S.X., Landry, D.W., Winger, G., and Woods, J.H. (2000). Natural and artificial enzymes against cocaine. I. Monoclonal antibody 15A10 and the reinforcing effects of cocaine in rats. *Journal of Pharmacology and Experimental Therapeutics, 295*(3), 1127-1134.

Benowitz, N.L., Jacob, P., III, Kozlowski, L.T., and Yu, L. (1986). Influence of smoking fewer cigarettes on exposure to tar, nicotine, and carbon monoxide. *New England Journal of Medicine, 315*(21), 1310-1313.

Berger, M., Shankar, V., and Vafai, A. (2002). Therapeutic applications of monoclonal antibodies. *American Journal of the Medical Sciences, 324*(1), 14-30.

Bonese, K.F., Wainer, B.H., Fitch, F.W., Rothberg, R.M., and Schuster, C.R. (1974). Changes in heroin self-administration by a rhesus monkey after morphine immunization. *Nature, 252*(5485), 708-710.

Bradbury, M.W., and Lightman, S.L. (1990). The blood-brain interface. *Eye, 4*(Pt 2), 249-254.

Byrnes-Blake, K.A., Carroll, F.I., Abraham, P., and Owens, S.M. (2001). Generation of anti-(+)methamphetamine antibodies is not impeded by (+)methamphetamine administration during active immunization of rats. *International Immunopharmacology, 1*(2), 329-338.

Carrera, M.R., Ashley, J.A., Zhou, B., Wirsching, P., Koob, G.F., and Janda, K.D. (2000). Cocaine vaccines: Antibody protection against relapse in a rat model. *Proceedings of the National Academy of Sciences, USA, 97*(11), 6202-6206.

Carrera, M.R., Ashley, J.A., Wirsching, P., Koob, G.F., and Janda, K.D. (2001). A second-generation vaccine protects against the psychoactive effects of cocaine. *Proceedings of the National Academy of Sciences, USA, 98*(4), 1988-1992.

Cerny, E.H., Levy, R., Mauel, J., Mpandi, M., Mutter, M., Henzelin-Nkubana, C., Patiny, L., Tuchscherer, G., and Cerny, T. (2002). Preclinical development of a vaccine against smoking. *Onkologie, 25*(5), 406-411.

Chiang, C.N., Hollister, L.E., Gillespie, H.K., and Foltz, R.L. (1985). Clinical evaluation of a naltrexone sustained-release preparation. *Drug and Alcohol Dependence, 16*(1), 1-8.

Comer, S.D., Collins, E.D., Kleber, H.D., Nuwayser, E.S., Kerrigan, J.H., and Fischman, M.W. (2002). Depot naltrexone: Long-lasting antagonism of the effects of heroin in humans. *Psychopharmacology, 159*(4), 351-360.

Drug Abuse Sciences. (2003). *Naltrexone depot for injectable suspension*. Available at http:www.drugabusesciences.com/products.asp [August 22, 2003].

Ernst, E. (1999). Second thoughts about safety of St John's wort [published erratum appears in *Lancet, 355*(9203), 580]. *Lancet, 354*(9195), 2014-2016.

Ettinger, R.H., Ettinger, W.F., and Harless, W.E. (1997). Active immunization with cocaine-protein conjugate attenuates cocaine effects. *Pharmacology, Biochemistry, and Behavior, 58*(1), 215-220.

Fiore, M.C., Bailey, M.C., and Cohen, S.J. (2000). *Treating tobacco use and dependence: Clinical practice guideline*. Rockville, MD: Public Health Service, U.S. Department of Health and Human Services.

Fox, B.S., Kantak, K.M., Edwards, M.A., Black, K.M., Bollinger, B.K., Botka, A.J., French, T.L., Thompson, T.L., Schad, V.C., Greenstein, J.L., Gefter, M.L., Exley, M.A., Swain, P.A., and Briner, T.J. (1996). Efficacy of a therapeutic cocaine vaccine in rodent models. *Nature Medicine, 2*(10), 1129-1132.

Gupta, R.K., Singh, M., and O'Hagan, D.T. (1998). Poly(lactide-co-glycolide) microparticles for the development of single-dose controlled-release vaccines. *Advanced Drug Delivery Reviews, 32*(3), 225-246.

Hardin, J.S., Wessinger, W.D., Proksch, J.W., and Owens, S.M. (1998). Pharmacodynamics of a monoclonal antiphencyclidine Fab with broad selectivity for phencyclidine-like drugs. *Journal of Pharmacology and Experimental Therapeutics, 285*(3), 1113-1122.

Hardin, J.S., Wessinger, W.D., Wenger, G.R., Proksch, J.W., Laurenzana, E.M., and Owens, S.M. (2002). A single dose of monoclonal anti-phencyclidine IgG offers long-term reductions in phencyclidine behavioral effects in rats. *Journal of Pharmacology and Experimental Therapeutics, 302*(1), 119-126.

Hatefi, A., and Amsden, B. (2002). Biodegradable injectable in situ forming drug delivery systems. *Journal of Controlled Release, 80*(1-3), 9-28.

Henningfield, J.E., Miyasato, K., and Jasinski, D.R. (1985). Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. *Journal of Pharmacology and Experimental Therapeutics, 234*(1), 1-12.

Hieda, Y., Keyler, D.E., Vandevoort, J.T., Kane, J.K., Ross, C.A., Raphael, D.E., Niedbalas, R.S., and Pentel, P.R. (1997). Active immunization alters the plasma nicotine concentration in rats. *Journal of Pharmacology and Experimental Therapeutics, 283*(3), 1076-1081.

Hieda, Y., Keyler, D.E., Ennifar, S., Fattom, A., and Pentel, P.R. (2000). Vaccination against nicotine during continued nicotine administration in rats: Immunogenicity of the vaccine and effects on nicotine distribution to brain. *International Journal of Immunopharmacology, 22*(10), 809-819.

Hughes, J.R., Hatsukami, D.K., Pickens, R.W., Krahn, D., Malin, S., and Luknic, A. (1984). Effect of nicotine on the tobacco withdrawal syndrome. *Psychopharmacology, 83*(1), 82-87.

Institute of Medicine. (1994). *Growing up tobacco free: Preventing nicotine addiction in children and youths*. Committee on Preventing Nicotine Addiction in Children and Youths. B.S. Lynch and R.J. Bonnie (Eds.). Washington, DC: National Academy Press.

Johnson, M.W., and Ettinger, R.H. (2000). Active cocaine immunization attenuates the discriminative properties of cocaine. *Journal of Experimental and Clinical Psychopharmacology, 8*(2), 163-167.

Kantak, K.M., Collins, S.L., Lipman, E.G., Bond, J., Giovanoni, K., and Fox, B.S. (2000). Evaluation of anti-cocaine antibodies and a cocaine vaccine in a rat self-administration model. *Psychopharmacology, 148*(3), 251-262.

Kantak, K.M., Collins, S.L., Bond, J., and Fox, B.S. (2001). Time course of changes in cocaine self-administration behavior in rats during immunization with the cocaine vaccine IPC-1010. *Psychopharmacology, 153*(3), 334-340.

Keyler, D.E., Hieda, Y., St. Peter, J., and Pentel. P.R. (1999). Altered disposition of repeated nicotine doses in rats immunized against nicotine. *Nicotine and Tobacco Research, 1*(3), 241-249.

Keyler, D.E., Shoeman, D., LeSage, M.G., Calvin, A.D., and Pentel, P.R. (2003). Maternal vaccination against nicotine reduces nicotine distribution to fetal brain in rats. *Journal of Experimental and Clinical Psychopharmacology, 305*(2), 587-592.

Killian, A., Bonese, K., Rothberg, R.M., Wainer, B.H., and Schuster, C.R. (1978). Effects of passive immunization against morphine on heroin self-administration. *Pharmacology, Biochemistry, and Behavior, 9*(3), 347-352.

Koetzner, L., Deng, S., Sumpter, T.L., Weisslitz, M., Abner, R.T., Landry, D.W., and Woods, J.H. (2001). Titer-dependent antagonism of cocaine following active immunization in rhesus monkeys. *Journal of Experimental and Clinical Psychopharmacology, 296*(3), 789-796.

Kosten, T.R., Rosen, M., Bond, J., Settles, M., Roberts, J.S., Shields, J., Jack, L., and Fox, B. (2002a). Human therapeutic cocaine vaccine: Safety and immunogenicity. *Vaccine, 20*(7-8), 1196-1204.

Kosten, T.R., Gonsai, K., St. Clair Roberts, J., Jack, L., Bond, J., Mitchell, E., and Fox, B. (2002b, June). *Phase II human study of cocaine vaccine TA-CD*. Paper prepared for the College on Problems of Drug Dependence Annual Meeting, June 8-13, Quebec City.

Kreek, M.J., LaForge, K.S., and Butelman, E. (2002). Pharmacotherapy of addictions. *Nature Reviews: Drug Discovery, 1*(9), 710-726.

Langer, R., Cleland, J.L., and Hanes, J. (1997). New advances in microsphere-based single-dose vaccines. *Advanced Drug Delivery Reviews, 28*(1), 97-119.

LeSage, M.G., Keyler, D.E., Hieda, Y., Valentine, J., Ross, C., Fattom, A., Ennifar, S., and Pentel, P.R. (2001). *Effects of a nicotine conjugate vaccine on the acquisition of nicotine self-administration in rats* (abstract). Society for Research on Nicotine and Tobacco Annual Meeting, March, Seattle, WA.

Lindblom, N., De Villiers, S.H., Kalayanov, G., Gordon, S., Johansson, A.M., and Svensson, T.H. (2002). Active immunization against nicotine prevents reinstatement of nicotine-seeking behavior in rats. *Respiration, 69*(3), 254-260.

Lindmayer, K., Horwith, G., Fattom, A., Naso, R., Fuller, S.A., Muenz, L., Kennedy, A., and Ennifar, S. (2002). *Results of a phase 1, double blinded, controlled safety and immunogenicity trial of NicVAX, a conjugated nicotine vaccine* (abstract). Paper presented at the 4th European Conference of the Society for Research on Nicotine and Tobacco, October, 2004, Santander, Spain.

Lopez-Arrieta, J.M., Rodriguez, J.L., and Sanz, F. (2004). Nicotine for Alzheimer's disease. In *The Cochrane Library* (Issue 1). Chichester, England: John Wiley & Sons.

Malin, D.H. (2001). Nicotine dependence: Studies with a laboratory model. *Pharmacology, Biochemistry, and Behavior, 70*(4), 551-559.

Malin, D.H. (2002). Passive immunization against nicotine attenuates dependence as measured by mecamylamine-precipitated withdrawal. *Society for Research on Nicotine and Tobacco Proceedings, 8*, RP1.

Malin, D.H., Lake, J.R., Lin, A., Saldana, M., Balch, L., Irvin, M.L., Chandrasekara, H., Alvarado, C.L., Hieda, Y., Keyler, D.E., Pentel, P.R., Ennifar, S., Basham, L.E., Naso, R., and Fattom, A. (2001). Passive immunization against nicotine prevents nicotine alleviation of nicotine abstinence syndrome. *Pharmacology, Biochemistry, and Behavior, 68*(1), 87-92.

Malin, D.H., Alvarado, C.L., Woodhouse, K.S., Karp, H., Urdiales, H., Lay, D., Appleby, P., Moon, W.D., Ennifar, S., Basham, L.E., and Fattom, A. (2002) Passive immunization against nicotine attenuates nicotine discrimination. *Life Sciences, 70*(23), 2793-2798.

Mantripragada, S. (2002). A lipid based depot (DepoFoam technology) for sustained release drug delivery. *Progress in Lipid Research, 41*(5), 392-406.

McMillan, D.E., Hardwick, W.C., Li, M., and Owens, S.M. (2002). Pharmacokinetic antagonism of (+)-methamphetamine discrimination by a low-affinity monoclonal anti-methamphetamine antibody. *Behavioral Pharmacology, 13*(5-6), 465-473.

Mets, B., Winger, G., Cabrera, C., Seo, S., Jamdar, S., Yang, G., Zhao, K., Briscoe, R.J., Almonte, R., Woods, J.H., and Landry, D.W. (1998). A catalytic antibody against cocaine prevents cocaine's reinforcing and toxic effects in rats. *Proceedings of the National Academy of Sciences, USA, 95*(17), 10176-10181.

Modesto-Lowe, V., and Van Kirk, J. (2002). Clinical uses of naltrexone: A review of the evidence. *Experimental and Clinical Psychopharmacology, 10*(3), 213-227.

Owens, S.M., and Mayersohn, M. (1986). Phencyclidine-specific Fab fragments alter phencyclidine disposition in dogs. *Drug Metabolism and Disposition, 14*(1), 52-58.

Owens, S.M., Zorbas, M., Lattin, D.L., Gunnell, M., and Polk, M. (1988). Antibodies against arylcyclohexylamines and their similarities in binding specificity with the phencyclidine receptor. *Journal of Pharmacology and Experimental Therapeutics, 246*(2), 472-478.

Pentel, P.R., and Keyler, D.E. (2004). Vaccination as a treatment for drug abuse: Nicotine, cocaine, phencyclidine. In M.M. Levine (Ed.), *New generation vaccines*. New York: Marcel Dekker.

Pentel, P.R., Malin, D.H., Ennifar, S., Hieda, Y., Keyler, D.E., Lake, J.R., Milstein, J.R., Basham, L.E., Coy, R.T., Moon, J.W., Naso, R., and Fattom, A. (2000). A nicotine conjugate vaccine reduces nicotine distribution to brain and attenuates its behavioral and cardiovascular effects in rats. *Pharmacology, Biochemistry, and Behavior, 65*(1), 191-198.

Plessinger, M.A. (1998). Prenatal exposure to amphetamines: Risks and adverse outcomes in pregnancy. *Obstetrics and Gynecology Clinics of North America, 25*(1), 119-138.

Proksch, J.W., Gentry, W.B., and Owens, S.M. (2000). Anti-phencyclidine monoclonal antibodies provide long-term reductions in brain phencyclidine concentrations during chronic phencyclidine administration in rats. *Journal of Pharmacology and Experimental Therapeutics, 292*(3), 831-837.

Putney, S.D., and Burke, P.A. (1998). Improving protein therapeutics with sustained-release formulations. *Nature Biotechnology, 16*(2), 153-157.

Sanderson, S.D., Cheruku, S.R., Padmanilayam, M.P., Vennerstrom, J.L., Thiele, G.M., Palmatier, M.I., and Bevins, R.A. (2003). Immunization to nicotine with a peptide-based vaccine composed of a conformationally biased agonist of C5a as a molecular adjuvant. *International Immunopharmacology, 3*(1), 137-146.

Sellers, E.M., Kaplan, H.L., and Tyndale, R.F. (2000). Inhibition of cytochrome P450 2A6 increases nicotine's oral bioavailability and decreases smoking. *Clinical Pharmacology and Therapeutics, 68*(1), 35-43.

Shoeman, D., Keyler, D.E., and Pentel, P. (2002). *Vaccination of female rats against nicotine reduces nicotine distribution to fetal brain* (abstract). Paper presented at the Society for Research on Nicotine and Tobacco Annual Meeting, February, Savannah, GA.

Simister, N.E., and Story, C.M. (1997). Human placental Fc receptors and the transmission of antibodies from mother to fetus. *Journal of Reproductive Immunology, 37*(1), 1-23.

St. Clair Roberts, J., Dobson, J., Wood, D., and Settles, M. (2002). *Safety and immunogenicity of a human nicotine conjugate vaccine (abstract)*. Paper presented at the College on Problems of Drug Dependence Annual Meeting, June, Quebec City.

Streeton, C., and Whelan, G. (2001). Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: A meta-analysis of randomized controlled trials. *Alcohol and Alcoholism, 36*(6), 544-552.

Tuncok, Y., Hieda, Y., Keyler, D.E., Brown, S., Ennifar, S., Fattom, A., and Pentel, P.R. (2001). Inhibition of nicotine-induced seizures in rats by combining vaccination against nicotine with chronic nicotine infusion. *Experimental and Clinical Psychopharmacology, 9*(2), 228-234.

Valentine, J.L., and Owens, S.M. (1996). Antiphencyclidine monoclonal antibody therapy significantly changes phencyclidine concentrations in brain and other tissues in rats. *Journal of Pharmacology and Experimental Therapeutics, 278*(2), 717-724.

Valentine, J.L., Arnold, L.W., and Owens, S.M. (1994). Anti-phencyclidine Fab fragments dramatically alter phencyclidine pharmacokinetics in rats. *Journal of Pharmacology and Experimental Therapeutics, 269*(3), 1079-1085.

Valentine, J.L., Mayersohn, M.M., Wessinger, W.D., Arnold, L.W., and Owens, S.M. (1996). Anti-phencyclidine monoclonal Fab fragments reverse PCP-induced behavioral effects and ataxia in rats. *Journal of Pharmacology and Experimental Therapeutics, 278*(2), 709-716.

Walburn, J., Gray, R., Gournay, K., Quraishi, S., and David, A.S. (2001). Systematic review of patient and nurse attitudes to depot antipsychotic medication. *British Journal of Psychiatry, 179*, 300-307.

Waldmann, T.A., and Strober, W. (1969). Metabolism of immunoglobulins. *Progress in Allergy, 13*, 1-110.

B

What Will We Learn from the FDA Clinical Trials Process and What Will We Still Want to Know About Immunotherapies and Depot Medications to Treat Drug Dependence?

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The National Academies created the Committee on Immunotherapies and Sustained-Release Formulations for Treating Drug Addition to examine issues related to the development of immunotherapies and depot medications targeted to treat drugs of abuse. This appendix was commissioned to examine the stage-wise strategy for completing clinical trials that will be part of the Food and Drug Administration (FDA) process for ensuring the safety and efficacy of these medications. The medications currently available for human use include vaccines for active immunizations against cocaine and nicotine and long- acting depot formulations of naltrexone, an opiate antagonist for alcoholism and opiate dependence. Monoclonal antibodies for passive immunotherapy are still in animal testing, but one for phencyclidine should be ready for human use within 2 years. The clinical trials to test these medications may involve individuals from three major categories: (1) addicts who *overdose*, (2) drug-dependent individuals who either volunteer for the medication or are mandated to use it by another agent to *prevent relapse*, and (3) nondependent persons who either volunteer or are inducted to receive the medication as a *protection* against initiating or increasing substance use (i.e., primary or second-

ary prevention, respectively). Particular attention is given to safety considerations of immunotherapies and depot medications, recognizing that some patients will continue to abuse various psychoactive substances and that these medications may be administered to pregnant women, adolescents, or children.

The FDA clinical trials process is designed to ensure safety and efficacy for specific uses or indications for new medications but not for off-label use in new diseases or in patient populations in which the medication was never studied. This appendix reviews the four phases of the FDA clinical trials process as it is likely to be implemented for the immunotherapies and depot medications currently in clinical or preclinical development. These products include depot formulations of naltrexone for alcohol and, potentially, opioid dependence; vaccination for cocaine and nicotine dependence; and monoclonal antibodies for phencyclidine (PCP), methamphetamine, and possibly cocaine. Also reviewed are the three types of treatment protocols: overdose, relapse prevention, and protection. Overall, the purpose here is to consider what might be learned during the FDA clinical trials process to inform later applications of these therapies and postmarketing experience. The surveillance that is an intrinsic part of the postmarketing experience should help to discourage premature examination of applications that may place certain populations at unacceptable risk.

TYPES OF INTERVENTION PROTOCOLS

The three types of treatment protocols—overdose, relapse prevention, and protection—are most suitably tested with different types of medication approaches: active immunization, passive immunization with monoclonal antibodies, or depot medications (Klein, 1998; Blaine et al., 1994). For example, overdose protocols most usefully employ monoclonal antibodies (passive immunization), while active immunization and depot medications have, at most, a limited role for this indication. Relapse prevention protocols can usefully employ any of these medication approaches, but different limitations exist for each approach. Protection protocols are the most speculative at present but could also use any of these three approaches. However, protection protocols must consider medical safety and frequency of administration as critical issues, since the individuals intended to benefit from these treatments do not require treatment for substance dependence. In addition, not all of the three types of intervention protocols are applicable to every abused substance. Overdose and relapse prevention protocols are very likely to be studied before these agents are approved for protection, but a protocol for protection from addiction is not likely to get controlled study because of several prac-

tical issues, such as the cost of such a long-term study in even a relatively high-risk group.

Protection protocols also are likely to be aimed at adolescents, since it is during adolescence that the majority of experimentation with substances is initiated and the potential for protection is greatest. However, protection protocols in adolescents may have three broad risks. First, they may result in medical harm to the adolescent, which will be covered in this appendix. Second, there may be psychological or social harm to the child-parent relationship resulting from parents "forcing" their adolescents to get treatments against their will or in a manner that harms parent-child trust. Third, there may be a misplaced biological focus for any antagonist protection in adolescents where much of the incentive to use illicit drugs or even tobacco is related to social, not pharmacological, effects. Adolescents want to impress peers, demonstrate rebelliousness to their parents, signal membership in a clique or subculture, and generally assert a social message. Pharmacological reinforcement of a drug may be a secondary motivation for use. Consequently, inhibiting this pharmacological reinforcement will have little effect on such motivations to use the substance and be much less cost effective than alternative protection strategies.

Overdose Protocols

A typical overdose protocol might use monoclonal antibodies to reverse an acute overdose of a drug such as PCP (Owens and Mayershohn, 1986; Valentine et al., 1996). However, since monoclonal antibodies can last up to several months, it is important that safety be considered in two areas (Proksch, Gentry, and Owens, 2000). First, if an individual is dependent on the overdosed substance, withdrawal will occur after the overdose is reversed, and this withdrawal will not be suppressed by treatment with the usual modest doses of a long-acting agonist from the same pharmacological class as the targeted overdose drug. Very large doses of the agonist might be required to overcome the antagonism produced by the antibody treatment. Second, when the patient who has recovered from the overdose leaves the emergency department, he or she will continue to have a relative blockade of the abused substance. Any attempts by the patient to override this blockade could lead to the use of large amounts of an abused substance. The effects of any adulterants included in an illicit street drug would be magnified by this more intensive self-administration. Thus only a single dose of the medication would be needed to provide acute treatment, but aftercare would be critical because of the potential for the intervention to be long lasting. Using monoclonal fragments (Fab) rather than the complete humanized antibodies will be an impor-

tant consideration for overdose reversal, since these fragments have considerably shorter half-lives and should have minimal efficacy within 24 hours, rather than lasting several weeks, as is typical of the complete antibody.

Nonetheless, the economic advantages of this type of intervention could be substantial if a single monoclonal antibody injection can keep a patient from entering an intensive care unit, at an expected cost of more than $1,000 per day. Thus the cost of treatment (approximately $2,000) would have to be justified in part by the cost of continued medical care (i.e., the high cost of a day in an emergency room or several days in intensive care). The aftercare costs for substance abuse relapse prevention (discussed below) after starting monoclonal treatment or after an intensive care unit stay should be the same, although the patient will be able to enter this aftercare much more quickly following reversal of the acute overdose by the monoclonal.

Relapse Prevention Protocols

A typical relapse prevention protocol might use any of the three types of agents to enhance compliance with treatment. The psychosocial backbone of these treatments may be quite variable, however, based on comorbid psychiatric or medical disorders as well as social supports. Overall, depot medications or immunotherapies are simply components of treatment for addictions. With depot medications a monthly injection might be given, though efforts to develop formulations of naltrexone, for example, that are active for up to 6 months are under way. One important issue in the use of depot medications in general is whether a test dose of the oral medication is required to ensure that the patient can tolerate the medication well. The need for a test dose is clear in the case of naltrexone for opioid dependence, because in an individual who is currently opioid dependent, naltrexone will precipitate a severe withdrawal syndrome that is irreversible until the medication is eliminated metabolically (Kleber and Kosten, 1984). In contrast, the use of this formulation in alcoholics may not require an oral test dose.

Based on the current technology, a year of treatment with a depot medication would involve monthly injections at a potential cost of $150 each. However, a depot medication is unlikely to be effective without a substantial psychosocial intervention that is delivered relatively frequently at first, with the potential for reduced frequency over time. Based on evidence of poor compliance with oral naltrexone, which has limited value in the treatment of opioid dependence, a major focus of the psychosocial intervention would be on promoting compliance with the depot injections (Kosten and Kleber, 1984). Efforts to enhance medication com-

pliance have included contingency management and other interventions with the patient as well as the involvement of family members. For opioid addicts this intervention would also include urine toxicology monitoring as well as self-reports of drug use. The psychosocial treatment to accompany a depot medication can be expected to add $5,000 to $10,000 to the cost of the medication itself. This estimate is based on twice weekly visits for up to 6 months, with gradual reduction to monthly visits over the second half of the year, or a total of approximately 75 visits, at a cost of up to $120 per visit (Rosenheck and Kosten, 2001; French et al., 1997). This cost may be mitigated in a relatively low-intervention criminal justice setting, where depot injections or even vaccinations of an antagonist could be part of monthly visits to probation or parole officers.

The use of long-acting depot formulations of antipsychotic medications, which have been well accepted, may provide a valuable model for dissemination of depot technology for the treatment of both alcohol and drug dependence. Johnson (1984) suggests several reasons why some patients who do not respond to an oral medication may respond to the depot formulation. First, the depot formulation overcomes the problems of oral drug absorption, yielding a more predictable and constant plasma level. Second, depot medications bypass hepatic metabolism, potentially resulting in a higher brain concentration of the parent compound. Third, depots help to reduce the noncompliance associated with daily drug administration. Although the use of depot antipsychotics in the treatment of schizophrenia appears to reduce patient noncompliance, evaluation of their benefits ideally requires a three-way, double-blind comparison of patients randomly assigned to a long-acting drug, the same drug given orally, or a placebo (Kane, 1984). Similar considerations apply to FDA testing of depot medications for the treatment of alcohol and drug dependence.

In addition, safety issues must be considered. Although initial study of one depot naltrexone formulation showed it to be well tolerated by alcoholics (Kranzler, Modesto-Lowe, and Nuwayser, 1998), severe local reactions to a similar formulation have subsequently been seen (Kranzler, unpublished observations). The need for careful monitoring of depot preparations was shown in a study of a long-acting formulation of somatostatin for the treatment of acromegaly (Ayuk et al., 2002). In that study, 3 of 22 patients showed impaired glucose tolerance that was attributable to the depot medication. Use of a depot formulation of a corticosteroid to treat severe seasonal allergic rhinitis, which resulted in severe bone damage to both hips of a patient (Nasser and Ewan, 2001), also underscores the risk associated with off-label use of depot formulations.

Relapse prevention using monoclonal antibodies (passive immuniza-

tion) would be very similar to a depot medication and might require injections as infrequently as every 2 months (Proksch et al., 2000; Casadevall, 1999). However, the initial administration of these monoclonal antibodies could be uncomfortable or even unsafe if given to a drug-dependent individual. Safety is a consideration because, like a depot antagonist, monoclonal antibodies would prevent the relief of withdrawal that ordinarily results from administration of a long-acting agonist. Long-acting agonists such as methadone for heroin-dependent individuals or benzodiazepines for those dependent on sedatives or alcohol are typically used for medical safety during detoxification treatment. The complications of withdrawal from sedatives or alcohol, for example, can be severe, including seizures. Helpful medications such as nicotine replacement therapy will also be neutralized by monoclonal antibodies. Therefore, before individuals are given long-acting monoclonal antibodies, they need to be adequately detoxified, which can take 3 to 14 days, depending on the abused substance and the severity of dependence (Kosten and O'Connor, 2003). As with depot medications, a relatively intensive psychosocial intervention will also be needed during at least the first few months of treatment. The cost of such an intervention is likely to be $5,000 to $10,000, not including the cost of the monoclonal antibody itself, based on twice weekly visits initially, with gradual reduction to monthly visits over time (Rosenheck and Kosten, 2001).

Relapse prevention using active immunization has several additional complications that are not present with monoclonal antibodies or depot medications. First, four or five injections administered over 8 to 12 weeks have been required in order to elicit an antibody response sufficient to antagonize the effects of the abused substance (Kosten et al., 2002). During this induction period other interventions will be needed to maintain individuals in treatment, and these may include monoclonal antibody treatment. Abusing drugs such as cocaine or taking replacement therapy such as nicotine during the induction period will not interfere with antibody production in response to the immunizations, but because of this delay in efficacy more intensive psychosocial interventions may be required with active than with passive immunization. Second, immunization will lead to a variable antibody response among individuals (Kosten and Biegel, 2002). While monoclonal antibodies can be given at a known dosage and concentration, which will not vary widely among individuals, some patients will be unresponsive to active immunization and will produce low antibody levels that will be ineffective at antagonizing the effects of the abused drug. Even in patients who respond well to initial immunization, booster immunizations about every 4 months will be required to maintain high antibody levels, and the cost per immunization might be

about $150 for the medication alone. Similar to the use of a depot medication, the inclusion of a psychosocial component will add substantially to the cost of relapse prevention via active immunization.

Protection Protocols

Protection protocols might use any of these three types of interventions, but the psychosocial issues raised earlier in this appendix as well as medical safety are important. Determining the safety of long-term exposure to these treatment agents in a relatively large number of individuals will be difficult and expensive (Sparenborg, Vocci, and Zukin, 1997; Cohen, 1997a). Thus, if a protection protocol is to be developed, it is unlikely to occur, even for those at high risk of drug abuse, until well after overdose or relapse prevention protocols are well established. Depot medications with no effects on normal functioning might be considered for this application, but even relatively inactive antagonists such as depot naltrexone for opiates have substantial risks that would likely preclude their use for such purposes. These risks include sustained elevations of various hormones such as cortisol and the sex hormones (e.g., follicle stimulating hormone) and potential liver toxicity (Kosten et al., 1986; Morgan and Kosten, 1990). Active immunization has the potential for producing a lifetime marker of immunization due to low levels of persistent antibody to the drug that could be detected in employment screenings or other nonmedical settings (Janeway et al., 1999). Passive immunotherapies, such as the monoclonals, are less likely to have safety issues than depot medications, such as naltrexone, and do not produce any lifetime markers of their use. However, compliance with 1- to 2-hour protein infusions that are administered every other month, the potential for overriding the antibody with large doses of the abused substance, and the substantial cost of the medication (about $12,000 per year, which represents six infusions at a cost of $2,000 per infusion) are limiting factors.

The potential harm of using large doses of an abused substance to overcome the blockade is well illustrated by nicotine, where a parental desire for immunotherapy of an adolescent child is a potential issue. If an immunized adolescent smoked cigarettes to obtain several times the usual dose of nicotine, he or she would also inhale several times the usual dose of various carcinogens that are in tobacco smoke without any antibody to block the adverse effects. Finally, as indicated earlier, protection against adolescent nicotine use by inhibiting pharmacological reinforcement may be ineffective because initiation of use is more closely related to peer acceptance and social factors than to pharmacological effects of the nicotine.

Several common threads run through all of these clinical protocols. First, immunotherapies and depot medications represent only a small part

of a comprehensive clinical intervention that requires substantially greater behavioral treatment than the monthly or even twice annual contact that may be needed to administer these therapies. Second, because these therapies are long lasting, they must build on a platform of treatment that is sustained for weeks and months. For example, reversal of overdose with these agents could commit the treatment provider to a substantially longer intervention than the hours ordinarily spent in an emergency department, particularly if a complete antibody rather than a Fab fragment is given. Third, the least expensive interventions to add on to existing treatment programs may best address relatively select patient populations, such as the 30 to 40 percent of methadone-maintained patients with combined heroin and cocaine dependence in whom active cocaine immunization could complement opioid agonist therapy (Brooner et al., 1997). Its advantage is that the marginal cost of such an intervention is less than for individuals not already receiving a variety of rehabilitative services. Fourth, polydrug abuse is common, and effective immunotherapies and depot medications may require that an individual receive multiple agents to treat a range of abused substances. The technology to develop such multiple target therapies is available and feasible (Kosten and Biegel, 2002). Furthermore, the medication and administration cost for such a multivalent vaccine would probably not be substantially greater than for a monovalent vaccine targeting a single abused drug. Fifth, any of these medications may be used in ways that are unlikely to be examined during clinical testing and the FDA approval process, such as for protection in nonabusing individuals (i.e., primary prevention) or among individuals identified as experimental users (i.e., secondary prevention), creating the possibility of adverse effects in an otherwise healthy population.

THE FDA CLINICAL TRIALS PROCESS

Phase I

The FDA clinical trials process, which is designed to assess safety and efficacy (but not cost efficiency) through four phases of testing, may raise specific issues in a substance-dependent population (Blaine et al., 1994). The purpose of Phase I is to establish the safety of escalating doses of medications, generally in healthy subjects. Realistically, though, some active immunotherapies can only be examined in the intended substance-abusing population, perhaps during extended abstinence, because active immunization is likely to leave a low level of antibody for a lifetime (Kosten et al., 2002). Health insurers or other agencies could use the presence of such an antibody as a marker of prior treatment for drug abuse or dependence. Active immunization requires that a series of doses be given;

no efficacy is likely from a single dose because several doses are needed for antibodies to be produced at an optimal level for efficacy. The use of multiple doses increases the risk of testing active immunization in healthy nonusers. In established drug users, testing of active immunization may need to occur in an inpatient setting for up to 3 months, to prevent the use of drugs that might interact with active immunization.

Monoclonal antibodies or depot medications can be tested with single doses in healthy nonusers or drug users who are currently abstinent, perhaps in a residential setting. The safety questions related to depot medications or monoclonals require no additional monitoring requirements beyond those involved in standard evaluations for related parenteral treatments in medicine. For monoclonal testing in abstinent drug users, the drug-free period might be up to 2 months to prevent unmonitored interactions between the antibody and the abused drug. For depot medications, safety testing is probably best done in the targeted substance abuser population but could be done in healthy nonusers. Phase I testing with drug abusers will most helpfully inform later studies in Phases II and III. Limiting testing to substance abusers also addresses ethical concerns over whether the risk of the interventions can be justified in nonusers (Cohen, 1997a).

Phase II

The purpose of Phase II is to establish preliminary efficacy by optimizing the dosage of the medication and may include comparison to a placebo. At this point the proposed indication for the medication is critical for determining which outcomes and populations to target. The simplest indication to study for substance dependence is probably reversal of overdose. However, drug-dependent users who have overdosed are a problematic population because they may be unable to give informed consent. Such problems can be addressed, since they were encountered with the initial evaluation of naloxone for reversing opiate overdose and flumazenil for benzodiazepine overdose. Furthermore, ongoing problems with obtaining informed consent exist when medications are tested for acute treatment of stroke patients in the emergency department while the patient is unconscious, obtunded, or in some other way unable to communicate informed consent. Hence, the conduct of such a study is possible, although it will likely require enrolling patients who meet predetermined criteria and obtaining consent for participation after the individual has regained the capacity to give informed consent.

If abstinence initiation is the outcome, interactions between the abused substance and the immunotherapy may need to be assessed in a human laboratory setting in which the abused substance is administered.

The laboratory assessment may also help establish blocking efficacy. Human laboratory assessments have been employed in testing naltrexone for opioid antagonism by using opioid agonist administration to evaluate the magnitude and duration of blocking effects (Kleber et al., 1985). This approach was recently applied to evaluate the effects of a depot naltrexone formulation (Comer et al., 2002).

During Phase II testing an additional risk that might be considered involves radiation exposure for receptor neuroimaging. Receptor neuroimaging can be very useful when used before and after immunotherapy to assess whether the antibodies effectively reduce entry of the abused drug into the brain. When the antibody is not present, a large amount of the receptor's radioligand (e.g., radioactive C-11 cocaine) should be displaced when the nonradioactive abused drug (e.g., cocaine), which binds to the same receptor, is taken. However, when the antibody is present, substantially less of the receptor's radioligand should be displaced following administration of the nonradioactive drug, thereby increasing the total dose of radiation detected in the brain. Imaging technology can also be applied to examine the time course of receptor occupancy by medications administered as a depot formulation. For example, mu-opioid selective receptor agents such as carfentanil could be used to examine the time course of mu-opioid receptor blockade following depot naltrexone administration (Fowler et al., 1999; Swanson and Volkow, 2002).

Another objective during Phase II testing can be to develop immunotherapies that target multiple abused substances, since these distinct antibodies should have no significant interactions. This multitarget approach should be considered as testing of a single treatment agent to facilitate examination in a polydrug-abusing population.

Depot medications in Phase II may provide a special case in which the efficacy of the oral medication is already established, so that a small Phase II study of efficacy may be sufficient. However, oral naltrexone was not compared to placebo for its initial approval as a treatment of opioid dependence and still has no evidence of superiority to placebo to support its efficacy (Kirchmayer, Davoli, and Verster, 2002). Because of the potential FDA requirement that depot naltrexone be demonstrated to have efficacy against placebo for opioid dependence, alcohol dependence has been the initial indication for developing depot naltrexone. This approach also takes into account the higher prevalence of alcohol dependence than opioid dependence (and a concomitantly greater market potential), previous success in showing that naltrexone was superior to placebo in alcohol dependence (Volpicelli et al., 1992; O'Malley et al., 1992), and the greater difficulty of conducting relapse prevention trials in opioid addicts compared with alcoholics (Srisurapanont and Jarusuraisin, 2002). However, given the modest overall effects of naltrexone for the treatment of alcohol

dependence (Kranzler and Van Kirk, 2001; Streeton and Whelan, 2001), demonstrations of the efficacy of depot naltrexone for this indication will require large patient samples to yield adequate statistical power.

Phase III

The purpose of Phase III is to establish efficacy and safety in one or more large-scale, placebo-controlled studies. The design of the studies and the specific outcomes of interest may differ with the potential indication being considered. Because the reversal of overdose has become an important consideration in the management of adverse effects of a variety of new drugs, including most recently gamma-hydroxybutyrate (Miro et al., 2002), consideration should be given to the evaluation of immunotherapies for this indication. If reversal of overdose is the outcome of interest, drug-dependent users who have overdosed will be given an immunotherapy that will probably last for several weeks beyond the time needed to reverse the overdose. This could provide the opportunity to examine relapse prevention as well. However, it involves a patient population that is likely to be very difficult to follow closely using urine toxicology testing and that may be at high risk of using large doses of the abused drug to override the blockade provided by the immunotherapy. Therefore, in these drug abusers it may not be feasible to assess the potential efficacy of the antibodies for relapse prevention; instead, a follow-up of the overdose episode would focus on safety considerations.

If relapse prevention is the outcome of interest, the focus would be on drug-dependent users who are abstinent, rather than those who have just experienced an overdose. Since the natural history of drug dependence is one of a chronic relapsing course with periods of binge use, several weeks of abstinence before randomization to the medication or placebo may be required to yield a meaningful relapse prevention study (Klein, 1998). Furthermore, because of a delay in efficacy for 6 to 8 weeks as antibody levels rise after active immunization, early treatment retention is critical and may require cointerventions such as intensive contingency management (Kosten and Biegel, 2002). To add to the complexity of subject selection and the initial procedures required for an efficacy trial, extended outcome monitoring over 6 to 12 months is needed after the initial period of abstinence to follow patients until the majority relapse back to drug use. These requirements will impose a selection bias in favor of an especially stable population of abusers of drugs such as cocaine. Finally, these efficacy studies will probably be restricted to adults and nonpregnant women using suitable methods of birth control and would not include nonabusers. Thus, these studies are likely to include a very selected population of patients and will require complex psychosocial treatment plat-

forms to assess efficacy, factors that will limit the generalization of these treatments to more usual clinical applications in actively drug-using populations. This appears to be an unavoidable limitation of a Phase III clinical trial.

Phase IV and Off-Label Uses

The purpose of Phase IV is to monitor use of the medication in clinical practice (i.e., once the medication has been approved for commercial use). This includes continued evaluation of the medication in populations not originally studied and assessment of relatively rare side effects (i.e., those occurring in less than 1 percent of patients). It is during this postmarketing phase that most of the many ethical and legal issues concerning the use of immunotherapies and, to a lesser extent, depot medications are likely to arise. Among the populations not likely to be studied in the initial three phases of FDA clinical trials process are adolescents, pregnant women, medically ill people, and prisoners. These populations may be considered for later controlled trials before off-label use becomes widespread. Off-label uses include treating patient groups with different disorders or using different types of interventions than originally approved. An example of a different disorder might be using depot naltrexone for relapse prevention in opioid dependence after it is approved for alcohol relapse prevention. An example of a different type of intervention might be using a monoclonal antibody that was approved for overdose reversal in a protection protocol. Early off-label use of immunotherapies will pose special issues for immunocompromised individuals with HIV infection or AIDS. While these patients may not be suitable for active immunization, they are potential candidates for passive immunotherapies such as monoclonal antibodies to help treat their substance dependence. These groups of medically ill patients with a relatively high prevalence among substance abusers may require the conduct of early Phase IV studies focusing on safety and not necessarily requiring placebo controls, for example.

Issues of stigmatization and coercion must be considered carefully in advance of Phase IV evaluation of immunotherapies and depot medications. Potential populations for evaluation during Phase IV may include long-term abstinent substance abusers at high risk for relapse to substance use. An example of such an application would be the prophylaxis of abstinent addicts following extended stays in prison or residential treatment settings (Cohen, 1997a). Prophylaxis or protection of high-risk substance abusers who have never been substance dependent (i.e., secondary prevention) may be considered for adolescents excluded from previous trials due to low severity of the disorder. Prophylaxis in high-risk groups with no personal history of abuse (i.e,, primary prevention), such as ado-

lescents with substantial family risk factors, may also be considered. With respect to immunotherapies, these populations should be tested using monoclonal approaches before active immunization is considered because persistent low levels of antibody to the abused drug resulting from active immunization will lead to a potential lifetime marker of substance abuse treatment.

Comparisons among treatments delivered in different settings will ultimately provide information on the most effective approach to treating a range of high-risk and affected individuals. Settings may vary in the degree to which they are suited to particular types of interventions, due to factors such as the level of medical care available on-site (Fiellin and O'Connor, 2002; Sindelar and Fiellin, 2001). For example, drug-free clinics may provide an opportunity to use depot medications because these medications have minimal need for ongoing medical evaluation after their initial administration. Although severe local reactions have been observed following some depot injections, only products with demonstrated safety in this regard are likely to receive FDA approval. Opioid agonist maintenance clinics (e.g., those dispensing methadone) have greater medical resources than do drug-free clinics, making them more feasible sites for immunotherapies that require careful medical assessments over a sustained period of time. Depot medications and immunotherapies should also be evaluated in primary care medical settings and emergency departments, since these are the settings in which drug abusers are often seen in the community.

Off-Label Uses

Before additional postmarketing clinical trials are completed, some physicians may decide to use these depot medications or immunotherapies for different diagnoses or in different types of intervention protocols than their approved indications. This off-label use extends beyond simply using the medication in an additional population that may not have been included in the Phase III clinical trials. Off-label use can involve a wide variety of patient groups. Generally, new medications will be used in patients with multiple illnesses, rather than in patients meeting the precise inclusion criteria of developmental trials. Although common, off-label use has raised ethical and practical issues (Cohen, 1997b; McIntyre et al., 2000; American Academy of Pediatrics, 2002).

Interestingly, one of the changes resulting from the FDA Modernization Act of 1997 was that pharmaceutical companies were allowed to disseminate articles from peer-reviewed journals about off-label use, which had previously been forbidden. The rationale for this approach was that,

since physicians had the legal right to prescribe drugs off label, information provided to them about uses not specifically approved by the FDA would make for more informed prescribing decisions (Reh, 1998). It was also hoped that this would motivate pharmaceutical companies to do the clinical studies necessary to get these indications added to drug labeling. However, such studies are unlikely in substance-dependent patients due to concerns about adverse effects related to substance abuse during the clinical trials. In general, off-label uses of medications, even in patient groups who do not abuse substances, is associated with a higher adverse drug reaction rate than that associated with labeled indications (Choonara and Conroy, 2002). Nevertheless, pediatric off-label uses of medications are quite common, and a specific study of the treatment of poisoning in children found that 60 percent of antidotes and other useful agents were not used according to the demands of licensing systems (Lifshitz, Gavrilov, and Gorodischer, 2001). This off-label use of antidotes for poisoning may be particularly relevant to the use of immunotherapies for overdose reversal in adolescents because the overdose agent may be unknown at the time that therapy is given, potentially resulting in the administration of multiple monoclonal antibodies. Furthermore, FDA clinical trials are likely to be conducted in adults, not children, so there will be limited or no prior experience with the use of these agents in adolescents.

While the development process and the postmarketing experiences differ across various therapies, when the FDA clinical trials process is completed and there is a successful new immunotherapy or depot medication, there may still be a number of unanswered questions relevant to the common practice of off-label medication use (Cohen, 1997b; McIntyre et al., 2000; American Academy of Pediatrics, 2002). For example, depot naltrexone is being developed for alcohol dependence, but the pharmacological specificity and utility for opioids are clear. Nevertheless, it is unclear whether similar efforts will be undertaken for a new drug application (NDA) to treat opioid dependence, and off-label use of depot naltrexone for opioid dependence is likely. Thus, what studies should be done with depot naltrexone in relation to the treatment of opioid dependence before the FDA grants an indication for alcohol dependence? Overall, many unanswered questions are likely to remain concerning which subgroups of substance-abusing patients will be most effectively treated pharmacologically with immunotherapies (Kosten, 1989). Nevertheless, at this juncture it would be useful to consider the indications for which an NDA or biological license might most readily be obtained for various depot medications and immunotherapies and how these indications might then be expanded by clinicians into off-label uses.

SPECIFIC ABUSED SUBSTANCES

This section addresses four issues related to generalization of the results of FDA clinical trials and the potential for off-label use of immunotherapies or depot medications that are in clinical development for treatment of a major abused substance. The first issue to be considered is the extent to which the study participants are representative of the general treatment population. Second is the range of potential therapeutic agents to be tested. Third is the need to develop multiple therapeutic targets, including integration of these agents with existing treatments. Fourth is the testing and clinical use of these treatments in settings other than specialty clinics, including primary care settings.

Nicotine

The FDA testing of immunotherapies or depot medications is likely to be more informative about the treatment of nicotine dependence than the treatment of any other abused substance. The participants in FDA trials for nicotine will likely be representative of the broad clinical target populations because the therapeutic goal for an NDA would be relapse prevention rather than the reversal of overdose. Second, because these therapies can have a relatively large market and the lower cost of active immunotherapies makes them attractive, both active and passive or monoclonal immunotherapies are likely to be tested. Third, because of the range of other pharmacotherapies available for nicotine dependence, combination therapies such as with antidepressants or nicotine replacement therapy (NRT; e.g., patches) are likely to be examined (Sutherland, 2002; Sullivan and Covey, 2002; Sims and Fiore, 2002). Monoclonal antibodies could not be combined with NRT because they would bind the nicotine from the patch, making NRT ineffective. However, the combination of NRT with active immunotherapies would provide an ideal and cost-effective combination that provides detoxification using the NRT, while antibody levels rise to therapeutic levels (Woolacott et al., 2002). Fourth, testing and use of these treatments would not be limited to specialty clinics; primary care settings could readily be used, since nicotine-dependent patients are commonly treated using NRT in primary care settings. Initial human testing of a nicotine vaccine has begun with no serious adverse events and the promise of rapid development (http://www.xenova.co.uk/dc_ta_nic.html).

The process of obtaining an NDA for adult smokers can address relapse prevention well, but protection protocols for prophylactic use in adolescents will require specific testing before off-label use should be allowed. Enforcement of such a prohibition on off-label use will provide

new challenges to the FDA clinical trials process. One approach that builds on the FDA requirement for testing new pharmacotherapies in children is represented by the 1998 final rule from the FDA that pediatric studies are required, the 2001 Subpart D—Final Rule: Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, and the Best Pharmaceuticals for Children Act (2002; Subpart D, Part 46, Title 45 CFR; http://www.fda.gov/OHRMS/DOCKETS/98fr/cd0030.pdf). Although this ruling has been overturned in the courts, it is under appeal by the FDA, and a new rule is being drafted in Congress to address the issue of mandating these studies in children.

Adolescent smoking is relatively common, and treatment interventions have been studied in this population. In addition, since a "smoking career" generally begins during adolescence, the greatest impact on reducing adult smoking rates will result from the prevention of adolescent smoking. Immunization could be used to alter the trajectory of early drug use—for example, among teenagers who smoke occasionally. This group has a greater than 70 percent chance of becoming regular smokers within a few years and so might provide a "high-incidence" target. An advantage of intervening at an early stage in the development of dependence, when the dose of the drug used is low, is that it would be more amenable to blockade by immunization. A specific consideration early in the development of dependence among adolescents, however, is that the initial incentives for drug use are more social than pharmacological. Consequently, the utility of a pharmacological intervention would probably not be substantial until the pharmacological effects of the drug become important in sustaining the dependence, such as occurs among smokers who use nicotine to reverse withdrawal. Furthermore, because development of any pharmacotherapy in adolescents raises a concern over potential interference with the normal growth process, an ideal intervention would be one that specifically targets nicotine without effects on organ or hormonal systems. Thus, immunotherapies would have to be tested first in adolescent smokers with demonstrated nicotine dependence in order to assess safety.

Passive immunization with monoclonal antibodies could be examined in relatively large groups of adolescents after initial approval of an immunotherapy for adults. This type of Phase IV study should be conducted within the context of the FDA drug development process and would provide an opportunity to consider secondary prevention in this younger patient group before any primary prevention is attempted. The use of depot formulations of nicotine, naltrexone, or bupropion in adolescents would require demonstration of the safety of the oral formulations of these medications in this age group. In addition, the safety of the depot prepa-

rations would have to be established in adults during at least 2 years of Phase IV monitoring.

Many of the same issues exist in relation to the treatment of nicotine dependence in pregnant smokers. Despite clear evidence of adverse outcomes among children born to women who smoke and the widespread acceptance of nicotine replacement therapy for smoking cessation, there is a paucity of research on pharmacological treatments for pregnant smokers (Oncken and Kranzler, 2003). Although nicotine replacement therapy is not approved for use in pregnant smokers, nearly half of obstetrics practitioners surveyed indicated that they prescribed nicotine to smokers in their practices (Oncken et al., 2000), which underscores the potential for off-label use of therapies in this population.

Cocaine and Amphetamines

Because a wide range of potential populations may not be tested in clinical trials directed toward an NDA for cocaine or amphetamines, these immunotherapies or depot medications may be poorly generalized to clinical populations for off-label use. First, in terms of populations studied, the passive immunotherapies could be most efficiently examined as overdose treatments, particularly using monoclonal antibodies that are designed to have a relatively short half-life (Carrera et al., 2001; Fox et al., 1996). Using these short-duration immunotherapies, an NDA could be obtained prior to the availability of information on the utility or safety of immunotherapies as a relapse prevention tool. Therefore, testing will need to examine the repeated administration of these monoclonal agents with no more than one or two half-lives between each administration. Such repeated dosing would be a simple extension of the labeled indication of the monoclonal for overdose reversal. Second, active immunotherapies are not useful for overdose reversal, but both active and passive or monoclonal immunotherapies are likely to be useful for relapse prevention. Because the lower cost of active immunotherapies makes them attractive in settings with limited resources, it may be critical to examine both approaches. Third, because polydrug abusers in general and stimulant abusers in particular can readily switch from cocaine to amphetamine to other "designer drug" stimulants (Petry and Bickel, 1998), multitarget immunotherapies might be encouraged to cover a range of stimulants and facilitate broader abstinence from these substances. Fourth, because of the difficulty in maintaining abstinence among stimulant abusers and the need for relatively comprehensive behavioral therapies, these immunotherapies will most likely succeed in specialty clinics. Primary care settings, which would not be likely testing sites, are also unlikely sites for off-label treatment.

Use of immunotherapies as protection protocols or for primary prevention in adolescents, prisoners, or pregnant women raises all of the issues listed above under Phase IV testing. Some applications, such as for abstinent prisoners with a prior history of cocaine dependence, are likely to be within the labeled use because the time since last stimulant use is not important to the administration of these immunotherapies. However, since no pharmacotherapy exists for these stimulants, significant social pressure may be exerted to examine the potential for immunotherapy in other off-label uses with these special groups (Kosten, 2002). Because of the potential for lifetime markers after active vaccination, this would not be a viable option for protection protocols. But even with monoclonal antibodies, the scientific information that might be obtained during the FDA clinical trials process will be inadequate to formulate guidelines for off-label uses in adolescents or pregnant women. Since animal models are the best available approximation of use in pregnant women, safety studies of immunotherapies and depot medications in pregnant animals should be a required part of any successful NDA.

No obvious candidates for depot medications to treat stimulant dependence exist. However, since disulfiram has shown some efficacy for cocaine dependence (Carroll et al., 1998), the active sulfoxide metabolite of disulfiram, which is highly potent (Hart and Faiman, 1992), is a potential agent for development as a depot formulation. Because of the potential for this medication to interact with alcohol, resulting in rare but potentially serious adverse effects, off-label uses would probably be discouraged by the liability concerns of practitioners (Wright and Moore, 1990).

Opioids

Although immunotherapies for opioids were developed in primate models over 30 years ago (Bonese et al., 1974), development did not continue due to the utility of methadone and naltrexone as pharmacological treatments for opioid dependence. Nevertheless, immunotherapies might be developed in trials that inform the four issues being considered here. It is likely that the first population to be studied with immunotherapies and depot medications would be representative of the general treatment population seeking relapse prevention. Because naloxone is so cost effective for the reversal of opioid overdose, overdose reversal may not seem a profitable target for development of this type of immunotherapy (Clarke and Dargan, 2002).

The range of potential therapeutic agents for treatment of opioid dependence is likely to be wide in order to compete with the cost-effective treatments of methadone maintenance or even naltrexone maintenance.

An inexpensive active immunotherapy or a depot form of naltrexone would be more likely to succeed than a relatively expensive monoclonal antibody.

The third issue of developing multiple therapeutic targets and integrating them with existing treatments will be of particular importance in the treatment of opioid dependence. While heroin is a predominant opioid of abuse, many other synthetic opioids are abused, including the treatment agents methadone and buprenorphine (National Institute on Drug Abuse, 1998; Kintz, 2001). Use of multiple therapeutic targets would be a reasonable approach, although the advantage of having high specificity for heroin while allowing the use of other opioids for pain relief might have some value in special populations. The integration of immunotherapies with methadone treatment provides interesting possibilities, including a potential slow detoxification starting with modest doses of methadone (e.g., 30 to 40 mg daily), while the antibody levels to heroin rise over 6 to 8 weeks. Depot naltrexone, like immunotherapy, addresses compliance issues, but naltrexone appears to offer advantages of very high levels of blockade compared to the competitive antagonism of active or passive immunotherapy. Obviously, however, the use of long-acting naltrexone, as with oral naltrexone, requires that detoxification be completed prior to initiation of therapy, to avoid a severe withdrawal reaction.

Although the testing and use of these treatments in settings other than specialty clinics pose the same challenges as with treatments for stimulant dependence, the structure and medical resources of methadone maintenance clinics make them excellent sites for the transfer of this technology into the community. Due to the difficulties inherent in blinding trials involving naltrexone for opioid dependence, limited placebo-controlled data are available on the oral formulation of this medication for the treatment of opioid dependence. Consequently, the design of placebo-controlled clinical trials of depot formulations of naltrexone for opioid dependence is likely to break new ground, because unmasking the blind will be relatively easy and is likely to occur.

Other Drugs of Abuse—Phencyclidine

While immunotherapies are theoretically possible for hallucinogens, cannabis, and "club drugs," such as MDMA (methylenedioxy-n-methylamphetamine) or ecstacy, the only monoclonal developed to date is PCP. This immunotherapy is specifically designed for the reversal of PCP overdose, but its long duration of action suggests that it also has potential for relapse prevention among PCP abusers (Owens and Mayershohn, 1986; Valentine et al., 1996; Proksch et al., 2000). Clinical trials to support an NDA might logically focus on the potential of this treatment to reverse

overdose, but its long duration of action dictates testing of its longer-term effects and its safety in outpatient substance abusers, particularly since once approved for overdose, it would likely be used off label.

The capacity to generalize the findings among study participants to general clinical use is a complex issue in relation to immunotherapies for PCP. Although as an overdose treatment the PCP monoclonal will be tested in precisely the population where it is intended for clinical use, follow-up of these patients after the overdose treatment may be very difficult. There is likely to be a low rate of contact for the weeks following overdose, since the patients are unlikely to be motivated to seek treatment or continued contact with the providers. Nevertheless, the weeks of follow-up will be most critical for assessing both the safety and potential efficacy for relapse prevention. This difficulty in follow-up suggests that a separate clinical trial may be needed to assess safety in active PCP abusers who have not had an overdose as the basis for monoclonal treatment. The availability of active vaccination as well as a passive monoclonal is important if this approach is considered for relapse prevention and not just overdose reversal. The need for multiple therapeutic targets is considerable, since the specific agent in overdoses with club drugs such as PCP, ketamine, or even MDMA is difficult to identify based on clinical presentation, and a broad-spectrum antidote would be most useful (Baskin and Morgan, 1997; Owens, 1997). The issue of using these treatments beyond the emergency department is a critical question because of the duration of their blocking effects. Unlike naloxone for opioids or flumazenil for benzodiazepines, both of which have brief durations of action, monoclonals are a sustained intervention that can be most important as an entry into treatment for substance abuse or dependence (Clarke and Dargan, 2002; Singh and Richell-Herren, 2000). This opportunity should be exploited for maximum clinical benefit and examined as part of the NDA process.

Alcohol

Immunotherapies are not possible for alcohol, but Phase III clinical trials of depot naltrexone are under way, and trials of depot formulations of other opioid antagonists such as nalmefene are being planned. Depot medications are not likely to have application in the treatment of either alcohol overdose (for which supportive measures and, at the extreme, hemodialysis, are the treatments of choice) or alcohol withdrawal (for which brain depressants or anticonvulsants are efficacious when administered for a relatively short period of time). Consequently, clinical trials are likely to be most informative to the degree that they extend findings of placebo-controlled trials of oral formulations of the candidate medications, which have focused on relapse prevention.

In addition to considering the development of these formulations in relation to the four issues of interest in regard to generalization of findings from the FDA clinical trials process, it is important to consider their potential application to the treatment of drug dependence. The large samples recruited for Phase III studies of these formulations should provide results that can be generalized to the population of treatment-seeking alcoholics, though as with oral naltrexone, it must be recognized that there is some selection of more motivated and compliant patients to participate in the trials. Given the difficulty of retaining opioid addicts in treatment with an opioid antagonist (Kleber and Kosten, 1984), it is likely that findings from Phase III studies of these formulations in opioid addicts will not be as readily generalized to the treatment-seeking population of opioid addicts. Consequently, once approved for the treatment of alcohol dependence, these medications are likely to be used off label for the treatment of opioid dependence. Consequently, FDA approval for alcohol dependence may necessitate evidence of the safety of these formulations for use in opioid addicts.

Since alcohol affects a variety of neurotransmitter systems, many of which have been implicated in the pathophysiology of alcohol dependence (Kranzler, 1995), the range of potential therapeutic agents to be tested in conjunction with a depot medication is great. Some of these systems (e.g., opioidergic or dopaminergic) are of obvious relevance to drug dependence, so that transfer of the technology to treat alcohol dependence will be relatively straightforward. However, depot formulations of drugs affecting neurotransmitter systems for which therapeutic effects in drug dependence are not as promising (e.g., the serotonergic system; Pettinati et al., 2000; Johnson et al., 2000) will be less readily applied across substances.

As with drug addicts, alcoholics often abuse a variety of substances (Gossop, Marsden, and Stewart, 2002), so a depot formulation that hits multiple targets could be very useful. Although the evidence supporting naltrexone treatment of nicotine dependence is not yet adequate to draw conclusions (David, Lancaster, and Stead, 2001), a depot medication that is efficacious for treatment of both alcohol and nicotine dependence would have considerable utility, given the high rate at which these disorders co-occur (Hughes, 1995). Combination therapy has not been widely used in alcoholism treatment. However, the diversity of neurotransmitter systems implicated in the disorder argues in favor of greater research attention being paid to this approach (Kranzler, 2000). The use of a targeted approach to oral therapies (Kranzler et al., 2003) raises the possibility of augmenting a depot treatment with intermittent use of an oral medication. This approach would facilitate a combination of medications to target different neurotransmitter systems—for example, depot naltrexone combined with targeted use of an alcohol-sensitizing drug to cope with high-

risk situations (Duckert and Johnsen, 1987; Annis and Peachey, 1992). As an example of an application of this strategy to the treatment of drug dependence, depot naltrexone could be combined with daily disulfiram to treat comorbid opioid and cocaine dependence (Petrakis et al., 2000).

There appears to be considerable potential for the use of depot formulations in settings other than specialty clinics, including primary care settings. In contrast to most specialty substance abuse treatment settings, the use of injectable medications is common in primary care practices. Consequently, the feasibility of their use in these settings will likely depend on demonstration in Phase III trials that low-intensity psychosocial interventions (i.e., those that can be readily applied to primary care settings) are adequate to support the efficacy of the medications.

CONCLUSIONS

Three broad types of intervention protocols might be tested in support of an NDA or expanded during the off-label use after approval of immunotherapies or depot medications: overdose, relapse prevention, and protection from abuse. The four-phase FDA clinical trials process to assess safety and efficacy will inform many of the important questions that must be answered prior to widespread use of these treatments. During Phases I and II, the safety of escalating doses of immunotherapies can be established in relevant patient groups and because polydrug abuse is common, multiple target approaches should be developed. The issue of multiple targets may be critical for overdose reversal with users of club drugs such as PCP because these abusers frequently do not know whether they have taken ketamine, MDMA, or other related substances and may be unaware that they are taking combinations. During Phase III, relapse prevention clinical trials would be most useful for both immunotherapies and depot medications and, where feasible, might include assessment of these treatments for abstinence initiation in active abusers. Relapse prevention studies are likely to enroll a very select population of patients, and complex (and costly) psychosocial treatment platforms may be used when assessing efficacy; both factors will limit their generalization to more usual clinical applications in actively drug-using populations. Nevertheless, these relapse prevention trials will be more relevant to the widespread application of these treatments than trials focusing on the reversal of overdose.

At best only some of the important questions will be answered during the FDA clinical trials process required for the approval of an NDA for immunotherapies and depot medications. The unanswered questions are likely to include how much behavioral treatment is needed to deliver these therapies effectively. This question includes both the frequency of treat-

ment contact (e.g., ranging from daily to monthly) and the duration over which behavioral treatment is required after the medication is administered. The setting for delivery of this care also needs to be considered to make the marginal cost of such an intervention affordable.

None of the Phase III studies are likely to address issues relevant to the prophylaxis of addiction in nonabusers (primary prevention) because of the substantial cost and long duration of this type of clinical trial to establish efficacy. Nevertheless, subjects with sustained abstinence, who are at high risk for relapse, might be approached for secondary prevention studies during Phase IV monitoring. Phase IV is where many ethical issues will arise as off-label uses of these immunotherapies or depot medications proliferate. New populations may be studied, including adolescents, prisoners, and pregnant women, and new treatment settings, such as primary care medical clinics, may be examined. The FDA testing process will provide only limited help in generalization to off-label uses, and the extent to which the process will help varies across the specific abused substances. Four issues will be important for this generalization: the nature of the NDA study population, the range of agents tested, the targeting of multiple therapeutic targets or integration with existing treatments, and the variety of settings where testing was done and treatment is provided. The issue of where treatment is provided may be a particular challenge, since many substance abuse treatment programs lack the infrastructure to deliver pharmacotherapies, particularly those that require greater medical support. Coordination between these programs and a medical setting where these immunotherapies or depot medications might be provided has typically not been successful and may lead to discontinuities in care for the patient. Off-label uses in these medical settings are likely to be provided most effectively for nicotine products. Off-label uses will probably be provided much more poorly for cocaine, amphetamines, and PCP. The difficulties with services for these drugs include limited information on their use from the FDA trials (e.g., reversal of overdose using monoclonal antibodies for PCP), the need for close coordination with substance abuse treatment settings that have limited medical backgrounds, and social pressure to make any effective treatment available. Use of depot medications such as naltrexone for alcoholism are likely to be well informed by the FDA process, but other uses of depot naltrexone such as for heroin dependence may be less thoroughly studied before the formulation is available for commercial use.

In summary, the FDA clinical trials process will provide a wealth of information about the safety and efficacy of these new medications. However, the wide range of unanswered questions posed by off-label use after approval needs ethical consideration to protect the many groups of indi-

viduals who may be offered or perhaps coerced into receiving these medical interventions.

REFERENCES

American Academy of Pediatrics. (2002). Uses of drugs not described in the package insert (off-label uses). *Pediatrics, 110*(1 Pt 1), 181-183.

Annis, H.M., and Peachey, J.E. (1992). The use of calcium carbamide in relapse prevention counseling: Results of a randomized controlled trial. *British Journal of Addiction, 87*(1), 63-72.

Ayuk, J., Stewart, S.E., Stewart, P.M., and Sheppard, M.C. (2002). Long-term safety and efficacy of depot long-acting somatostatin analogs for the treatment of acromegaly. *Journal of Clinical Endocrinology and Metabolism, 87*(9), 4142-4146.

Baskin, L.B., and Morgan, D.L. (1997). Drugs detected in patients suspected of acute intoxication. *Texas Medicine, 93*(9), 50-58.

Blaine, J.D., Ling, W., Kosten, T.R., O'Brien, C.P., and Chiarello, R.J. (1994). Establishing the efficacy and safety of medications for the treatment of drug dependence and abuse: Methodological issues. In R. Prien and E. Robinson (Eds.), *Clinical evaluation of psychotropic drugs: Principles and guidelines*. New York: Raven Press.

Bonese, K.F., Wainer, B.H., Fitch, F.W., Rothberg, R.M., and Schuster, C.R. (1974). Changes in heroin self-administration by a rhesus monkey after morphine immunization. *Nature, 252*(5485), 708-710.

Brooner, R.K., King, V.L., Kidorf, M., Schmidt, C.W., Jr., and Bigelow, G.E. (1997). Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Archives of General Psychiatry, 54*(1), 71-80.

Carrera, M.R., Ashley, J.A., Wirsching, P., Koob, G.F., and Janda, K.D. (2001). A second-generation vaccine protects against the psychoactive effects of cocaine. *Proceedings of the National Academy of Sciences, USA, 98*(4), 1988-1992.

Carroll, K.M., Nich, C., Ball, S.A., McCance, E., and Rounsaville, B.J. (1998). Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction, 93*(5), 713-727.

Casadevall, A. (1999). Passive antibody therapies: Progress and continuing challenges. *Clinical Immunology, 93*(1), 5-15.

Choonara, I., and Conroy, S. (2002). Unlicensed and off-label drug use in children: Implications for safety. *Drug Safety, 25*(1), 1-5.

Clarke, S., and Dargan, P. (2002). Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Intravenous bolus or infusion of naloxone in opioid overdose. *Emergency Medicine Journal, 19*(3), 249-250.

Cohen, P.J. (1997a). Immunization for prevention and treatment of cocaine abuse: Legal and ethical implications. *Drug and Alcohol Dependence, 48*(3), 167-174.

Cohen, P.J. (1997b). "Off-label" use of prescription drugs: Legal, clinical and policy considerations. *European Journal of Anaesthesiology, 14*(3), 231-235.

Comer, S.D., Collins, E.D., Kleber, H.D., Nuwayser, E.S., Kerrigan, J.H., and Fischman, M.W. (2002). Depot naltrexone: Long-lasting antagonism of the effects of heroin in humans. *Psychopharmacology, 159*(4), 351-360.

David, S., Lancaster, T., and Stead, L.F. (2004). Opioid antagonists for smoking cessation. In *The Cochrane Library* (Issue 1). Chichester, England: John Wiley & Sons.

Duckert, F., and Johnsen, J. (1987). Behavioral use of disulfiram in the treatment of problem drinking. *International Journal of the Addictions, 22*(5), 445-454.

Fiellin, D.A., and O'Connor, P.G. (2002). Clinical practice: Office-based treatment of opioid-dependent patients. *New England Journal of Medicine, 347*(11), 817-823.

Fowler, J.S., Volkow, N.D., Wang, G.J., Ding, Y.S., and Dewey, S.L. (1999). PET and drug research and development. *Journal of Nuclear Medicine, 40*(7), 1154-1163.

Fox, B.S., Kantak, K.M., Edwards, M.A., Black, K.M., Bollinger, B.K., Botka, A.J., French, T.L., Thompson, T.L., Schad, V.C., Greenstein, J.L., Gefter, M.L., Exley, M.A., Swain, P.A., and Briner, T.J. (1996). Efficacy of a therapeutic cocaine vaccine in rodent models. *Nature Medicine, 2*(10), 1129-1132.

French, M.T., Dunlap, L.J., Zarkin, G.A., McGeary, K.A., and McLellan, A.T. (1997). A structured instrument for estimating the economic cost of drug abuse treatment. The Drug Abuse Treatment Cost Analysis Program (DATCAP). *Journal of Substance Abuse Treatment, 14*(5), 445-455.

Gossop, M., Marsden, J., and Stewart, D. (2002). Dual dependence: Assessment of dependence upon alcohol and illicit drugs, and the relationship of alcohol dependence among drug misusers to patterns of drinking, illicit drug use and health problems. *Addiction, 97*(2), 169-178.

Hart, B.W., and Faiman, M.D. (1992). In vitro and in vivo inhibition of rat liver aldehyde dehydrogenase by *S*-methyl *N*, *N*-diethylthiolcarbamate sulfoxide: A new metabolite of disulfiram. *Biochemical Pharmacology, 43*(3), 403-406.

Hughes, J.R. (1995). Clinical implications of the association between smoking and alcoholism. In J.B. Fertig and J.P. Allen (Eds.), *Alcohol and tobacco: From basic science to clinical practice* (National Institute on Alcohol Abuse and Alcoholism Research Monograph No 30. NIH Publ. No. 95-3931, pp. 171-186). Washington, DC: U.S. Government Printing Office.

Janeway, C.A., Travers, P., Capra, J.D., and Walport, M.J. (1999). *Immunobiology. The immune system in health and disease*, 4th ed. New York: Garland.

Johnson, B.A., Roache, J.D., Javors, M.A., DiClemente, C.C., Cloninger, C.R., Prihoda, T.J., Bordnick, P.S., Ait-Daoud, N., and Hensler, J. (2000). Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. *Journal of the American Medical Association, 284*(8), 963-971.

Johnson, D.A.W. (1984). Observations on the use of long-acting depot neuroleptic injections in the maintenance therapy of schizophrenia. *Journal of Clinical Psychiatry, 45*(5 Pt 2), 13-21.

Kane, J.M. (1984). The use of depot neuroleptics: Clinical experience in the United States. *Journal of Clinical Psychiatry, 45*(5 Pt 2), 5-12.

Kintz, P. (2001). Deaths involving buprenorphine: A compendium of French cases. *Forensic Science International, 121*(1-2), 65-69.

Kirchmayer, U., Davoli, M., and Verster, A. (2004). Naltrexone maintenance treatment for opioid dependence. In *The Cochrane Library* (Issue 1). Chichester, England: John Wiley & Sons.

Kleber, H.D., and Kosten, T.R. (1984). Naltrexone induction: Psychological and pharmacological strategies. *Journal of Clinical Psychiatry, 45*(9 Pt 2), 29-38.

Kleber, H.D., Kosten, T.R., Gaspari, J., and Topazian, M. (1985). Non-tolerance to the opioid antagonism of naltrexone. *Biological Psychiatry, 20*(1), 66-72.

Klein, M. (1998). Research issues related to development of medications for treatment of cocaine addiction. *Annals of the New York Academy of Sciences, 844*, 75-91.

Kosten, T.R. (1989). Pharmacotherapeutic interventions for cocaine abuse: Matching patients to treatments. *Journal of Nervous and Mental Disease, 177*(7), 379-389.

Kosten, T.R. (2002). Pathophysiology and treatment of cocaine dependence. In K.L. Davis, D. Charney, J.T. Coyle, and C. Nemeroff (Eds.), *Neuropsychopharmacology: The fifth generation of progress* (pp. 1461-1473). Baltimore, MD: Williams and Wilkins.

Kosten, T.R., and Biegel, D. (2002). Therapeutic vaccines for substance dependence. *Expert Review of Vaccines, 1*(3), 363-371.

Kosten, T.R., and Kleber, H.D. (1984). Strategies to improve compliance with narcotic antagonists. *America Journal of Drug and Alcohol Abuse, 10*(2), 249-266.

Kosten, T.R., and O'Connor, P.G. (2003). Current concepts—management of drug withdrawal. *New England Journal of Medicine, 348*(18), 1786-1795.

Kosten, T.R., Kreek, M.J., Ragunath, J., and Kleber, H.D. (1986). Cortisol levels during chronic naltrexone maintenance treatment in ex-opiate addicts. *Biological Psychiatry, 21*(2), 217-220.

Kosten, T.R., Rosen, M., Bond, J., Settles, M., Roberts, J.S., Shields, J., Jack, L., and Fox, B. (2002). Human therapeutic cocaine vaccine: Safety and immunogenicity. *Vaccine, 20*(7-8), 1196-1204.

Kranzler, H.R. (1995). *The pharmacology of alcohol abuse*. New York: Springer-Verlag.

Kranzler, H.R. (2000). Pharmacotherapy of alcoholism: Gaps in knowledge and opportunities for research. *Alcohol and Alcoholism, 35*(6), 537-547.

Kranzler, H.R., and Van Kirk, J. (2001). Efficacy of naltrexone and acamprosate for alcoholism treatment: A meta-analysis. *Alcoholism, Clinical and Experimental Research, 25*(9), 1335-1341.

Kranzler, H.R., Modesto-Lowe, V., and Nuwayser, E.S. (1998). Sustained-release naltrexone for alcoholism treatment: A preliminary study. *Alcoholism, Clinical and Experimental Research, 22*(5), 1074-1079.

Kranzler, H.R., Armeli, S., Tennen, H., Blomqvist, O., Oncken, C., Petry, N., and Feinn, R. (2003). Targeted naltrexone for early problem drinkers. *Journal of Clinical Psychopharmacology, 23*(3), 294-304.

Lifshitz, M., Gavrilov, V., and Gorodischer, R. (2001). Off-label and unlicensed use of antidotes in paediatric patients. *European Journal of Clinical Pharmacology, 56*(11), 839-841.

McIntyre, J., Conroy, S., Avery, A., Corns, H., and Choonara, I. (2000). Unlicensed and off label prescribing of drugs in general practice. *Archives of Disease in Childhood, 83*(6), 498-501.

Miro, O., Nogue, S., Espinosa, G., To-Figueras, J., and Sanchez, M. (2002). Trends in illicit drug emergencies: The emerging role of gamma-hydroxybutyrate. *Journal of Toxicology—Clinical Toxicology, 40*(2), 129-135.

Morgan, C., and Kosten, T.R. (1990). Potential toxicity of high dose naltrexone in patients with appetitive disorders. In L. Ried (Ed.), *Opioids, bulimia, and alcohol abuse and alcoholism* (pp. 261-274). New York: Springer-Verlag.

Nasser, S.M., and Ewan, P.W. (2001). Lesson of the week: Depot corticosteroid treatment for hay fever causing avascular necrosis of both hips. *British Medical Journal (Clinical Research Edition), 322*(7302), 1589-1591.

National Institute on Drug Abuse (1998). *National survey results on drug use from Monitoring the Future survey*. Rockville, MD: National Institute on Drug Abuse.

O'Malley, S.S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E., and Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence: A controlled study. *Archives of General Psychiatry, 49*(11), 894-898.

Oncken, C.A., and Kranzler, H.R. (2003). Pharmacotherapies to enhance smoking cessation during pregnancy. *Drug and Alcohol Review, 22*(2), 191-202.

Oncken, C.A., Pbert, L., Ockene, J.K., Zapka, J., and Stoddard, A. (2000). Nicotine replacement prescription practices of obstetric and pediatric clinicians. *Obstetetrics and Gynecology, 96*(2), 261-265.

Owens, S.M. (1997). Antibodies as pharmacokinetic and metabolic modifiers of neurotoxicity. *NIDA Research Monograph, 173*, 259-272.

Owens, S.M., and Mayershohn, M. (1986). Phencyclidine-specific Fab fragments alter phencyclidine disposition in dogs. *Drug Metabolism and Disposition, 14*(1), 52-58.

Petrakis, I.L., Carroll, K.M., Nich, C., Gordon, L.T., McCance-Katz, E.F., Frankforter, T., and Rounsaville, B.J. (2000). Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction, 95*(2), 219-228.

Petry, N.M., and Bickel, W.K. (1998). Polydrug abuse in heroin addicts: A behavioral economic analysis. *Addiction, 93*(3), 321-335.

Pettinati, H.M., Volpicelli, J.R., Kranzler, H.R., Luck, G., Rukstalis, M.R., and Cnaan, A. (2000). Sertraline treatment for alcohol dependence: Interactive effects of medication and alcoholic subtype. *Alcoholism, Clinical and Experimental Research, 24*(7), 1041-1049.

Proksch, J.W., Gentry, W.B., and Owens, S.M. (2000). Anti-phencyclidine monoclonal antibodies provide long-term reductions in brain phencyclidine concentrations during chronic phencyclidine administration in rats. *Journal of Pharmacology and Experimental Therapeutics, 292*(3), 831-837.

Reh, M. (1998). Changes at FDA may speed drug approval process and increase off-label use. *Journal of the National Cancer Institute, 90*(11), 805-807.

Rosenheck, R., and Kosten, T. (2001). Buprenorphine for opiate addiction: Potential economic impact. *Drug and Alcohol Dependence, 63*(3), 253-262.

Sims, T.H., and Fiore, M.C. (2002). Pharmacotherapy for treating tobacco dependence: What is the ideal duration of therapy? *CNS Drugs, 16*(10), 653-662.

Sindelar, J.L., and Fiellin, D.A. (2001). Innovations in treatment for drug abuse: Solutions to a public health problem. *Annual Review of Public Health, 22*, 249-272.

Singh, P.K., and Richell-Herren, K. (2000). Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Flumazenil and suspected benzodiazepine overdose. *Journal of Accident and Emergency Medicine, 17*(3), 214.

Sparenborg, S., Vocci, F., and Zukin, S. (1997). Peripherial cocaine-blocking agents: New medications for cocaine dependence. *Drug and Alcohol Dependence, 48*(3), 149-151.

Srisurapanont, M., and Jarusuraisin, N. (2004). Opioid antagonists for alcohol dependence. In *The Cochrane Library* (Issue 1). Chichester, England: John Wiley & Sons.

Streeton, C., and Whelan, G. (2001). Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: A meta-analysis of randomized controlled trials. *Alcohol and Alcoholism, 36*(6), 544-552.

Sullivan, M.A., and Covey, L.S. (2002). Nicotine dependence: The role for antidepressants and anxiolytics. *Current Opinion in Investigational Drugs, 3*(2), 262-271.

Sutherland, G. (2002). Current approaches to the management of smoking cessation. *Drugs, 62*(Suppl 2), 53-61.

Swanson, J.M., and Volkow, N.D. (2002). Pharmacokinetic and pharmacodynamic properties of stimulants: Implications for the design of new treatments for ADHD. *Behavioural Brain Research, 130*(1-2), 73-78.

Valentine, J.L., Mayersohn, M., Wessinger, W.D., Arnold, L.W., and Owens, S.M. (1996). Antiphencyclidine monoclonal Fab fragments reverse phencyclidine-induced behavioral effects and ataxia in rats. *Journal of Pharmacology and Experimental Therapeutics, 278*(2), 709-716.

Volpicelli, J., O'Brien, C., Alterman, A., and Hayashida, M. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry, 49*(11), 867-880.

Woolacott, N.F., Jones, L., Forbes, C.A., Mather, L.C., Sowden, A.J., Song, F.J., Raftery, J.P., Aveyard, P.N., Hyde, C.J., and Barton, P.M. (2002). The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: A systematic review and economic evaluation. *Health Technology Assessment, 6*(16), 1-245.

Wright, C., and Moore, R.D. (1990). Disulfiram treatment of alcoholism. *American Journal of Medicine, 88*(6), 647-655.

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Putting Addiction Treatment Medications to Use: Lessons Learned

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INTRODUCTION

The medications development program of the National Institute on Drug Abuse (NIDA) was formed in 1989 following congressional legislation with appropriations specifically targeted for that purpose. At the time of the legislation the Food and Drug Administration (FDA) had no formal guidelines for determining whether an addiction treatment medication was safe and effective, even though several had been widely accepted and used for many years. Among these were benzodiazepines for alcohol withdrawal, disulfiram for the prevention of relapse to alcohol dependence, phenobarbital for detoxification from sedative dependence, clonidine and methadone for detoxification from opioid dependence, methadone for opioid maintenance; naltrexone for prevention of relapse to opioid dependence, and nicotine replacement therapy for nicotine dependence.

The role of the pharmaceutical industry was seen as important in advancing the medications development program. Thus one of the first tasks of the new NIDA program was to develop guidelines so that companies would know the criteria used by the FDA in order for a medication to gain approval. A task force was established that worked in conjunction with the FDA, NIDA, industry representatives, and a wide range of consultants to develop guidelines. A series of meetings were held over a period of 2 years, and guidelines were written and approved by the FDA in 1996.

Knowing that the guideline development and approval process could take several years, and with the above-mentioned precedents in mind,

NIDA chose a director and staff for the medications program and immediately began work. The highest priorities were to complete the testing of LAAM (levo-alpha acetyl methadol) for opioid maintenance and submit the data for FDA approval, find a medication that was useful in treating cocaine dependence, and continue studies of buprenorphine for opioid detoxification and maintenance. The importance of this effort was high due to the limited number of medications available to treat addiction, the size of the target populations, the limitations of currently available therapies, and the emergence of HIV disease along with data showing that addiction treatment reduced the chances for HIV infection (Avins et al., 1997; Metzger, Navaline, and Woody, 1998; Shoptaw et al., 1997; Woody et al., 2003).

Implicit in these efforts was the assumption that *both the short- and long-term* outcomes of addicted individuals could be improved with medication. This assumption was consistent with data showing that detoxification alone usually did not alter the long-term course of addiction, and with prior experience and data showing that some medications were safe and effective for specific indications.

Although the medications development program was anchored in the broader tradition of clinical drug testing and the need to meet FDA standards, many clinicians thought that treatment outcome was often maximized when medication was used in combination with psychosocial interventions such as counseling or psychotherapy (Resnick et al., 1981; Khantzian, 1985). The early methadone maintenance studies by Dole and Nyswander (1965) emphasized this point, as did the first FDA methadone regulations, and later studies confirmed it (McLellan et al., 1993). It was also clear that some addicted persons were able to achieve remission with psychosocial treatment alone (DeLeon, 1984; Hubbard et al., 1997) and that others remitted spontaneously or by attending self-help groups (Bailey and Leach, 1965). But despite their demonstrated benefits, it was clear that many addicted individuals failed to achieve optimal results with the current medications and drug-free treatments. The new program was simply an attempt to expand the available options by additional testing of medications that had shown promise, getting them approved by FDA, and finding new medications for addictions such as cocaine and other stimulant dependencies for which none currently existed.

The medications program has tested more than 50 pharmacotherapies for cocaine dependence and obtained FDA approval for LAAM, conducted studies that further documented the safety and efficacy of methadone maintenance, guided studies that contributed to the recent FDA approval of sublingual buprenorphine/naloxone (Suboxone) and buprenorphine (Subutex), facilitated the development of depot naltrexone for preventing

relapse to opioid dependence, and studied lofexidine and dextromorphan for opioid detoxification.

Despite the demonstrated efficacy of methadone and LAAM in altering the long-term course of opioid dependence, these medications are used by less than 20 percent of the opioid-dependent population in the United States at any single point in time. This figure is calculated using the Office of National Drug Control Strategy (2002, p. 22) estimate of 898,000 heroin-dependent people in 2000, adding the fact that persons addicted to prescription opioids were not in the estimate and accepting the Center for Substance Abuse Treatment figure of 205,000 persons on methadone or LAAM in 2001 (R. Lubran, personal communication, May 2001). Naltrexone, initially developed to prevent relapse to opioid dependence and later found to be effective for preventing relapse to alcohol dependence, appears to be used by less than 5 percent of the target populations in the United States. Notable exceptions to these gaps between treatment need and actual use are medications to treat withdrawal—benzodiazepines for alcohol, clonidine for opioid, and phenobarbital or benzodiazepines for sedatives (Kosten and O'Connor, 2003).

There are many reasons for this lack of penetration of methadone, LAAM, and naltrexone into the target populations, but onerous regulation and lack of political support are among the foremost. An example of these problems is the absence of methadone or LAAM treatment programs in six states (M. Parrino, personal communication, 2003). This appendix discusses both general and specific factors that have inhibited the use of addiction treatment medications in the United States, specifically methadone, LAAM, and naltrexone. It will also speculate on the reasons that similar inhibitions have not occurred with detoxification medications and end with lessons learned from the experience with addiction treatment medications that might be useful in the effort to develop and apply vaccines to prevent or modify the course of substance use disorders.

GENERAL FACTORS

Unresolved Ambivalence About the Nature of Addiction

One of the greatest barriers to wider use of methadone, LAAM, and naltrexone has been unresolved ambivalence about whether addiction is a morality/self-control problem or a medical disorder. This ambivalence has a long history that has flip-flopped between these two positions in the United States and other countries (Lowinson et al., 1992; Fischer et al., 2002), and it has very important treatment implications. For example, if addiction is a medical disorder characterized by abnormal biological pro-

cesses, then use of medications and other biologically based therapies to treat it would seem appropriate. However, if addiction represents a failure of morality or self-control, then psychosocial, religious, or criminal interventions would seem more appropriate. Think of how foolish it would appear to try to develop a vaccine for marital infidelity or stock market manipulation!

It is clear that the prevailing view in the United States throughout most of the 20th century was that addiction is a morality/self-control problem (Lowinson et al., 1992). This emphasis is seen clearly in the large proportion of funds spent for law enforcement compared to treatment and by strict antidrug laws and liberal use of prison sentences as opposed to treatment for large numbers of drug offenders. It is also seen by the marked reductions in money spent on substance abuse treatment over the past 10 years. For example, in the private sector between 1988 and 1998 the value of health insurance in medium to large companies decreased by 12 percent, while there was a 75 percent decrease in funds spent for substance abuse treatment (Galanter et al., 2000). In the public sector between 1995 and 2000, the Department of Veterans Affairs withdrew 47.5 percent of the funds it had been spending on specialty substance abuse treatment while at the same time increasing funds for other medical services by 10 percent (Chen, Wagner, and Barnett, 2001).

The increased use of mandated treatment rather than incarceration for nonviolent drug offenders and the rapid expansion of drug courts (Shichor and Sechrest, 2001) can be interpreted as an attempt to find a middle ground between the morality/self-control and medical views. The benefits that may result from a combination of legal pressure and treatment are seen in a study of the Delaware prison system showing improved outcomes for individuals who received treatment while in prison, with even better outcomes if treatment continued following prison release (Martin et al., 1999; Inciardi, Martin, and Butzin, in press). Unfortunately, funds to support the increased numbers of individuals who are or could be mandated to receive treatment have not always been made available. In addition, few private insurance plans pay for maintenance treatment, and courts rarely refer opioid-dependent patients to methadone maintenance, which, paradoxically, is the single treatment with the greatest level of empirical support (National Institutes of Health Consensus Panel, 1998). These practices further reduce the chances of narrowing the gap between the theoretical and actual uses of this medication.

Interestingly, the dominance of the morality/self-control view does not appear to have affected the use of detoxification agents in most treatment settings. Physicians and the public at large readily accept the fact that alcohol and opioids can produce physiological dependence and that certain medications are safe, effective, and needed for detoxification. Most

insurance companies seem to agree because they usually pay for medically assisted detoxification, at least for a few days if done in outpatient settings. Prison settings are an exception since patients often report that detoxification services are not available during incarceration, a problem that was confirmed in a nationwide survey of jails it which it was found that only 20 percent provided detoxification (Peters, May, and Kearns, 1992), which is still probably true today.

If these funding patterns reflect underlying assumptions about the cause of and cure for addiction, it would appear that the general public, many political leaders, insurance companies, and many physicians do not accept the fact that some individuals need medication to prevent relapse and alter the long-term course of addiction. Put another way, the idea that addiction is for many a chronic and relapsing disorder with significant environmental and behavioral components, such as hypertension, diabetes, and asthma, that can be helped by medication (McLellan et al., 2000) does not seem to have been widely accepted outside the area of addiction research and treatment (Leshner, 1999).

Lack of Consumer Advocacy

Advocacy with the impact of groups such as ACT-UP or the National Association for the Mentally Ill has never existed for addiction treatment with one exception—addicted Vietnam War veterans. During the later stages of the war there were numerous reports of heroin addiction among troops, including stories that veterans were going into opioid withdrawal on flights home from Vietnam. These reports caused widespread concern resulting in a political consensus that Vietnam service was contributing to heroin dependence. There were two powerful and well-supported responses: (1) rules were developed mandating that military personnel could not leave Vietnam until they provided a drug-free urine sample and (2) special funding was allocated by Congress for the Department of Veterans Affairs to establish addiction treatment programs.

Funds for the new VA programs were protected by legislation that prevented the money from being spent on anything but specialty substance abuse treatment. The programs grew, as did the number of veterans treated for substance use disorders within this funding structure until the mid-1980s when the funds lost their special protection and were merged with general hospital budgets. At about this time the rate of program growth slowed and then began a sharp decline in 1995 in association with the funding cuts described above. Congressional hearings on whether to restore funding and services to the 1995 levels were held in 1999 (Report of Minority Staff Review of VA Programs for Veterans with Special Needs to Senator Rockefeller, July 27, 1999) but have not yet had their intended

result. Interestingly, the advocacy that started the VA programs was not generated by consumers but rather by popular and congressional concerns about heroin addiction being associated with military service in Vietnam.

One factor contributing to this absence of consumer advocacy is that many persons who have recovered or are doing well in treatment are very reluctant to speak out for fear of adverse social consequences. This is especially true for persons who have been addicted to heroin, cocaine, and other illegal drugs (Parrino, personal communication, 2002). In addition, many addicted persons have serious behavioral problems that generate negative emotional responses from neighbors, the general public, and sometimes even their own families, thus making it difficult to obtain support for anything other than an expansion of criminal justice responses to the problem.

Narrow Interpretation of the 12-Step Approach

The fact that benefits could result from collaboration between 12-step programs and the medical profession was mentioned in the writings of the founders of Alcoholics Anonymous (1955). But somehow that message became modified such that many 12-step programs developed a drug-free philosophy to such an extent that individuals being treated in residential programs or participating in 12-step meetings were pressured to stop all psychoactive medication even if they were taking it for major depression or other nonsubstance-related mental disorders (Woody, 2003). In many cases, the result was an institutionalized opposition to the use of medication except for detoxification.

Staffing Patterns

Much addiction treatment in this country developed outside the existing medical system. Addiction treatment was essentially neglected in medical education, and very few physicians became involved in it. The result was that for many years Alcoholics Anonymous was the only place to turn for help, and treatment became dominated by a nonmedical approach involving staff with little or no medical training. A current example of this problem was seen in an informal survey of staffing patterns in 150 addiction treatment programs that had been randomly selected from Substance Abuse and Mental Health Services Administration records. It was found that none except the methadone programs had a physician and that many of the methadone programs had only enough medical coverage to write prescriptions and satisfy minimal regulatory requirements (A.T. McLellan, 2003, personal report).

Weak Efficacy of Some Approved Medications

Naltrexone has been shown to be effective for preventing relapse to alcohol dependence in the majority of controlled studies where the naltrexone condition showed a 15 to 20 percent advantage over a placebo (Morris et al., 2001). Unfortunately, the largest study done to date showed no differences between the naltrexone and control groups, though patients in each group improved significantly (Krystal et al., 2001). A conclusion that can be drawn from an overview of these studies is that naltrexone has an effect on preventing relapse to alcohol dependence but that overall it is relatively weak. Were the effect to be strong, some positive effect of naltrexone over the control condition likely would have emerged in the VA study. This weak efficacy, combined with the resistance of many treatment staff to using medications for relapse prevention, and the fact that many patients with alcohol dependence respond to psychosocial treatment alone have contributed to the low acceptance of naltrexone. New evidence has shown that a subgroup of naltrexone patients with one or two copies of the Asp40 allele of the gene coding the mu opioid receptor may have a robust response to naltrexone as compared to subjects without this allele (Oslin et al., 2003). If this finding is replicated, the overall weak effect of naltrexone may not generalize to this subgroup.

The experience with nicotine replacement therapies and buproprion treatment for nicotine dependence shares a few commonalities with the naltrexone/alcohol studies and methadone maintenance. Although nicotine in the form of tobacco has been used since early history, its use did not become highly problematic for large populations until the introduction of the cigarette. Although movements existed in Europe in the 17th century to ban tobacco, it was used primarily as snuff and did not affect the wider society. However, with the introduction of machine-made cigarettes and sophisticated advertising campaigns, the general population was exposed to an extremely efficient nicotine delivery system and large numbers of people became dependent on nicotine in tobacco. Initially, the use of cigarettes was not considered a health problem, but some people did think it was a bad habit. It was not until the negative health consequences of tobacco use became significant and well known, especially lung cancer and cardiovascular disease, that physicians began to recommend that patients not smoke. It quickly became apparent that large numbers of smokers, despite good intentions, were unable to stop. Ways to assist smokers in achieving abstinence began to be explored. Medically, it was soon obvious that one of the factors in continued tobacco use was a nicotine-specific abstinence syndrome. Various forms of nicotine replacement were studied, and today there are currently four forms of nicotine replacement available in the United States (Hurt et al., 2003), two of which (nicotine gum and nicotine patches) are over-the-counter medications.

The over-the-counter mode of making medications available has implications that both favor and inhibit their appropriate use. On the one hand, the medications are available without seeing a physician and going to the trouble and expense of receiving and filling a prescription; however, the easy availability of OTC medications decreases the probability that patients will receive appropriate education on how to administer the medication and tobacco cessation counseling. For instance, will patients buying nicotine gum know that it should not be chewed the same way regular gum is chewed but rather in a specific way to optimize sublingual absorption of the nicotine? Do patients who use this medication receive counseling from their physicians other than brief advice? In addition, most health insurance plans will not pay or reimburse for OTC medications.

It is important that the treatment process be made as effective as possible because, short of inpatient hospitalization and treatment, even with nicotine patches there is only a 20 to 30 percent success rate for long-term abstinence (Hays et al., 2001). Given the potential drawbacks of the OTC approach, it is likely that the overall effectiveness of the patch or the gum is reduced because OTC use far outpaces prescription nicotine nasal spray or inhaler. Another barrier to effective utilization of nicotine replacement therapies is that all are marketed for short-term use, thus indicating that, like other addiction treatment situations, there is general acceptance of medication for detoxification but a resistance to using it for long-term relapse prevention. However, many patients use nicotine replacement as maintenance therapy but without formal instructions or approval, implying perhaps that they are misusing the medications and "exchanging one addiction for another," which is a frequent criticism of methadone and LAAM maintenance.

A nonnicotine approach to the treatment of nicotine dependence is the use of antidepressants, specifically bupropion. But the lack of strong evidence of therapeutic efficacy is probably the largest barrier to bupropion's acceptance as a treatment for nicotine dependence. While it has been shown in clinical trials to be more effective than a placebo in helping subjects achieve abstinence (Hurt et al., 1997), it has also been shown to have limited efficacy in producing sustained abstinence (Hall et al., 2002). It is available only by prescription, and the manufacturer decided it was necessary to come out with a new formulation and name for bupropion for the indication of smoking cessation. This change distinguishes it from the bupropion to be used to treat depression and can be interpreted as indicating a reluctance on the part of the manufacturer to associate a medication with known efficacy for an "acceptable" indication (depression) with a "tainted" disorder like addiction.

Poor Patient Acceptance of Some Medications

The best example of this problem is naltrexone used for the prevention of relapse to opioid dependence. Studies have shown that less than 5 percent of patients for whom it is suggested end up taking it for 30 days or more (Greenstein et al., 1981). This figure can be improved by contingency management (Carroll et al., 2001), and it is higher for persons who are under social or legal pressure to comply, such as a physician whose license is contingent on doing well in treatment or a person on probation or parole who will be returned to jail if he or she relapses to opioid dependence (Cornish et al., 1997). Poor compliance with treatment has been particularly frustrating to treatment providers because naltrexone is, in a pharmacological sense, an ideal medication for preventing relapse to opioid dependence due to its effective blockade of mu opioid receptors.

A second though less extreme example is clonidine for opioid detoxification. Though widely used, dropout rates have been two to three times higher than with methadone or other opioid agonists (Ling, 2003).

Perception That Addiction Treatment Does Not Work

The perception that addiction treatment does not work results from the observation that patients in treatment may substantially reduce their drug use but do not always stop; that relapse occurs even among patients who have been abstinent for weeks, months, or even years; and that investments in treatment are not worth the money (McFarland et al., 2003). It contributes to the gap between treatment need and availability—why spend money for something that does not work?—and appears to stem from the belief that sustained abstinence is not simply the optimal but the *only* clinically meaningful outcome. It seems closely related to the belief that addiction is a moral problem for which reductions in severity, even if accompanied by improvements in quality of life, reduced chances for HIV infection, increased employment, less crime, and lower death rates, do not count because the immoral behavior has merely improved but not completely stopped.

This perception is inconsistent with data discussed above that for many people addiction more closely resembles a chronic relapsing disorder like diabetes or hypertension rather than an acute disorder such as appendicitis or a broken leg. If seen as a medical disorder that for many is chronic and relapsing, reductions in severity are meaningful but not ideal outcomes. For example, lowering the blood sugar of a diabetic from 400 to 150 or the blood pressure of a hypertensive person from 200/120 to 140/90 are meaningful but not ideal outcomes, though widely considered as evidence that treatment is effective. An analogy with addiction treatment

would be reducing heroin use with methadone maintenance from three times a day, 7 days a week to once a day, 2 days a week, or reducing cocaine use from 10 days a month to 1 day a month (Crits-Christoph et al., 1997; Woody et al., 2003). In each case the severity of the addiction was substantially reduced and, though not eliminated, was accompanied by meaningful benefits.

An example of the same phenomenon in the case of alcohol treatment was seen in a study in which 150 subjects who met the criteria for alcohol dependence of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) were randomly assigned to topiramate or placebo. At the end of 12 weeks, subjects on topiramate had 2.88 fewer drinks per day, 3.1 fewer drinks per drinking day, 27.6 percent fewer heavy drinking days, 26.2 percent more days abstinent, lower levels of gamma glutamyl transferase, and less craving than subjects receiving placebo (Johnson et al., 2003). Here, as in other addiction treatment studies, a reduction in the severity of the target symptom (drinking) and evidence of improved liver function were considered successful outcomes even though full, sustained remission was not generally achieved.

A similar situation could arise in vaccine development. Efforts are being made to develop both preventive and therapeutic vaccines for HIV disease (Check, 2003). It is likely that therapeutic vaccines would be considered effective if they reduced the viral load of an HIV-infected person and prolonged his or her life. The very same result could occur with a therapeutic vaccine for addiction; however, it would be considered ineffective if the only acceptable outcome was permanent cessation of drug use.

Efforts to Reduce Health Costs

Using medication requires medical personnel, who are the most expensive treatment staff. Administrators trying to reduce health care costs have strong incentives to minimize the number (and salaries) of doctors and nurses working in addiction treatment programs. Such reductions in personnel were seen in the changes that occurred at the VA that were described earlier. These financial pressures may serve as disincentives for medically trained persons to become involved in addiction treatment and further diminish the chances for the staffing patterns that are necessary when medications are used.

Reluctance of Pharmaceutical Companies to Become Involved

Pharmaceutical companies have been the leaders in medication development, but costs are very high and few new molecular compounds reach

the market; thus a company must have a chance at making a profit simply to cover development costs. The poor reimbursement and financial pressures to hold down costs of addiction treatment are clearly disincentives for companies to engage in developing addiction treatment medications. High levels of comorbidity and adverse events that could be attributed to a new medication further reduce incentives for companies to become involved in this area.

These problems contributed to NIDA's involvement in the development of LAAM, which was a very slow process, partly due to NIDA's inexperience in drug development at the time and also partly due to bad luck relating to the failure of a key contractor to provide credible preclinical data on LAAM. It will be very important for NIDA to partner with the National Institute of Allergy and Infectious Diseases (NIAID), the AIDS Vaccine Coalition, or other entities that have experience in vaccine development so as to avoid these problems.

SUBSTANCE-SPECIFIC FACTORS

Incorrect Information About Treatment

This problem has most prominently focused on methadone maintenance and is reflected in statements made by political leaders. For example, in October 1998 three senators submitted a resolution, which stated that ". . . the Federal Government should adopt a zero-tolerance drug-free policy that has as its principal objective the elimination of drug abuse and addiction, including both methadone and heroin" (Congressional Record, Senate Resolution 295- S12186-S12187, 1998). This resolution was followed by introduction of the Addiction Free Treatment Act of 1999, which proposed to reduce the availability of maintenance treatment using methadone and LAAM (Addiction Free Treatment Act of 1999, 106th Congress S. 423). The resolution added: "Heroin addicts and methadone addicts are unable to function as self-sufficient, productive members of society" and concluded that "Congress should work . . . to develop an effective drug control policy that . . . is based on detoxification and the comprehensive treatment of the pathology of drug addiction."

Considering the source, these statements are difficult to understand and inconsistent with the large amount of data showing that efforts to treat the "comprehensive pathology of drug addiction" have often failed, which is the reason that methadone was developed, and that patients on methadone are often able to function and be "self-sufficient, productive members of society." In addition, the beliefs expressed in this proposed legislation are easily interpreted as disincentives to use medication to treat addiction since the only acceptable policy involved being drug-free.

Federal and State Regulations

The Institute of Medicine published a comprehensive report on the effect of regulations on access to treatment with methadone or LAAM. The report led to a shift in monitoring methadone programs from the regulatory approach of the FDA to accreditation involving the Joint Commission on Accreditation of Healthcare Organizations, the Commission on Accreditation of Rehabilitation Facilities, or state agencies. This change was only recently put into effect; thus its results are unclear.

The problems identified in the IOM report provided the basis for the Addiction Treatment Act of 2000, which allows agonist and other medications that are classified as Schedule III or below and approved for addiction treatment to be used under less restrictive circumstances than has been the case with methadone. Related to this legislation was the approval of buprenorphine/naloxone (Suboxone) for maintenance treatment of opioid dependence as a Schedule III medication. This congressional action is clearly intended to make addiction treatment medications more available and less stigmatized; however, its effects are unclear since the changes only went into effect in October 2002.

LESSONS LEARNED

The public and the medical profession accept the fact that medicines are needed to treat withdrawal, but fewer believe they are needed over the long term. This belief seems to result from the view that addiction is a moral rather than a medical problem. Lack of appreciation that addiction is a medical disorder and that many individuals need long-term treatment is likely to negatively impact the use of vaccines.

Research should continue on the biological aspects of substance dependence. The work of authors who successfully make public data showing that addiction has biological as well as behavioral components and that addiction more closely resembles a medical disorder than a moral problem should be extended (Leshner, 1997; McLellan et al., 2000). Data can help resolve the ambivalence about the nature of addiction.

The perception that meaningful treatment outcome is an all-or-nothing phenomenon is widely held but often untrue. Many treatments used in medicine would be considered failures if held to the same standard. The same problem could emerge with vaccines. Data showing that treatment can often produce meaningful benefits to individuals and society even though the ideal outcome—complete and sustained abstinence—does not occur should be presented and reviewed. Data are available to make this point from almost every addiction treatment study that has ever been done and concluded that treatment is effective.

The lack of medical staff in addiction treatment prevents more widespread use of medications. This problem is closely related to the issue of whether addiction is a problem of morality or a medical disorder. It is also related to the more general issues of parity in mental health and to attempts to hold down treatment costs that involve disproportionate cuts in funding for substance abuse treatment. Any effort that can achieve parity in mental health and addiction treatment and that can minimize the costs of effective vaccines will help, as would a political consensus that addiction is a treatable disorder.

Lack of positive effects or the presence of adverse effects will discourage staff acceptance and patient compliance. Painful vaccines, especially if they need to be administered frequently, are not likely to be widely used. These points should be strongly considered in vaccine development. Good efficacy and few side effects are especially important goals for medications or vaccines used to treat individuals with substance use disorders since their tolerance for adverse effects can be limited.

Lack of experience in medications development and bad luck contributed to the slow approval of LAAM. It will be very important for NIDA to partner with NIAID, the AIDS Vaccine Coalition, pharmaceutical companies, or other entities that have experience in vaccine development so as to avoid these problems.

REFERENCES

Alcoholics Anonymous. (1955). *The story of how many thousands of men and women have recovered from alcoholism, 2nd ed*. New York: AA World Services.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders*, 4th ed. Washington, DC: American Psychiatric Association.

Avins, A.L., Lindan, C.P., Woods, W.J., Hudes, E.S., Boscarino, J.A., Kay, J., Clark, W., and Hulley, S.B. (1997). Changes in HIV-related behaviors among heterosexual alcoholics following addiction treatment. *Drug and Alcohol Dependence, 44*(1), 47-55.

Bailey, M.B., and Leach, B. (1965). *Alcoholics Anonymous: Pathway to recovery: A study of 1058 members of the AA fellowship in New York City.* New York: National Council on Alcoholism.

Carroll, K.M., Ball, S.A., Nick, C., O'Connor, P.G., Egan, D.A., Frankforter, T.L., Triffleman, E.G., Shi, J., and Rounsaville, B.J. (2001). Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence—efficacy of contingency management and significant other involvement. *Archives of General Psychiatry, 58*(8), 755-761.

Check, E. (2003). AIDS researchers seek criteria for vaccines. *Nature, 423*(6936), 107.

Chen, S., Wagner, T.H., and Barnett, P.G. (2001). Expenditures for substance abuse treatment in the Department of Veterans Affairs: 1993-1999. *Health Affairs, 20*(4), 169-175.

Cornish, J.W., Metzger, D., Woody, G.E., Wilson, D., McLellan, A.T., Vandergrift, B., and O'Brien, C.P. (1997). Naltrexone pharmacotherapy for opioid dependent federal probationers. *Journal of Substance Abuse Treatment, 14*(6), 529-534.

Crits-Christoph, P., Siqueland, L., Blaine, J.D., Frank, A., Luborsky, L., Onken, L.S., Muenz, L., Thase, M.E., Weiss, R.D., Gastfriend, D.R., Woody, G.E., Barber, J.P., Butler, S.F., Daley, D., Bishop, S., Najavits, L.M., Lis, J., Mercer, D., Griffin, M.L., Moras, K., Beck, A. (1997). The National Institute on Drug Abuse Collaborative Cocaine Treatment Study. *Archives of General Psychiatry, 54*(8), 721-726.

DeLeon, G. (1984). *The therapeutic community: Study of effectiveness.* Rockville, MD: National Institute on Drug Abuse.

Dole, V.P., and Nyswander, M.E. (1965). A medical treatment for diacetylmorphine (heroin) addiction. *Journal of the American Medical Association, 193*, 646-650.

Fischer, B., Rehm, J., Uchtenhagen, A., and Kirst, M. (2002). Compulsory treatment—what do we know and where should we go? *European Addiction Research, 8*(2), 52-53.

Galanter, M., Keller, D.S., Dermatis, H., and Egelko, S. (2000). The impact of managed care on substance abuse treatment: A report of the American Society of Addiction Medicine. *Journal of Addictive Diseases, 19*(3), 13-34.

Greenstein, R.A., O'Brien, C.P., Woody, G., Long, M., Coyle, G., Grabowski, J., and Vittor, A. (1981). Naltrexone: A short-term treatment alternative for opiate dependence. *American Journal of Drug and Alcohol Abuse, 8*(3), 291-300.

Hall, S.M., Humfleet, G.L., Rues, V.I., Munoz, R.F., Hartz, D.T., and Maude-Griffin, R. (2002). Psychological intervention and antidepressant treatment in smoking cessation. *Archives of General Psychiatry, 59*(10), 930-936.

Hays, J.T., Wolter, T.D., Eberman, K.M., Croghan, I.T., Offord, K.P, and Hurt, R.D. (2001). Residential (inpatient) treatment compared with outpatient treatment for nicotine dependence. *Mayo Clinic Proceedings, 76*(2), 124-133.

Hubbard, R.L., Craddock, S.G., Flynn, P.M., Anderson, J., and Etheridge, R.M. (1997). Overview of 1-year follow-up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). *Psychology of Addictive Behaviors, 11*(4), 261-278.

Hurt, R.D., Sachs, D.P.L., Glover, E.D., Offord, K.P., Johnston, J.A., Dale, L.C., Khayralla, M.A., Schroeder, D.R., Glover, P.N., Sullivan, R., Croughan, I.T., and Sullivan, P.M. (1997). A comparison of sustained-release bupropion and placebo for smoking cessation. *New England Journal of Medicine, 337*(17), 1195-1202.

Hurt, R.D., Ebbert, J.O., Hays, J.T., and Dale, L.C. (2003). Pharmacologic interventions for tobacco dependence. In A.W. Graham (Ed.), *Principles of addiction medicine, 3rd ed.* Chevy Chase, MD: American Society of Addiction Medicine.

Inciardi, J.A., Martin, S.S., and Butzin, C.A. (in press). Five-year outcomes of therapeutic community treatment of drug-involved offenders after release from prison. *Crime and Delinquency*.

Johnson, B.A., Ait-Daoud, N., Bowden, C.L., DiClemente, C.C., Roache, J.D., Lawson, K., Javors, M.A., and Ma, J.Z. (2003). Oral topiramate for treatment of alcohol dependence: A randomized controlled trial. *Lancet, 361*(9370), 1677-1685.

Khantzian, E.J. (1985). The self-medication hypothesis of addictive disorders: Focus on heroin and cocaine dependence. *American Journal of Psychiatry, 142*(11), 1259-1264.

Kosten, T.R., and O'Connor, P.G. (2003.) Management of drug and alcohol withdrawal. *New England Journal of Medicine, 348*(18), 1786-1795.

Krystal, J.H., Cramer, J.A., Krol, W.F., Kirk, G.F., and Rosenheck, R.A. (2001). Naltrexone in the treatment of alcohol dependence. *New England Journal of Medicine, 345*(24), 1734-1739.

Leshner, A.I. (1997). Addiction is a brain disease, and it matters. *Science, 278*(5335), 45-47.

Leshner, A.I. (1999). Science-based views of drug addiction and its treatment. *Journal of the American Medical Association, 282*(14), 1314-1316.

Lowinson, J.H., Payte, J.T., Joseph, H., Marion, I.J., and Dole, V.P. (1992). Methadone maintenance. In J.H. Lowinson, P. Ruiz, R.B. Millman, and J.G. Langrod (Eds.), *Substance abuse: A comprehensive textbook* (pp. 405-414). Philadelphia: Williams and Wilkins.

Martin, S.S., Butzin, C.A., Saum, C.A., and Inciardi, J.A. (1999). Three-year outcomes of therapeutic community treatment for drug-involved offenders in Delaware: From prison to work release to aftercare. *Prison Journal, 79*(3), 294-320.

McFarland, B.H., Lierman, W.K., Penner, N.R., McCamant, L.E., and Zani, B.G. (2003). Employee benefits managers' opinions about addiction treatment. *Journal of Addictive Diseases, 22*(2), 15-29.

McLellan, A.T., Arndt, I.O., Metzger, D.S., Woody, G.E., and O'Brien, C.P. (1993). The effects of psychosocial services in substance abuse treatment. *Journal of the American Medical Association, 269*(15), 1953-1959.

McLellan, A.T., O'Brien, C.P., Lewis, D., and Kleber, H.D. (2000). Drug addiction as a chronic medical illness: Implications for treatment, insurance and evaluation. *Journal of the American Medical Association, 284*(13), 1689-1695.

Metzger, D.S., Navaline, H., and Woody, G.E. (1998). Drug abuse treatment as AIDS prevention. *Public Health Reports, 113*(Suppl 1), 97-106.

Morris, P.L., Hopwood, M., Whelan G., Gardiner, J., and Drummond, E. (2001). Naltrexone for alcohol dependence: A randomized controlled trial. *Addiction, 96*(11), 1565-1573.

National Institutes of Health Consensus Conference. (1998). Effective medical treatment of opiate addiction. *Journal of the American Medical Association, 280*(22), 1936-1943.

Office of National Drug Control Strategy. (2002). *2002 Final report on the 1998 National Drug Control Strategy: Performance measures of effectiveness*. Available: http://www.whitehousedrugpolicy.gov/publications/policy/02pme/pmepdf/pme.pdf [January 2, 2004].

Oslin, D.W., Berrettini, W., Kranzler, H.R., Penninati, H., Gelernter, J., Volpicelli, J.R., and O'Brien, C.P. (2003). A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology, 28*(8), 1546-1552.

Peters, R.H., May, R.I., and Kearns, W.D. (1992). Drug treatment in jails: Results of a nationwide survey. *Journal of Criminal Justice, 20*, 283-295.

Resnick, R.B., Washton, A.M., and Stone-Washton, N. (1981). Psychotherapy and naltrexone in opioid dependence. In L.S. Harris (Ed.), *Problems of drug dependence* (pp. 109-115). Rockville, MD: U.S. Department of Health and Human Services.

Shichor, D., and Sechrest, D. (2001). Introduction: Special issue on drug courts. *Journal of Drug Issues, 31*, 1-6.

Shoptaw, S., Frosch, D.L., Rawson, R.A., and Ling, W. (1997). Cocaine abuse counseling as HIV prevention. *AIDS Education and Prevention, 9*(6), 511-520.

Woody, G.E. (2003). Treating dually diagnosed patients. *Psychiatric Times, 20*(1), 29-30.

Woody, G.E., Gallop, R., Luborsky, L., Blaine, J., Frank, A., Gastfriend, D., Crits-Christoph, P., and the Cocaine Psychotherapy Study Group. (2003). HIV risk reduction in the NIDA cocaine psychotherapy study. *Journal of Acquired Immune Deficiency Syndromes, 33*(1), 82-87.

D

Adoption of Drug Abuse Treatment Technology in Specialty and Primary Care Settings

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OVERVIEW

Investments in neuroscience and the development of pharmacotherapies for drug abuse treatment seem to be near fruition. Changes in federal legislation coupled with the approval of Subutex (buprenorphine hydrochloride) and Suboxone (buprenorphine hydrochloride in combination with naltrexone) for the treatment of opioid dependence offer an opportunity to engage primary care physicians directly in the treatment of dependence on heroin and other drugs. Advances in immunotherapy and depot medications are also promising. New pharmacotherapies, however, will only be effective to the extent they are accepted by clinicians and their use is facilitated through adequate financing and organizational and community support.

Newly approved pharmacotherapies are usually rapidly and widely adopted in general medicine. For substance abuse treatment, however, diffusion of medications has been a slower and less predictable process. Naltrexone for alcoholism treatment, for example, reached only a fraction of its expected market. Differences in the structure of the substance abuse treatment environment (less often built around a physician delivery model and commonly in specialty treatment settings) and differences in financing of substance abuse treatment have contributed to slower adoption of naltrexone and other such therapies. With the development of additional new pharmacological-based treatments for addictions, more individuals may be drawn to receive treatment in primary care settings. These patients often have different needs than most patients typically found in primary

care and family medicine settings. Difficulties in developing linkages between primary care and the ancillary services used in addiction treatments may pose barriers to the adoption of new treatment technologies. Specialty treatment settings may also be limited in their ability or interest in adopting new pharmacotherapies due to philosophical resistance and lack of training and/or resources.

This appendix applies a framework from health services research on technology diffusion to identify elements that may be important in understanding the adoption of treatment technologies in the substance abuse field. Literature on the adoption of substance abuse treatment technologies is reviewed, and particular challenges and opportunities are outlined—including the organization, financing, and delivery of specialty addiction treatments that may inhibit rapid adoption. Implications for primary care and other treatment settings are discussed relative to the availability of new pharmacology-based interventions. Finally, strategies for making these medications available and encouraging their appropriate use are examined.

ADOPTION OF INNOVATIONS IN MEDICAL CARE

Classical diffusion theory suggests the nature of the technology, the organizational structures and associated financial influences in which the technology is disseminated, characteristics of the providers and patients, and the communication methods (by whom and through what channels) affect the rate and direction of the adoption pattern (Banta and Luce, 1993; Office of Technology Assessment, 1994; Rogers, 1995). Figure D-1 shows a conceptual model of the factors contributing to technology adoption, described below.

Technology Attributes

Adoption depends in part on the attributes of the innovation and how practitioners perceive them (Meyer and Goes, 1988; Rogers, 1995). Characteristics affecting an innovation's adoption include the relative advantages over existing technologies, whether in economic, clinical, or social terms; compatibility with values, experiences, and needs of potential users; complexity or simplicity of use; "trialability," or the potential to try on a limited basis without significant risk; and the extent to which results are observable (Rogers, 1995). After a new technology is introduced, uncertainty often remains regarding its use. Emerging technologies are commonly used in ways other than initially intended (Gelijns and Rosenberg, 1994). Modification of the technology occurs after initial adoption (Greer, 1988),

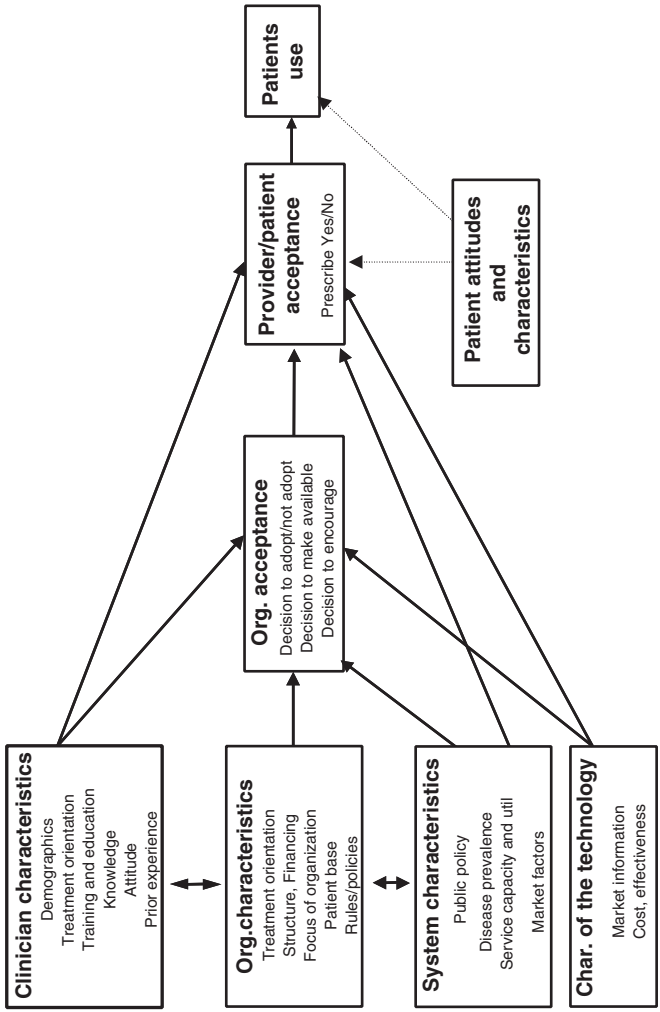

FIGURE D-1 Conceptual model for adoption of new substance abuse pharmaceutical technologies.
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and uneven use occurs at a high rate early in the diffusion process (Wennberg, 1988).

While similar diffusion patterns exist for medications, devices, and surgical procedures, medications may have a lower adoption "threshold"—it is easier to write a prescription than learn a new procedure or approach (Fendrick and Schwartz, 1994). While medications and devices must first gain approval from the Food and Drug Administration for use in general clinical practice, different combinations and uses of pharmacotherapies in practice are not well evaluated (Sisk and Glied, 1994), and uses by physicians of medications on the market for indications or in combinations other than that for which they received FDA approval (so-called off-label prescribing) is thought to be common.

Although physicians are able to prescribe medications upon FDA approval, a number of factors may inhibit adoption. Innovations that depart from existing practices and are counter to prevailing attitudes are much less likely to be adopted (Office of Technology Assessment, 1994). Physicians may reject new medication therapy because of what it might do to the physician's case mix, because other practice costs will rise, or because of inadequate time for patient visits. They may also reject a new therapy if there is inadequate evidence of cost-effectiveness (particularly in comparison to existing approaches).

In summary, immunotherapy and depot medications can present promising new strategies for treating drug dependence and abuse if they have potential relative advantage over existing treatments, compatibility with current drug treatment practices, and both providers and patients find them easy to use. But it is likely that ways in which clinicians and treatment settings perceive the new interventions will affect adoption.

Provider Attributes

Members of the social system and professional networks are an important element in the diffusion process (Rogers, 1995). Typically in general health care, exponential growth in the use of new treatments often ensues in an "epidemic" pattern throughout the larger provider community, as information disseminates regarding the new technology through professional networks, media, and advertising and following positive reports from initial users and demand from patients. However, at the same time, if incentives, education, and resources are not in place to adopt new treatment strategies, physicians can be somewhat resistant (Eisenberg, 1993).

Research has examined the characteristics of individuals associated with innovation as independent practitioners (Kimberly and Evanisko, 1981) and as leaders of organizational policy (D'Aunno, Vaughn, and McElroy, 1999; Friedmann, Alexander, and D'Aunno, 1999b). Variables

including younger age (Alexander et al., 1997; Counte and Kimberly, 1974), more education (Rogers, 1995), more urban practice, higher certification, specialization (Alexander et al., 1997; Counte and Kimberly, 1974; Rogers, 1995), academic affiliation, and group rather than individual practice were associated with earlier adoption of new technologies (Coleman, Katz, and Menzel, 1966; Fendrick and Schwartz, 1994; Freiman, 1985). Decisions to adopt have also been linked to factors such as authority roles among peers and the relationships of providers within an organization (Posner, Gild, and Winans, 1995).

Studies of physicians' prescribing behavior suggest that the decision to write a prescription is a complex process, influenced by organizational rules, training, treatment philosophy, experience, information, and opinion leaders. Physician characteristics (Dybwad et al., 1997), provider assessments of the need for a prescription, likelihood of patient compliance, and the likely outcome of treatment (Brown et al., 1997; Denig, Haaijer-Ruskamp, and Zijsling, 1988; Lambert et al., 1997; Turk and Okifuji, 1997) do not fully explain variations in prescribing patterns. Advertising, education, and patient demand also affect prescribing patterns (Hemminki, 1975).

Organizational Structures and Financing of Treatment

The organization, its internal structure, and its response to external influences, such as competition or reimbursement on rates of technology acquisition and use affect adoption (Escarce et al., 1995; Hodgkin and McGuire, 1994; Romeo, Wagner, and Lee, 1984; Teplensky et al., 1995). Factors that are positively associated with earlier and more thorough adoption of innovation include size (Moch and Morse, 1977), resources (D'Aunno et al., 1999; Nohria and Gulati, 1995), academic network, leader behavior (Becker, 1970; Chilingerian and Glavin, 1994), system openness, organizational slack, a more competitive marketplace, and favorable reimbursement for the innovation. Thus, having resources available to explore and adopt a new innovation and having leadership with interest in and commitment to innovation are important factors in technology adoption.

The treatment setting's environment—that is, "the specific collection of organizations providing the critical sources of inputs, and markets for outputs, required for an organization's survival" (Scott, 1993, p. 292)—includes its competitors, state and federal regulators, parent organizations, managed care organizations, pharmaceutical companies, and potential clients. Each group exerts different demands or poses particular threats or incentives to the focal treatment setting that may drive it to adopt and encourage or reject and discourage new pharmacotherapies for drug de-

pendence (see Strang and Soule, 1998). Thus, managed care organizations and insurers may promote adoption of new pharmacotherapies by including them in the formulary or by issuing treatment guidelines that advocate their use. States can encourage the use of particular medications by covering treatment under Medicaid benefits. Regional location may influence decisions to accept and encourage pharmacotherapy in addiction treatments. Methadone treatment units in the northeastern United States used more effective treatment practices than those in other regions (D'Aunno and Vaughn, 1992). This may be due to the high concentration of top-tier medical schools and academic health centers in the area and the resulting exposure to and competition to remain at the cutting edge of medical science. Other treatment organizations may influence the decision to adopt particular medications, particularly if competitors have done so (Abrahamson, 1991; DiMaggio and Powell, 1988; Tolbert and Zucker, 1983; Westphal, Gulati, and Shortell, 1997). Professional organizations (e.g., American Society of Addiction Medicine) may improve an organization's appraisal of immunotherapy and depot medications through official endorsements and dissemination of information about treatments. Pharmaceutical companies may also encourage adoption through marketing campaigns, particularly direct and repeated marketing to the focal organization (Van den Bulte and Lilien, 2001).

If a pharmacotherapy is perceived as a cost-effective treatment or a highly effective treatment, superior to other methods, organizations will experience substantial pressure to adopt it in order to enhance their performance and compete with other treatment organizations for individual and group clients (i.e., managed care contracts, state contracts). Cultural attitudes toward new pharmaceuticals in treatment will drive the pressures from the institutional environment. A shared view that pharmacotherapy represents the cutting edge of treatment for drug dependence may encourage physicians and organizations to adopt new pharmacotherapies in order to enhance their reputation or increase their market. Alternatively, if professional organizations and treatment organizations begin to accept these innovations, others may follow and come to view accepting particular new pharmacotherapies as a necessary move.

Channels of Communication

Channels of communication influence what information is transferred to potential users and its credibility. Professional information regarding a technological innovation is generally transferred in several ways, both formal (scientific literature, meetings, training) and informal (opinion leaders, colleagues, advertising, and press reports). However, while scientific evidence is an important factor, most adoption decisions depend

on the transfer of subjective information regarding the treatment from one member of a group who has already tried the innovation to another person in the group (Rogers, 1995). The change agent tends to be most effective when it is someone much like the potential adopter.

A major method of communicating information regarding new pharmaceuticals that has been particularly effective is marketing by drug manufacturers. In recent years the medications with the greatest growth in sales have been those that have been heavily marketed (National Institute of Health Care Management, 2002). However, marketing of prescription drugs can be a double-edged sword: While the message regarding the availability of new pharmacotherapies has been effectively communicated and can reach new potential audiences, information provided by manufacturers may be biased and must be complemented by additional objective sources. Further, there is some concern that extensive marketing efforts in the case of new medications in general medicine can lead to overprescribing and inappropriate use (Altman and Thomas, 2002). However, in the case of new drug treatment pharmacotherapies, marketing efforts, which are known to be a powerful driver of adoption of new medications, may be limited by how manufacturers perceive the profitability of new treatments.

The transtheoretical stages-of-change model (Prochaska and DiClemente, 1983) provides an additional framework for assessing behavioral changes and communication strategies. Adoption of innovations is viewed as a multistep process, integrating the practice setting and an ability to move through a continuum of five steps: precontemplation (no knowledge yet regarding the action), contemplation (awareness of the new behavior and motivation to adopt), action (development of a strategy to use the technique), implementation of the technique, and maintenance. Rather than examine the structural characteristics of a health care system, studies assess organizational and individual readiness to accept new treatment strategies (Backer, 1995). Investigators focus on the dynamics of the change process in order to understand differences between early- and late-adopter individuals and organizations and to improve technology transfer. Studies of cancer screenings and treatments (Johnson, Warnecke, and Aitken, 1996; Kaluzny et al., 1990) and cessation of addictive behaviors (Prochaska et al., 1994) illustrate the model's broad base of support and the value of matching interventions with readiness to change.

Summary

Rogers's (1995) framework for the diffusion of technology and the transtheoretical model of change provide structures for disaggregating the process of diffusion and analyzing critical components. The adoption

of pharmacotherapies for the treatment of drug abuse disorders, particularly in primary care, may be particularly sensitive to the characteristics of the medication (compatibility, complexity, and observability), the use of people in recovery as change agents, analyses of the persuasion process, and the nature of the social and organizational systems found in drug treatment programs. While the historical pattern in the United States is that of relatively rapid adoption of new pharmacotherapies, there are reasons to believe that the adoption of medications to treat drug and alcohol dependence will be more reserved. The use of medications as complementary interventions with behavioral therapies represents a vast change in the nature of treatment of drug abuse challenging current practitioner and provider structures. Multiple professional and social obstacles may offset the easy "trialability" of pharmacotherapy. Furthermore, to the extent that substance abuse treatment medications are used to enhance the efficacy of existing therapies, they may significantly contribute to increased costs of addiction treatment. The literature on adoption of technology in alcohol and drug abuse treatment may be informative.

ADOPTION OF TECHNOLOGIES IN THE TREATMENT OF ALCOHOL AND DRUG ABUSE

The peer-reviewed literature on the adoption of new technologies in alcohol and drug abuse treatment settings is surprisingly limited; systematic empirical investigations are uncommon. A review of the literature finds one randomized trial of dissemination methods, a few analyses of the adoption of naltrexone for the treatment of alcohol dependence, and a handful of essays reflecting on barriers to adoption and strategies to address the barriers.

Randomized Trial

A randomized trial tested dissemination strategies to promote an evidence-based practice to improve employment among patients in drug treatment (Job Seekers Workshop; Sorensen et al., 1988). Drug treatment programs (n = 172) were randomized to four levels of information about the employment training intervention: (1) training materials only (i.e., a 20-page summary of the workshop and effectiveness data plus a manual on conducting the workshop), (2) the training materials plus one day of on-site technical assistance, (3) the training materials plus an expenses-paid 2-day training, and (4) a nonintervention comparison where training materials were provided after the follow-up period. A questionnaire mailed three months after the interventions assessed the extent to which the training materials had been used and the number of workshops con-

ducted. Adoption was higher among programs that received a technical assistance site visit (28 percent) or participated in the 2-day training (19 percent) than at the sites that received only printed materials (4 percent) and among programs in the nonintervention group (0 percent). Hands-on, in-person demonstrations appear to be an important element in the adoption of new drug abuse treatment interventions. Despite the strength of the finding, dissemination efforts continue to emphasize distribution of brochures and manuals.

The Sorensen et al. study remains the only randomized trial that tested interventions to promote the adoption of an empirically supported drug abuse treatment technology. Subsequent investigations examined differences between practitioners who adopted or did not adopt new technologies and provide useful insights into variables associated with adoption. But in the absence of random assignment, multiple factors may contribute to the observed differences in adoptions.

Adoption of Naltrexone

Using naltrexone for the treatment of alcohol dependence remains an intriguing example of limited adoption of a medication for addiction treatment. A mail survey conducted in Massachusetts, Tennessee, and Washington state among physicians with a substance abuse specialization (135 responses, 63 percent response rate) and certified addiction counselors (1,116 responses, 65 percent response rate) found limited use of naltrexone (Thomas, 2000; Thomas et al., 2003). Most (80 percent) of the physicians reported current or prior use of naltrexone, but only 15 percent prescribed it often (11 percent) or for almost all patients (4 percent). A majority (54 percent) of counselors, in contrast, had never suggested use of naltrexone to patients, and few recommended it often (4 percent) or for almost all of their patients (1 percent). Logistic regression models suggested that adoption was more likely among physicians involved in research (odds ratio = 19.7) and physicians located in organizations that promoted the use of naltrexone (odds ration = 11.6). Physicians in recovery (odds ratio = 0.2) and physicians with multiple degrees (odds ratio = 0.1) were less likely to prescribe naltrexone. Organizational support to use naltrexone was the strongest influence on counselors recommending it to patients (odds ratio = 7.9). Counselors who reported receiving marketing information on naltrexone were also more likely to recommend its use (odds ratio = 3.2).

Patient access to insurance that covered naltrexone also affected counselor behavior. Counselors with a higher proportion of Medicaid patients were more likely to prescribe naltrexone, and those with more patients funded through block grant and self-pay were less likely. (Medicaid in all

three states covered naltrexone prescriptions, while block grant funding did not pay for it.) Washington state actively encouraged counselors to support the use of naltrexone, and counselors in Washington (compared to Massachusetts and Tennessee) were more likely (odds ratio = 1.5) to recommend that their patients use naltrexone. Recovery status did not have a significant influence on counselor use of naltrexone. Overall, these results suggest that organizational support, financing mechanisms, and state policies may influence the adoption of medications to treat alcohol and drug abuse.

Roman and Johnson (2002) examined organizational influences on the adoption of naltrexone. In a sample of 400 alcoholism treatment centers, 44 percent reported current use of naltrexone. Levels of use among patients, however, were low among both alcohol- (13 percent of the caseload) and opiate-dependent (11 percent of the caseload) patients. Logistic regression suggested that any naltrexone use was greatest in centers where counselors were more likely to have master's degrees (odds ratio = 1.7) and with more patients in commercial health maintenance organization and preferred provider organization health plans (odds ratio = 1.02). Centers that were older and those with higher caseloads of patients with a history of relapse also were more likely to use naltrexone. Importantly, structural characteristics of the organization (e.g., hospital setting, larger corporation, physician availability) were not significant influences when tested in multivariate models. The investigators suggest that addiction treatment programs have not encountered rapid change in technology, so older, more experienced programs and administrators are more willing to assume the risk of adoption. They also noted that levels of education among clinical staff are a key factor in the adoption of naltrexone but that the overall magnitude of use is still minimal (Roman and Johnson, 2002).

In a Researcher in Residence Program piloted in New York state, nationally recognized investigators provided hands-on technical assistance to facilitate adoption of research-based technologies for alcoholism treatment (Hilton, 2001). Investigators provided one to three days of on-site assistance and at three sites either a reconnaissance visit or a booster session. Participating programs requested assistance with the use of naltrexone (two sites), clinical assessment (two sites), motivational interviewing (one site), and services for patients with comorbidities (one site). Interviews with program directors and clinical staff were conducted three to six months after visits to assess impacts and adoption. Case studies were prepared for each of the six sites, and commonalities were abstracted. Hilton (2001) concluded that the site visits fostered adoption but that organizational change is difficult, takes time, and requires sustained leadership. The Researchers in Residence Program provided clinical staff with opportunities to have personal experience with the new technolo-

gies, and that experience seemed to promote adoption and use. Staff turnover, however, inhibited follow-through and adoption was observed in some but not all of the clinical settings. When adoption required more change in practice style, change was slower and less likely to be observed in a short follow-up. Surprisingly, limited reimbursement for prescription medications and negative staff attitudes toward the use of medications did not inhibit the use of naltrexone (Hilton, 2001). The results of the Researcher in Residence Program echo the findings from Sorensen et al. (1988)—hands-on technical assistance is often an essential aspect of adopting a new treatment technology.

Essays on Adoption

The most common, but still infrequent, papers on the adoption of technologies in addiction treatments are personal reflections on variables that contributed to or inhibited adoption of evidence-based drug abuse treatment technologies. Brown's thoughtful essays review linkages between research and practice, lament the lack of strategies to foster technology transfer, and encourage adoption of research findings (Brown, 1987, 1995, 1997, 1998, 2000; Brown and Flynn, 2002). Backer summarizes the technology transfer and dissemination literature and generalizes from classic work on technology diffusion to the adoption and use of drug abuse prevention and treatment technologies (Backer, 1991, 1995; Backer and David, 1995; Backer, Rogers, and Sopory, 1992). Naranjo and Bremner describe their efforts and frustrations implementing the use of a clinical tool (the Clinical Institute Withdrawal Assessment for Alcohol) to improve detoxification services in rural areas of Canada (Naranjo and Bremner, 1996). Similarly, Morgenstern (2000) reflects on his experiences promoting the use of cognitive behavioral therapies in traditional 12-step treatment settings.

Most recently, the focus has shifted toward viewing technology transfer as a process of organizational change. The Addiction Technology Transfer Centers promote an organizational change model to support the adoption of evidence-based practices in alcohol and drug abuse treatment centers. *The Change Book* offers a 10-step structure to foster organizational change and support the adoption and use of new drug abuse treatment technologies (Addiction Technology Transfer Centers, 2000). Finally, in a promising development, Simpson (2002) reviews the literature on technology transfer and drafts a model of the factors that contribute to organizational change and the adoption of new technologies for drug abuse treatment; early results are encouraging. It is critical, therefore, to have an overview of the financing and organization of specialty drug and alcohol treatment programs.

SPECIALTY DRUG AND ALCOHOL TREATMENT SERVICES

The specialty clinics that constitute much of the nation's alcohol and drug abuse treatment system trace their roots to the narcotics hospitals in Lexington, Kentucky, and Fort Worth, Texas (which opened in 1932 and 1938, respectively) and the lack of access to medical and psychiatric facilities in the 1960s and 1970s (Institute of Medicine, 1990a, 1990b, 1997, 1998). As a result, the financing and structure of the services developed idiosyncratically and are relatively autonomous from the nation's primary care system.

Financing of Services

The nation's expenditures for treating alcohol and drug disorders were estimated as $11.9 billion in 1997, or about 1 percent of total expenditures on health care ($1,057 billion) and 14 percent of expenditures on behavioral health ($82.2 billion; Coffey et al., 2001; Mark et al., 2000). The distribution of expenditures by provider type begins to illustrate the idiosyncratic nature of the treatment system for alcohol and drug abuse. Hospitals and specialty treatment centers account for nearly three-quarters of the expenditures for chemical dependency treatment services. Alcohol and drug treatment services primarily occur in hospitals (40 percent of total expenditures) for inpatient detoxification and in specialty clinics (33 percent of total expenditures) for outpatient and residential counseling services.

Hospitals also account for the largest portion of expenditures for total health care (35 percent) and for mental health treatment (30 percent), but specialty substance abuse treatment services make invisible contributions (less than one percent) to expenditures for mental health and health care services. Independent practitioners, mental health centers, and prescription drugs account for little of the expenditures in alcohol and drug abuse treatment but for substantially greater proportions of mental health and general health care: independent practitioners (health care = 26.5 percent; mental health = 28.5 percent; substance abuse = 11.1 percent); mental health centers (health care = less than 1 percent; mental health = 15 percent; substance abuse = 9 percent); prescription drugs (health care = 7.5 percent; mental health = 12.3 percent; substance abuse = 0.3 percent) (Coffey et al., 2001; Mark et al., 2000).

Expenditure analyses also show that payers differ (Coffey et al., 2001; Mark et al., 2000). Alcohol and drug treatment services rely more on federal funding other than Medicaid and Medicare (16 percent of expenditures) compared to mental health and total health care (4 percent each). This reflects the role of the federal Substance Abuse Prevention and Treat-

ment Block Grant. Medicare makes less of a contribution to funding for alcohol and drug treatment (8 percent of expenditures) compared to treatment for mental health (12.3 percent) and general health care (20.3 percent). Patients also contribute proportionately less out-of-pocket revenues for substance abuse treatment (9.2 percent) than for mental health services (16.9 percent) and general health care (17.7 percent). State and local revenues make up more of the funding for mental health and substance abuse services (20 percent each) than for general health care (6.6 percent), but general health care receives more support from private insurance (33 percent versus 24 percent for mental health and substance abuse treatment).

The summary of expenditures for alcohol and drug abuse treatment suggests that integration of alcohol and drug treatment with primary care and general health care services is inhibited by differences in financing and differences in treatment settings and practitioners. The presence of a large and autonomous system of specialty chemical dependency treatment settings reflects a legacy of poor service for alcohol and drug disorders in health care and mental health care settings, limited coverage in insurance plans, and the resulting divergence in payer sources and regulatory mechanisms.

Specialty Chemical Dependency Treatment Services

The most current source of data on facilities that offer drug and alcohol treatment is the 2000 National Survey of Substance Abuse Treatment Services (N-SSATS; previously called the Uniform Facilities Data Set—UFDS; Substance Abuse and Mental Health Services Administration, 2002). The report is available through the SAMHSA Website at http://www.samhsa.gov/oas/dasis.htm#nssats2. N-SSATS is an annual census and point prevalence recording of program and patient characteristics. The 2000 N-SSATS found 13,428 facilities offering treatment for alcohol and drug dependence that served slightly more than one million patients as of October 1, 2000. Six of 10 (60 percent) treatment centers are nonprofit and about one in four (26 percent) operate as for-profit organizations; the remainder are operated by state and local governments (11 percent), federal agencies (2 percent), and tribal governments (1 percent; Substance Abuse and Mental Health Services Administration, 2002).

Most (61 percent) designate themselves as substance abuse treatment settings rather than combined substance abuse and mental health organizations (25 percent), mental health care organizations (9 percent), or health care settings (3 percent). Facilities are most likely to offer outpatient treatment (78 percent), 26 percent offer residential rehabilitation, and about 8 percent provide inpatient detoxification; 9 percent of facilities reported

using methadone. Treatment services vary, but more than two of three reported offering assessment (94 percent); individual therapy (95 percent); group therapy (88 percent); discharge planning (80 percent); urine screens for drug use (79 percent); relapse prevention, family counseling, and aftercare (77 percent); and case management (68 percent). Medical services were provided less routinely: pharmacotherapy and prescription medications (42 percent), tuberculosis screening (38 percent), testing for HIV (33 percent), hepatitis (25 percent), and sexually transmitted diseases (25 percent). Programs tend to be small—45 percent reported an active caseload of less than 30 patients, and 78 percent served fewer than 100 patients. Thus, the picture that emerges from the N-SSATS census is of a treatment system composed of small specialty outpatient clinics that provide limited medical services and have little overlap with the larger general medical system of care. Current financing systems, however, do not encourage greater integration of substance abuse and primary care services. What steps have been taken to encourage more integration with primary care?

INTEGRATION OF ADDICTION TREATMENT WITH PRIMARY CARE

Similarities between drug and alcohol dependence and chronic illnesses like diabetes, asthma, and heart disease (e.g., diagnosis, genetic heritability, etiology, pathophysiology, treatment response, rates of retreatment) suggest that addiction could be viewed as a chronic disorder (McLellan, Lewis, O'Brien, and Kleber, 2000). Primary care settings with linkages to support and counseling services, therefore, may be appropriate environments for treating alcohol and drug dependence. Editorials in the *Journal of the American Medical Association* (Stein and Friedmann, 2001) and the *Journal of General and Internal Medicine* (O'Connor and Samet, 2002), in fact, encourage expanded roles for primary care clinicians because abuse of alcohol, tobacco, and other drugs is common among patients, it co-occurs with HIV/AIDS and psychiatric disorders, and it is a chronic health problem.

Two models have been described for integrating primary care and addiction treatment: centralized and distributed (Samet, Friedmann, and Saitz, 2001). Centralized models offer primary care and behavioral health services (substance abuse and/or mental health care) at a single location. Delivering both services at the same location eliminates geographic distance and travel time as barriers to linkage and facilitates access for patients who may have limited motivation to seek care and whose lives are often disorganized. Distributive models recognize that reimbursement mechanisms and licensing requirements inhibit co-location of services and seek to optimize the existing pattern of independent service settings for

primary care and behavioral health services. Strong referral mechanisms are required, and practitioners in both settings need to recognize and acknowledge problems that require referral. Case management can facilitate appointments and transitions between service settings.

Barriers to a fuller integration of treatment systems include provider education, financing mechanisms and disincentives, confidentiality requirements and concerns, and the persistent presence of stigma (Samet et al., 2001). The distributive and centralized models of integrated care implicitly recognize that primary care clinicians are unlikely to assume full responsibility for caring for alcohol and drug disorders. Stein and Friedmann (2001) acknowledge that only a small portion of primary care clinicians will choose to specialize in patients with alcohol and drug disorders, but they recommend that all physicians should be able to screen for potential alcohol and drug abuse problems and to make appropriate interventions and referrals.

A recent clinical trial demonstrated the value of integrating primary care physicians into an addiction treatment setting (Weisner et al., 2001). Patients who entered treatment for chemical dependency in a large health maintenance organization were randomly assigned to receive primary care in the addiction treatment setting or continue with their usual primary care clinician located in a separate clinic. Six months after randomization the rates of abstinence did not differ significantly among the patients who received integrated care (68 percent) compared to the treatment as usual—independent primary care (63 percent). Patients with a substance abuse-related medical condition, however, were significantly more likely to achieve abstinence when treated in an integrated setting (69 percent) rather than when primary care was provided in a different setting (55 percent). Costs were not significantly higher in the integrated setting and, consequently, the cost-effectiveness ratio was substantially better for integrated care (Weisner et al., 2001).

Studies of drug abuse treatment services, however, find that most do not provide on-site primary care. A 1995 survey of outpatient drug abuse treatment programs, for example, reported that 48 percent provided on-site physical examinations, and 40 percent offered routine medical care on-site (Friedmann et al., 1999a). The outpatient programs that were most likely to provide on-site primary care were certified by the Joint Commission on Accreditation of Healthcare Organizations and offered methadone treatment. Similarly, an analysis of the 96 programs participating in the Drug Abuse Treatment Outcome Study reported that 15 percent offered complete medical care on-site and 34 percent used a combination of on-site services and referrals (Friedmann, McCullough, and Saitz, 2001). Use of medical services during the first month of drug abuse treatment was generally low (30 to 40 percent of patients). When all services were pro-

vided on-site, however, 27 percent of patients received at least three medical visits compared to 10 to 14 percent in all other programs (Friedmann et al., 2001).

Despite the apparent value of integrating primary care and interventions for alcohol and drug use disorders, adoption in primary care settings has been relatively limited. Studies of screening and brief intervention and the adoption of buprenorphine to treat opioid dependence suggest that there is great opportunity for higher levels of impact and adoption.

Screening and Brief Interventions

Research suggests that individuals with high-risk patterns of alcohol and drug use can be identified in health care settings. Moreover, relatively brief interventions by physicians and other health care professionals lead to significant reductions in levels of alcohol use (Fleming et al., 1997; Ockene et al., 1999). Despite the strength of these findings, physicians often neglect to screen for alcohol and drug use. A survey of physician screening practices (57 percent response rate) reported that 88 percent screen new patients for alcohol use but that only 13 percent use formal screening tools (Friedmann et al., 2000) and 68 percent inquire about drug use (Friedmann et al., 2001). Psychiatrists were more likely to screen than primary care clinicians and more likely to intervene (Friedmann et al., 2000, 2001). A minority but still substantial number of primary care physicians miss the opportunity to examine their patients' use of alcohol and other drugs (Friedmann et al., 2000).

Saitz et al. (2000, 2003) identified two types of barriers that inhibit adoption of screening and intervention tools: *clinician-specific barriers* (negative attitudes toward addicted patients, limited knowledge and experience regarding treatments, lower professional satisfaction, lack of perceived responsibility for treatment of addictions) and *resource-related barriers* (limited time, inadequate reimbursement mechanisms, limited office support for such services, and inadequate linkages with referrals).

Screening and interventions for smoking cessation are becoming more widely implemented in primary care as well. Availability of medications in treatment has changed how physicians approach smoking. While significant evidence indicates the importance of smoking cessation for personal health and the overall health care system, screening and intervention have still not been universally adopted in primary care (Cornuz et al., 2000; Fiore, 2000; Fiore et al., 2000; Jaen et al., 2001). Similar to other addiction disorder treatments, barriers to successful adoption have included lack of medical education in this area (Spangler et al., 2002), low provider expectations for success, and little office support (Gottlieb et al., 2001; McIlvain et al., 2002). However, tobacco cessation guidelines now exist

(Fiore, 2000; Fiore et al., 2000), evidence regarding their cost effectiveness in primary care has been published (Cromwell et al., 1997; U.S. Veterans Administration, 1999a), and screening is now recommended as part of standard healthcare systems and health plan evaluation criteria (U.S. Veterans Administration, 1999b; U.S. Public Health Service, 2000).

Adherence to guidelines is improved with organizational support and policies for implementation (including screening systems and prompting), better physician familiarity with the guidelines, improved counseling skills, and greater belief on the part of physicians in the effectiveness of treatment (Fiore, 2000; Fiore et al., 2000; Stone, et al., 2002; Vaughan et al., 2002). Successes in tobacco cessation treatment have also likely been encouraged in part by pharmaceutical manufacturers' marketing to both clinicians and patients in the presence of a vast potential market, in combination with the development of accepted guidelines for treatment.

An emerging and more challenging frontier is office-based treatment of opioid dependence. Recent approval of buprenorphine for the treatment of opioid dependence offers opportunities for primary care physicians to become more directly involved in the treatment of drug use disorders.

Adoption of Buprenorphine

In the United States, policy makers and advocates see potential for primary care and specialist physicians to take leadership roles in the treatment of patients dependent on opioids because of increased options for opioid maintenance and detoxification medications (Fiellin and O'Connor, 2002; Merrill, 2002). The Food and Drug Administration (FDA) approved the use of Subutex (buprenorphine hydrochloride) and Suboxone (buprenorphine hydrocholoride plus naltrexone) for the treatment of opioid dependence in October 2002. Within eight months, SAMHSA's Buprenorhine Physician Locator Web page (http://buprenorphine.samhsa.gov/bwns_locator/dr_search.htm) listed 1,028 physicians as qualified to write prescriptions (this reflects only the physicians who chose to be listed and is an undercount of the number with waiver approval). The relatively small number of listed practitioners suggests that the challenge of promoting adoption among physicians is substantial.

Office-based dispensing and prescribing of maintenance medications are expected to increase access to treatment, reduce the stigma associated with seeking drug treatment, and provide better patient care (Fiellin and O'Connor, 2002). Randomized clinical trials suggest that physicians can treat opioid-dependent patients effectively in office-based practices. In one study, opioid-dependent patients were randomly assigned to receive buprenorphine three times a week in either a primary care clinic or a

traditional narcotics treatment program (a methadone maintenance center; O'Connor et al., 1998). Patients treated in the primary care clinic had a higher 12-week retention rate (78 versus 52 percent), had lower rates of urine positive for opioids (63 versus 85 percent), and were more likely to achieve at least three weeks of abstinence from opioids (43 versus 13 percent; O'Connor et al., 1998). It is important to note that the primary care clinic was affiliated with a drug abuse treatment service and patients participated in a weekly group counseling session at the clinic—drug abuse treatment services were integrated into the primary care clinic. A 6-month trial of office-based methadone maintenance also found that maintenance medication could be provided safely and effectively in a primary care setting (Fiellin et al., 2001).

Given the brief time since FDA approval and the requirements for receiving a waiver, information is limited on the adoption of buprenorphine in the United States. France, however, approved its use for the treatment of opiate dependence in 1995. Within a year, 25,000 French citizens were receiving prescriptions from general practitioners (Moatti et al., 1998). An April 1996 telephone survey of nearly 1,200 randomly selected and eligible general practitioners in France (70 percent response rate) found that one in four (24 percent) reported caring for patients who injected drugs (Moatti et al., 1998). Physicians with experience caring for injection drug users were more willing to prescribe buprenorphine (31 versus 7.5 percent) (Moatti et al., 1998). A second assessment found that 27 percent of French physicians prescribed and 52 percent of pharmacists dispensed buprenorphine at least once in the first two years of availability (Vignau et al., 2001). Mean dosage levels (6 mg per day), however, suggested that doses for many patients were below recommended therapeutic levels (6 to 16 mg per day) and may indicate "a lack of experience and training" in the treatment of opiate dependence. Another study showed that the mean daily dose among French general practitioners was higher (11.5 mg), accompanied by high levels of concurrent benzodiazepine use by some patients (Thirion et al., 2002). Variations in dosing and concurrent pharmacotherapy suggest that practitioner training is a critical element in promoting adoption, diffusion, and effective use of buprenophine.

Primary Care and Addiction Interventions

Options and models for integrating primary care and drug abuse treatment services are emerging. Because alcohol use and abuse are more common than drug abuse, research has tended to emphasize patients with alcohol-related problems. There has been much less work on integrating services for drug-dependent patients (Samet et al., 2001). It may be more challenging to develop effective integration for drug patients because of

less experience with drug-dependent individuals and more suspicion of their motives for seeking care. An ethnographic study of the treatment of opiate-dependent patients in a teaching hospital, for example, concluded that attending and resident physicians were inexperienced and unskilled in working with addicted patients and the lack of skill inhibited better care (Merrill et al., 2002). Patients, moreover, perceived inconsistent and hesitant care and concluded that they were being treated poorly because of their drug use. Most physicians are untrained in the treatment of alcohol and drug disorders and are unlikely to seek greater skill. Physician training and education, however, are key to effective integration of primary care and services for alcohol and drug dependence.

INTEGRATION OF IMMUNOTHERAPIES AND DEPOT MEDICATIONS INTO TREATMENT SETTINGS

The reviews of technology adoption in alcohol and drug services, specialty treatment programs, and treatment of alcohol and drug disorders in primary care settings suggest general implications for dissemination of immunotherapies and depot medications. There are also implications for specialty and primary care settings.

The transfer of new technologies into treatment for alcohol and drug abuse may be challenging. Brown (1995) enumerates factors important to support technology transfer and noted that the absence of any one feature can inhibit dissemination: the relevance and timeliness of the innovation, style of communication regarding the innovation, credibility of the source as well as the message, availability of resources to adopt the innovation, acceptability of the innovation within current treatment orientations, and consistency of the innovation with current organizational mandates. In many programs, staff training relies on an apprenticeship (experiential training) emphasizing traditional approaches rather than the more theoretical and academic perspective found in graduate education. Diffusion studies consistently report that early adopters of new technologies tend to be more highly educated (Rogers, 1995). Counselors with formal postgraduate training, therefore, may respond differently than those without graduate training. The heterogeneous structure of the substance abuse workforce may require different change messages and change agents for different subgroups of counselors. The innovation decision process must be examined for both groups.

Progress in the development of medications for the treatment of drug dependence will lead to little application of pharmacotherapy if drug abuse treatment practitioners and programs are not ready, willing, and able to embrace medication technologies. Six broad sets of barriers to the diffusion and adoption of emerging technologies in drug abuse treatment

settings were identified in the Institute of Medicine's (1998) analysis of the linkages between research and practice:

- Structure—small programs with limited resources may be unable to afford the medical staff and training required to fully utilize medications.
- Financing—the multiple funding streams that support drug treatment may have unique rules and may not provide coverage for new therapies, including medications.
- Education and training—in many programs training for staff relies more heavily on an apprenticeship (experiential training) emphasizing traditional approaches rather than the more theoretical and cosmopolitan perspective found in graduate education.
- Stigma—ignorance and prejudice about drug abuse contribute to inadequate training in graduate programs and medical schools, inhibit the construction and location of facilities, and reduce investments in technology development.
- Lack of knowledge about technology transfer—a lack of systematic research on technology adoption in drug abuse treatment settings slows the development of more effective dissemination strategies.
- Policy—local, state, and federal policies sometimes restrict the types of services available and the individuals who receive those services.

Individuals seeking treatment and their families are the most direct beneficiaries of effective pharmacotherapy. Their attitudes toward medications and their beliefs about the efficacy and effects of medications will be critical in the adoption and diffusion of new pharmacotherapies. Moreover, because of the value of group support to recovery, there is a whole social system of individuals in recovery whose attitudes and beliefs could have substantial impact on the acceptability of medications to the field. Similarly, counselors communicate their beliefs and opinions to clients and as authority figures can potentially facilitate or inhibit the use of medications. Social and normative influences must be considered when assessing the cognitive factors that contribute to behavioral decisions, because much of what clients know about treatment comes from interactions with counselors and other clients.

Specialty Settings

Despite the potential of new and emerging medication therapies for substance abuse treatment, the drug and alcohol treatment field appears reticent to embrace them. The winter 2002 issue of *Hazelden Voice*, for ex-

ample, includes a commentary on "the pros and cons of addiction medications" (available on the Web at http://www.hazelden.org/newsletter_detail.dbm?id=1345; Owen, 2002). (Hazelden is one of the nation's most recognized specialty programs for the treatment of chemical dependency.) The essay suggests that adoption of medications will be inhibited in many specialty alcohol and drug abuse treatment centers because of experience with recovery without the use of medications, concern about unanticipated side effects and addiction potential, discomfort with the research supporting the use of medications, and perceived incompatibilities with traditional treatment approaches. The potential value of medications is acknowledged, but there is a strong sense of resistance and skepticism. Four negatives associated with the potential use of medications were noted:

- "We are puzzled why some providers are so enthusiastic about medications, when we see, for our patients, that recovery is possible without them."
- "We worry that some medications . . . may prove to be mood-altering."
- "Research findings . . . are often framed in non-familiar and in fact sometimes non-desirable outcomes (e.g., 'reduced alcohol use,' 'fewer drinking days' or 'fewer drinks per drinking day'). For abstinence-based programs these are not necessarily impressive outcomes."
- "It is possible that addicts/alcoholics may believe the medication will help them control their substance use rather than focusing on the goal of abstinence" (pp. 3, 12).

At the same time, the essay identified four reasons for considering medications:

- "We know that not everyone is helped by our treatment approach; maybe other methods would help."
- "As a disease, alcohol/drug dependence has a biological basis. Could a medication be part of the multidimensional approach?"
- "Medications are used as part of a treatment regimen for other diseases that have a behavioral component, such as heart disease or diabetes."
- "Incorporation of new ideas is part of the 'Minnesota Model'" (p. 12).

The essay concludes that medications may eventually prove to be an effective facet of a comprehensive addiction treatment program but that

medications alone are unlikely to be sufficient to ensure a stable recovery. Hazelden, therefore, "will watch the research . . . [and] when it becomes clear that other approaches have something significant to offer that fits with our model of care, Hazelden will incorporate them" (Owen, 2002, p. 12).

The Hazelden commentary provides insight and perspective on the challenges that await efforts to foster adoption of new medication technologies in the programs that treat alcohol and drug dependence. A treatment organization's internal structure, staffing, and other resources have a large influence on the adoption of new technologies. For instance, staff expertise, availability of physicians, and adequate training are essential for adoption of innovation. This has particular significance for specialty treatment organizations, which are not centered around physicians and thus do not have the clinical expertise and a medical approach to the management of addictions, nor do nonphysicians have the ability to prescribe medications. Adoption of new pharmacotherapies, especially in these settings, requires significant physician involvement in the management of patients.

Management structures, norms, and expectations about appropriate and expected behaviors, reimbursement mechanisms, and state and federal policies also affect the flow of information and the response to emerging medications and immunotherapies. In treatment organizations, decisions about innovation may be optional (each clinician and patient chooses), collective (choices are made as a group), or authoritative (policy is set by management). Thus training must include the counselors and a recognition that staff turnover is high in many treatment programs. Finally, financing for medications is not usually included in the reimbursement provided for most specialty drug abuse treatments. New financing mechanisms must be developed before rapid adoption is likely in publicly funded treatment centers.

Primary Care Settings

Implementation challenges are also apparent for medical settings. Primary care settings (physicians' offices and clinics) are typically organized around procedural services and medications as the focus of treatment. While a portion of primary care has always been devoted to the management of conditions that require ongoing psychosocial therapy, the linkages with psychosocial support systems have for the most part been secondary to medical therapy. Primary care physicians who are willing to address problems of addiction have not yet done so due to several factors: lack of training or skills specific to substance abuse screening or treatment, lack of linkages between service systems, limited provider time and

financial resources to address problems of substance abuse, and the stigma often associated with patients who have addiction problems. Additional challenges in promoting linkages between primary and specialty services include difficulties communicating across settings, confidentiality standards for the treatment of alcohol and drug disorders that often inhibit sharing medical and psychosocial information, and concerns regarding coerced treatment.

Confidentiality Regulations

Alcohol and drug abuse treatment records have a unique level of federal protection. In most cases, information in the clinical record may not be shared without the specific consent of the patient. Authority for confidentiality standards for alcohol dependence treatment records was included in the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970 (Hughes Act, P.L. 91-616) and extended to drug abuse treatment records in the Drug Abuse Prevention, Treatment, and Rehabilitation Act of 1972 (P.L. 92-255; Lopez, 1994). The regulations were designed to protect the privacy of individuals entering care (Legal Action Center, 1991). The strict confidentiality requirements prohibit disclosure of information from a "federally assisted" treatment program unless the patient provides a valid consent to the release or specific conditions are met for a court-ordered release (Legal Action Center, 1991). "Federally assisted" is broadly defined to include any form of federal funds, a grant of tax-exempt status, an authorization to conduct business, or an agency of federal, state, or local government. As a result, the rules apply to all facilities that are licensed or authorized by state regulations.

State regulations may be more restrictive but cannot permit disclosures that are prohibited by the federal regulations. The strict limits on disclosure are unique to alcohol and drug abuse treatment programs. Medical records and mental health records do not enjoy the same level of protection. As a result, primary health care practitioners may be unaware that their patients are simultaneously receiving treatment for alcohol and drug disorders. The confidentiality regulations complicate efforts to integrate care. The recent implementation of stricter confidentiality standards for medical records (Health Insurance Portability and Accountability Act) does not obviate the stricter standards applied to alcohol and drug abuse treatment records but may foster consistent strategies for releasing and sharing information, including treatment for alcohol and drug disorders in health care settings.

Financing

Differences in financing between general medical care and mental health/substance abuse treatment will also challenge adoption of new treatments. First, many insurance programs limit funding for counseling and recovery support. Second, in cases in which care is fully or partially capitated (either all services or carved out to specialty substance abuse programs), new medications and treatments may need to prove they are cost effective in order to be adopted onto formularies and incorporated into treatment.

Chronic Care Model

A valuable approach to the management of addiction treatment in primary care settings would be to apply principles of optimal chronic disease management. A recently demonstrated approach to managing chronic illness was applied to tobacco addiction (Bodenheimer, Wagner, and Grumbach, 2002a, 2002b). This model recognizes and operationalizes linkages across the systems in which chronic care takes place—community resources and health care, financing, and provider organizations. Proactive teams address six essential elements of care: community resources and policies, health care organization, self-management support, delivery system design, decision support, and clinical information systems. The chronic care model improved outcomes of care and in some cases reduced costs for certain conditions. However, payment incentives are not always in alignment with the chronic care model approach and can provide obstacles to coordination of care.

Emergency Medicine

Finally, the emergency medical setting must be considered a potential setting for adoption and implementation of immunotherapies or depot medications. The prevalence of substance abuse in emergency room patients is estimated at 15 to 24 percent (Teplin, Abram, and Michaels, 1989; Cherpitel, 1996). Emergency personnel, however, detect and refer only a small proportion of substance abuse problems (Fortney and Booth, 2001). As treatment options for overdose and relapse prevention increase, physicians and hospitals will have to make decisions to adopt interventions that may require better detection of drug dependence. Protocols will have to be developed and individualized to the particular setting. Some issues in emergency care may be the same as those of primary care, in particular lack of training specific to addiction problems and inadequate

linkages or follow-up for individuals treated in emergency rooms. Additional barriers are specific to emergency departments:

- A high proportion of emergency care is uninsured, so reimbursement for expensive interventions will be difficult to obtain.
- Many individuals treated in emergency departments are lost to follow-up, so linkages to care will be critical.
- Prioritizing and triaging patients are important components of emergency care, but some individuals being treated for addictions may receive lower priority than others needing urgent care.

Thus, the adoption of immunotherapies and depot medications will be challenging whether in specialty settings, primary care, or emergency medicine.

CONCLUSIONS

Extensive literature indicates that adoption of innovations is the result of characteristics of the provider, treatment setting, financing strategies, the technology itself, and the manner in which information is communicated. Several characteristics of the substance abuse treatment system have in the past worked to diminish the speed and extent to which innovations have been adopted in addiction treatment. Addiction treatment technologies have achieved less than anticipated success in the market, most recently in the case of naltrexone, where financing, education, and questions regarding effectiveness have played a large part in the lack of adoption. Studies suggest that many of the barriers to adoption of new substance abuse treatments may be amenable to policy interventions, including appropriate education, adequate financing, and improved linkages between primary care and specialty treatment. Specific approaches to technology transfer can promote new therapies for drug abuse treatment and may have particular significance for the successful diffusion of depot medications and immunotherapies. These innovations have the potential to reach a wide population at need and bring primary care settings to play a greater role in addiction treatment. However, in order to do so, policy makers and providers must influence financing strategies, organizational structures, and educational approaches that will facilitate use of these innovations. See Figure D-1 for a summary of the health care system components that must be addressed to promote appropriate adoption of immunotherapies and depot medications for the treatment of drug dependency disorders.

Integration of treatment of substance abuse disorders is not universally implemented in primary care. However, research suggests that

several factors can facilitate appropriate and informed use of new medications. These strategies can be considered prior to widespread availability of immunotherapies and depot medications.

A necessary step prior to making immunotherapy and depot medications available is to develop professional standards that guide the application of the therapies to specific patient groups, including adolescents. Guidelines for prophylaxis are also needed. Several areas have made progress in the development of practical guidelines for screening and treatment. Particularly effective are alcohol screening tools and smoking cessation programs. These approaches, however, must be applied regularly in practice in order to be effective. Therefore, an accompanying approach is provider education. It is clear from the literature that multifaceted education efforts for physicians and other providers must be in place to inform them about all aspects of the use of these therapies. As has been shown with naltrexone, a lack of information supported a host of other questions surrounding the drug's effectiveness, and adoption in primary care has been negligible.

On the other hand, in the case of buprenorphine, a multipronged approach is taking place in which guidelines are being developed by the federal government, providers are being certified through professional societies to treat patients in office settings, it is being incorporated on formularies, and patient education materials are being developed. The importance of linkages between primary care and related support services is being addressed, although it presents a continuing challenge. How this pharmacotherapy is addressed in primary care, and how this innovation may affect the treatment of substance abuse disorders, will be important to document.

Education directed toward providers must be complemented by efforts to educate the public regarding both the chronic disease nature of addiction disorders and the importance of screening and treatment. With regard to immunotherapies and depot medications that may be available for prophylaxis, particular problems may arise regarding appropriate use and public perceptions surrounding this approach to management.

Additionally, insurance and financing are necessary components of successful adoption of any therapy into practice. It is essential to understand the structure of the market for immunotherapies and depot medications, so that manufacturers' efforts to promote these medications can be balanced by objective information from other sources. It is important to note that financing for substance abuse treatments occurs through various avenues in the public and private sectors. While inclusion on insurers' formularies is important for the private sector, funding through public programs at the federal and state levels is essential after a medication becomes available.

Finally, managing the use of immunotherapies and depot medications will require strong linkages between primary care and a spectrum of services. As noted, an important approach to promote is the chronic care model, which incorporates both medical and psychosocial treatments. As this type of care is still implemented on only a limited basis, demonstrations and evaluations of such care models will be essential to identify the most effective implementation approaches for various populations.

In conclusion, immunotherapies and depot medications have great potential to improve access to treatment for alcohol and drug dependence. Before the medications can be used most effectively, however, policy makers and practitioners must prepare the field. Strategies to improve linkages with primary care, to train primary care practitioners, and to educate drug abuse treatment programs are essential to the long-term adoption of these emerging technologies.

REFERENCES

Abrahamson, E. (1991). Managerial fads and fashions: The diffusion and rejection of innovation. *Academy of Management Review, 16,* 586-612.

Addiction Technology Transfer Centers. (2000). *The change book: A blueprint for technology transfer*. Kansas City, MO: Addiction Technology Transfer Center National Office.

Alexander, J.A., Lichtenstein, R., D'Aunno, T., McCormick, R., Muramatsu, N., and Ullman, E. (1997). Determinants of mental health providers' expectations of patients' improvements. *Psychiatric Services, 48*(5), 671-677.

Altman, S.A., and Thomas, C.P. (2002). Controlling spending for prescription drugs [Editorial]. *New England Journal of Medicine*, *346*(11), 855-856.

Backer, T. E. (1991). *Drug abuse technology transfer*. Rockville, MD: National Institute on Drug Abuse.

Backer, T.E. (1995). Assessing and enhancing readiness for change: Implications for behavior change. In T.E. Backer, S.L. David, and G. Soucy (Eds.), *Reviewing the behavioral science knowledge base on technology transfer*. Rockville, MD: National Institute on Drug Abuse.

Backer, T.E., and David, S.L. (1995). Synthesis of behavioral science learnings about technology transfer. In T.E. Backer, S.L. David, and G. Soucy (Eds.), *Reviewing the behavioral science knowledge base on technology transfer* (pp. 262-279). Rockville, MD: National Institute on Drug Abuse.

Backer, T.E., Rogers, E.M., and Sopory, P. (1992). *Designing health communication campaigns: What works?* Thousand Oaks, CA: Sage.

Banta, H.D., and Luce, B.R. (1993). *Health care technology and its assessment*. Oxford, England: Oxford University Press.

Becker, M.H. (1970). Sociometric location and innovativeness: Reformulation and extension of the diffusion model. *American Sociological Review, 35,* 262-282.

Bodenheimer, T., Wagner, E.H., and Grumbach, K. (2002a). Improving primary care for patients with chronic illness. *Journal of the American Medical Association, 288*(14), 1775-1779.

Bodenheimer, T., Wagner, E.H., and Grumbach, K. (2002b). Improving primary care for patients with chronic illness: The chronic care model, part 2. *Journal of the American Medical Association, 288*(15), 1909-1914.

Brown, B.S. (1987). Networking between research and service delivery. *International Journal of the Addictions, 22*(4), 301-317.

Brown, B.S. (1995). Reducing impediments to technology transfer in drug abuse programming. In T.E. Backer, S.L. David, and G. Soucy (Eds.), *Reviewing the behavioral science knowledge base on technology transfer*. Rockville, MD: National Institute on Drug Abuse.

Brown, B.S. (1997). Staffing pattern and services for the war on drugs. In J.A. Egertson, D.M. Fox, and A.I. Leshner (Eds.), *Treating drug abusers effectively* (pp. 99-124). Malden, MA: Blackwell Publishers and the Milbank Memorial Fund.

Brown, B.S. (1998). Making a difference: Is journal publication enough? *Journal of Substance Abuse Treatment, 15*(2), 87-88.

Brown, B.S. (2000). From research to practice: The bridge is out and the water's rising. *Advances in Medical Sociology, 7*, 345-365.

Brown, B.S., and Flynn, P.M. (2002). The federal role in drug abuse technology transfer: A history and perspective. *Journal of Substance Abuse Treatment, 22*(4), 245-257.

Brown, R.L., Saunders, L.A., Castelaz, C.A., and Papasouliotis, O. (1997). Physicians' decisions to prescribe benzodiazepines for nervousness and insomnia. *Journal of General Internal Medicine, 12*(1), 44-52.

Cherpitel, C.J. (1996). Drinking patterns and problems and drinking in the event: An analysis of injury by cause among casualty patients. *Alcohol: Clinical and Experimental Research, 20*(6), 1130-1137.

Chilingerian, J.A., and Glavin, M.P. (1994). Temporary firms in community hospitals: Elements of a managerial theory of clinical efficiency. *Medical Care Review, 51*(3), 289-335.

Coffey, R.M., Mark, T., King, E., Harwood, H., McKusick, D., Genuardi, J., Dilonardo, J., and Chalk, M. (2001). *National estimates of expenditures for substance abuse treatment, 1997*. Rockville, MD: Center for Substance Abuse Treatment.

Coleman, J.S., Katz, E., and Menzel, H. (1966). *Medical innovation: A diffusion study*. Indianapolis, IN: Bobbs-Merrill.

Counte, M.A., and Kimberly, J.R. (1974). Organizational innovation in a professionally dominated system: Responses of physicians to a new program in medical education. *Journal of Health and Social Behavior, 15*(3), 188-198.

Cromwell, J., Bartosch, W.J., Fiore, M.C., Hasselblad, V., and Baker, T. (1997). Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. *Journal of the American Medical Association, 278*(21), 1759-1766.

Cornuz, J., Ghali, W.A., DiCarlantonio, D., Pecoud, A., and Paccaud, F. (2000). Physicians' attitudes toward prevention: Importance of intervention-specific barriers and physicians' health habits. *Family Practice, 17*(6), 535-540.

D'Aunno, T., Vaughn, M., and McElroy, P. (1999). An institutional analysis of HIV prevention efforts by the nation's outpatient drug abuse treatment units. *Journal of Health and Social Behavior, 40*(2), 175-192.

D'Aunno, T.A., and Vaughn, T.E. (1992). Variations in methadone treatment practices: Results from a national study. *Journal of the American Medical Association, 267*(2), 253-258.

Denig, P., Haaijer-Ruskamp, F.M., and Zijsling, D.H. (1988). How physicians choose drugs. *Social Science and Medicine, 27*(12), 1381-1386.

DiMaggio, P.J., and Powell, W.W. (1988). The iron cage revisited: Institutional isomorphism and collective rationality in organizational fields. *American Sociological Review, 48,* 147-160.

Dybwad, T.B., Kjolsrod, L., Eskerud, J., and Laerum, E. (1997). Why are some doctors high-prescribers of benzodiazepines and minor opiates? *Family Practice, 14*(5), 361-368.

Eisenberg, J.M. (1993). Economics. *Journal of the American Medical Association, 270*(2), 198-200.

Escarce, J.J., Bloom, B.S., Hillman, A.L., Shea, J.A., and Schwartz, J.S. (1995). Diffusion of laparoscopic cholecystectomy among general surgeons in the United States. *Medical Care, 33*(3), 256-271.

Fendrick, M.A., and Schwartz, J.S. (1994). Physicians' decisions regarding the acquisition of new technology. In A.C. Gelijns and H. Dawkins (Eds.), *Adopting new medical technology* (pp. 71-84). Committee on Technological Innovation in Medicine, Institute of Medicine. Washington, DC: National Academy Press.

Fiellin, D.A., and O'Connor, P.G. (2002). Office-based treatment of opioid-dependent patients. *New England Journal of Medicine, 347*(11), 817-823.

Fiellin, D.A., O'Connor, P.G., Chawarski, M., Pakes, J.P., Pantalon, M.V., and Schottenfeld, R.S. (2001). Methadone maintenance in primary care: A randomized controlled trial. *Journal of the American Medical Association, 286*(14), 1724-1731.

Fiore, M.C. (2000). U.S. Public Health Service clinical practice guidelines: Treating tobacco use and dependence. *Respiratory Care, 45*(10), 1200-1262.

Fiore, M.C., Bailey, W.C., Cohen, S.J., Dorfman, S.F., Goldstein, M.G., Gritz, E.R., Heyman, R.B., Jaen, C.R., Kottke, T.E., Lando, H.A., Mecklenburg, R.E., Mullen, P.D., Nett, L.M., Robinson, L., Stitzer, M.L., Tommasello, A.C., Villejo, L., and Wewers, M.E. (2000). *Treating tobacco use and dependence: Clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services.

Fleming, M.F., Barry, K.L., Manwell, L.B., Johnson, K., and London, R. (1997). Brief physician advice for problem alcohol drinkers: A randomized controlled trial in community-based primary care practices. *Journal of the American Medical Association, 277*(13), 1039-1045.

Fortney, J., and Booth, B.M. (2001). Access to substance abuse services in rural areas. In M. Galanter (Ed.), *Recent developments in alcoholism, Vol. 15, Services research in the era of managed care* (pp.177-208). New York: Plenum Press.

Freiman, M.P. (1985). The rate of adoption of new procedures among physicians: The impact of specialty and practice characteristics. *Medical Care, 23*(8), 939-945.

Friedmann, P.D., Alexander, J., and D'Aunno, T. (1999). Organizational correlates of access to primary care and mental health services in drug abuse treatment units. *Journal of Substance Abuse Treatment, 16*(1), 71-80.

Friedmann, P.D., Alexander, J.A., Jin, L., and D'Aunno, T.A. (1999). On-site primary care and mental health services in outpatient drug abuse treatment units. *Journal of Behavioral Health Services and Research, 26*(1), 80-94.

Friedmann, P.D., McCullough, D., Chin, M.H., and Saitz, R. (2000). Screening and intervention for alcohol problems: A national survey of primary care physicians and psychiatrists. *Journal of General Internal Medicine, 15*(2), 84-91.

Friedmann, P.D., McCullough, D., and Saitz, R. (2001). Screening and intervention for illicit drug abuse: A national survey of primary care physicians and psychiatrists. *Archives of Internal Medicine, 161*(2), 248-251.

Gelijns, A., and Rosenberg, N. (1994). The dynamics of technological change in medicine. *Health Affairs, 13*(3), 28-46.

Gottlieb, N.H., Guo, J.L., Blozis, S.A., and Huang, P.P. (2001). Individual and contextual factors related to family practice residents' assessment and counseling for tobacco cessation. *Journal of the American Board of Family Practice, 14*(5), 343-351.

Greer, A.L. (1988). The state of the art versus the state of the science: The diffusion of new medical technologies into practice. *International Journal of Technology Assessment in Health Care, 4*(1), 5-26.

Hemminki, E. (1975). Review of literature on factors affecting drug prescribing. *Social Science and Medicine, 9*(2), 111-116.

Hilton, M.E. (2001). *Researcher in residence program: Experiences from New York state*. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism.

Hodgkin, D., and McGuire, T. (1994). Payment levels and hospital response to prospective payment. *Journal of Health Economics, 13*(1), 1-29.

Institute of Medicine. (1990a). *Broadening the base of treatment for alcohol problems*. Committee on Treatment of Alcohol Problems. Washington, DC: National Academy Press.

Institute of Medicine. (1990b). *Treating drug problems, volume 1*. Committee for the Substance Abuse Coverage Study. D.R. Gerstein and H.J. Harwood (Eds.). Washington, DC: National Academy Press.

Institute of Medicine. (1997). *Managing managed care: Quality improvement in behavioral health*. Committee on Quality Assurance and Accreditation Guidelines for Managed Behavioral Health Care. M. Edmunds, R. Frank, M. Hogan, D. McCarty, R. Robinson-Beale, and C. Weisner (Eds.). Washington, DC: National Academy Press.

Institute of Medicine. (1998). *Bridging the gap between practice and research: Forging partnerships with community-based drug and alcohol treatment*. Committee on Community-Based Drug Treatment. S. Lamb, M.R. Greenlick, and D. McCarty (Eds.). Washington, DC: National Academy Press.

Jaen, C.R., McIlvain, H.E., Pol, L., Phillps, R.L., Flocke, S., and Crabtree, B.F. (2001). Tailoring tobacco counseling to the competing demands in the clinical encounter. *Journal of Family Practice, 50*(10), 859-863.

Johnson, T.P., Warnecke, R.B., and Aitken, M.J. (1996). Changing practice patterns. In A.D. Kaluzny and R.B. Warnecke (Eds.), *Managing a health care alliance: Improving community cancer care* (pp. 105-128). San Francisco: Jossey-Bass.

Kaluzny, A.D., Morrissey, J.P., and McKinney, M.M. (1990). Emerging organizational networks: The case of the Community Clinical Oncology Program. In S.S. Mick (Ed.), *Innovations in health care delivery*. San Francisco: Jossey-Bass.

Kimberly, J.R., and Evanisko, M.J. (1981). Organizational innovations: The influence of individual, organizational, and contextual factors on hospital adoption of technological and administrative innovations. *Academy of Management Journal, 24*(4), 689-713.

Lambert, B.L., Salmon, W.J., Stubbings, J., Gilomen-Study, G., Valuck, R.J., and Kezlarian, K. (1997). Factors associated with antibiotic prescribing in a managed care setting: An exploratory investigation. *Social Science and Medicine, 45*(12), 1767-1779.

Legal Action Center. (1991). *Confidentiality: A guide to the federal laws and regulations*. New York: Author.

Lopez, F. (1994). *Confidentiality of patient records for alcohol and other drug treatment*. Rockville, MD: Center for Substance Abuse Treatment.

Mark, T.L., Coffey, R.M., King, E., Harwood, H., McKusick, D., Genuardi, J., Dilonardo, J., and Buck, J.A. (2000). Spending on mental health and substance abuse treatment, 1987-1997. *Health Affairs, 19*(4), 108-120.

McIlvain, H.E., Backer, E.L., Crabtree, B.F., and Lacy, N. (2002). Physician attitudes and the use of office-based activities for tobacco control. *Family Medicine, 34*(2), 114-119.

McLellan, A.T., Lewis, D.C., O'Brien, C.P., and Kleber, H.D. (2000). Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. *Journal of the American Medical Association, 284*(13), 1689-1695.

Merrill, J.O. (2002). Policy progress for physician treatment of opiate addiction. *Journal of General Internal Medicine, 17*(5), 361-368.

Merrill, J.O., Rhodes, L.A., Deyo, R.A., Marlatt, G.A., and Bradley, K.A. (2002). Mutual mistrust in the medical care of drug users: The keys to the "narc" cabinet. *Journal of General Internal Medicine, 17*(5), 327-333.

Meyer, A.D., and Goes, J.B. (1988). Organizational assimilation of innovations: A multilevel contextual analysis. *Academy of Management Journal, 31,* 897-923.

Moatti, J.P., Souville, M., Escaffre, N., and Obadia, Y. (1998). French general practitioners' attitudes toward maintenance drug abuse treatment with buprenoprhine. *Addiction, 93*(10), 1567-1575.

Moch, M.K., and Morse, E.V. (1977). Size, centralization and organizational adoption of innovation. *American Sociological Review, 42,* 716-725.

Morgenstern, J. (2000). Effective technology transfer in alcoholism treatment. *Substance Use and Misuse, 35*(12-14), 1659-1678.

Naranjo, C.A., and Bremner, K.E. (1996). Dissemination of research results regarding the pharmacotherapy of substance abuse: Case examples and critical review. *Substance Abuse, 17,* 39-50.

National Institute of Health Care Management. (2002). *Prescription drug expenditures in 2000: Another year of escalating costs*. Available: www.nihcm.org/spending2001.pdf [December 24, 2003].

Nohria, N., and Gulati, R. (1995). Is slack good or bad for innovation? *Academy of Management Journal, 39,* 716-725.

O'Connor, P.G., and Samet, J.M. (2002). Substance abuse: The expanding role of general internal medicine. *Journal of General Internal Medicine, 17*(5), 398-399.

O'Connor, P.G., Oliveto, A.H., Shi, J.M., Triffleman, E.G., Carroll, K.M., Kosten, T.R., Rounsaville, B.J., Pakes, J.A., and Schottenfeld, R.S. (1998). A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *American Journal of Medicine, 105*(2), 100-105.

Ockene, J.K., Adams, A., Hurley, T.G., Wheeler, E.V., and Hebert, J.R. (1999). Brief physician- and nurse practitioner-delivered counseling for high-risk drinkers: Does it work? *Archives of Internal Medicine, 159*(18), 2198-2205.

Office of Technology Assessment. (1994). *Identifying health technologies that work: Searching for evidence.* Washington, DC: U.S. Congress, Office of Technology Assessment.

Owen, P. (2002). The pros and cons of addiction medications. *Hazelden Voice, 7,* 3-12.

Posner, K.L., Gild, W.M., and Winans, E.V. (1995). Changes in clinical practice in response to reductions in reimbursement. *Medical Anthropology Quarterly, 9*(4), 476-492.

Prochaska, J.O., and DiClemente, C.C. (1983). Stages and processes of self-change in smoking: Towards an integrative model of change. *Journal of Consulting and Clinical Psychology, 51*(3), 390-395.

Prochaska, J.O., Velicer, W.F., Rossi, J.S., Goldstein, M.G., Marcus, B.H., Rakowski, W., Fiore, C., Harlow, L.L., Redding, C.A., Rosenbloom, D., and Rossi, S.R. (1994). Stages of change and decisional balance for 12 problem behaviors. *Health Psychology, 13*(1), 39-46.

Rogers, E.M. (1995). *Diffusion of innovations*, *4th ed*. New York: The Free Press.

Roman, P.M., and Johnson, J.A. (2002). Adoption and implementation of new technologies in substance abuse treatment. *Journal of Substance Abuse Treatment, 22*(4), 211-218.

Romeo, A.A., Wagner, J.L., and Lee, R.H. (1984). Prospective reimbursement and the diffusion of new technologies in hospitals. *Journal of Health Economics, 3*(1), 1-24.

Saitz, R., Sullivan, L.M., and Samet, J. (2000). Training community-based clinicians in screening and brief intervention for substance abuse problems. *Substance Abuse, 21*(1), 21-31.

Saitz, R., Horton, N., Sullivan, L., Moskowitz, M., and Samet, J. (2003). Addressing alcohol problems in primary care: A cluster randomized controlled trial of a systems intervention. *Annals of Internal Medicine, 138*(5), 372-382.

Samet, J.M., Friedmann, P.D., and Saitz, R. (2001). Benefits of linking primary medical care and substance abuse services. *Archives of Internal Medicine, 161*(1), 85-91.

Scott, W.R. (1993). The organization of medical care services: Toward an integrated theoretical model. *Medical Care Review, 50*(3), 271-303.

Simpson, D.D. (2002). A conceptual framework for transferring research to practice. *Journal of Substance Abuse Treatment, 22*(4), 171-182.

Sisk, J.E., and Glied, S.A. (1994). Innovation under federal health care reform. *Health Affairs, 13*(3), 82-97.

Sorensen, J.L., Hall, S.M., Loeb, P., Allen, T., Glaser, E.M., and Greenberg, P.D. (1988). Dissemination of a job seekers' workshop to drug treatment programs. *Behavior Therapy, 19,* 143-155.

Spangler, J.G., Goerge, G., Foley, K.L., and Cradell, S.K. (2002). Tobacco intervention training: Current efforts and gaps in U.S. medical schools. *Journal of the American Medical Association, 288*(9), 1102-1109.

Stein, M.D., and Friedmann, P.D. (2001). Generalist physicians and addiction care: From turfing to sharing the turf. *Journal of the American Medical Association, 286*(14), 1764-1765.

Stone, T.T., Longo, D.R., Phillps, R.L., Hewett, E., and Riley, S.L. (2002). Health care system and insurer support for smoking cessation guideline implementation. *Journal of Health Care Finance, 29*(2), 78-86.

Strang, D., and Soule, S.A. (1998). Diffusion in organizations and social movements: From hybrid corn to poison pills. *Annual Review of Sociology, 24,* 265-290.

Substance Abuse and Mental Health Services Administration. (2002). *National Survey of Substance Abuse Treatment Services (N-SSATS): 2000. Data on substance abuse treatment facilities*. Rockville, MD: Author.

Teplensky, J.D., Pauly, M.V., Kimberly, J.R., Hillman, A.L., and Schwartz, J.S. (1995). Hospital adoption of medical technology: An empirical test of alternative models. *Health Services Research, 30*(3), 437-465.

Teplin, L.A., Abram, K.M., and Michaels, S.K. (1989). Blood alcohol level among emergency room patients: A multivariate analysis. *Journal of Studies on Alcohol, 50*(5), 441-447.

Thirion, X., Lapierre, V., Micallef, J., Ronfle, E., Masut, A., Pradel, V., Coudert, C., Mabriez, J.C., and Sanmarco, J.L. (2002). Buprenorphine presription by general practitioners in a French region. *Drug and Alcohol Dependence, 65*(2), 197-204.

Thomas, C.P. (2000). *No magic bullet: Adoption of naltrexone by clinical providers.* Dissertation, Brandeis University.

Thomas, C.P., Wallack, S., Lee, S.S., McCarty, D., and Swift, R. (2003). Research to practice: Factors affecting the adoption of naltrexone in alcoholism treatment. *Journal of Substance Abuse Treatment*, *24*(1), 1-11.

Tolbert, P.S., and Zucker, L.G. (1983). Institutional sources of change in the formal structure of organizations: The diffusion of civil service reform. *Administrative Science Quarterly, 28,* 22-39.

Turk, D.C., and Okifuji, A. (1997). What factors affect physicians' decisions to prescribe opioids for chronic noncancer pain patients? *The Clinical Journal of Pain, 13*(4), 330-336.

U.S. Public Health Service. (2000). *Treating tobacco use and dependence—A systems approach. A guide for health care administrators, insurers, managed care organizations, and purchasers.* Available: http://www.surgeongeneral.gov/tobacco/systems.htm [December 24, 2003].

U.S. Veterans Administration. (1999a). Relative cost effectiveness of tobacco use cessation pharmacotherapies. *Pharmacoeconomic Center Update,* 8.

U.S. Veterans Administration. (1999b). Tobacco use cessation in the primary care setting. *Pharmacoeconomic Center Update,* 1.

Van den Bulte, C., and Lilien, G.L. (2001). Medical innovation revisited: Social contagion versus marketing effort. *American Journal of Sociology, 106,* 1409-1435.

Vaughan, T.E., Ward, M.M., Doebbing, B.N., Uden-Holman, T., Clarke, W.T., and Woolson, R.F. (2002). Organizational and provider characteristics fostering smoking cessation practice guideline adherence: An empirical look. *Journal of Ambulatory Care Management, 25*(2), 17-31.

Vignau, J., Duhamel, A., Catteau, J., Legal, G., Pho, A.H., Grailles, I., Beauvillain, J., Petit, P., Beauvillain, P., and Parquet, P.J. (2001). Practice-based buprenorphine maintenance treatment (BMT): How do French healthcare providers manage the opiate-addicted patients? *Journal of Substance Abuse Treatment, 21*(3), 135-144.

Weisner, C., Mertens, J., Parthasarathy, S., Moore, C., and Lu, Y. (2001). Integrating primary medical care with addiction treatment: A randomized controlled trial. *Journal of the American Medical Association, 286*(14), 1715-1723.

Wennberg, J. (1988). Improving the medical decision-making process. *Health Affairs, 7*(1), 99-106.

Westphal, J.D., Gulati, R., and Shortell, S.M. (1997). Customization or conformity? An institutional and network perspective on the content and consequences of TQM adoption. *Administrative Science Quarterly, 42,* 366-394.

E

The Use of Immunotherapies and Sustained-Release Formulations in the Treatment of Drug Addiction: Will Current Law Support Coercion?

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Immunotherapies and sustained-release medications may be the hope of the future for many individuals addicted to drugs who are willing, even eager, to access state-of-the-art treatment. They may also seem attractive to a society seeking to lower the high social and economic costs of addiction among such populations as recidivist drug offenders, homeless individuals addicted to drugs, and drug-abusing pregnant women and mothers. Experience suggests, however, that in these populations and others, some individuals will refuse treatment or participate for only a time and then drop out. They may participate or adhere to treatment regimens only if they are mandated to do so.

For that reason this appendix addresses the following question: Will current law support the coercive use of immunotherapies against drugs of addiction? The discussion, in outline, runs as follows. Authority to coerce treatment is derived from the government's responsibility to provide for public health and comfort but is substantially constrained by the countervailing rights of individuals for self-determination in medical treatment. Those rights typically assume the competence of the individuals making the self-determination. Certain classes of individuals may be regarded as lacking that competence; however, a clear legal foundation for broad attribution of incompetence to persons with drug dependence is not found. Even given competence, though, the interests of the state may prevail over those of the individual within certain classes of people, particularly among those who may have effectively waived their right of refusal. In such cases, coercion might be legally sustainable, and this appendix discusses potentially pertinent statutes and case law bear-

ing on the ability of the state to justify the use of coercion. It is concluded that for some classes of individuals and in some situations, coerced immunotherapy is likely to be legal, subject to the constraints of due process and establishment of the modality's safety and effectiveness. Assuming a situation in which immunotherapy may be legally coerced, the appendix concludes with some reflections on fairness in implementing coercion policy.

The entire discussion here is necessarily subject to substantial uncertainty. Given the novelty of immunotherapies, no law has been developed pertaining to them, so likely legal authority must be inferred from a set of successively more generalized or analogous areas of law: first, from the very sparse law pertaining to coercion of other modalities of substance abuse treatment; second, from the law pertaining to coercion of substance abuse treatment in general, also sparse; and third, from the law pertaining to coercion of treatment for mental illness, which is more developed but only analogous. While this approach cannot lead to very confident predictions, it may well mirror the thinking of courts as they review precedents to inform their future decisions regarding coercion of immunotherapy.

THE GOVERNMENT'S RIGHT TO COMPEL TREATMENT FOR DRUG ADDICTION

The law permits the government to enforce addiction treatment under *parens patriae* and police powers. Although the U.S. Constitution generally confers broad autonomy to individuals, *parens patriae* and police powers are invoked by the government to limit the actions of individuals when broader societal interests are at stake.

Parens patriae, translated literally from the Latin, means "parent of the country." This power lies with the states, where it has been broadly interpreted as the right to protect interests such as the health and welfare of the people. For example, all states permit the civil commitment of individuals with mental disorders. The rationale for civil commitment is to provide treatment for mentally disordered individuals as well as to prevent harm to the larger society.

Overlapping *parens patriae* are police powers. These are derived from the Tenth Amendment to the U.S. Constitution, which reserves to the states any powers not explicitly delegated to the federal government. Under their police powers, states (and by delegation localities) may "adopt such laws and regulations as tend to prevent the commission of fraud and crime, and secure generally the comfort, safety, morals, health and prosperity of its citizens by preserving the public order, preventing a conflict of rights in the common intercourse of citizens, and insuring to

each an uninterrupted enjoyment of all the privileges conferred upon him or her by the general laws" (*Black's Law Dictionary*, 5th ed.).

While states possess significant power under these principles, the Fifth Amendment of the U.S. Constitution also provides that no person shall be "deprived of life, liberty or property without due process of law." It is this due process clause that has provided a balance of protection for individuals in situations where the power of the state and the autonomy of individuals come into conflict.

THE RIGHT OF INDIVIDUALS TO DETERMINE THEIR OWN MEDICAL TREATMENT

Generally, competent adults have the right to make their own decisions about whether to accept or reject medical treatment, free from interference by anyone, including the government. These rights are found in the common law and the U.S. Constitution and are maintained through the doctrine of informed consent.

Informed Consent and Refusal

The doctrine of informed consent generally provides that physicians may not perform any medical procedure on a *competent adult* patient in a nonemergency situation without explaining the risks and benefits of the procedure and obtaining the patient's voluntary consent. This informed consent doctrine is founded in tort law and state statutes. (For a review of statutes, see Andrews, 1984.) As established in the former, consent must be *knowing, voluntary, and competent*.[1]

In *Cruzan v. Missouri Director of Health*, the U.S. Supreme Court held that the right to refuse treatment is a part of the constitutional right of privacy.[2] Justice Rehnquist, writing for the majority, stated: "The logical corollary of the doctrine of informed consent is that the patient generally possesses the right not to consent, that is, to refuse treatment."[3] In other words, if individuals are competent to consent to treatment, they might choose to refuse it instead. If they are not competent to consent/refuse treatment, the government might be in a better position to coerce. If informed consent applies only to competent adults, what about individuals addicted to drugs and children?

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[1]*Kaimowitz v. Department of Mental Health for the State of Michigan*, No. 73-194AW (Cir. Ct., Wayne County, Mich., July 10, 1973).

[2]*Cruzan v. Director, Missouri Department of Health*, 497 U.S. 261 (1990).

[3]Id. at 270.

Consent by Persons with a Substance Use Disorder

Addiction may be a factor limiting competence. It is widely acknowledged that consent should not be pursued while a person is acutely intoxicated. However, what if a person is addicted but not acutely intoxicated when a decision about treatment is to be made? Does addiction make someone *per se* incompetent to provide informed consent for treatment?

At least one court has weighed in on the issue of per se incompetence. The California Supreme Court in its opinion in *In re: Jones* stated that addiction does not render an individual per se incompetent to voluntarily submit to addiction treatment.[4] Support for this notion is found in the case law on mental illness, where the courts have ruled that people with mental disorders enjoy a *presumption of competence* absent an adjudication of incompetence,[5] even though it is widely recognized that mental disorders may affect cognition and judgment.[6]

However, states have an obligation to assure that voluntary consent is truly voluntary. In *Zinermon v. Burch*, staff at a state mental hospital allowed a mentally ill individual to sign voluntary admission papers while psychotic, disoriented, and heavily medicated.[7] The implication of the U.S. Supreme Court ruling in *Zinermon* is that states are obliged to pursue civil commitment, with its due process protections for the individual, where there is a question of competence to voluntarily consent to treatment.

Even in the case of adjudicated incompetence, the state does not necessarily have the right to make a decision about treatment for the individual if there are others available to act on his or her behalf. The courts have recognized the right of incompetent individuals to bodily integrity and to consent or refuse treatment through guardians or other representatives.[8]

Consent by Children or Adolescents

How is the issue of competence handled in the case of children? Those under the age of majority are legally incompetent to make medical decisions for themselves. Generally, parents are the substitute decision makers for their children.

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[4]61 Cal. App. 2d 325 (1964), cert. denied, 379 U.S. 980 (1965).

[5]*Rogers v. Commissioner of the Department of Mental Health*, 458 N.E.2d 308 (Mass. 1983).

[6]For a report on empirical work on decision-making capacity among people with mental illness, see Appelbaum and Grisso (1995) and Grisso, Appelbaum, Mulvey, and Fletcher (1995).

[7]494 U.S. 113, 113 (1990).

[8]See *Cruzan*, 497 U.S. 261; *In re: Quinlan*, 355 A.2d 647 (N.J. 1976).

Adolescents—usually defined as children between the ages of 14 and 18—are regarded as minors by the courts. However, state statutes allow adolescent decision making without parental review in particular areas of health care, including substance abuse treatment. As of 2002, statutes of this type had been passed in 29 states (Hartman, 2002).

These laws, however, address access to desired care, not consent to potentially undesired care—or, by implication, its refusal. Hartman emphasizes that the "refusal of unwanted medical treatment is noticeably absent from the statutory provisions that afford legal autonomy to adolescents for medical decision-making" (p. 418). Case law in this area is sparse and not directly relevant to this appendix's purposes.[9] Thus, there is little guidance on how the courts would handle the situation of a parent attempting to enforce the use of immunotherapy on an unwilling adolescent.

GOVERNMENT PREEMPTION OF THE INDIVIDUAL'S RIGHT TO REFUSE TREATMENT

The U.S. Supreme Court in *Cruzan v. Missouri Director of Health* specifically acknowledged that the right to refuse treatment was not absolute:

> But determining that a person has a liberty interest under the Due Process Clause does not end the inquiry; whether respondent's constitutional rights have been violated must be determined by *balancing his liberty interests against the relevant state interests*. (emphasis added)[10]

Something can be learned about how courts might balance these interests in the case of immunotherapies by examining the involuntary administration of psychotropic medications to persons with mental illness. The courts have enunciated a *qualified* right of mentally ill individuals to refuse psychotropic medications, finding that there are circumstances in which the government's interest in compelling treatment outweighs the individual's right to refuse treatment. For example, in *Riggins v. Nevada* the U.S. Supreme Court allowed the administration of psychotropic medication over the refusal of a criminal defendant when the purpose of treatment was to restore competence to stand trial. However, the court found that due process would be violated without there being a finding that the medication was justified by safety considerations and that there were no less intrusive means to accomplish the same result.[11]

The court recently clarified the standard for permitting forced medication in *Sell v. United States*.[12] Justice Breyer, writing for the majority,

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[9]See, for example, Hartman's (2002:414) discussion of end-of-life cases.
[10]497 U.S. 261, 279 (1990).
[11]504 U.S. 127 (1992). See also Winick (1997).
[12]123 S. Ct. 2174 (2003).

stated that the government interests at stake must be important, forced medication must significantly further those state interests, there must be no less intrusive treatments likely to achieve substantially the same result, and the treatment must be medically appropriate.[13] Judicial review is not necessarily required to override refusals. State courts have found that administrative boards within institutions to which mentally ill persons were civilly committed were sufficient to protect the qualified right of patients to refuse medication.[14]

Interestingly, as Mossman (2002) points out in his recent review of this area of the law, side effects have figured prominently in the analysis by the courts. In *Rennie v. Klein* the court emphasized that doctors must consider whether and to what extent the patient will suffer harmful side effects. Mossman reports that decisions by state courts since *Rennie* have continued to focus on the medical appropriateness of the medication and whether there are less intrusive alternatives.

Under what other circumstances or for what classes of people can the government override the individual's right to refuse treatment? Legislatures and courts have approved the exercise of government power to mandate treatment for various classes of addicted individuals, who might broadly be divided into those who have committed crimes and those who have not. The limits of government power, and the protections afforded persons who abuse or are dependent on drugs by statute or by the U.S. Constitution, are briefly described below.

Prison Inmates

Some states (e.g., California) mandate treatment for prison inmates with some history of substance abuse.[15] While there is no case law on inmate refusal of substance abuse treatment, in *Washington v. Harper* the U.S. Supreme Court addressed the issue of involuntary psychotropic medication for inmates with mental illness.[16] Of the decision in *Harper*, Siegel, Grudzinskas, and Pinals (2001) wrote:

> [T]he court recognized the core substantive due process right implicated by involuntary psychotropic medication—even for a defendant who had already been convicted and who unquestionably presented some threat. It concluded, however, as a matter of substantive due process, that the

[13]Id. at 12-14.

[14]653 F.2d 836 (3d Cir. 1981) (en banc), vacated and remanded, 458 U.S. 1119 (1982). See also *Rogers v. Okin*, 634 F.2d 650 (1st Cir. 1980), vacated and remanded sub nom. *Mills v. Rogers*, 457 U.S. 291 (1982).

[15]*People v. Peel*, 17 Cal. App. 4th 594 (1993), review den. S034883, 1993 Cal LEXIS 5602 (Cal. October 20, 1993), *cited in* 25 Am. Jur. 2d Drugs and Controlled Substances § 253 (2002).

[16]494 U.S. 210 (1990).

> imposition on liberty was justified based on the needs of correctional management, and that the process used to determine the need for medication was adequate, given the limited procedural rights accorded convicted criminals. (p. 307)

Therefore, it seems reasonable to conclude that inmates would have a right to refuse medication unless their mental illness made them a threat to themselves or others. Would immunotherapies meet the definition of justified involuntary treatment under *Harper*? It is not clear that they would, since control of violent behavior is not a byproduct of immunotherapy. That would be especially true if there were other addiction treatments that the inmate was not refusing.

As for due process protections, these legal scholars strongly urge that the decision to override refusal of medication be made by a court or an independent administrative body within the institution. They also recommend that the state be obligated "to establish the need for the medication and medical appropriateness of the drug" by *clear and convincing evidence*.[17]

Parolees and Probationers

Many persons who abuse or are dependent on drugs in the criminal justice system are on parole or probation. Parole is the release of incarcerated individuals after they have served some portion of their sentence. Probation permits a person convicted of a crime to go free with a suspended sentence. Conditions are attached to each, and violation of those conditions can result in incarceration (Petersilia, 1998). One such condition might be participation in an addiction treatment program.[18]

Probation and parole are both privileges, not rights.[19] Release under parole or probation is made with conditions, which may include random drug testing and addiction treatment, and therefore persons with substance use disorders can be said to have, in a sense, "volunteered" for treatment. Failure to follow through with treatment or failure to pass drug tests may be grounds for revocation of parole or probation.

Can parolees or probationers deliberately refuse treatment? This issue does not seem to have been addressed, perhaps because opportunities for probationers or parolees to receive any kind of community-based substance abuse treatment are reported to be few (Petersilia, 1999). However, while parolees and probationers may be free to reject specific modalities

[17]Id. at 375-378.

[18]See the requirements of the federal parole system, United States Parole Commission, *U.S. Parole Commission Rules & Procedures Manual* § 2.40 (l)(2) and § 2.40 (c) (2001).

[19]See *Weaver v. Pennsylvania Board of Probation and Parole*, 688 A.2d 766 (Pa. 1997).

of treatment, the administrative agencies and the courts may respond by revoking probation or parole for noncompliance with the conditions on which the release was made.

Arrestees and Convicted Persons Diverted to Treatment

In a number of states prosecutors are empowered to withdraw criminal charges or hold them in abeyance so that arrestees can enter drug treatment rather than being incarcerated. In addition, states may allow judges to order drug treatment for those already convicted of a crime but not yet sentenced.[20]

One well-publicized method of diversion is the drug court. Drug courts have been defined as "separately identified criminal court dockets that provide judicially supervised treatment and case management services for drug offenders in lieu of criminal prosecution or incarceration."[21] Drug courts vary across jurisdictions, but they tend to include ongoing judicial supervision, random urinalysis testing, mandatory participation in addiction treatment, and the imposition of graduated sanctions for noncompliance with any established condition.

The legal "hold" that drug courts have on their clients is that they typically enter a guilty plea to criminal charges or are required to stipulate to the facts in the arrest report as a condition of being accepted. Once that is done, termination from the program (for noncompliance) would result in conviction and sentencing.[22] Because clients agree to the program's conditions in advance, they can be said to have "volunteered" for treatment. Generally, it is left to addiction professionals, in consultation with the presiding judge, to determine the course of treatment.

In at least two states (California and Arizona), voters have passed diversion laws that do not rely on drug courts.[23] In California, under Proposition 36, any nonviolent offender charged with simple drug possession or use is diverted from criminal prosecution and placed on probation, conditional on addiction treatment (Cal. Penal Code § 1210.1)

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[20]*State v. Manning*, 605 So. 2d. 508 (Fla. 1992), cited in 25 Am. Jur. 2d Drugs and Controlled Substances § 253 (2002).

[21]For a comprehensive description of the drug court model, see generally National Association of Drug Court Professionals (1997).

[22]Id.

[23]California Substance Abuse and Crime Prevention Act of 2000, 2000 Cal. Legis. Serv. Prop. 36 (West) codified at Cal. Health & Safety Code § 11999.4 and Cal. Penal Code §§ 1210-1210.1, 3063.1 (Deering, 2003), and Arizona Drug Medicalization, Prevention and Control Act of 1996, Ariz. Rev. Stat. § 13-3412.01 (2003). For a discussion of the merits of the California law and like-minded diversion programs, see generally Riley, Ebener, Chiesa, Turner, and Ringel (2000).

(Deering, 2003). Offenders who complete drug treatment are entitled to have their arrest and conviction expunged.

For purposes of treatment compliance, participation in such programs, like participation in drug courts, is "voluntary" on the part of offenders. Decisions about what kind of treatment to mandate are made by treatment providers, according to their professional judgment. There is nothing in the law to suggest that participants who have agreed to the conditions of the diversion program can then refuse to participate in the specific treatment offered, including any prescribed medication. However, California law does provide for a full panoply of due process protections.

Homeless Individuals

More than any other class of noncriminal persons with a substance use disorder, homeless individuals are likely to draw attention regarding treatment coercion. Various strategies have been used to encourage homeless individuals with behavioral health problems to enter treatment. The strategies have included efforts to bring people into treatment by first addressing needs for food and shelter, as well as more coercive measures such as threats of criminal charges for loitering, public intoxication, and so forth, unless treatment is undertaken. Some newer statutes have allowed for outpatient commitment (or "assisted outpatient treatment"), though typically to address mental illness, not addiction (Ridgely, Borum, and Petrila, 2001). It is noteworthy for our purposes, however, that some of those statutes (e.g., those in Michigan and New York) do *not* empower authorities to medicate individuals against their will. Special court orders are necessary. In New York the government can obtain such an order only upon finding that a patient lacks the capacity to make treatment decisions.[24]

Parents with a Substance Use Disorder and Child Protective Services

Congress, state legislatures, and the courts have from time to time attempted to create drug-related incentives or disincentives within the fabric of social welfare programs not directly related to addiction. In 1996, Congress passed the Personal Responsibility and Work Opportunity Reconciliation Act, which contained provisions affecting people with addictions. For example, it authorized states to develop programs to condition the payment of welfare benefits on drug testing (21 U.S.C. § 862b (2003)).

Michigan enacted a statute authorizing a pilot program to test welfare beneficiaries for drugs in three counties (Mich. Comp. Laws. § 400.57 et.

[24]*Rivers v. Katz*, 67 New York 2d 485 (1986).

seq. (2003)). The statute also required that individuals who tested positive complete substance abuse treatment. The Michigan law went into effect in 1999 but was almost immediately blocked by a federal judge.[25] U.S. District Judge Victoria Roberts ruled that the plaintiffs were likely to succeed on the merits of their claim that such indiscriminate drug testing was an unconstitutional search, and this decision was allowed to stand by the federal appeals court.[26] Since Michigan was the only state to attempt to institute drug testing in response to the congressional invitation via federal welfare reform, the federal court's action will likely put a chill on any further such legislation at the state level.

In her decision, Judge Roberts emphasized that the state of Michigan had other means to address the effects of addiction on child abuse and neglect (e.g., child protective services). Under statutes in Michigan and other states, child protective services agencies may remove neglected children from their homes, terminate parental rights, and put the children up for adoption. Addiction can provide the basis for a finding of neglect. Such agencies may also require parents with a substance use disorder to undergo evaluation and treatment for addiction (Paltrow, Cohen, and Carey, 2000).

Courts in various states have upheld the right of child protective services agencies to implement sanctions for the failure of parents with a substance use disorder to comply with treatment recommendations. For example, the Supreme Court of Montana in *In re: J.B.* upheld the termination of a mother's parental rights on her failure to complete a treatment plan.[27] The Ohio courts have also upheld terminations for noncompliance with reunification plans that included addiction treatment.[28] Oregon courts have ruled that the right to due process in these types of proceedings is not violated as long as the proceedings are fundamentally fair.[29] But courts in at least two states have ruled on the termination of parental rights based on proof by *clear and convincing evidence* that the parent has not complied with the treatment conditions of the plan.[30]

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[25]*Marchwinski v. Howard*, 113 F.Supp.2d 1134 (E.D. Mich. 2000), rev'd, 309 F.3d 330 (6th Cir. 2002), vacated and reh'g en banc granted, 319 F. 3d 258 (6th Cir. 2003), aff'd 60 Fed. Appx. 601 (6th Cir. 2003).

[26]*Marchwinski*, 113 F. Supp. 2d at 1135.

[27]No. 99-527, 2001 Mont. LEXIS 330 (Mont. May 10, 2001).

[28]See *In re: Jones*, No. 01AP-376, 2001 Ohio App. LEXIS 5676 (Ohio Ct. App. December 18, 2001) and *In re: Evans*, No. 2000CA00127, 2000 Ohio App. LEXIS 4715 (Ohio Ct. App. October 2, 2000).

[29]*In re: Graham*, CA No. A78417, 1993 Ore. App. LEXIS 1527 (Or. Ct. App. September 22, 1993).

[30]See *Hadley v. States (In re: K.C.)*, 46 P.3d 1289 (Okla. 2002) and *In re: Daniel C.*, 1999 Conn. Super. LEXIS 1933 (Conn. Super. Ct. July 22, 1999).

What seems clear is that child protective services agencies can mandate that parents seek evaluation for addiction and follow through with treatment. Whether agreement to these terms can be considered voluntary given the sanctions involved is arguable. No case law was found to suggest that there are limits to specific modalities of treatment that can be mandated under these statutes. However, it is safe to assume that experimental treatment would probably fall outside the bounds of what the courts would deem reasonable.

Pregnant Women with a Substance Use Disorder

Much publicity in the past several years has surrounded the use of criminal and child abuse laws to address the problem of prenatal addiction. According to the Alan Guttmacher Institute, as of January 2003 no state had enacted a statute specifically criminalizing drug use during pregnancy. However, prosecutors and other public officials have used existing laws for several purposes: to criminally prosecute pregnant women, to evaluate parenting ability or terminate parental rights (Paltrow et al., 2000), to require reporting or testing by health care professionals, and to civilly commit women with a substance use disorder during the term of their pregnancy (Alan Guttmacher Institute, 2003).

The U.S. Supreme Court has spoken on one such policy, striking down a prosecution-focused collaboration among police, prosecutors, and a university hospital in South Carolina. The case before the court was brought by 10 women who were tested for drugs without a warrant or their consent while receiving prenatal care at the hospital, which turned over the results of positive drug tests to local prosecutors. In *Ferguson v. City of Charleston*, the U.S. Supreme Court found that these practices violated the Fourth Amendment right to be free from unreasonable searches.

Interestingly, the South Carolina Supreme Court continues to be the only one to have upheld lower court rulings on arrest and prosecution of pregnant women for drug use.[31] Given that state attempts to prosecute pregnant women have been curbed by the courts, some have suggested mandated treatment as a "compromise" that can less punitively accomplish public health goals. What would be the legal means of mandating treatment? Most states have civil commitment statutes that can be used for such a purpose, but whether a fetus can be defined as an "other" (to meet the commitment criteria of "danger to self or others") is not clear (Chavkin, 1991). Treatment also can be used as an alternative to trial or incarceration or as a precondition for retaining custody of children.

[31]*Whitner v. South Carolina*, 328 S.C. 1 (1997). For a discussion of state responses to substance abuse among pregnant women, see Alan Guttmacher Institute (2003).

Given, however, that the overall goal of intervening in the lives of pregnant women with a substance use disorder is to safeguard their fetuses from exposure to drugs, what implications are raised by the use of pharmacological addiction treatments? It is very unlikely that pregnant women will have participated in premarketing clinical trials for immunotherapies. There will, therefore, be no safety data on the potential toxicity to pregnant women and their fetuses, which would undermine justification for enforcing the use of immunotherapies by pregnant women (Chavkin, 1991).

SUMMARY OF LEGAL BASIS FOR COERCING IMMUNOTHERAPY

In a nutshell, and subject to the uncertainties discussed at the outset, this appendix's findings may be stated as follows:

- People with a substance use disorder are not *per se* incompetent simply by virtue of their addiction, although a substance use disorder may compromise their ability to give informed consent to treatment.
- The law regarding adolescents is insufficiently developed to allow prediction of what the courts might decide as to their ability to refuse immunotherapy if their parents consent to it.
- The interests of the state may override individual rights and permit coercion of treatment generally in the case of violent prison inmates but not immunotherapy in particular.
- Persons who accept parole, probation, or diversion to treatment have effectively "volunteered" for treatment and probably can refuse immunotherapy only if they are willing to risk the consequences of such refusal (i.e., probable incarceration).
- Most likely, immunotherapy cannot be forced on competent adults who abuse or are dependent on drugs but have not been convicted of a crime (e.g., homeless people, parents under the purview of child protective services, pregnant women). However, parenting women may risk consequences related to nonadherence to treatment generally.

ISSUES OF FAIRNESS IN COERCING THE USE OF IMMUNOTHERAPIES AND SUSTAINED-RELEASE MEDICATIONS

Should legislatures and the courts decide that coercion of immunotherapies is permissible, either narrowly or broadly, that does not neces-

sarily imply that it is appropriate in all situations allowed. Two aspects of fairness in implementing a coercion policy are addressed here: issues of safety and effectiveness and issues of coercion within relationships of trust.

Safety and Effectiveness

Many of the legal rulings to date have invoked the caveat that pharmacological addiction treatments must be deemed safe and effective. For whom will these treatments be so? Premarketing clinical trials are often not able to represent every ethnic, racial, and age group and typically do not include children, adolescents, or pregnant women. The groups most likely to be considered for mandatory treatment are individuals involved in the criminal justice system (disproportionately represented by ethnic and racial minorities), adolescents, and pregnant women. This mismatch argues for caution in the coercive use of these therapies until adequate safety data can be gathered across the broad spectrum of potential users.

Effectiveness also includes issues of adherence to protocols. If immunotherapy results in insufficient antibody production to completely "capture" the drug circulating in the body, some drug users might seek to overcome the blockade by using a larger drug quantity. That may result in side effects that clinical trials did not uncover. Also, because drug-dependent individuals will not be able to easily ascertain their circulating antibody levels, their supernormal doses may be taken to challenge an antibody effect that is no longer there, potentially leading to accidental overdose.

Coercion and Trust

Coercion, especially in noncriminal justice settings, has great potential for harming the relationship between the parties involved. Deterioration of a parent-child relationship could lead to greater risk taking, rather than less. In the case of pregnant women, coercive use of immunotherapy could result in fewer persons with a substance use disorder presenting for prenatal care in order to avoid being subjected to unwanted testing and treatment.

The literature on mandated treatment in the mental health arena suggests that there are situations where coercion may be arguably necessary (and certainly legal), but good clinical practice should attempt to minimize its negative effects. Regarding persons with mental disorders who were involuntarily treated, the recent MacArthur coercion studies (Lidz et al., 1995) concluded:

> Patients in the admissions process who reported that others acted out of concern for them, treated them fairly, in good faith, with respect, and without deception, provided them with an opportunity for voice, and took what they said seriously were much less likely to experience coercion. When these moral norms reflecting patient attitudes about how they should be treated are adhered to, many apparently coercive acts seem to be accepted by the patient as morally legitimate. (Winick, 1997, p. 1159)

While the MacArthur studies did not demonstrate that perceptions of coercion were related to treatment adherence (Rain et al., 2003), care should still be taken to assure fairness and respect in determining who should be required to accept immunotherapy treatments and in administering such treatments.

This appendix does not attempt a broad argument against immunotherapies. These new therapies might have tremendous benefits for society—if they prove safe and effective for all groups of potential recipients and if trust-building measures are taken where coercion is necessary. The importance of those conditions is simply emphasized.

REFERENCES

Alan Guttmacher Institute. (2003). *State policies in brief: Substance abuse during pregnancy.* Available: http://www.agi-usa.org/pubs/spib_SADP.pdf [January 2, 2004].

Andrews, L.B. (1984). Informed consent statues and the decisionmaking process. *Journal of Legal Medicine, 5*(2), 163-217.

Applebaum, P., and Grisso, T. (1995). The MacArthur Treatment Competence Study: I. Mental illness and competence to consent to treatment. *Law and Human Behavior, 19*(2), 105-126.

Chavkin, W. (1991). Mandatory treatment for drug use during pregnancy. *Journal of the American Medical Association, 266*(11), 1556-1561.

Grisso, T., Appelbaum, P., Mulvey, E., and Fletcher, K. (1995). The MacArthur Treatment Competence Study: II. Measures of ability related to competence to consent to treatment. *Law and Human Behavior, 19*(2), 127-148.

Hartman, R.G. (2002). Coming of age: Devising legislation for adolescent medical decisionmaking. *American Journal of Law and Medicine, 28*(4), 409-453.

Lidz, C.W., Hoge, S.K., Gardner, W., Bennett, N.D., Manaham, J., Mulvey, E.P., and Roth, L.H. (1995). Perceived coercion in mental hospital admission: Pressure and process. *Archives of General Psychiatry, 52*(12), 1034-1039.

Mossman, D. (2002). Unbuckling the "chemical straight jacket": The legal significance of recent advances in the pharmacological treatment of psychosis. *San Diego Law Review, 39*(4), 1033.

National Association of Drug Court Professionals. (1997). *Defining drug courts: The key components*. Washington, DC: U.S. Department of Justice, Office of Justice Programs.

Paltrow, L.M., Cohen, D.S., and Carey, C.A. (2000). *Year 2000 overview: Governmental responses to pregnant women who use alcohol or other drugs*. Available: http://www.drugpolicy.org/library/governmental_response_p1.cfm [January 2, 2004].

Petersilia, J. (1998). Probation and parole. In M. Tonry (Ed.), *The handbook of crime and punishment* (p. 563). New York: Oxford University Press.

Petersilia, J. (1999). Parole and prisoner re-entry in the United States. In M. Tonry and J. Petersilia (Eds.), *Prisons: Crime and justice* (p. 502). Chicago: University of Chicago Press.

Rain, S.D., Williams, V.F., Robbins, P.C., Manahan, J., and Steadman, H.J. (2003). Perceived coercion at hospital admission and adherence to mental health treatment after discharge. *Psychiatric Services, 54*(1), 103-105.

Ridgely, M.S., Borum, R., and Petrila, J. (2001). *Effectiveness of involuntary outpatient treatment: Empirical evidence and the experience of eight states*. (MR-1340-CSCR). Santa Monica, CA: RAND Corporation.

Riley, K.J., Ebener, P.A., Chiesa, J.R., Turner, S., and Ringel, J.S. (2000). *Drug offenders and the criminal justice system: Will Proposition 36 treat or create problems?* (IP-204). Santa Monica, CA: RAND Corporation.

Siegel, D.M., Grudzinskas, A.J., Jr., and Pinals, D.A. (2001). Old law meets new medicine: Revisiting existing involuntary psychotropic medication of the criminal defendant. *Wisconsin Law Review, 307*, 313.

Winick, J. (1997). Symposium on coercion: An interdisciplinary examination of coercion, exploitation, and the law: III. Coerced confinement and treatment. *Denver Univiversity Law Review, 74*, 1145.

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Ethical Issues in Immunotherapies and Depot Medications for Substance Abuse

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Soon it may be possible to treat an overdose of phencyclidine (PCP) with a kind of passive immunotherapy, a monoclonal antibody (mAB) specifically engineered to neutralize the effects of PCP. It is passive in the sense that instead of stimulating an individual's immune system and waiting for it to produce its own antibodies, as traditional vaccines do, mAB therapy provides ready-made antibodies. Monoclonal antibody therapy for PCP overdose is in development. But it represents only one modality among several targeted for one specific problem—overdoses—associated with substance abuse. Other uses are being contemplated. To get a better grasp of the range of potential new interventions and their uses, consider the following hypothetical case.

Imagine a young professional woman, in her mid-20s perhaps, concerned about the use of so-called date-rape drugs. She worries that at the parties she occasionally attends on weekends some unscrupulous man might slip such a drug unnoticed into her drink. Then she learns about a new medication—a long-lasting intervention that would protect her against date-rape drugs by physiologically short-circuiting her body's vulnerability to the drugs. Someone might succeed in getting her to consume such a powerful drug, but she would be immune to its effects. So, safely, she leaves the party for home.

It would be difficult to see this as anything but a good use of one of the developing technologies for interfering with the physiological action of drugs of abuse. The young adult in this story uses the new medication voluntarily, fully informed of its risks and potential benefits, and for a clearly good purpose—to avert what would have been a terrible wrong—

a possible sexual assault that she might otherwise have been rendered powerless to avoid.

In cases real or hypothetical, the facts, explicit or implicit, are important. In this case the young woman is an adult, not an adolescent or a child. That she is a professional implies that she is functionally competent, even perhaps with a sophisticated grasp of the implications of using the new medication. We must make a few additional assumptions about her—for example, that she is not incapacitated with mental illness, nor does she have a cognitive disability that would make questionable her capacity to understand and appreciate the consequences of her choices. That she is free to attend weekend parties implies that she is free in a more general sense—she is neither incarcerated nor institutionalized. Nor for that matter is she likely to be under the active surveillance of the criminal justice system, as might be the case with someone on probation after being convicted of illegal drug use. There is no reason to suppose that she is addicted to the date-rape drug whose effect she wishes to avoid, so we do not have to consider whether addiction impairs her ability to give free, voluntary, and informed consent. And she is making this decision by and for herself. Neither is she the object of some other person's would-be benevolence nor is she choosing on someone else's behalf. Finally, the purpose for which she is using the new medication seems an entirely worthy one. In short, this hypothetical case includes a set of facts that incline us to approve of her decision. In the messier world in which these new medications might be used, the facts will often be murkier and the ethical judgments more complex.

- Suppose she was an adolescent or child rather than an adult.
- Suppose she had a mental illness or mental disability that interfered with her ability to understand or appreciate what using the new intervention would mean for her.
- Suppose she was in prison or a residential drug treatment facility.
- Suppose undergoing this treatment was a condition of her parole for substance abuse and she accepted it grudgingly.
- Suppose she was powerfully addicted to the drug that the intervention was meant to counteract. Would her consent to treatment mean the same?
- Suppose the drug itself was not illegal—that it was alcohol or nicotine rather than some banned substance.
- Suppose the intervention was imposed on her by another party: her parents, her employer, the government.
- Suppose the intervention was being marketed aggressively, perhaps directly to consumers, by its manufacturer.

- Suppose her reason for taking—or being given—the treatment was not to avoid the unequivocal evil of a sexual assault but for a morally ambiguous purpose.

The properties of the interventions themselves are important. For each one, what are its benefits and risks? For how long do its effects persist? For how long can one detect that such an intervention had been attempted (in the case of active immunizations, perhaps a lifetime)? Looking beyond mere physiology, might a treated person's behavior change in ways that would increase or diminish the risks to his or her own health or to others' safety and well-being?

To have a clear apprehension of the ethical implications of making available interventions like this, the many likely contexts in which they might be used must be anticipated, not merely the most favorable and ethically unambiguous ones. Also to be considered is how we get from here—where we are currently in terms of our scientific understanding of such interventions, especially their clinical effects—to there. As with all potent new drugs and biologicals, the technologies intended to disarm substances of abuse must undergo a thorough evaluation of their benefits and risks via clinical research. To put it another way, both the *ethics of research* and the *ethics of use* must be considered.

After a brief discussion of the intervention technologies themselves and the dimensions of these technologies that are most likely to affect our ethical evaluation of them, this appendix considers first the *ethics of research*. Along the way what makes informed consent ethically significant and what makes it meaningful in practice are discussed. Then the discussion turns to the *ethics of use*, focusing on one of the most ethically complex possibilities for use—when parents want to administer these technologies to their children in order to discourage or prevent them from engaging in substance abuse.

FEATURES OF THE POSSIBLE INTERVENTIONS WITH SPECIAL ETHICAL RELEVANCE

Immunotherapies or depot medications might be used for three purposes. The first is to treat an overdose by administering passive immunotherapy in the form of mABs. That is, instead of exposing the immune system to a modified form of the antigen and waiting for the body to mount its own antibody response, passive immunotherapy provides ready-made antibodies. Such a therapy could be life-saving. But like all potent interventions, it will have additional effects. One strategy for helping a person through withdrawal from addiction is to use a modified form

of the drug. The mABs may neutralize such treatments just as effectively as they neutralize the addictive substance, leaving the addict without relief for the symptoms of withdrawal. Another possible danger arises when the person recovers from the overdose but remains in the throes of addiction and may once again seek the drug. As long as the passive immunotherapy is active, the person will need higher doses of the drug in order to achieve the experience that reinforces the addiction. For example, if a person needed to take five times the usual dose to get high from an illegal narcotic, he or she would be exposed to five times as much adulterants or impurities present in the drug.

The second purpose would be to prevent relapse. For this any of the three available modalities might be useful: passive immunotherapy, active immunotherapy, and depot medications. In addition to concerns about the expense of relapse prevention protocols, which would require parallel intensive psychosocial interventions, there will be concerns about the meaningfulness of the person's informed consent to research or treatment. To the extent that the individual may suffer from a comorbid mental illness, his or her capacity to consent may be impaired. If the relapse prevention protocol is tied in any way to the legal system—as an alternative to incarceration, a condition of probation, or the like—voluntariness is suspect. As an additional observation on active immunotherapies, biological traces, such as persistent antibodies or memory lymphocytes, of active immunotherapy may persist at detectable levels for a very long time, perhaps even a lifetime. This would be true for active immunotherapies used either for relapse prevention or, in the third likely purpose of use, protection protocols.

The desire to protect individuals or populations from substance abuse may prompt the use of protection protocols. Here the analogy with traditional immunotherapies for infectious diseases is at its strongest. Research on such protocols may present significant ethical challenges, but the most difficult problems are likely to arise if and when such products are approved for marketing and when parents seek them for their children.

There is an important observation well known to physicians and others familiar with prescription drug policy in the United States, but probably not broadly understood by the public. Once a drug is approved for marketing in this country, physicians can prescribe it for indications or populations not included in the official Food and Drug Administraion (FDA) approval. Physicians could, for example, take an active immunotherapy approved for relapse prevention in adults and prescribe it for the purpose of "protecting" a young child from becoming addicted to the same substance. Pharmaceutical companies have devised ways to encourage such off-label use.

CHALLENGES IN THE ETHICS OF RESEARCH: FROM IDEA TO PRACTICE

To get from a promising idea to an effective treatment, the immunotherapies and depot medications under consideration must undergo thorough evaluation in clinical research. The ethical challenges posed by clinical research on these particular interventions on the likely populations of interest and at risk are particularly daunting. This section attempts to identify the challenges. Where clear conclusions can be drawn and confident recommendations made, that will be done. But many problems will go unresolved. For these the nature of the problem is described along with the values at stake.

The world of clinical research is itself beset with criticisms these days (Angell, 2000; Bodenheimer, 2000). Substantive matters for concern include the following: Who gets recruited as clinical research subjects and why? What are the ethical implications involved in study design, methodology, and outcome measures? How can informed consent be made to serve in practice the noble ethical purposes it is presumed to serve in theory (see Faden, Beauchamp, and King, 1986)? Less ethically complex forms of clinical research may struggle with subject recruitment, study design, and the like; all forms of clinical research must confront the challenge of making informed consent meaningful (Feussner and Murray, 2002).

Who Will the Subjects of Research Be?

Though there will certainly be overlap, the three purposes of treatment—overdose protocols, relapse prevention, and protection—have features that distinguish them from each other.

Once overdose protocols move into the stage of testing for efficacy, the subjects of research will include, unsurprisingly, individuals who have taken an overdose of a drug of abuse. The clinical state of such individuals may vary considerably as a function of the particular drug taken, the dose, the time elapsed since taken, and their overall health, among other factors. In some cases in which the urgency is low, time is available, and the person is conscious, competent, and communicative, it may be possible to inform the person and get his or her voluntary consent to participate in research. In other instances, however, the person may be confused, incoherent, or unconscious; whatever intervention is to be made must be begun urgently; and the person may be in police custody, transported from an institution, or otherwise unfree.

Informed consent has been the fulcrum of the ethics of research with human subjects at least since the Nuremberg Code. Informed consent performs double duty: It demonstrates respect for the person being asked to participate in research and, by providing an account of the risks and ben-

efits, gives the individual the opportunity to exercise her or his own preferences and hence is believed to promote the most appropriate overall balance of benefit and risk.

Many factors can impair informed consent in practice. Some can be described as *subject-specific* factors, which can be further subdivided into those factors that affect a person's *capacity* and those that affect the person's *voluntariness*. In addition, there are factors related to the *person requesting consent* and the *setting*—in the broadest sense—in which the consent is being sought.

Subject-specific factors affecting capacity include the ability to understand the information being conveyed (including cognitive capacity, familiarity with the language used, and literacy if printed information is used), the ability to appreciate the significance of that information for the decision to be made, and the likelihood of avoiding the cognitive biases and errors that infect so much decision making (Holmes-Rovner and Wills, 2002; Ubel, 2002).

If a person is severely intoxicated, disoriented, or muddled, his or her capacity to consent is put into question. People with mental disorders interfering with their capacity to understand and appreciate the implications of a decision to enroll in a research protocol may not be able to give a morally meaningful and valid informed consent to research (National Bioethics Advisory Commission, 1998; Appelbaum, 2002). If a person is unconscious (which will be the case for some people for whom overdose protocols are designed), the capacity for consent is, at that time at least, nil. To deal with this last category of persons, those requiring emergency medical treatment while not competent to give consent, a new set of rules has been adopted (61 *Federal Register* 51, 1996).

New rules were needed to extricate us from an ethical Catch-22. On the one hand, emergency room physicians were permitted, ethically and legally, to try innovative therapies to help their patients, even when patients were unable to give consent. On the other hand, under the rules governing research with human subjects, those physicians were not permitted to do the research necessary to learn whether these new interventions worked better or worse than the old ones, thus the Catch-22. The new rules for research with patients unable to give consent in the emergency room create stringent safeguards to protect such patients against abuse or frivolous experimentation while permitting research on the therapies that might benefit those same patients. One of the safeguards requires seeking and obtaining what is being called "community consent." The details of community consent are being worked out. Deciding what constitutes adequate community consent for research on persons suffering from drug overdoses will be a challenge. Serious work on that problem should begin immediately.

What to make of the capacity to consent to participate in research when a person is addicted to a substance of abuse is a more complex question (McCrady and Bux, 1999). In general, we do not act as if we believe that addiction relieves people of all moral and legal responsibilities when they do something wrong. Rather, it is assumed that people are accountable for their actions in the absence of convincing reasons to think otherwise. That presumption does not carry over straightforwardly to the context of research. In recruiting people as research participants, especially for anything involving more than minimal risk, the presumption is that they should be informed competent volunteers. Evidence of some impairment of voluntariness or of cognitive capacity can be enough to disqualify someone from enrolling in a research protocol (Nelson and Merz, 2002). Therefore, the fact that someone is addicted may carry more weight in the judgment on whether to permit that person to volunteer for research than it carries in a criminal courtroom.

A recent discussion about consenting to participate in a research study involving prescription medication for heroin argues that the decisional impairments characteristic of heroin addiction, which include compulsion, intoxication, and withdrawal, compromise both understanding and voluntariness (Charland, 2002). But relapse prevention studies are likely to differ from heroin administration studies in important ways. The interventions given in relapse prevention studies may reduce the compulsion, prevent intoxication, and diminish or eliminate the symptoms of withdrawal. The desire to *escape from addiction* should be distinguished from the addiction itself.

Subject-specific factors affecting *voluntariness* include being incarcerated, institutionalized, or otherwise under the control or influence of other parties such that one's liberty to consent or refuse to consent is diminished.

Some substances of abuse are illegal; others, such as alcohol, cause intoxication that can result in entanglement with law enforcement through, for example, driving while impaired or fighting. Many potential research subjects will have had interactions with the criminal justice system (McCrady and Bux, 1999). Some may be in prison; some may be on probation or under some form of surveillance; others may believe they are being offered a choice between being punished or enrolling in research. In all such cases, voluntariness may be in question.

Factors involving the *person requesting consent* may also pose challenges to obtaining fully voluntary and informed consent for research on immunotherapies and depot medications for substances of abuse. In situations in which a treating physician recommends to a patient that she or he consider enrolling in a clinical trial, the usual issues include concerns about possible conflicts of interest on the physician's part—for example, if the physician has any financial interest in the drug or device being tested

or has been offered incentives for recruiting research subjects (Bekelman, Li, and Gross, 2003). Such concerns are common to a broad range of research protocols and subject recruitments; they may be pertinent to research on immunotherapies and depot medications for substances of abuse as well. But the person requesting consent for research on these particular interventions may have a more complex relationship with the prospective subject (Chen, Miller, and Rosenstein, 2002).

The requester may be perceived by the prospective subject to be in a position of potentially coercive authority. How did the potential research subject come into contact with the requester? There is no one scenario likely to account for all cases, but it may be instructive to consider plausible cases for the three categories of intervention mentioned earlier: overdose treatments, relapse prevention protocols, and protection protocols.

For prospective research subjects in overdose treatment protocols, some, perhaps most, may be unconscious, intoxicated, or so muddled as a consequence of their overdose that fully informed consent is impossible. Leaving such cases aside, some individuals may present voluntarily for treatment at an emergency room for fear they have taken an overdose. There they may encounter a specialist in emergency medicine who is collaborating in a clinical trial of passive immunotherapy (mABs) to treat an overdose of PCP. In all likelihood they will have no previous relationship with this physician. If the drug ingested is illegal, like PCP, they may fear arrest; if they have a previous record of drug-related crimes, they may be wary of giving any personal information to emergency room staff; indeed, they may give a false name. In the best of cases, they will be truthful about the drug and their own identity and health history; the emergency room physician will explain carefully and thoroughly what the research protocol entails and offer the patient the right to consent or refuse, making it completely clear that the patient will receive appropriate treatment in either case; and the investigators will have taken the permitted steps to protect subjects' confidentiality, so that enrolling in the clinical trial will not increase their risk of criminal prosecution. Life, of course, does not always present the best of cases.

The possibility of participating in research on relapse prevention protocols presupposes that a prospective subject has experienced addiction to one or more substances of abuse (otherwise it would not be a *relapse*). The person inquiring about whether a prospective subject would be interested in enrolling in the research may be the individual's primary care physician. It seems more likely though that the requester specializes in the treatment of substance abuse and hence may work in a substance abuse clinic or resident treatment facility. The physician's role may be more confrontational, more controlling than the typical primary care doctor; the physician's role may also include what sociologists call the "dirty

work" of medicine—social control functions such as those performed by occupational physicians who certify whether an employee is fit to return to work or whether an injury was job related (Murray, 1986). The substance abuse clinic physician may hold the power to declare whether a patient is "clean," if it is safe to release the individual from the facility, or if the individual is complying with the demands of her or his probation. Whenever the physician or someone perceived as that physician's agent makes the request, the prospective research subject may feel compelled to agree—because of the requester's power over the person.

Research on protection protocols is likely to come only after the interventions have been vetted in overdose and relapse prevention studies. Only plausible speculation can be offered about the circumstances of protection protocols. In the ethically simplest case, a study of a well-characterized intervention with only a few minor side effects is offered to free competent adults. The "protection" intervention might be a passive immunization with mABs that interfere with the action of date-rape drugs—the example used at the beginning of this chapter. (Designing an ethically acceptable protocol to test the safety and clinical efficacy of such an intervention for this purpose would be a challenge.) Who would conduct such a study? In what institutional settings might it be done? Who would have the interest and the resources to fund such a study? If these questions could be answered satisfactorily, use of such an intervention for such a purpose could be thought of as a version of a "Ulysses contract"; just as Ulysses had his crew bind him to the mast so that he could not yield to the Sirens' temptation, so a woman immunizing herself against the action of a date-rape drug is trying to protect against yielding to the seductive temptations of the drug (Dresser, 1984).

In practice, it appears much more likely that the principal demand for protection protocols will come from parents anxious to prevent their children from becoming dependent on substances of abuse, whether illegal or legal. This section focuses on the context of research, so the discussion of likely scenarios in which parents might seek such protective interventions for their children is deferred until later in this appendix. The initial research on protection protocols is virtually certain to have competent adults as its first subjects. Enrolling informed adults with full capacity to consent, whose participation is clearly voluntary, simplifies the ethical analysis of such trials. All the usual questions about the ethics of research—the nature and extent of the risks, the possibility of benefit to the subjects and to others, the protections afforded to subjects' privacy, the absence of troublesome conflicts of interest among the investigators, and so on—will still need to be asked and satisfactorily answered.

Suppose that these initial clinical trials are done and that they confirm that the intervention is relatively safe and effective. If, as seems likely for

many of the interventions imagined, its most likely practical use is in children and adolescents, decisions will need to be made as to whether studies must or should be done with such subjects who are not fully competent or independent and, if so, how those studies should be designed and what will count as ethically adequate consent (from parents or legal guardians) and assent (from the subjects themselves) (Kopelman, 2000; Food and Drug Administration, 2001).

The last topic under the ethics of research is the *setting* in which potential research subjects are identified, recruited, and enrolled. Of the principal settings in which most clinical research subjects are recruited—the physician's practice and the specialty clinic or hospital—the former is likely to be less commonly employed for the studies under consideration here, and the latter, in these cases the substance abuse clinic, has properties that place it outside the usual clinic environment, especially the social control aspects of treatment for substance abuse and the fact that much of the conduct creating the need for treatment may be illegal. Other settings include the emergency room (especially for overdose treatment protocols) and the family, for protection protocols used in children and adolescents.

One potential problem lies at the intersection of the patient, the person requesting consent, and the setting; it goes by the name of *therapeutic misconception*. People being recruited as research subjects for clinical trials often fail to appreciate the difference between medical care and research—a phenomenon dubbed the therapeutic misconception, defined as occurring "when a research subject fails to appreciate the distinction between the imperatives of clinical research and [those] of ordinary treatment, and therefore inaccurately attributes therapeutic intent to research procedures. Most often, this will occur in clinical research, but it can also occur in nonclinical settings" (Lidz and Appelbaum, 2002, V-57). Patients often appear to believe that their physicians would only recommend that they enroll in research when those physicians are convinced that doing so is in the patients' best interests. The norms that guide clinical care and those that guide research differ in important respects. Good clinical care embodies individualized care; good research requires standardized treatment. Clinical care is aimed at benefiting a single patient; research is aimed at creating generalizable knowledge and benefiting future patients.

There are data to support the existence and significance of the therapeutic misconception. A study published in 1995 reported that 78 percent of Americans did not know what "randomly" meant and 83 percent could not explain "double blind" (Waggoner and Mayo, 1995). In a study of research subjects in four chemotherapy Phase I trials—toxicity and dosage studies—at the National Institutes of Health, all 127 subjects said that the trial had treatment as well as research aims (Schaeffer et al., 1996).

Lidz and Appelbaum (2002) exhort researchers to try to dispel the

therapeutic misconception. They acknowledge that some people may decline to participate in research when they understand fully the difference between standardized research protocols and individualized treatment, but they point to plausible advantages for the research enterprise: fewer angry subjects during and after the conclusion of studies; the possibility of fewer dropouts in the course of studies; and the preservation of public trust in research and researchers, including the willingness to participate as research subjects.

Is the therapeutic misconception a problem for research on immunotherapies and depot medications for substance abuse? If the subjects in these studies are less well educated and less sophisticated about scientific research, they may be more susceptible to the therapeutic misconception. If, on the other hand, they are more suspicious or mistrustful of the health professionals providing their clinical care, they may not presume that the principle of personal care governs their relationship with their clinicians and may be less likely to fall prey to the therapeutic misconception. To the extent that the populations from which subjects are drawn for research are already mistrustful of researchers, the therapeutic misconception and the resentment that may follow once it is corrected may exacerbate those communities' suspicion of research. This would be a particularly unfortunate outcome for everyone.

CHALLENGES IN THE ETHICS OF USE: FROM IDEAL TO MUNDANE REALITY

It is not difficult to imagine situations in which using an immunotherapy or depot medication would be welcome by the person using it and deemed a good thing by informed observers. The hypothetical case with which this chapter began is an example. The principal virtue of a hypothetical case is, of course, that its creator can load it with whatever details he or she wants to elicit the desired response. But there is an associated trap: Rarely does reality conform to the hypothetical. Life brings heaps of complexity, and people's judgments, rather than being clear and ringing, are often shadowed by ambiguity and uncertainty. Using depot medications and immunotherapies for substance abuse will be no exception to the rule of complexity and ambiguity.

We may worry more intensely and systematically about informed consent in the context of research, but informed consent is important in treatment as well. This is especially so when there are reasons to fear that the person may lack elements of the capacity to make meaningful and informed decisions or when the voluntariness of a person's consent may be in doubt. The same characteristics that lead us to worry about the capacity of people to consent to research will also cause concern about the

meaningfulness of their consent to treatment: cognitive and emotional maturity, mental illness and mental disability, addiction. The same situations that lead us to worry about the voluntariness of consent to research will be relevant again in the context of treatment—that a person is incarcerated or under the threat of incarceration, that an individual is under the power of some other person or entity such as a government agency. The fact that many substances of abuse are illegal and that others that are legal may nonetheless be linked to actions that can get someone in trouble with the law (like driving under the influence) adds complexity to the analysis. Finally, there is a certain moralism attached to substance abuse that may affect how health care professionals regard and act toward people seeking treatment for substance abuse (Klerman, 1972). That moralism may incline physicians toward harsher interventions and may make them less sensitive to privacy and confidentiality with such patients.

How significant are these concerns likely to be? Looking again at the three categories of likely treatment protocols reveals important differences among them. First, overdose treatment protocols that use passive immunotherapies raise the fewest red flags. People for whom this is an indicated treatment have either been brought to or presented themselves at an emergency room. If they are conscious and competent, they can consent to the intervention. If they are unconscious or incompetent, the treating physician has a professional ethical obligation to provide appropriate treatment; if passive immunotherapy is proven to be superior to other interventions, the physician is simply fulfilling his or her professional duty by applying it.

This is not to say that passive immunotherapies carry no short- or long-term risks, medical or otherwise. In the example mentioned in the committee's report, a person treated for an overdose in this way might face some risks for the interval—as long as several months—during which the mABs remained active. If the person experienced withdrawal, one treatment strategy for withdrawal would be rendered more difficult—that is, treatment with an agonist that ameliorates the pangs of withdrawal. The mABs may interfere with the action of the agonist just as it blocks the activity of the substance of abuse. Treating withdrawal then might require much higher doses of the agonist, with whatever risks attend such doses. If the person tries using the drug again while the mABs are still active, he or she will have to use larger doses in order to overcome the antagonistic activity of the mABs. If the drug itself has toxic effects or if as a street drug it contains adulterants, the risks of physical harm increase as the amount used increases. These risks are contingent on the actions of the person treated. Some people may get additional benefits from passive immunotherapy if they choose to forego further substance abuse while the mABs are in their bodies.

On the whole, passive immunotherapy in an overdose treatment protocol raises relatively few novel or difficult ethical problems. Attention will have to be given to follow-up for the interval during which the mABs remain active. But with reasonable attention to informed consent and treatment under emergency circumstances, to patient confidentiality, and to the training of health care professionals to gain perspective on the perils of moralizing, this category of interventions is not especially ethically problematic.

Relapse prevention protocols present a wider spectrum of possible interventions as well as contexts of treatment. Like overdose treatment, passive immunotherapy could be used. Unlike overdose treatment, the therapy would have to follow a period of detoxification and be readministered periodically in conjunction with psychosocial interventions. Depot medications would also require repeated treatment and psychosocial interventions, possibly accompanied by urine testing for compliance. Active immunization is more complicated still. Like the other two categories, it is likely to require multiple administrations (to induce antibody production) and periodic readministration to keep antibody levels up as necessary. In contrast to passive immunotherapy in which the quantity of antibodies administered is known, people's antibody production in response to active immunization can be highly variable. Also, active immunization may become a kind of "scarlet letter," leaving lifelong markers of interest to others (e.g., military, police, employer, insurer, even a future spouse).

Beyond the clinical complications, relapse prevention protocols are likely to be given in contexts fraught with ethical complexities. In the discussion of research on such protocols, some of these complexities were mentioned: the reality that the patient has a substance abuse problem and, very possibly, has had or is at risk of encounters with the law; the clinicians treating such patients may have complex relationships with them, including indirect power over their liberty or their eligibility for treatment. Typical sources of power discrepancies between physicians and patients become magnified and may be more numerous in relapse prevention treatments. Differences in education, social class, and institutional power have greater significance when physicians exert control over patients' destinies in more than a narrowly medical sense.

There may also be times when the physician acts explicitly as an agent of the state. For example, the patient may be given the option of relapse prevention as an alternative to prison, or the patient may be compelled to see the physician for treatment and monitoring as a condition of parole. Of the options available to the patient, this may be the least undesirable. The implications for informed consent, the physician-patient relationship, and the role of the physician are serious and must be given full weight in designing acceptable policies.

Protection protocols have potentially the widest scope for application and also raise the most novel and challenging ethical issues. Again, the hypothetical case that began this paper is an example of a protection protocol that seems, on balance, well justified. Alter the facts of the case, however, and matters may not seem so clear anymore. A less than fully competent or voluntary patient, a dubious ratio of risk to benefit, or uncertainty about long-term effects raise provocative ethical questions. The questions become most urgent and difficult when contemplating a likely—perhaps the most likely—use of protection protocols: parents wishing to have the intervention for their children.

PARENTS, CHILDREN, AND PROTECTION AGAINST SUBSTANCE ABUSE

Parents allow their children to be vaccinated in an effort to prevent them from being harmed by diseases that used to cause widespread suffering and death. Even parents who refuse to have their children vaccinated may be acting from a similar motivation; they may be convinced that the vaccine is a greater risk to their children than the disease itself. Parents in both cases are trying to protect their children from harm. It should be no surprise if and when immunotherapies and depot medications against substances of abuse are approved for marketing that some parents will seek such interventions for their children. Policy makers and clinicians will be called on to anticipate and respond to such requests. Among the factors to be considered are:

- Is the substance of abuse itself legal for *any* population, such as adults (e.g., alcohol, nicotine) or illegal (e.g., opiates, PCP, marijuana)?
- What are the risks of the particular intervention?
- What is the duration of action of the intervention? Will its effects outlast childhood?
- Will the biological evidence that such an intervention was made survive into adulthood and with what medical or social consequences?
- Will intervening now foreclose choices when the individual reaches adulthood?
- Might there be distinct social patterns to the use of such interventions? Will it be more attractive to people in cities or suburbs? To the relatively wealthy, poor, or middle class? To people with different religious commitments? To people whose insurer will cover the cost?

The one certainty here is that parents will have a vast range of reactions. Some parents, out of conviction, experience, or fear may leap to immunotherapies or depot medications as the best way to ensure that their children do not become addicted to one or more drugs of abuse, from alcohol and nicotine to heroin, cocaine, or other illegal drugs. Other parents, out of caution, skepticism, confidence, or beliefs about their children's risks, may spurn the interventions. Initially at least, not all parents will know about them. And depending on their cost, some parents may decide they cannot afford immunotherapies or depot medications even if they think the interventions are desirable. Also, lobbying efforts can be expected from those hoping to profit from the sale of immunotherapies and depot medications to encourage or compel insurers to pay for their use.

A remote and unlikely alternative would be a state or federal policy requiring, for example, that all children be immunized against one or more substances of abuse, the way childhood immunizations are required for common infectious diseases. Or perhaps there could be voluntary programs promoting periodic administration of depot medications or active immunotherapies (that require regular reimmunization) on the model of the annual flu shots aimed at vulnerable populations. Such programs would require very different risk-benefit judgments than currently exist; the risks of the interventions would have to be seen to be very low and the benefits fairly clear and certain, while the risks of substance abuse would have to be seen as severe enough to be worth the risk and expense. Unfortunately, drug policy in the United States has at times been shaped more by fear and misinformation than solid science, so the possibility of government initiatives to promote such immunotherapies and depot medications, even in the absence of clear evidence of their wisdom, cannot be dismissed.

Before people begin contemplating using immunotherapies or depot medications as public health measures—coercive or quasi-voluntary—and likely even well before these interventions are tested or approved for use in children, some parents will seek to use them on their children. Similar behavior has occurred, arguably for a much less compelling purpose, with human growth hormone (hGH; Murray, 1987).

Cadaveric hGH was introduced for use in children suffering from deficiencies in physiologically active hGH—either because low levels were produced or because what was produced was biologically inactive. By the early 1980s some parents were seeking hGH for their children who did not have evidence of hGH deficiency and who may—or may not—have been short for their age. That this was happening was confirmed in many ways, including articles in the scholarly literature (Benjamin, Muyskens, and Saenger, 1984) and in one instance a conversation with a

pediatric endocrinologist at an FDA hearing at which this author was asked to testify. (This doctor also said that all or virtually all the requests she had received came from physicians.) Such parental pleas came despite consistent opposition by the Ad Hoc Committee on Growth Hormone Usage (1983) and the American Academy of Pediatrics (1997). At least some physicians gave in to these pleas (Cuttler et al., 1996).

Parents who sought hGH for their non-hGH-deficient children did so, it appears, from a variety of motives. In some cases they may have wanted to spare their children from the social disadvantages, and at times discrimination, visited on adolescents and adults of short stature. Discrimination of this sort has been dubbed "heightism," like racism, sexism, or ageism—that is, treating or regarding a person according to an attribute that is irrelevant to the matter at hand. The flip side of heightism is exemplified by parents who seek hGH for their children because of the perceived advantages of being taller. These parents, rather than attempting to spare their children from the disadvantages of heightism, instead seek to exploit it for their children's benefit.

With hGH, parents may be motivated by a desire to help their child overcome a disease (a lack of physiologically active hGH), a disability (severe idiopathic short stature), or a disadvantage (idiopathic short stature that is not severe—e.g., less than two standard deviations from the population average). Some parents have sought a comparative advantage for their children. A pediatric endocrinologist directing the hGH program at a major American academic medical center told me of a teenage girl, 5'9", whose parents wanted her treated with growth hormone. She played volleyball and her coach had told them that if she were 4 inches taller she would surely be offered a scholarship from any college with a women's volleyball program.

As it happens, the evidence is mixed that hGH given within a physiologically normal dosage range increases the height of non-hGH-deficient children. Some studies show a slight increase in height; other studies show no difference. The studies are mostly small and typically fail to follow the children into adulthood. The cost of height attained, if any, is estimated at no less than $14,000 per centimeter, or roughly $35,000 per inch—and that assumes the best response found in studies of children with idiopathic short stature on optimized treatment with both hGH and gonadotropin-releasing hormone (Kaplowitz, 2001). It is an enormous financial investment for an uncertain anatomical outcome. Perhaps more important, years' worth of hGH injections may focus undue attention on a single criterion by which that child literally "comes up short" rather than on the child's strengths and talents. Whether hGH treatment is *on the whole* a benefit to a child with idiopathic short stature—where final adult height may be a disadvantage but not a disability—is open to question.

In the case of immunotherapies and depot medications for substances of abuse, parents' motivations are more likely to reflect a desire to prevent harm to their child rather than to seek a competitive advantage, making it similar to the use of hGH to treat disease or to ameliorate disability. But a child put on a protection protocol does not yet have a disease, as does a child with diagnosable hGH deficiency. The closest analogy then is with children with severe idiopathic short stature. These children have no known disease, but they are at risk of the sort of harm that often faces people of severe short stature; these risks are due mostly to human choices in the construction of our human-made physical environment and to the attitudes, beliefs, and actions of the people they encounter.

When parents have their children put on immunotherapies or depot medications to protect them against substance abuse, the parents here, like the parents of children with severe idiopathic short stature, are attempting to protect their children against what the parents regard as the risk of serious harm. In both cases, parents may perceive their children as being *vulnerable*. But the vulnerabilities are different. Children with severe short stature are vulnerable precisely because in this respect they are *unlike* other children of similar age and circumstances. Children enrolled in protection protocols are vulnerable precisely because they are *like* other children; their lack of maturity and wisdom, their susceptibility to peer pressure, the propensity of young people to experiment are all attributes that are widely shared.

Another factor distinguishing children in the two cases is the likelihood of harm. Children with severe short stature *will* suffer harms associated with disability; the question is only how often and how deleteriously. Parents do have nonmedical options for helping their children. They can build their child's sense of self-worth, emphasize the child's strengths, and find communities that welcome their child. Society can also become more accommodating to differences and less prone to the prejudice of heightism. But however resourceful and strong parents may be, children with severe short stature will likely be exposed to some types of harm, some of the time.

Children placed on protection protocols may have no elevated risk of harm from substance abuse. Merely being a child or adolescent does not mean that an individual will suffer the harms associated with substance abuse. Some children avoid abuse altogether; others experiment briefly but either cease such use completely or in time adopt a pattern of use of, for example, alcohol, that is mature and controlled. The benefits of protection protocols are, therefore, less certain in the degree that the harms are also less certain.

A broad range of plausible scenarios can be imagined in which parents

seek immunotherapies or depot medications for their children. In the hypothetical case with which this appendix began, we need only make the young woman an adolescent and have the decision made by her parents. Physicians may face ethical challenges in such cases depending on the age of the child or adolescent, their child's acceptance or resistance to the parents' wishes, and the intervention's duration of action. Suppose that parents present for protection a relatively young child. The younger the child, the more willing society is to accept the parents' authority to make medical decisions on the child's behalf. Suppose the child does not want the intervention. When may an intervention be imposed on a child against her or his will? Suppose that the intervention lasts for months, years, decades, or even a lifetime. Should we be less quick to apply such interventions when the consequences for the child are long lasting?

In a study of the issues raised by enhancement via gene transfer, Juengst distinguishes among three types of control: personal, professional, and policy. "Personal" refers to the decisions made by individuals or, in the case of children, by their parents. These decisions are shaped by individual moral beliefs and broad cultural forces. "Professional" refers to the standards, formal or informal, that govern the practices of professionals. The American Academy of Pediatrics and Lawson-Wilkens Endocrine Society's guidelines for using hGH in children are examples of professional standards that regulate practices in the absence of governmental laws or regulations (Lawson Wilkins Pediatric Endocrine Society, 1995; American Academy of Pediatrics Committee on Drugs and Committee on Bioethics, 1997). Professional standards can be quite effective if they are clear and widely respected. However, even if a consensus is formed among physicians to strictly limit access to immunotherapies and depot medications for substance abuse, some physicians might, out of fear of drug dependency or because of sentiments strongly in favor of parental discretion, accede to parental requests for such access. Control by "policy" refers to formal governmental actions whether by legislation or regulation.

It seems plausible that immunotherapies and depot medications will at least initially be available only by prescription. Anyone seeking these interventions through legally approved sources, then, will presumably consult a physician or other professional entitled by law to prescribe them. What will parents request and what should clinicians do in response? What public policies should there be to cope with these interventions? Consider two scenarios. In the first, parents ask a physician to prescribe a depot medication for nicotine addiction for their 12-year-old child. In the second, parents ask that a new very long-lasting vaccine—an active immunotherapy—against response to opiates be administered to their 15-year-old child.

DEPOT THERAPY AGAINST NICOTINE ADDICTION

The savvy parents of 12-year-old Vicky understand—almost as well as the tobacco companies—that people who do not begin smoking cigarettes during adolescence or childhood rarely become addicted to nicotine. Vicky's parents also understand the power of peer pressure at the relatively affluent school their daughter attends. Vicky has not given her parents any particular reason to worry, but she is a bit shy and terribly eager to please her fellow students in the hope that they will become her friends. Some of Vicky's classmates are experimenting with smoking as a form of adolescent rebellion and because they believe it gives them an aura of maturity. Vicky's parents are worried that she might take up smoking as a way of ingratiating herself with the "popular" clique at school. Though they recognize that it will not affect Vicky's underlying desires for acceptance, they ask her pediatrician for a prescription for the new depot medication against nicotine for their daughter.

A VACCINE AGAINST OPIATE ADDICTION

Larry's parents are worried that their 15-year-old son will fall prey to the heroin dealers that infest their neighborhood. So far, they believe, he has stayed clean. But the children of three friends have become addicts and one has died of an overdose. Recently, a vaccine against opiates was approved by the FDA. It is an active vaccine that spurs the body to produce antibodies, some of which are likely to be detectable for many years. There is uncertainty about just how long the immunological effect will linger. This particular vaccine works very well and seems to provide long-lasting protection, but to be safe the current recommendation is to have periodic booster shots.

CHALLENGES TO PARENTS, HEALTH CARE PROFESSIONS, AND PUBLIC POLICY

What would a good and responsible parent do with respect to depot medications or immunotherapies for substances of abuse? This is not a simple question, and it does not invite easy answers. People who think that they *know* the right answer are likely to be confronted by other people equally certain that *they* know the right—and precisely opposite—answer.

The Worth of a Child (Murray, 1996) proposes an understanding of the relationship between parents and children in which each depends on the other for the conditions necessary for their individual and mutual flourishing. Actions, practices, policies, and laws are defensible to the degree to which they create or support conditions conducive to the family flourishing and to the values central to family life—both those values intrinsic to

healthy families, such as love, loyalty, steadfastness, and forgiveness, and those values made possible by such families, such as emotional resiliency, the capacity for enduring relationships, and generativity.

Thinking about the ethics of parenting in the framework of flourishing and mutuality is not meant as a way to find easy answers, but it is intended to protect against oversimplification—to ensure that what is morally most important about families remains at the center of our ethical reasoning and that no significant morally relevant consideration gets left out. Other ways of framing the ethical issues for parents may appear simpler at first glance, but in practice are at least as complex.

Take the case of Vicky and her parents. It should be easy for most parents to understand the parents' desire to protect their daughter against nicotine addiction. They want to spare her from the diseases that accompany exposure to cigarette smoke. They might invoke a parent's duty to protect their minor child from sources of harm, whether the actual harm occurs now or in the future. Vicky's parents may be trying to balance the risks and benefits of using one of these interventions. It is never a trivial matter to decide which risks and benefits are relevant. If her parents focus exclusively on the risks and benefits to health, the decision may seem obvious: use whatever interventions are available to prevent nicotine addiction. Parenthood, unfortunately, is rarely that simple. By attending only to the direct risks to health, Vicky's parents leave out many other important factors, such as the possibility that struggles with their daughter over control will impair the growth of mutual trust and respect and may lead to rebellion and backlash. Or Vicky may choose another, more rapidly destructive means of declaring her independence from parental control.

The point here is not that parents should absolve themselves from such decisions. They have an ethical obligation to make decisions about exactly this sort of issue. No, the point is that such decisions can be complicated ones, fraught with implications that go far beyond the near-term consequences for health. So, if as a framework the balance between risks and benefits is chosen, either all but a small subcategory of such risks and benefits must be set aside—those pertaining to health and safety—or the full range of relevant considerations must be acknowledged, deciding which ones are most important and weighing and balancing them.

Vicky's parents could approach this decision with a different moral framework—for example, the one suggested by such scholars as Dena Davis and Joel Feinberg. This framework gives priority to preserving Vicky's liberty to decide for herself, a liberty that would be constricted by addiction. The latter motive, preserving Vicky's ability to choose, is captured in the ethical concept of the *right to an open future*. Davis (2001) offers a wonderfully clear summary of Feinberg's (1980) classic distinction of four kinds of rights:

> First, there are rights that adults and children have in common (the right not to be killed, for example). Second, there are rights that are generally held only by children (or by "child-like" adults). These "dependency-rights" . . . derive from the child's dependence on others for such basics as food, shelter, and protection. Third, there are rights that can be exercised only by adults (or at least by children approaching adulthood), for example, the right to choose and to practice one's religion. Finally, there are rights that Feinberg calls "rights-in-trust," rights that are to be "*saved* for the child until he is an adult." These rights can be violated by adults now, in ways that cut off the possibility that the child, when she or he achieves adulthood, can exercise them.

The concept of the child's right to an open future gives wide discretion to parents' judgments about how best to prepare their child for adult life. But it does not leave unlimited discretion. Parents who want to have their young child sterilized, perhaps because they believe that having children is a terrible burden they wish to spare their own child, would violate their child's right to an open future by cutting off a life choice that is central to human flourishing—the decision whether to have and raise a child.

The right to an open-future framework gives a clear and resounding answer in a case such as sterilization. But, like other frameworks, the devil is in the details of the case. Feinberg and Davis disagree about a touchstone legal case that reached the U.S. Supreme Court in 1972. The dispute was over whether a state could insist that children remain in school beyond the eighth grade. An Amish community argued that requiring their children to stay in school could destroy their way of life and that their children were well prepared to function in Amish society. Feinberg concluded that the relatively minor infringement of a child's right to an open future—perhaps 2 fewer years of schooling—was outweighed by the constitutional obligation not to unduly burden the Amish community's religious beliefs. Davis (2001) strikes the balance on the opposite side. Once again, a variety of morally important considerations are at play, and once again, judgments are open to disagreement.

Other scholars defend a strong presumption in favor of parental authority over matters of health. Ross argues that "when there is parent-child disagreement, the child's decision should not be decisive nor should health care providers . . . seek third party mediation. Rather . . . there are both moral and pragmatic reasons why the parents should have final decisionmaking authority" (Ross, 1997, p. 44).

A well-considered ethical decision will have to attend to the facts of the case. How effective is the vaccine? Is it safe? What is known about other young persons' reactions to it? Do they substitute other risky behaviors for smoking, or does the vaccine reduce their overall risk? Further, a wise ethical decision will require reflecting on the implications

for Vicky's developing moral character and for her relationship with her parents. Has Vicky been trustworthy? (Of course, as most parents of adolescents know, their children can be placed under enormous pressure to do unwise things and even very responsible teenagers can succumb, so "trustworthiness" remains a relative term.) Instead of a vaccine, might it be preferable to extract a promise not to use tobacco? If the promise is broken, privileges can be withdrawn. This option reinforces Vicky's role as a moral agent rather than as someone who must always be protected against her own foolish choices. It also attempts to build mutual trust and respect between parents and child. Which decision is best depends on many factors—the medical facts, the child's character and setting, the values at the heart of the family's life.

An honest analysis will be no less complex in the second scenario: fifteen-year-old Larry and a vaccine against opiate addiction. Larry's parents, most of all, want Larry to survive and not be drawn into the world of drug use, violence, and addiction. Their experience shows that this is a realistic danger for adolescents in their community. The medical risks of the immunotherapy must be taken into account, as well as the possible unintended consequences. For example, should Larry decide to try opiates despite having received the vaccine, he may have to use much larger doses to get high, which might pose even greater danger to his health. Responsible parents will want to know all they can about the medical risks and benefits, but also about the unintended but foreseeable medical, social, and legal consequences.

Individual physicians will need to be informed about all of these issues. If and when effective and apparently safe depot medications and immunotherapies are approved for marketing, some people will approach physicians to prescribe them for off-label use, even in the complete absence of data on their safety and effectiveness for such use, especially by children and adolescents. As soon as a clear picture of such requests emerges, professional associations should begin work on professional standards to guide physicians on how to respond.

Through law and regulation, public officials will be positioned to influence the patterns of use. If the potential for misuse were deemed high, the FDA could restrict access to some or all of these interventions. Other policy options could encourage their use by, for example, subsidizing them or requiring insurers to cover their cost.

In a climate in which substance abuse is seen as a scourge, many scenarios can be imagined. Might a state concerned about teenage drinking and driving make a depot medication against alcohol a condition for obtaining a driver's license? Might a city rocked by the violence and chaos of a thriving market for cocaine or heroin embark on a mass vaccination program intended to dry up the market for these drugs? The rough

analogy here is with herd immunity in vaccinations against infectious diseases. Vaccinate a sufficient percentage of the population and the infection will not spread; vaccinate enough of the community against opiates and the dealers will move on to more lucrative markets.

CONCLUDING REFLECTIONS

Immunotherapies and depot medications for substance abuse are promising technologies with complex ethical implications. In thinking about these implications it is helpful to distinguish clearly between the issues that will arise in *research* and those stemming from their *use*. Likewise, in both research and use it is important to take into account the different *modalities* and the different *purposes* to which they might be put. This appendix discusses three modalities: *active immunotherapies* on the model of traditional vaccines but utilizing new methods for presenting small-molecule antigens to the immune system; *passive immunotherapies* such as mABs; and *depot medications*, including long-lasting forms of currently available drugs. The appendix also discusses three purposes of use: as *therapy for overdose*, for which mABs are the most promising of the three modalities; in *relapse prevention protocols*; and for *protection protocols*. All three modalities might be explored for both relapse prevention and protection purposes.

Responding to the challenges posed by immunotherapies and depot medications for substance abuse will require attention to the medical and scientific aspects of these interventions, as well as their social, economic, legal, and ethical implications. We must accept the great need to educate the public, health care professionals, and policy makers about the realities of substance abuse and its causes, prevention, and treatment. Failure to respond to the enormous educational challenge will contribute to misuse of these new interventions.

Once interventions that might be used in prevention protocols are approved by the FDA, clear and enforceable public policies will be needed to deal with off-label uses. These responses should include clear policies on the promotion of off-label use by manufacturers or others and clear guidance to the professionals, primarily physicians, who will have the power to control access to such interventions.

Finally, it should be anticipated that some, perhaps many, parents will seek to use certain interventions in the belief that they will protect their children against substance abuse, sparking a broad and heartfelt debate over the nature and limits of good parenting. This debate may well be the most far-reaching and long-lasting ethical consequence of immunotherapies and depot medications for substance abuse.

REFERENCES

Ad Hoc Committee on Growth Hormone Usage. (1983). Growth hormone in the treatment of children with short stature. *Pediatrics, 72*(6), 891-894.

American Academy of Pediatrics Committee on Drugs and Committee on Bioethics. (1997). Considerations related to the use of recombinant growth hormone in children. *Pediatrics, 99*(1), 122-129.

Angell, M. (2000). Is academic medicine for sale? *New England Journal of Medicine, 342*(20), 1516-1518.

Appelbaum, P.S. (2002). Involving decisionally impaired subjects in research: The need for legislation. *American Journal of Geriatric Psychiatry, 10*(2), 120-124.

Bekelman, J.E., Li, Y., and Gross, C.P. (2003). Scope and impact of financial conflicts of interest in biomedical research: A systematic review. *Journal of the American Medical Association, 289*(4), 454-465.

Benjamin, M., Muyskens, J., and Saenger, P. (1984). Short children, anxious parents: Is growth hormone the answer? *Hastings Center Report, 14*, 5-9.

Bodenheimer, T. (2000). Uneasy alliance—Clinical investigators and the pharmaceutical industry. *New England Journal of Medicine, 342*(20), 1539-1544.

Charland, L.C. (2002). Cynthia's dilemma: Consenting to heroin prescription. *American Journal of Bioethics, 2*(2), 37-47.

Chen, D.T., Miller, F.G., and Rosenstein, D.L. (2002). Enrolling decisionally impaired adults in clinical research. *Medical Care, 40*(Suppl 9), V20-V29.

Cuttler, L., Silvers, J.B., Singh, J., Marrero, U., Finklestein, B., Tannin, G., and Neuhauser, D. (1996). Short stature and growth hormone therapy: A national study of physician recommendation patterns. *Journal of the American Medical Association, 276*(7), 531-537.

Davis, D.S. (2001). *Genetic dilemmas: Reproductive technologies, parental choices, and children's futures.* New York: Routledge.

Dresser, R. (1984). Bound to treatment: The Ulysses contract. *Hastings Center Report, 14*(3), 13-16.

Faden, R.R., Beauchamp, T.L., and King, N.M.P. (1986). *A history and theory of informed consent.* New York: Oxford University Press.

Feinberg, J. (1980). The child's right to an open future. In W. Aiken and H. LaFallette (Eds.), *Whose child? Children's rights, parental authority, and state power* (pp. 124-153). Totowa, NJ: Littlefield, Adams.

Feussner, J.R., and Murray, T.H. (2002). Making informed consent meaningful: A state-of-the-art conference. *Medical Care, 40*(Suppl 9), V1-V3.

Food and Drug Administration. (2001). Additional safeguards for children in clinical investigations of FDA related products. *Federal Register, 66*(79), 20589-20600.

Holmes-Rovner, M., and Wills, C.E. (2002). Improving informed consent: Insights from behavioral decision research. *Medical Care, 40*(Suppl 9), V30-V38.

Kaplowitz, P.B. (2001). If gonadotropin-releasing hormone plus growth hormone (GH) really improves growth outcomes in short non-GH-deficient children, then what? *Journal of Clinical Endocrinology and Metabolism, 86*(7), 2965-2968.

Klerman, G.L. (1972). Psychotropic hedonism vs. pharmacological Calvinism. *Hastings Center Report, 2*(4), 1-3.

Kopelman, L.M. (2000). Children as research subjects: A dilemma. *Journal of Medicine and Philosophy, 25*(6), 745-764.

Lawson Wilkins Pediatric Endocrine Society. (1995). Guidelines for the use of growth hormone in children with short stature. A report by the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. *Journal of Pediatricss, 127*(6), 857-867.

Lidz, C.W., and Appelbaum, P.S. (2002). The therapeutic misconception: Problems and solutions. *Medical Care, 40*(Suppl 9), V55-V63.

McCrady, B.S., and Bux, Jr., D.A. (1999). Ethical issues in informed consent with substance abusers. *Journal of Consulting and Clinical Psychology, 67*(2), 186-193.

Murray, T.H. (1986). Divided loyalties dilemmas for physicians: Social context and moral problems. *Social Science and Medicine, 23*(8), 827-832.

Murray, T.H. (1987). The growing danger from gene-spliced hormones. *Discover, 8*(2), 88, 90, 92.

Murray, T.H. (1996). *The worth of a child*. Berkeley and Los Angeles: University of California Press.

National Bioethics Advisory Commission. (1998). *Research involving persons with mental disorders that may affect decisionmaking capacity.* Rockville, MD: National Bioethics Advisory Commission.

Nelson, R.M., and Merz, J.F. (2002). Voluntariness of consent for research: An empirical and conceptual review. *Medical Care, 40*(Suppl 9), V69-V80.

Ross, L.F. (1997). Health care decisionmaking by children: Is it in their best interest? *Hastings Center Report, 27*(6), 41-45.

Schaeffer, M.H., Krantz, D.S., Wichman, A., Masur, H., Reed, E., and Vinicky, J.K. (1996). The impact of disease severity on the informed consent process in clinical research. *American Journal of Medicine, 100*(3), 261-268.

Ubel, P.A. (2002). Is information always a good thing? Helping patients make "good" decisions. *Medical Care, 40*(Suppl 9), V39-V44.

Waggoner, W.C., and Mayo, D.M. (1995). Who understands? A survey of 25 words or phrases commonly used in proposed clinical research consent forms. *IRB, 17*(1), 6-9.

G

Costs and Benefits of Immunotherapies or Depot Medications for the Treatment of Drug Abuse

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SUMMARY

Two related but distinct cost-benefit questions could be asked about a proposed immunotherapy or depot medication designed to prevent a given drug of abuse from crossing the blood-brain barrier. One is whether the application of such a treatment technique to some particular patient or class of patients would be cost-justified, once it had been developed, approved, and marketed. For a treatment with high efficacy and acceptable side effects, answering that question will turn out to be trivially easy as applied to patients with severe and chronic substance abuse disorders because the benefits per application will be very large multiples of the marginal cost of production and administration.[1]

An efficacious immunotherapy or depot medication administered to a chronic heavy user of a low-recovery-rate drug (such as tobacco, heroin, alcohol, or cocaine) might easily cut years from the otherwise expected length of that patient's active addiction career. A very rough calculation (given below under "Example: Cigarette Smoking") suggests that the excess of costs over benefits for a month of active heavy cigarette smoking is on the order of $500. The comparable figures for active cocaine or heroin use might exceed that by an order of magnitude. Thus the expected gross

[1]The estimated total monetary societal (external) cost of substance abuse (excluding alcohol and tobacco use and abuse) was $143.4 billion a year for 1998, the most recent year available (Office of National Drug Control Policy, 2001). That estimate has been criticized as too low because it omits nonfinancial costs, losses to the families of those suffering from substance abuse disorders, and losses to the sufferers themselves (see Kleiman, 1999).

benefits of administering an effective antismoking treatment to a long-term smoker would be in the range of thousands of dollars per patient. The amount would be substantially higher for a chronic alcoholic and higher still—in the tens of thousands of dollars— for someone addicted to heroin or cocaine.

It is hard to imagine that the financial costs of making an immunotherapy agent, administering it to a patient, and doing the necessary follow-up could even approach such levels. Current estimates are that the treatments will cost on the order of a thousand dollars per administration and that each administration will be efficacious for a few months. So if a highly efficacious, low-side-effect immunotherapy were developed for any of the major drugs of abuse, its application to anyone with an established chronic problem with that drug would almost certainly be cost-justified.

If the efficacy were only partial, if side effects were substantial, or if substitution of other drugs turned out to be a major problem, the calculation would become more challenging. An immunotherapy that prevented three-quarters of an abusable drug from getting to the brain might have much less than three-quarters of the benefits of a completely effective immunotherapy, or it might have virtually the same benefits, depending on behavioral responses that as yet can only be guessed at. (Partial interception would be equivalent in some ways to a price increase, and the behavioral response would reflect an analog of the price elasticity of demand. The more elastic [sensitive] consumption of a drug is to its price, the greater the benefit of a partially effective immunotherapy.)

Use in patients with less chronic conditions, or prophylactically in those without established drug problems but engaged in drug-taking patterns that threaten to escalate, would be less beneficial per case but might still be cost-justified in some instances (National Research Council, 2001).

The second kind of cost-benefit question that might be raised involves expenditures on the development of such therapies. That development analysis uses the patient-by-patient analysis as its starting point, but the relevant part of the patient-by-patient analysis is not the part that deals with the interesting close questions such as the possibility of prophylactic use or use in cases of a relatively mild abuse disorder or a disorder not yet shown to be chronic. Instead it is the benefits in the cases that are most obvious in the patient-by-patient analysis—patients with severe, chronic disorders—that need to be summed and then measured against the costs of a development effort and its probability of success. This appendix will pass over the questionable cases to concentrate on the clear ones. (It would be somewhat perverse to oppose the development of a medication on the grounds that, if developed, it might then be used badly in some instances, though far from perverse to try to anticipate and forestall such usages.)

In considering whether to attempt to develop an immunotherapy or depot medication, the relevant comparison is between, on the one hand, the aggregate amount by which the benefits of use would exceed the costs, summing over total applications and, on the other hand, the development costs, appropriately adjusted both for the risks of failure—failure to develop a safe and efficacious medication, failure to secure regulatory approval, failure of adoption by providers and patients—and for the time value of money (Hubbard and French, 1991).

In addition to the benefits that accrue to patients who use the new therapy in place of other treatments, there would be another, potentially much larger, flow of benefits from patients attracted to try desistance from heavy use by the availability of a treatment that might be less effortful as well as more likely to succeed.

Against those benefits must be set the costs, including the opportunity cost of the treatment dollars that would pay for administration of a new therapy. But that sort of opportunity-cost analysis implicitly assumes that the overall level of funding is invariant to the range of therapies available, and that assumption may not be valid in this case. There are reasons to expect that an effective immunotherapy or depot medication might turn out to have characteristics more appealing to those who make decisions about drug treatment than its current competitors. The most demonstrably effective drug treatments in use today are the opiate substitution therapies, which are highly acceptable to many, though far from all, persons suffering from opiate dependency but which remain controversial politically because they do not promise a "cure" for the underlying addiction. Other treatments, while no one doubts their utility for some patients, face lower success rates and more resistance among potential clients, as reflected in both reluctance to enter treatment and high rates of dropout and treatment recidivism. These facts constitute part of the political background against which funding decisions are made and also of the professional background against which medical providers make treatment decisions, insurers make coverage decisions, and medical schools and other educators of health care professionals design curricula. It is not at all far-fetched to imagine the development of effective immunotherapies as a catalyst for changes in attitudes that would lead to changes in funding.

The sheer magnitude of the social costs of substance abuse means that even development programs with modest probabilities of success will be cost-justified. A treatment for smoking that had net benefits per patient measured in thousands of dollars, and a potential patient base measured in tens of millions, would have development benefits that might rise into the tens of billions. The potential patient base for treatment of cocaine addiction is more than an order of magnitude smaller, but the potential gains per patient are in the range of an order of magnitude greater, sug-

gesting comparable potential for aggregate social gain (see Office of National Drug Control Policy, 2001).

That suggests that a $50 million development effort with a 1 percent chance of a "home run" success against cocaine or nicotine would easily be worth the investment. In practice, development efforts are not decided on all at once. Funding is allocated sequentially, with several opportunities to put a losing project out of its misery. (Formally, this could be modeled using decision analysis or dynamic programming; practically, the gains in understanding from doing so now would be modest at best.) In addition, it suggests that pursuing more than one approach per drug might be justified, both because that would increase the probability of developing at least one successful therapy and because the marginal benefit of having more than one therapy available for a given drug of abuse might still be very substantial, if different therapies turn out to appeal to only partially overlapping populations of potential treatment clients.

In the case of alcohol the benefits would be greater still, perhaps not great enough to justify making substantial investments now in the face of apparently discouraging technical facts, but great enough to justify some continued basic studies. The social damage from heroin is currently probably comparable to that from cocaine, especially considering its role in the spread of infectious disease, but the existence of a set of efficacious substitution pharmacotherapies somewhat lowers the potential benefits of developing a new treatment, and the wide variety of closely substitutable opiates and opioids would tend to reduce the value of an immunotherapy targeted at only a single molecule. The social gain from developing a treatment for methamphetamine (high damage per month but a small and largely transient population of heavy users) and cannabis (more problem users at any one time but lower damage per month and moderate chronicity under current conditions) would be smaller than the others but still in the billions.

It could reasonably be suggested that the data on which to perform such calculations with anything approaching precision do not exist. The cost of developing a therapy, its costs in use, its efficacy in a technical sense (what proportion of the population would derive benefit from it, the proportion of the abusable drug the new therapy would trap before it reached the brain), its clinical utility (depending on the drug-taking behavior of actual patient populations, which may be different from the reactions of participants in clinical trials, in the face of an imperfect barrier between drug-taking and enjoying the desired psychological effects of the drug), the effect of immunization against the effect of one drug on consumption of other drugs, the side effects profile of the new medication, its acceptability among different categories of potential clients, difficulties in achieving regulatory approval, and adoption by treatment

providers are all matters of speculation. Moreover, the probability of success is not a single number. Any actual research program might produce a range of results from a "home run" to a medication capable of gaining regulatory approval but of only marginal clinical utility. Even those factors in the calculation that relate to current rather than hypothetical facts—the number of persons suffering from a severe and chronic substance abuse disorder for any given drug, the rate of turnover in that population, and the cost (to the affected individual, to his or her intimates, to other individuals such as potential crime victims, and to the budgets and functioning of institutions such as police and health care providers) associated with active abuse that would be averted by successful treatment—are not nearly as well measured as they ought to be (National Research Council, 2001).

To undertake a formal sensitivity analysis around such poorly grounded calculations would itself suggest more certainty than the data will actually support. But simple critical value calculations are enough to support the idea that, if development seems technically plausible, the risk of funds is likely to be thoroughly cost-justified. As long as the probability of a highly successful development is at least a few percent, elaborate calculations are probably superfluous. Moreover, the extremely discouraging histories of pharmacotherapies for substance abuse other than the opiate maintenance agents give some reassurance that the opportunity cost of funds taken from other parts of the National Institute of Drug Abuse's medication development effort to support work on immunotherapies and depot medications is unlikely to be very high (see, for example, Tai, Chiang, and Bridge, 1997).

As is always the case in thinking about the social benefits to be derived from pharmaceutical development, the mechanics of pricing create a potential problem. Pricing near marginal cost will not recoup the investment in development efforts; pricing designed to recoup that investment will inefficiently squeeze some patients out of the market.

The fact that patent protection permits pricing well above marginal cost, in principle, ought to be ignored in a full cost-benefit analysis of the decision to administer a drug; the producer's surplus from supra-marginal-cost pricing is a mere transfer from whoever pays for the treatment to whoever holds the patent. From a cost-benefit perspective, the relevant comparison is between the marginal social cost of producing, distributing, and administering an additional unit of the medication and the benefit that could be derived from that treatment, over and above the benefits, minus the costs, of whatever treatment is the next-best. Of course, if high price will lead to low utilization, that reduction in volume is a fact about the world that ought to be incorporated into the analysis of the development decision.

If the proposed therapies came to represent anything approaching a reliable "cure" for drug addiction, the possibility exists that introducing them will have unwanted effects on the rates of initiation to the drugs whose abuse syndromes they treat. That issue presents both conceptual and empirical challenges that probably put it outside the reach of any numerical cost-benefit analysis. Those risks lurk in the background of any decision about development. Depending on the extent of the effect and the long-term harm from nonchronic bouts of substance abuse, the losses on the prevention side might (or might not) substantially cut into the benefits on the treatment side; it is conceivable that the prevention losses might even exceed the treatment benefits.[2]

Whether and how to consider such risks in deciding on the development of treatments for a life-threatening group of diseases pose tricky problems in bioethics. It might plausibly be argued, as it has in the partially analogous case of medication development for HIV/AIDS,[3] that it would be wrong to deny treatment to those currently suffering from some disorder out of concern that treating them might, through one mechanism or another, increase the rate of incidence of that disorder. Fortunately for the author, those issues are beyond the scope of this appendix.

A CONCEPTUAL MODEL

Assume the introduction of a new treatment, T, for abuse and dependency related to drug D. In particular, let T be a depot medication or immunotherapy designed to reduce or eliminate, for a period of months, the bioavailability of D to a patient given T.

The relevant direct costs are the costs of T itself, the effort required to induce clients to accept it, and the ancillary treatment required to make it effective, plus whatever negative value is assigned to the side effects. Insofar as T competes for resources or clients with other forms of drug treatment, the benefits of whatever other treatment is foregone are an opportunity cost of T, and the costs associated with those foregone treatment episodes are a benefit of T. Thus it will matter greatly whether the clients treated with T would otherwise have pursued other forms of treatment.

Treatment cost is also influenced by the extent of treatment recidivism (a somewhat unfortunate but now established term for repeated rounds of treatment and relapse [see, e.g., McKay et al., 1996]). A treatment that is expensive per treatment episode but has a high rate of long-

[2]Compensatory responses to reductions in risk are well established in a number of risk domains (see, for example, MacCoun, 1993, and Goldberg and Fischoff, 2000).

[3]For example, in response to work on HIV therapies by Blower, Schwartz, and Mills (2003).

term success may be less costly in the long run than one that is cheaper per episode but that generates multiple episodes. Whether to treat these savings as adjustments to the cost side of the calculation or to include them as benefits is partly an arbitrary choice of analytic conventions, but the choice ought to depend in part on the impacts of various sorts of savings on the treatment system. Nothing guarantees that the opportunity cost of a treatment dollar expended or saved will be exactly or even nearly $1. It might be much more than $1 if existing treatment is highly cost- beneficial and resource-constrained and less than $1 for ineffective treatments.

In some cases the alternative to T will not be some other form of substance abuse therapy but rather jail or prison. That situation requires a different analysis; the resource savings if T is used instead of incarceration are likely to be large, but those savings may not accrue in a way that makes it possible to recycle them into other treatment efforts.

The benefit picture is much more complicated, and estimating it numerically will require constructing a number of counterfactual hypotheticals concerning what would have happened had T not been available or not been used. One place to start is with a single representative individual, A, at risk of a drug abuse disorder involving D, in a world without T. Moore (1990) has described a quasi-Markov process[4] that provides a basis for estimating the damage done to and by A as a result of D (Figure G-1).

Starting as a nonuser of D, in each period (say, arbitrarily, each month) A has some probability of starting to use D. Assume that all initiations are, in the first instance, to occasional, casual, or use not meeting diagnostic criteria for abuse or dependency. Still, A might suffer and/or impose on others, on a probabilistic basis, some monthly flow of harm (net of whatever benefit A receives from use of D).

[4]Note that this is not a true Markov process in several respects: (1) The individuals in a given state are heterogeneous with respect to transition probabilities from that state. (2) A given individual in a given state may have transition probabilities that vary with, for example, his or her age or how long he or she has been in that state. (3) Not all transitions are created equal. Someone who transitions from heavy heroin use to abstinence as a result of a religious conversion or participation in a therapeutic community will in general have a lower probability of relapse than the same person making the same transition as a result of a detoxification program. (4) The system is open rather than closed. New potential users are born (or reach some minimum age of risk) every day, and users die (at nontrivial rates for long-time heavy hard-drug users). Abstracting from all these difficulties, a transition probability model provides a good conceptual basis for thinking about the probabilistic process by which drug users incur and inflict harm and the impacts of a new treatment technology on that process.

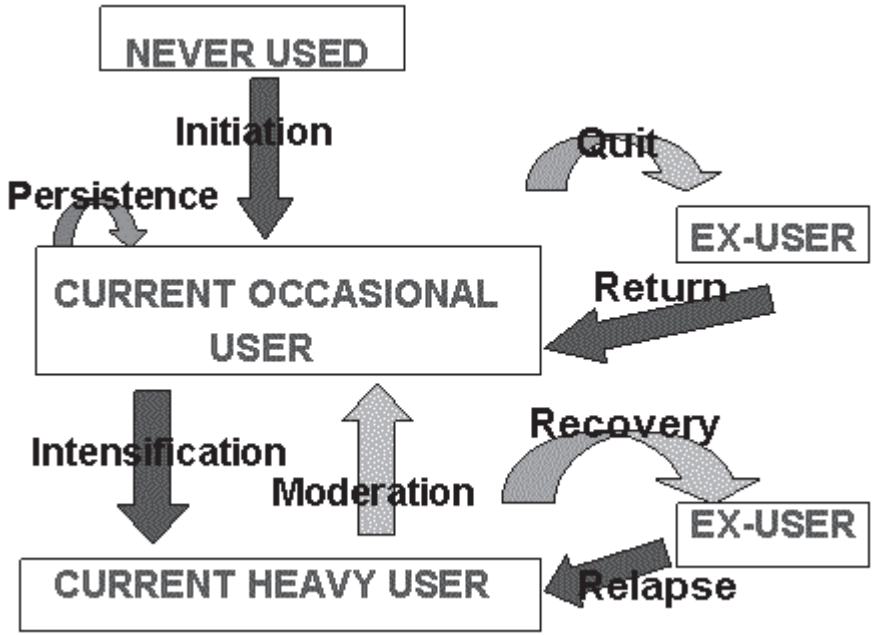

FIGURE G-1 Drug taking as a system of states and transition probabilities.

In every month in which A uses D on a casual basis, A has some probability of desisting from use and some probability of intensifying to heavy or problematic use amounting to diagnosable substance abuse disorder. (Obviously, this treats as a set of discrete states what in fact is a continuum; a more adequate model would have to be more complex. But for purposes of exposition this simplified model displays most of the relevant features of the situation.)

If A desists from using D, A faces some monthly risk of resuming use. If A progresses to heavy use, the monthly flow of harms increases compared to continuing casual use. A then has monthly probabilities of moderating his or her use—going back to being a casual user—or quitting altogether and/or going into recovery. (Ex-casual users and ex-heavy users may continue to suffer harm due to their past use, but for these purposes it is better to attribute damage on an "accrual" rather than a "cash" basis, charging each month with the future as well as current consequences of that month's use.)

Thus we have identified, in the abstract, a small number of rates that, among them, determine total expected harm to A due to drug D: the initiation rate, the quit and intensification rates from casual use, the rate of

harm from casual use, the return rate from former occasional use, the rates of recovery and moderation from heavy use, the rate of harm from heavy use, and the relapse rate from recovery. Persistence in casual use is the reciprocal of the sum of the quit and intensification rates. The chronicity of heavy use depends on the recovery, moderation, and relapse rates. With estimates of these we could in principle solve the model for A's expected lifetime damage from D. Moreover, we ought to be able to understand the impact of any proposed intervention in terms of its impact on initiation, persistence, return, intensification, moderation, recovery, relapse, and the two harm rates.

The sources of harm, both to the person suffering from a substance abuse disorder and to others, are multifarious and will vary from drug to drug. A partial list might include:[5]

- Physical toxicity
  - Direct (to user)
  - Indirect (e.g., environmental tobacco smoke)
- Behavioral toxicity (crimes and accidents due to intoxication)
  - Damage to victims
  - Damage to community
  - Damage to intoxicated person (including risks of punishment)
- Psychological toxicity (and associated health care costs)
- Infectious disease risks (and associated health care costs)
  - User's infection risk
  - Risk of re-transmission
- Expenditures of drugs
- Costs to users
  - Costs to users' family members
  - Support for illicit markets
    - Increasing supply to other current and future users of the same drug
    - Generating illicit-market side-effects
      - Violence
      - Disorder
      - Corruption
      - Damage to juveniles employed in illicit trade
    - Enforcement costs
      - Budget costs
      - Losses to dealers and their families due to incarceration

[5]A formal taxonomy of drug-related harms can be found in MacCoun, Reuter, and Schelling (1996).

Again simplifying for concreteness, harm can be identified with the use rate itself. That will be more appropriate for cigarette use, for example, than for cocaine or heroin use, but even for the "hard drugs" total damage is likely to track, albeit imperfectly, total consumption.

In this model a treatment technology appears as something that increases the rates of recovery and moderation, decreases the relapse rate, or decreases the flow of harm from heavy use. The greater the chronicity of heavy D use in the absence of some new treatment, and the greater the harms associated with continued heavy use, the greater the potential benefit of a new treatment. The net outflow, after adjusting for relapse, among individuals with long-established tobacco or heroin problems appears to be on the order of 3 percent per year,[6] though other individuals pass through the heavy-use state relatively quickly and remain out of it once they leave (see Goldstein, 2001, pp. 261-263; Trosclair et al., 2002). Recent aggregate-level data seem to suggest that heavy cocaine use, especially cocaine smoking, may create a condition of comparable chronicity.[7]

The fact that heavy users of a given drug are likely to be heterogeneous with respect to the length of the "addiction careers" they face (even evaluated *ex ante*, on an expected-value basis) will greatly complicate the task of assigning a value to any new treatment technology because the group that volunteers to be treated with it may not be a random draw from the population suffering from the substance abuse disorder to which the treatment applies.

The rate of recovery—quitting from heavy use—can be decomposed into a monthly probability, P(a), that someone with a D problem will attempt to recover in that month and another probability, P(s), that a given recovery attempt will be successful. Any treatment that influences P(s) may also influence P(a), since the risk of failure is known to be one deterrent to attempting to desist from problem drug use (Institute of Medicine, 1990).

The hypothetical new treatment, T, can change these rates in several ways. Obviously, it can increase the success probability conditional on

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[6]Note that, although some 70 percent of smokers express a desire to quit (a figure undoubtedly higher than comparable proportions of heavy users of heroin and cocaine), only 4.7 percent of daily smokers were able to quit for more than 3 months in any given year, according to a recent report (see Trosclair et al., 2002). Kleber has estimated that, with 40 million Americans having quit smoking cigarettes over a period of 20 years, the actual cessation rate (net of relapse) may be closer to 2 percent (http://www.nationalfamilies.org/update/dau-111001.html). Heroin addiction may be even more intractable; see Hser et al., 2001). This study showed "remarkably stable use patterns" in a cohort of heroin users over at least 11 years since a previous survey of the same group of addicts.

[7]Rydell and Everingham (1994:17-19) discuss the differences in consumption patterns between "light" and "heavy" users and a "Two-State Markovian Model" of cocaine consumption ("demand"). For further details, see Chapter 2 in Everingham and Rydell (1994).

attempting to quit, P(s). More subtly it can also decrease the perceived costs to the sufferer from attempting to quit; reportedly, much of the unpleasantness associated with quitting is the constant struggle with temptation and the constant fear of backsliding, and patients who arrange to physically isolate themselves from any possibility of acquiring their drug of abuse appear to have a much easier time of quitting than those for whom a decision to backslide could be executed within minutes (DeLeon, 2000).

(In this regard, some empirical work could be done on opiate-dependent physicians and other health care professionals required to take narcotic antagonists daily on a "Directly Observed Medication" basis as a condition of maintaining their licenses. The reported high success rates in such attempts are often attributed to the subjects, having a great deal to lose and an unusual amount of self-discipline, but it may be the case that the temptation-reduction benefits of a daily dose of an antagonist in fact make quitting easier for this group than for other detoxified opiate-dependent individuals who do not take an antagonist.[8] A vaccine or depot medication would have this advantage to an even greater degree, since there would not even be a potential daily inner struggle over whether to take the medication, attempt to fake taking it, or leave the program entirely.)

Reduced stress associated with the recovery attempt and increased probability of succeeding will tend to increase the rate at which patients undertake recovery attempts if T is present, compared to its being absent. Thus so far there are three classes of benefit from T: increased success probability, P(s), due to the efficacy of T; increased attempt probability, P(a), due to increased perceived benefits from attempting to recover; and further increased attempt probability due to decreased perceived costs (in the economist's generalized sense of that term) of attempting to recover. (For some patients the irreversibility of T will appear as a disadvantage and a source of discouragement to attempt T, but that will not reduce P(a) compared to what it would have been, since alternative technologies, including unassisted quitting, would still be available.)

Finally, an immunotherapy or depot medication might reduce the relapse rate, especially in the early months of recovery when that risk is typically at its highest. That would seem to be among the strongest advantages of an immunotherapy or depot medication over, for example, traditional detoxification. The opportunity to extend the period of protection by readministering T would accentuate this advantage.

[8]For a discussion of the use of Directly Observed Medication to improve treatment outcome, see Johnson, Rosenblum, and Kleber (2003).

If we were to imagine a repeatable vaccine or depot medication that provided complete and non-dose-overridable protection, the cost to the patient of the substance abuse disorder in question would then be effectively capped at the cost of the treatment itself. If, say, four injections per year costing $1,000 each could entirely prevent a cocaine abuser from getting any psychoactive effect from cocaine, then that person could ensure against any risk of relapse (at least any relapse to cocaine) at an annual cost of $4,000. Because the decision not to use cocaine could be made only four times a year rather than having to be made again and again whenever the temptation presented itself, the risk of relapse through weakness of will would be greatly reduced, along with the stress of the struggle to maintain abstinence.

An open question—the answer to which will probably vary from treatment to treatment, drug to drug, and patient to patient—is the level of craving and the relapse probability after the immunological (or other pharmacological) effect has dissipated. While the option of readministration to extend the treatment's active life makes this question less crucial than it would otherwise be, it remains an important one and would be more important if diminishing efficacy or accumulating side effects made long-term application unattractive.

Competing considerations make it unclear whether the post-direct efficacy relapse rates would be higher or lower for remissions secured through immunotherapies or depot medications than for remissions occurring as a result of other treatment approaches, through group self-help, or "spontaneously." On the one hand, a period of months of abstinence with no, or reduced, cravings due to the effective unavailability of the drug of abuse might make long-term success more likely. On the other hand, if many who would have relapsed quickly under other treatment regimens succeed using T, that population may be selected to be less relapse-resistant than those who managed to abstain for a period in the face of active temptation.

Thus a depot medication or immunotherapy can reduce the average length of the combined active phases of an addiction career in three ways. It can do so directly by increasing the probability that a given quit attempt will succeed and by decreasing the relapse rate. (Call these effects "efficacy improvements.") Efficacy improvements, especially if combined with decreased discomfort through reduced cravings, will make attempts to quit more attractive, thus increasing their number ("treatment demand" effects). If such therapies are actually more cost-effective than conventional therapies, and if the resulting cost savings are available to be recycled into the treatment effort itself, the result could be an effective expansion of the capacity of the treatment system, which might be called the "treatment supply effect." (The importance of these two latter classes

of effects will depend in part on external conditions. The treatment supply effect will be of more importance when funded treatment slots are scarce compared to volunteers; the treatment demand effect will be more important when volunteers are scarce compared to slots.)

Efficacy, treatment demand, and treatment supply effects will all contribute to a reduction in the average number of months of heavy drug use in a typical addiction career. The benefits of such reductions will depend on the costs of addiction careers of different lengths, which costs are likely to vary with characteristics of the underlying drug, existing therapies, the client, and the context, in particular the nature and extent of pressures on clients to participate.

Obviously, highly toxic, illegal, expensive drugs with highly socially disruptive markets, high chronicity, and poor alternative treatment options offer greater potential savings per month of active heavy use avoided than drugs with the opposite characteristics. Drugs with close and comparably harmful pharmacological substitutes not affected by the proposed therapy will be less attractive candidates for treatment insofar as some users make the substitution and wind up comparably dependent on the substitute (e.g., see Fairbank, Dunteman, and Condelli, 1993).[9] On the other hand, treating dependency on drugs that are frequently used in combination (e.g., cocaine with alcohol) will tend to have carry-over benefits in reducing abuse of the complementary drugs.

Examples, even with made-up numbers, may be more illuminating here than the mere exposition of principles. Tobacco and cocaine present such different pictures that they may nearly bracket the range of variation among target drugs.

EXAMPLE: CIGARETTE SMOKING

Assume an immunotherapy for nicotine of such high efficacy that 90 percent or more of patients report no subjective effect of smoking a cigarette in the 3 months following immunization. Also, assume low side effects of the therapy (apart from those of quitting itself, such as weight gain, depression, and reduced productivity).

Imagine a person now suffering from nicotine dependency in the form of cigarette smoking who expresses a desire to quit (as about 90 percent of smokers do). Each additional pack of cigarettes smoked does some amount of expected damage to his or her health, wallet, and other people (e.g., family), net of whatever value the smoker places on the pleasure,

[9]Note that two drugs do not have to be substitutes in any pharamacological sense to be substitutes in an economic sense. A stimulant may be substituted for an opiate, for example.

comfort, or capacity for concentration, or relaxation provided by smoking. That net marginal cost of smoking a pack of cigarettes is presumably a declining function of cumulative packs smoked and of the smoker's age and presumably varies with other factors as well, but for concreteness and simplicity assume that it is $10.[10]

Again simplifying, assume that the person, a male, smokes a little more than a pack and a half a day, or 50 packs per month. Thus his smoking generates a net loss of $500 per month. That person also has some probability, P(q), of trying to quit in any given time period (say a month); the probability certainly varies from person to person and may vary with the availability and efficacy of various treatment options as perceived by the smoker. If he tries to quit, he has some probability, P(s), of succeeding, where success means (say) going a whole month without smoking (at all or over some low threshold). The product P(q)P(s) is his monthly probability of a successful quit. Once he quits, he faces some (probably declining) monthly probability, P(r), of relapsing. From assumptions about those probabilities, his expected lifetime months of smoking could be computed. (That calculation would be complicated by the impact of his smoking on his life expectancy and by the time-value of money, but those problems can be ignored for now.)

In particular, one could calculate the reduction in expected cumulative months of smoking that will result if there is a successful quit attempt in the current month. Again for concreteness, assume that a successful quit reduces the expected cumulative lifetime periods of smoking—the length of the active addiction career—by 20 months, a fairly modest estimate given that smoking careers are typically measured in pack-years and that the median successful cigarette quitter succeeds in quitting and not relapsing on about the sixth try. That would put a value on successful quitting of $\$500 \times 20 = \$10{,}000$.

Against this must be offset the costs of quitting, such as weight gain and psychological distress. For most smokers those effects will be tolerable, but not for all. Smoking is such a major health risk that those who treat it tend to ignore its benefits. Since relapse is always an option, those patients who really cannot function without nicotine presumably usually

[10]Assume a smoker who consumes 50 packs a month for 40 years and loses as a result 7 years of life expectancy. If that person has a willingness to pay for longevity of $100,000 per life-year, then he or she consumes 24,000 packs and foregoes $700,000 worth of life expectancy. If his or her real (after-inflation) discount rate is 4 percent, the lag between the average pack smoked and the average life-year lost is 25 years, the present-value cost of the foregone life expectancy is $11 per pack. So for the estimate used to be appropriate, the other costs of smoking, financial and nonfinancial, would have to roughly come within $1 per pack of balancing the benefits of smoking.

do relapse. An immunotherapy, assuming it is irreversible during its term, might actually pose some risks—directly in the form of reduced productivity, bad behavior, or psychiatric disorder and indirectly through substitution of other drugs or other bad habits (overeating, for example) for the unavailable cigarettes. This might be considered a side-effect risk of immunotherapy absent from, for example, the nicotine-substitution therapies. Part of the clinical development of any nicotine immunotherapy ought to be exploration of the size of the population that cannot function well without nicotine and the means of determining whether a given candidate for immunotherapy is part of that subpopulation.

Assume that P(s/T), the conditional probability of success in any given quit attempt in which the smoker uses T, is higher than P(s/~T)). The smoker has a better chance of success if he uses T than if he does not. Then the gain in success probability from using T is P(s/T)–P(s/~T). Again for concreteness, assume that P(s/~T) is 20 percent and P(s/T) is 90 percent.[11] Then the value of T is an additional 70 percent chance of success; if a success is worth $10,000, the gross value of T (before reckoning financial costs and side effects) would be $7,000. (Where T substitutes not for an alternative quit attempt but for no quit attempt, the benefit is $9,000.)

So far we have considered T merely as a means of increasing the probability that a quit attempt will succeed rather than fail. If T were sufficiently low in side effects so that it could be repeated prophylactically to prevent relapse, a successful quit using T will in fact be much more valuable (much longer lasting on average) than the average successful quit. Relatively few ex-smokers report *deciding* to go back to smoking, as opposed to succumbing to temptation (Office on Smoking and Health, 1989). Thus (again assuming low side effects) the renewal rate might be high and the net relapse rate low. The value of T might then be a multiple of the $7,000 figure, though of course repeated use would also increase cost.

Moreover, since the discomfort of attempting to quit and the fear of failure are important barriers to quitting, and since it has been reported that the subjective discomfort of being deprived of nicotine is dramatically less if cigarettes are simply unavailable than if the temptation to smoke must be battled moment-to-moment, there could be a significant treatment demand effect from T, especially if T-assisted quitting proved more successful, more durable, and more comfortable than quitting using other means. A therapy T as assumed might in fact convert nicotine

[11]That is, assume that, if the treatment is effective in nearly eliminating bioavailability, it will result in some period of nonsmoking.

dependency into a reliably treatable disorder, which would in turn further increase P(q) by increasing the social pressures on smokers to quit.

The social value of having T available would be the value of the total additional reduction in expected cumulative lifetime smoking generated by T treatment compared to the next-best treatment, plus the additional reduction generated by increased quit attempts (T treatment as opposed to no treatment), plus the value of reduced discomfort from T-assisted quit attempts compared to non-T-assisted quit attempts, plus the saved financial costs of non-T-assisted quitting.

That would have to be compared with the costs of T, both the capital cost of developing it and the costs of T-assisted quitting itself. But thousands of dollars in gross benefit per treatment, minus costs probably measured in the hundreds, times tens of millions of long-term-dependent cigarette smokers suggests total gains in the range of tens of billions of dollars.

Assuming that 30 million of the roughly 37 million current smokers are nicotine-dependent, that one in six of them would try T, that trying T increased the probability of a successful quit that month by 70 percent, that a successful quit cuts 20 months off the active smoking career, and that the net cost of an active month is $500, the total gross benefits would come to $35 billion and total costs, after development, to about a seventh of that ($1,000 per treatment times 5 million treatments is $5 billion), leaving nearly $30 billion in gross social surplus (an analog to "profit") from having developed the treatment.

Even adjusting that figure down for the time lag between research and development expenditures and having the treatment available, not adjusting it upward for the annual flow of new potential treatment candidates, and assigning no value to the development of a treatment with less attractive characteristics than hypothesized or to the possibility that more than one-sixth of today's dependent smokers decided to try T, a development effort with a price tag of $50 million would be cost-justified even if its chance of producing such a successful result were even one-half of 1 percent.

This estimate is most sensitive to reductions in the assumed length of remission. If the therapy costs $1,000 but needs to be repeated every 3 months, two-thirds of its benefit disappears. If remission from a single treatment is as long-lasting as assumed, even doubling the estimated cost of treatment has very little effect on that answer directly (net benefit per treatment falls only from $6,000 to $5,000) because the benefits of treatment so far outstrip the costs. However, a higher price would be expected to reduce benefits by reducing the rate of uptake of the new therapy. The price of the treatment would be much more significant a factor if it turned out that maintaining recovery required frequent readministration.

The calculation is also sensitive to reductions in the assumed probability of success and reductions in the assumed uptake rate. However, even if figures given above for market penetration, efficacy, and duration of remission are halved, the breakeven value of the success probability for a $50 million effort remains below 5 percent. That being the case, any approach that seems technically plausible is probably worth pursuing. Moreover, the sensitivity of the calculation to cost and duration of action suggests the value of achieving a longer-lasting and/or lower-cost treatment, even at the expense of greater development cost.

EXAMPLE: COCAINE

Now assume a treatment with the same high efficacy but for cocaine rather than nicotine. The same basic framework of analysis can be used, but all the other facts will be different. The costs of active heavy cocaine use are much higher, both to the user and to the people around him or her. The drug is more toxic and much more likely to lead to dangerous behavior. Unlike cigarette smoking, heavy cocaine use tends to be inconsistent with good performance in work or family roles. It is also illegal and therefore very expensive. A typical member of the population of 2 million or so heavy cocaine users in this country is estimated to spend $10,000 to $15,000 per year on the drug (Office of National Drug Control Policy, 2001). Since only a small proportion of heavy cocaine users have access to that much extra cash from licit sources, much of the money involved is the product of illicit activities—theft, prostitution, cocaine dealing. The portion derived from theft has a social cost that is some multiple of the base amount, both because stolen property typically yields far less to the thief than its loss cost the owner and because of the costs of the precautions that potential victims take against theft. Cocaine dealing, in addition to its contribution to the spread of cocaine abuse and dependency, is associated with neighborhood disruption and violence.

Moreover, all of these illegal activities are likely to force the cocaine-dependent individual into the arms of the criminal justice system. It has been estimated that three-quarters of heavy cocaine users are arrested in the course of any given year. Arrest, conviction, and incarceration generate costs for the public and perhaps even greater costs for the individual involved. In particular, a criminal record greatly complicates the problem of reentry into the workforce. In addition, even users who do not participate in the cocaine market as sellers still participate as buyers and thus as contributors to the revenue base that keeps the market turning, with the resultant costs in violence, disruption, and the recruitment of new dealers (especially juveniles).

Any attempt to sum all of the losses (evaluated in willingness-to-pay

terms) involved in a month of heavy cocaine use by a criminally active cocaine user, while it would run into very substantial problems of both data and conceptualization—particularly regarding the benefit that should be counted for the pleasures of cocaine use itself—could hardly reach an answer that was not some multiple of the dollar cost of the cocaine itself, thus putting it in the range of thousands of dollars.

Heavy cocaine users who are not criminally active (other than as cocaine buyers) almost certainly generate less in the way of external costs (at least extra family costs) than their criminally active counterparts, but they are on average wealthier, which would be expected to increase their own willingness-to-pay to be shed of their destructive habit. Moreover, their family members are presumably wealthier than the family members of criminally active cocaine users; the family members' willingness-to-pay will also be correspondingly greater. Again, it would be foolish to pretend that the arithmetic could be done with anything approaching precision, but a reasonable estimate would probably put total monthly net social cost in the same thousands-of-dollars range as the costs of cocaine abuse among the criminally active.[12]

An alternative calculation reaches an answer of the same order of magnitude. If the external financial costs of substance abuse actually totaled $150 billion per year (Office of National Drug Control Policy, 2001), if the nonfinancial external costs and the net costs to the substance abusers themselves came to an equal amount, if half the total were attributable to cocaine, and if 80 percent of the cocaine-related damage is due to 2 million heavy cocaine users, then the damage per person per year is $60,000, or $5,000 per month.

With a cocaine-dependent population about one-fifteenth the size of the nicotine-dependent population, and the benefits of a month's remission from cocaine about 10 times those of a month's nicotine remission, the total potential gain from a "cure" for cocaine abuse would therefore be of the same order of magnitude as the total potential gain from a "cure" for cigarette smoking, assuming that the two problems turn out to be comparably chronic in the absence of such a breakthrough.[13] (The apparent stabilization in aggregate national consumption of cocaine suggests that the outflow from the heavy-cocaine-using population is slower than was

[12]An introspective thought experiment: If you had a cocaine-dependent child or spouse, what would you be willing to pay per month of remission? Would the figure be less than one-tenth of your monthly family income?

[13]Many in the public health community will find the assertion that cocaine has aggregate social costs comparable to tobacco very hard to swallow; many in the criminal justice community and most elected officials and the citizens they represent would be dumbfounded at the suggestion that cigarette smoking is anything like as large a problem as cocaine.

once hoped, so comparable chronicity may be a reasonable guess; only time will tell.)

The effect on treatment demand among heavy cocaine users from the introduction of a therapy with a high probability of success and free from the moment-to-moment struggle with temptation is an open question. Given the extreme misery and social dislocation created by heavy cocaine use, especially cocaine smoking and especially among the criminally active population, a strong motivation to quit, or at least to have quit, should surely be present. However, cravings are by no means the only source of discomfort for heavy users trying to stop. Anhedonia is widely reported, and a cocaine immunotherapy would likely do little if anything to ease it. (The depression that can accompany nicotine withdrawal seems to be more treatable.)

Moreover, many heavy cocaine users would be quite miserable even if they were free of their drug dependency; both personal distress and social distress are often among the causes of taking up cocaine in the first place and among the sequelae of heavy use itself. It seems plausible that the proportion of heavy cocaine users who will find themselves unable to live without cocaine (or some substitute, not necessarily another stimulant) will be higher than the proportion of heavy smokers who find themselves unable to live without nicotine and that enough of the current heavy users would fear that they fell into that class to limit demand for such a therapy were it introduced.

On the other hand, while virtually all attempts at tobacco cessation are more or less voluntary (made, perhaps, under family or social pressure, but not legal compulsion), a significant number of heavy cocaine users today find themselves facing legal demands that they quit or at least accept treatment. Abstinence from illegal drug use is a routine condition of probation, though probation departments tend to be lax in enforcing that requirement. Drug treatment in lieu of punishment is already fairly standard in the criminal justice system. A major limitation of the approach is the difficulty in getting those who are ordered into treatment, or who "volunteer" for treatment when the alternative is prison, to actually carry through on their end of the bargain.

In a typical diversion program, as many as half of the offenders referred never show up even for a first treatment appointment, and in most places the capacity of the probation system to chase absconders is not high enough to be an effective deterrent. Observing treatment attendance, treatment compliance, and desistance from drug use are difficult in part because every day is a new day, and the criminal justice system has proven largely incapable of administering programs that deliver consistent low-intensity sanctions for deviating from its orders. Thus the legal demands that criminally active heavy cocaine users desist from cocaine

use are so imperfectly enforced as to be of only limited use in reducing the cocaine-dependent population.

By contrast, whether a probationer has shown up at the clinic to receive a cocaine vaccination is easy to determine, and, if the person has and the vaccination is highly effective, there is much less need to attempt to observe whether the person continues to take cocaine. (Testing might still be needed to deter, or detect, substitution of other drugs.)

Thus an immunotherapy or depot medication would greatly simplify the challenge faced by criminal justice agencies and the courts in converting their legal hold over criminally active cocaine users into effective pressure on them to quit. A judge might reasonably require an offender offering to undergo vaccination as part of a sentence bargain to actually receive the vaccine before the judge formally enters the sentence. While attendance at and compliance with treatment are matters of more and less and to some extent matters of opinion, receiving a vaccination is an observable, yes-or-no phenomenon. That might make enforcement considerably easier.

Since, as noted, most of the population of heavy cocaine users comes to the attention of the criminal justice system in the course of any given year, the combination of a new therapy with the power of the state might lead to a far more dramatic increase in the exit rate from heavy cocaine use than could be achieved for cigarette smoking.

The ethical question of mandating a pharmacological treatment with potential side effects (as opposed to attendance at counseling sessions) is outside the scope of this analysis, except to note that both courts and treatment providers will have to wrestle with the question (National Research Council, 2001, Chapters 6 and 8, Appendix E). But the operational issues are also substantial and likely to reduce the benefits and increase the costs of administering immunotherapies or depot medications. The criminal justice system, not being fundamentally a diagnostic enterprise, may well mandate such therapies for individuals suffering from transient, rather than chronic, cocaine abuse or from no diagnosable substance abuse disorder. That is already an issue with the various drug diversion programs, including drug courts, and an immunotherapy is exactly the sort of "magic bullet" likely to catch the imagination of some judges and other officials. If the costs are modest and the side effects mild, administration of such a therapy to some people not really in need of it may be a tolerable price to pay. If the side effects are significant, a therapy that would still be a blessing for someone with no other way out of chronic cocaine abuse may be a very poor idea for someone merely arrested for cocaine possession.

The benefits of such a therapy would also be lower, and the costs higher, if many of those who receive it involuntarily or semivoluntarily under criminal justice pressure found life without cocaine intolerable.

They might well substitute other drugs, not necessarily stimulants. There is no way to guess in advance how the damage done as a result of the use of those substitutes might compare to the damage avoided from cocaine. Nor is there any good basis for estimating what proportion of court-mandated cocaine immunotherapy patients would in fact be unable to function without cocaine or would attempt substitution from mere disinclination to attempt a nonintoxicated life-style.

Still, the potential aggregate benefits from developing an immunotherapy or depot medication for treating cocaine dependency would be enormous. Assume that one-third of the roughly 1.5 million criminally active heavy cocaine users in this country could be induced to accept such a therapy and that the result of that therapy was, as assumed for tobacco, a 70 percent increase in the chance of a successful quit attempt, where a success would cut 20 months, valued at $5,000 per month, off the expected length of the active addiction career (net of substitution with other drugs). That gives gross benefits of 500,000 treatments $\times$ 0.7 $\times$ 20 $\times$ $5000, or about $35 billion, or roughly the same figure (given the error bands) as the estimate given earlier for nicotine. Per-patient costs dealing with an involuntary criminally active population would be far higher than in the case of nicotine, but the number of patients treated would be much smaller, leaving comparable net benefits as well.

While the nicotine calculation was sensitive to the assumed duration of remission after a single administration and, if that duration proved to be short, to the cost of the treatment itself, the very high cost of a month of cocaine use makes the calculation for cocaine robust in that regard. Even if the treatments cost $2,500 each and need to be repeated every 3 months, the cost of a treatment would still be only one-sixth of its benefits. The value of an immunotherapy for cocaine depends almost entirely on its efficacy, the number of heavy users who can be induced to accept it, and the rate of substitution of other drugs. That suggests that, insofar as there are tradeoffs to be made, the development effort should focus on improving efficacy rather than reducing cost or extending duration.

ADDITIONAL ISSUES

Other Drugs

Other than the efficacy, costs, and side effects of a treatment, all of which are hard to gauge in advance, the key factors in determining the benefits of developing an immunotherapy or depot medication for a given drug are the size of the population of long-term heavy users, the chronicity of the disorder in that population, and the social cost per month of heavy use.

While alcohol generates no illicit market and thus no illicit-market

crime, and while its users typically do not engage in income-producing crime in order to buy it, the aggregate costs associated with long-term heavy alcohol use probably exceed those associated with any other drug because of the very high prevalence of alcohol use and its moderate "capture rate" to abuse (estimated at 17 percent of all drinkers on a lifetime basis), the extreme chronicity of heavy drinking among the minority of problem drinkers whose problem recurs, and the physical and behavioral toxicity of the drug itself, in particular its relationship to both accidents and violent crimes. The potential benefits of developing an efficacious immunotherapy or depot medication are therefore extremely high, even compared to the benefits of developing such treatments for cocaine or nicotine. However, even a very high reward for success cannot justify a major development effort unless and until a technically plausible approach is invented.

The costs of heroin addiction are second only to those of cocaine addiction among the illicit drugs because of its high chronicity and its links to income-producing crime and the spread of infectious diseases. However, by contrast with cocaine, opiate addiction can be managed with substitution therapies (methadone, and more recently buprenorphine and LAAM [levo-alpha acetyl methadol]). That somewhat reduces the urgency of developing a heroin immunotherapy, and the sheer variety of opiates and opioids that are relatively closely intersubstitutable (in addition to diacetylmorphine [heroin], morphine itself, oxycodone [the active agent in Percodan and Oxycontin], hydrocodone [Vicodin], hydromorphone [Dilaudid], meperidine [Demerol], and the fentanil compounds) would tend to reduce the value of an immunotherapy targeted at only a single molecule.

Methamphetamine has costs per month of heavy use that are comparable to those of cocaine, perhaps higher if the long-term physical and psychological sequelae of heavy use are considered, but a far smaller number of heavy users (perhaps one-quarter as many) and probably significantly higher "natural" turnover among that population because of the drug's punishing side effects (see National Household Survey on Drug Use, 2001). Lower chronicity reduces the benefit of treating any given patient and thus the aggregate benefits unless a mechanism were developed to identify heavy methamphetamine users relatively early in their use careers and induce them to undergo treatment quickly. The sheer population size difference suggests that methamphetamine is only about one-quarter as attractive a target as cocaine, and the higher turnover rate would reduce that even further. Still, the aggregate gross benefits of successful development would surely be in the billions of dollars.

Cannabis has more heavy users than any other illicit drug. No firm estimate exists, but 3 million, or about half again as large as the cocaine

population, seems to be a rough consensus figure. How many of them want to quit is an open question. Historically, demand for cannabis treatment among adults has been small, though there is some evidence this is changing, perhaps due to the falling age of onset to heavy cannabis use. Early onset has also increased the number of teenagers in need of treatment. The damage from a month of heavy use is greater than that associated with cigarette smoking but far less than that associated with any other intoxicant. The median duration of the first period of heavy use (daily use over a period of months) has been estimated at nearly 4 years. The proportion of heavy users who have recurrent spells of heavy use has not been estimated, so overall chronicity cannot be known with anything like certainty. The value of developing an immunotherapy for cannabis would clearly be smaller, perhaps by as much as an order of magnitude, than the value of developing such a treatment for nicotine or cocaine, but more precision than that is not possible given the paucity of data.

The Pricing Problem

The actual marginal cost of an immunotherapy or depot medication—the cost of administering it to an additional patient once it is available—is likely to be so far below the benefit of that administration in cases of well-established heavy use of any of the intoxicants as to make a cost-benefit analysis superfluous. (That might not be true for cigarette smoking if the treatment has to be repeated frequently.) But the price of any such therapy, if it is developed along conventional pharmaceutical company lines, will be much greater than its marginal cost.

That must be true as long as the costs of drug development, including the costs and risks of the regulatory process, are borne by private entities under the incentive provided by the promise of patent-protected monopoly. The owner of the patent on an efficacious immunotherapy for cocaine (if there were only one on the market) might well want to price it near its perceived expected benefit to high-income cocaine users, as the producers of the nicotine patch have priced their product near the price of the cigarettes it displaces.

That sort of pricing would greatly reduce the social benefit available from the original drug development by pricing out of the market large numbers of potential patients whose willingness or ability to pay for treatment is lower. Even if the potential benefits from reducing cocaine use in the criminally active population are measured in the tens of billions of dollars, the agencies involved are highly unlikely to come up with billions of dollars to pay for it.

Thus the cost-benefit analysis is not invariant to the pricing structure, and if public or charitable money is to go into the development of these drugs, there ought to be agreements in advance with the potential patent holders or licensees regarding the pricing issue.

Imperfect Efficacy

The discussion to this point has been about high-efficacy therapies. That need not mean therapies that are efficacious for all, or almost all, of the population. A therapy that worked well for half the population and completely failed for the other half would have about half the benefits of a therapy that worked for everyone.

Unfortunately, however, it would not be the case that a therapy that reduced bioavailability by 75 percent in all patients would be 75 percent as beneficial as a therapy that reduced bioavailability effectively to zero. If three out of four molecules are put out of action before they reach the brain, a user who can acquire four times his or her normal dose can overcome the effects of the vaccine.[14] The result resembles a fourfold price increase for the drug.

Fortunately, the old opinion that drug demand among dependent individuals is highly inelastic (i.e., unresponsive) to changes in effective price is no longer in vogue. Current opinion holds that demand is fairly elastic to price. That makes it unlikely that many users will make a habit of "shooting over" the vaccines. The animal data are also reassuring on this point.

But it is not at all unlikely, if it is known that a large dose can reproduce something like the old drug effect, that a substantial number of users will make the attempt occasionally. The combined uncertainties about the quantity and purity of drugs acquired on the illicit market, how effective the therapy is, and how much a user's tolerance declines because of a period of abstinence might create significant overdose risk with respect to cocaine, heroin, or methamphetamine.

In the case of cigarette smoking, overdose seems unlikely to be a risk, but if the word were to spread among smokers that, say, smoking two cigarettes in quick succession, and doing so with attention to maximizing nicotine absorption, would get enough nicotine through the blockade to do its job, the temptation-reducing aspect of the immunotherapy or depot medication would be noticeably reduced, at least for some patients.

[14]In the methadone literature, this phenomenon is known as "swamping" or "shooting over" the drug blockade.

Substitution of Immunotherapy or Depot Medication for Noncriminal Justice Social Sanctions

Physicians and other health care professionals who use drugs illegally risk losing their licenses and when caught are frequently put on a kind of professional probation (sometimes in the case of opiate or opioid users, involving a requirement to take, under observation, a daily dose of a narcotic antagonist). Workers in the transportation industry also can lose their jobs if drugs are found in their systems. Members of the armed services are subject to dismissal. Mothers can lose custody of their children. Immunotherapies and depot medications, if developed, might be used in any of these circumstances, and the benefits and costs in those cases would be different from either the truly voluntary case or the case of coercion from the criminal justice system.

Prophylactic Administration

Vaccination is usually a prophylactic rather than a therapeutic procedure. The discussion up to now has assumed that (except for possibly overenthusiastic application to offenders) immunotherapies and depot medications would be used only in the treatment of persons with diagnosed substance abuse disorders. But the level of fear among parents about illicit drug use by their children is such that some parents would want their children "immunized" against, for example, cocaine, if such a treatment were available. Some might want "immunization" against cigarette smoking. Clearly, the cost-benefit ratio in such applications would be far lower than in the cases assumed above.

An intermediate case would involve children found to be using one or another drug but who are not yet diagnosably dependent on it. Here the parental demand would be more insistent and the justification at least somewhat more plausible. In each case, parent-child conflict is a possibility, and health care providers might find themselves caught in the middle.

It is also possible that some drug users not (yet) diagnosably abusing or dependent might find their own use of some drug so worrisome, and their confidence in their self-command so shaky, that they would want to undergo immunotherapy or depot medication. The benefits of such prophylactic administration, while far lower than the benefits of therapeutic administration, might still exceed the costs.

Risk Compensation

The concern that improved access to drug treatment will have a perverse impact on initiation and escalation rates has long been dismissed by

those familiar with the phenomenon of drug abuse. After all, few people who start to use abusable drugs expect to become addicted, and drug treatment to date has been sufficiently unreliable and unpleasant that its availability does not offer much comfort to someone contemplating the risk of addiction even if they do think about it. But that does not mean that the fear of addiction—thought of as a mysterious, incurable, relapsing condition—does not play an important role in reducing initiation and making most users of most drugs watchful over their own use patterns or that changing the meaning of "addiction" by making dependency curable might not substantially change the initiation rate.

A "home run" immunotherapy of the kind imagined above would substantially change the risk analysis, from the user's viewpoint, of "experimenting" with the drug whose addiction it treats. It seems hard to deny that the increased curability of some sexually transmitted diseases certainly contributed to a rise in risky sexual activity, and this case might be similar. An immunotherapy sounds enough like a "magic bullet" treatment that the problem of "risk compensation"—increased participation in a risky activity as a result of a reduction in the risk—needs to be considered.

If the dependency syndrome around any of the major drugs of abuse became a curable illness in the same sense that tuberculosis or syphilis is curable, the long-term effects on people's opinion of the drug might be profound. It is not obvious that the net result would be undesirable, but it might be very much so. It might be found that lowering the chronicity of the substance abuse disorder increased its incidence substantially, with unknown impacts on steady-state prevalence. That risk would be especially severe if the efficacy of the new therapy as perceived by potential drug users, especially young people, exceeded its efficacy in practice. In addition, even if aggregate problems from addiction went down, problems associated with casual use, which in the case of alcohol constitute a nontrivial fraction of the total social cost, might go up.

The risks of an upsurge in drug initiation as a result of the promise of an effective and relatively low-stress treatment are virtually impossible to quantify, even by the loose standards of quantification used elsewhere in this paper. But that does not mean that those risks ought to be ignored in planning for a world in which such therapies become available.

REFERENCES

Blower, S.M., Schwartz, E.J., and Mills, J. (2003). Forecasting the future of HIV epidemics: The impact of antiretroviral therapies and imperfect vaccines. *AIDS Reviews, 5*(2), 113-125.

DeLeon, G. (2000). *The therapeutic community: Theory, model, and method*. New York: Springer-Verlag.

Everingham, S.S., and Rydell, C.P. (1994). *Modeling the demand for cocaine.* Santa Monica, CA: RAND Corporation.

Fairbank, J.A., Dunteman, G.H., and Condelli, W.S. (1993). Do methadone patients substitute other drugs for heroin? Predicting substance use at 1-year follow-up. *American Journal of Drug and Alcohol Abuse, 19*(4), 465-474.

Goldberg, J., and Fischoff, B. (2000). The long-term risks in the short-term benefits: Perceptions of potentially addictive activities. *Health Psychology, 19*(3), 299-303.

Goldstein, A. (2001). *Addiction: From biology to drug policy* (Second Edition). New York: Oxford University Press.

Hser, Y., Hoffman, V., Grella, C.E., and Anglin, D. (2001). A 33-year follow-up of narcotics addicts. *Archives of General Psychiatry, 58*(5), 503-508.

Hubbard, R.L., and French, M.T. (1991). New perspectives on the benefit-cost and cost-effectiveness of drug abuse treatment. In W.S. Cartwright and J.M. Kaple (Eds.), *Economic costs, cost-effectiveness, financing, and community-based drug treatment* (pp. 94-113). Rockville, MD: National Institute on Drug Abuse.

Institute of Medicine. (1990). *Treating drug problems, volume 1.* Committee for the Substance Abuse Coverage Study, D.R. Gerstein and H.J. Harwood (Eds.). Washington, DC: National Academy Press.

Johnson, B.D., Rosenblum, A., and Kleber, H. (2003). *A new opportunity to expand treatment for heroin users in New York City: Public policy challenges for bringing buprenorphine into drug treatment programs and general medical practice.* White paper for New York City Department of Health and Mental Hygiene. Available: http://www.nyc.gov/html/doh/pdf/public/dmh/whitepaper.pdf [August 21, 2003].

Kleiman, M.A.R. (1999). Economic cost measurements, damage minimization and drug abuse control policy. *Addiction, 94*(5), 638-641.

MacCoun, R.J. (1993). Drugs and the law: A psychological analysis of drug prohibition. *Psychological Bulletin, 113*(3), 497-512.

MacCoun, R.J., Reuter, P., and Schelling, T. (1996). Assessing alternative drug control regimes. *Journal of Policy Analysis and Management*, *15*(3), 330-352.

McKay, J.R., Rutherford, M.J., Cacciola, J.S., Kabasakalian-McKay, R., and Alterman, A.I. (1996). Gender differences in the relapse experiences of cocaine patients. *Journal of Nervous and Mental Disease, 184*(10), 616-622.

Moore, M.H. (1990). Supply reduction and drug law enforcement. In M. Tonry and J.Q. Wilson (Eds.), *Drugs and crime* (pp. 109-158). Chicago: University of Chicago Press.

National Household Survey on Drug Use. (2001). *Methamphetamine usage data.* Available: http://www.samhsa.gov/oas/NHSDA/2k1NHSDA/vol2/appendixh_1.htm [August 21, 2003].

National Research Council. (2001). *Informing America's policy on illegal drugs: What we don't know keeps hurting us.* Committee on Data and Research for Policy on Illegal Drugs. C.F. Mansiki, J.V. Pepper, and C.V. Petrie (Eds.). Committee on Law and Justice and Committee on National Statistics. Commission on Behavioral and Social Sciences and Education. Washington, DC: National Academy Press.

Office of National Drug Control Policy. (2001). *The economic costs of drug abuse in the United States, 1992-1998.* Washington, DC: Executive Office of the President. Available: http://www.whitehousedrugpolicy.gov/publications/pdf/economic_costs98.pdf [August 21, 2003].

Office on Smoking and Health. (1989). *Reducing the health consequences of smoking: 25 years of progress: A report to the Surgeon General*. Washington, DC: U.S. Department of Health and Human Services.

Rydell, C.P., and Everingham, S.S. (1994). *Controlling cocaine: Supply versus demand programs.* Santa Monica, CA: RAND Corporation.

Tai, B., Chiang, N., and Bridge, P. (Eds.). (1997). *Medication development for the treatment of cocaine dependence: Issues in clinical efficacy trials*. Rockville, MD: National Institute on Drug Abuse. Available: http://www.drugabuse.gov/pdf/monographs/monograph175/download175.html [August 21, 2003].

Trosclair, A., Husten, C., Pederson, L., and Dhillon, I. (2002). Cigarette smoking among adults—United States, 2000. *Morbidity and Mortality Weekly Report, 51*(29), 642-645. Available: http://cisat.isciii.es/mmwr/preview/mmwrhtml/mm5129a3.htm [August 21, 2003].

H

Anticipating Unintended Consequences of Vaccine-Like Immunotherapies and Depot Medications for Addictive Drug Use

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Immunotherapy or depot medication (henceforth I/DM) programs that would prevent addiction or relapse to such drugs as tobacco or cocaine are largely unprecedented. These interventions differ in important respects from other pharmacological treatments for drug addiction and, for that matter, from vaccines used to prevent viral diseases. I/DMs may significantly alter the complex system of relationships among users, sellers, treatment providers, and social control agents. These actors are likely to change their behavior in both desirable and unintended ways.

Given the novelty of such interventions and uncertainty about how they might be implemented, it is not possible to forecast either the likelihood or the magnitude of unintended behavioral responses. Nevertheless, it is desirable to design I/DM interventions that might minimize such risks. This appendix identifies plausible mechanisms by which I/DMs might produce unintended consequences and reviews available evidence on the effects of these mechanisms in the research and clinical literatures on drug use and other risky behaviors. "Plausible" is defined here as something more than simply possible but not necessarily "more likely than not."

Judgments about whether and how to implement I/DM programs should not necessarily be based solely on worst-case scenarios. Economists and risk analysts have long noted the opportunity costs in foregone benefits that can result from extreme risk aversion (e.g., Viscusi, 1992; cf.

Shrader-Frechette, 1991).[1] But the literature on technological risks also documents the dangers posed by excessive optimism on the part of enthusiastic program designers (e.g., Janis, 1983; MacCoun, 1998a; Tenner, 1996; Vaughan, 1996). Thus, in the spirit of "devil's advocacy," it has been chosen in this appendix to err on the side of caution, giving greater attention to arguments in support of various unintended consequences than to possible counterarguments (which are nevertheless noted).

CONCEPTUAL FRAMEWORK

Program Prototypes

The committee has identified three types of immunotherapy or depot medication treatment protocols: overdose treatment, relapse prevention, and protection from addiction. *Overdose treatment* appears to be less susceptible than the other two categories to unintended consequences created by behavioral responses to the intervention, at least with respect to the mechanisms considered here. And to the extent that overdose treatment might operate via those mechanisms, its effects are likely to be similar to those of a relapse prevention program, only weaker. Thus, this appendix focuses primarily on *relapse prevention* and secondarily on the somewhat more remote prospect of *addiction protection*.

For simplicity the focus here is on interventions that target tobacco and cocaine use. Tobacco illustrates issues involved in pharmacological treatments for a legal, commercially available drug, and cocaine exemplifies issues posed for an illicit recreational drug.

Relevant Actors and Drug Use States

Psychoactive drug use is a multidimensional behavior characterized by many continuous parameters: age of onset, length of drug-use career, variety of drugs used, frequency of use, quantity consumed per use, and so on. To simplify the discussion, all this detail is abstracted away and drug use is characterized in terms of four mutually exclusive states. Figure H-1 presents a stochastic flow diagram, modified from a similar diagram used by Everingham and Rydell (1994). The figure depicts drug-using careers as patterns of movement among four "states": never used, light use, heavy use, and former use. Among users, program participants are distinguished from nonparticipants and use of the target drug versus

[1]The argument that risk-averse choices impose opportunity costs is analytical; the question of whether we should be more risk neutral is a value judgment.

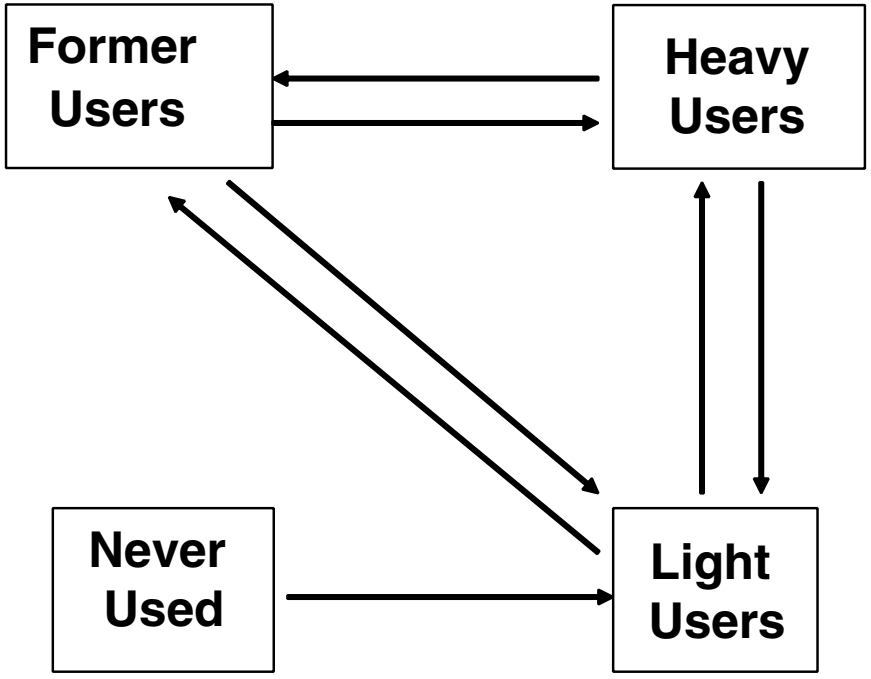

FIGURE H-1 Drug use conceptualized in terms of flows among four distinct drug use states.

use of other drugs. Behavioral effects on drug dealers, politicians, and the general public are also considered.

Presumably a relapse prevention program would target some fraction of heavy users. If effective, it should increase the flow of heavy users into nonuse and reduce the flow of nonusers back into use. An addiction protection program would target some fraction of light users and perhaps (not shown) newly heavy users and (more controversially) those at high risk who have never used. If effective, it should increase the flow of light users into nonuse and reduce the flow of nonusers into use.

In addition to these flows, it is important to consider the "stocks"—the distribution of individuals across these states. The distribution of consumption across users is strongly positively skewed for most drugs (see Everingham and Rydell, 1994; Skog, 1993)—though less dramatically so for tobacco than cocaine. As a result, the harmful consequences of substance use are not uniform but are disproportionately concentrated among the heaviest users.

The relative viability of targeting the median user versus hard-core users in the right tail of the distribution will probably vary as a function of several factors (Edwards et al., 1994; MacCoun, 1998b; Rose, 1992). Everything else being equal, it will be more effective to target typical users when the dose-response curve for various harms rises very quickly with small doses and when typical users account for a large fraction of total consumption. It will be more effective to target heavy users when the dose-response curve for various harms rises slowly at low doses and when the statistical distribution of consumption is heavily skewed. Relapse prevention I/DMs would disproportionately target right-tail users; addiction protection I/DMs would presumably include individuals from the whole range of the use distribution (even including some who would never use anyway), depending on their recruitment process and our accuracy at predicting who is "at risk" for addiction. But of course the choice of users to target for a pharmacological intervention will also be determined by legal, ethical, economic, and political considerations not considered in this chapter.

Voluntary Versus Mandated Participation

The consequences of an I/DM program are likely to differ depending on whether participation is solely voluntary versus mandated by legal or other authorities (e.g., employers). The voluntary-mandatory distinction hinges in part on the legal status of the drug in question. MacCoun and Reuter (2001) and MacCoun, Reuter, and Schelling (1996) examine the effects of a drug's legal status on its prevalence and harmful consequences. Here a few key points of relevance to the comparison of pharmacological interventions for a licit drug (e.g., tobacco) versus an illicit drug (e.g., cocaine) are summarized.

- Prohibition almost certainly raises the price of a prohibited substance, probably substantially (MacCoun and Reuter, 2001; National Research Council, 2001; cf. Miron, 2003). This is one reason why cocaine users might be more likely than tobacco users to commit income-generating crimes, even in the absense of any pharmacologically mediated disinhibition or aggression.
- Prohibited drugs are marketed quite differently from licit drugs; there is less quality control and far greater violence. The lack of quality control may make it more difficult to determine appropriate pharmacological dosages for cocaine addicts than for tobacco addicts. And the nature of black markets creates a risk that pharmacological interventions for illicit drugs might have nonpharmacological effects on violence.

- Prohibition increases the stigma associated with a drug, although stigma can have both desirable and undesirable consequences (see "Social Norm Effects" this appendix).

In addition to a drug's legal status, a related consideration is whether participation in a pharmacological program would be voluntary or mandatory.[2] Voluntary relapse prevention for either drug seems most feasible and would face few ethical and legal obstacles. For cocaine, mandatory participation would pose thorny ethical, legal, and political questions, but the drug's illicit status makes such programs plausible (see National Research Council, 2001, Chapters 6 and 8 and Appendix E). On the other hand, *mandatory* participation in a relapse or addiction prevention seems implausible for tobacco, a licit drug.

Although the distinction between voluntary and mandatory programs has legal and political relevance, it may have less clinical and behavioral relevance. Many experts contend that mandatory treatment is as effective as voluntary treatment,[3] and that conclusion seems even more plausible for these pharmacological interventions than for more traditional psychotherapeutic modalities. The behavioral mechanisms examined here seem as applicable to voluntary as to mandatory programs, given the severe self-control problems involved in drug addiction. Indeed, the very concept of "voluntariness" is problematic in the case of addictions, which are often characterized as "diseases of will" (see Elster and Skog, 1999; Vuchinich and Heather, 2003).

EFFECTS OF PRICE CHANGES

The first mechanism considered here involves the behavioral effects (on use and on criminality) of a change in drug prices brought about by I/DM programs.

[2]The term "mandatory" is used here to refer to a program in which clients are required to participate under threat of formal legal sanctions. The term "coerced" is commonly used in the treatment literature but is ambiguous because many clients are "coerced" into treatment via the threat of *informal* sanctions—divorce, loss of a job, expulsion from school.

[3]For evidence on this point, see Anglin and Hser (1990), Farabee, Prendergast, and Anglin (1998), Inciardi et al. (1997), Lawental et al. (1996), Maxwell (2000), Miller and Flaherty (2000), and Nishimoto and Roberts (2001). Manski et al. (2001) raise concerns about the methodologies used in these studies and also the possibility that mandated treatment has a "net-widening" effect on the scope of criminal justice activity.

Price Elasticity of Demand

Some readers may question the relevance of a drug's price for the behavior of a consumer who is addicted. Traditionally, many have assumed that addicts, by the very nature of their addiction, are oblivious to price changes; they will obtain their drug no matter what the cost, committing income-generating crime if need be to finance their habit. Thus, it has been surprising to learn that illicit drug use is in fact fairly sensitive to price variations.

Economists estimate sensitivity to prices in terms of the price elasticity of demand—the percentage change in consumption for a 1 percent change in price. Estimates for the price elasticity of cigarette demand are in the –0.3 to –0.5 range (Chaloupka and Pacula, 2000; Manning et al., 1991), suggesting that a 10 percent increase in the price of cigarettes would reduce overall consumption by only 3 to 5 percent. Thus tobacco users are in fact somewhat but not completely unresponsive to price. Cocaine users are more price sensitive; low estimates are around –0.4, but some studies find elasticities of –1.0 or more (see reviews by Caulkins and Reuter, 1996, and Chaloupka and Pacula, 2000). A drawback is that most estimates are based on users in the household population and may overrepresent casual users. But Reuter and Kleiman (1986) argue that, if anything, budget constraints tend to make heavy users more rather than less price sensitive. And Caulkins (2001) has shown that trends in emergency room incidents involving cocaine are highly responsive to trends in cocaine price, suggesting that heavy users are also price sensitive.

Assumptions Underlying a Shift in Demand

The analysis of drug price effects presented here is premised on four "best-case" assumptions about the effectiveness of I/DM programs. Later mechanisms will challenge each of these assumptions; to the extent that these assumptions are false, any price effects will probably be smaller than those contemplated here. Specifically, assume that: (1) targeted users cooperate fully with the intervention program; (2) the intervention completely discourages use of the target by program participants; (3) participants do not substitute other psychoactive drugs; and (4) the program has no direct effect on the behavior of nonparticipants, and any *indirect* effects are benign. Under these conditions, a successful psychopharmacological relapse or addiction prevention program ought to shift the demand curve downward, such that less cocaine (or tobacco) is demanded at any price. The magnitude of the demand shift would be determined by the number of users targeted and their previous levels of consumption.

Effects Predicted by a Traditional Model of Supply and Demand

Figure H-2 presents a rudimentary "comparative statics" analysis of the implications of this shift in drug demand. In this type of microeconomic analysis, a product's price and the quantity supplied are inferred from the equilibrium point where the supply curve (reflecting supplier responses) and the demand curve (reflecting consumer responses) intersect. Ceteris paribus, a downward shift in the demand curve ought to produce a reduction in the quantity supplied and a drop in the equilibrium price of the drug.[4]

In the short run, this reduced price should not in itself lead to increased use; by definition, the equilibrium price and quantity already reflect consumer and supplier preferences. But in the long run, reduced prices pose a risk of increased consumption, for two reasons. First, existing drug users may be more responsive to price changes over the long run than the short run (e.g., Reuter and Kleiman, 1986; Caulkins, 2001). Second, adolescents may be more likely to initiate use if they perceive the drug as inexpensive rather than expensive. This latter effect may be qualitative as well as quantitative; the reputation of a drug as "cheap" versus "expensive" can change over time. Compare cocaine's reputation in the late 1970s versus the late 1980s.

On the other hand, a consequence of reduced cocaine demand is that any "psychopharmacological" criminality produced by the direct effects of the drug (Goldstein, 1985) should be reduced.[5] Moreover, a price drop might reduce crime even among users not enrolled in an I/DM program. Presumably, some fraction of those nonparticipant cocaine users commit income-generating crimes to finance their use—what Goldstein calls "economic-compulsive" criminality. A reduction in price means that they might be expected to reduce their criminal involvement—a collateral benefit of a successful program. The effects of a price change on criminality, if any, will depend in part on whether the users who participate in I/DM programs differ from nonparticipants in their price sensitivity. If the two

[4]Caulkins and Harwood each suggest that the I/DM effect could be modeled as a downward shift in the supply curve—supply reduction rather than demand reduction—in the sense that these treatments block the supply of drug to the brain. But it seems preferable to model the effects with respect to demand for two reasons. First, the supply function is usually conceptualized with respect to supplier behavior rather than consumer physiology or phenomenology. Second, I/DM programs, if effective, will reduce the demand of participants but will not necessarily affect the supply to nonparticipant users, at least not directly.

[5]Of course, neither of these crime reduction benefits seems very likely for a tobacco program. Tobacco has not been causally linked with significant increases in psychopharmacological criminality, and because prices are lower (and the average user is more socially integrated), few users commit crimes to buy cigarettes.

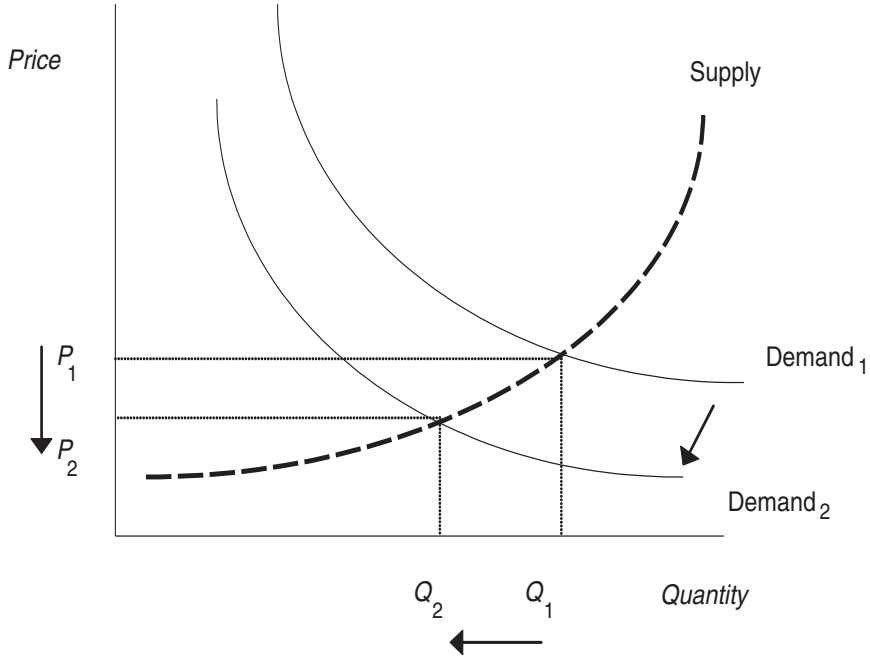

FIGURE H-2 Price and quantity decreases following a downward shift in demand, assuming a traditional supply curve.
NOTE: P_1 = initial price, P_2 = new price; Q_1 = initial quantity supplied, Q_2 = new quantity supplied.

classes of users differ, I/DM programs might alter the slope of the demand function by changing the composition of the remaining user pool.

Predicted Effects if the Supply Function Is Downward Sloping

The traditional analysis in Figure H-2 is plausible as a qualitative depiction of the tobacco market.[6] But several experts (e.g., Kleiman, 1993;

[6]Nevertheless, despite a substantial drop in demand, the non-tax price of tobacco has actually approximately doubled since 1985 (calculations for the author by Rosalie Pacula, senior economist at RAND, 11 November 2003). This increase is not fully understood, but it appears that the shift in the demand curve may have been accompanied by a shift in the supply curve, due to increased advertising expenses, tort litigation expenses, and other factors (personal communication to the author from Frank Chaloupka, University of Illinois at Chicago, 18 November 2003). It seems unlikely that an I/DM program for tobacco would have similar effects on supply costs.

Reuter and Kleiman, 1986; Reuter et al., 1988; Rydell and Everingham, 1994) argue that the illicit nature of the cocaine business might produce a supply curve that is downsloping, as seen in Figure H-3. This conclusion follows if the marginal cost of producing a kilogram of cocaine does not increase with the total number of kilograms produced and the per-unit risk of seizures and other enforcement actions falls with the total quantity of cocaine that is produced. The assumption of a downward sloping cocaine supply curve is controversial (see Caulkins, Chiesa, and Everingham, 2000; National Research Council, 1999) but is important to consider because it has implications for the effect of a downward shift in the demand curve.

Figure H-3 indicates that with a downsloping supply curve a downward shift in the demand curve would still produce a reduction in the quantity supplied, but prices would actually rise. This is obviously a desirable effect if users not receiving an I/DM intervention are price sensitive because they can be expected to reduce their consumption *even though they are not in the program*. Moreover, the higher prices should discourage potential users from initiating drug use.

On the other hand, if those still using cocaine are relatively price insensitive, they might increase their rate of income-generating crime to

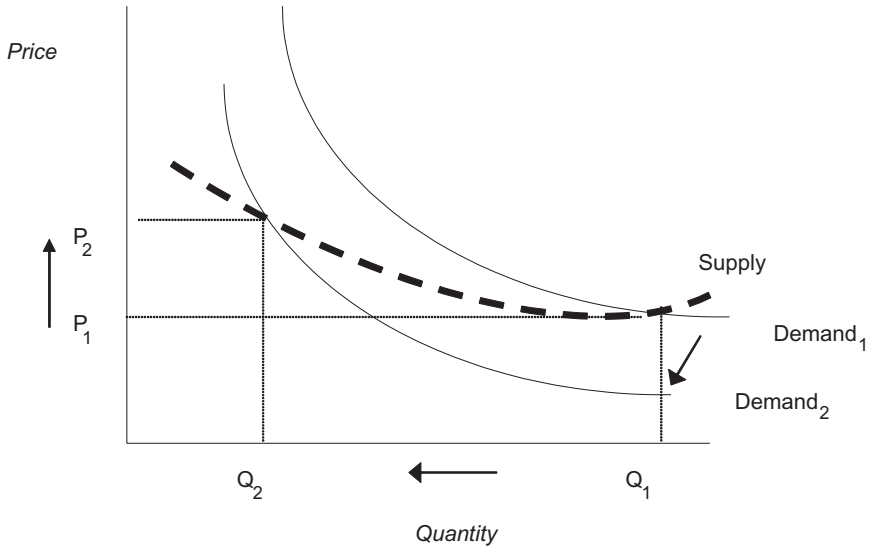

FIGURE H-3 Price increase and quantity decrease following a downward shift in demand, assuming a downsloping supply curve
NOTE: P_1 = initial price, P_2 = new price; Q_1 = initial quantity supplied, Q_2 = new quantity supplied.

maintain their preferred level of consumption—clearly an unintended consequence of the program. This effect would be mitigated to the extent that those users targeted for the program were the ones most heavily involved in criminal activity—as might occur through a court-mandated program.

This discussion of price and criminality effects suggests the importance of additional empirical research on users' responsiveness to price changes. To accurately predict the consequences of an I/DM intervention on drug markets, better information is needed on short- versus long-run price elasticities and on differences in the price sensitivity of likely participants versus other users.

NONPARTICIPATION AND NONCOMPLIANCE

The analysis of price effects presented above was premised on the best-case assumption that I/DM programs produce their intended shift in demand. The remaining mechanisms considered here each challenge that assumption. The simplest and least speculative challenge to the best-case scenario is the likelihood that some nontrivial fraction of targeted users will fail to participate.

It may be difficult to enroll targeted participants at high rates and sustain their participation for the desired length of time. In the Drug Abuse Treatment Outcome Study, a nationwide naturalistic examination of nonexperimental treatment settings, median retention in treatment ranged from 29 to 177 days across 18 long-term residential programs and from 42 to 144 days for 16 outpatient drug-free programs (Joe, Simpson, and Broome, 1998). Methadone clinics fared somewhat better, with a median of 117 to 583 days across 13 programs; across these programs, half of all clients participated for at least a year. But an examination of the evidence from a variety of at least partially analogous interventions suggests that high dropout rates are the norm.[7]

Evidence from Partially Analogous Programs

Smoking Cessation Programs

The smoking cessation evaluation literature has largely ignored the question of program attrition. For example, dropout rates are not ana-

[7]These high dropout rates do not necessarily imply that those dropping out receive no treatment (see Simpson, Joe, and Brown, 1997) or do not stop using on their own (see Shadish et al., 1998); they simply suggest that high levels of participation in a vaccine program cannot be taken for granted.

lyzed in many major metanalyses of this literature (e.g., Cepeda-Benito, 1993; Viswesvaran and Schmidt, 1992). In a recent methodological analysis of seven carefully controlled clinical trials (Shadish et al., 1998), the dropout rate ranged from 0 to 30 percent, with a mean of 13 percent But Borrelli et al. (2002, p. 23) suggest that "proactive recruitment and population-based studies demonstrate no-show rates approaching 50 percent."

Pharmacological Treatment of Cocaine Dependence

Table H-1 summarizes data from 45 clinical trial arms on the effects of 15 different pharmacological interventions for cocaine dependence, computed from data presented in a recent metanalysis by Silva de Lima et al. (2002). Discouragingly, no significant effects from any of these interventions were found. But the participation rates were also discouraging, with dropout rates ranging from 15 to 79 percent, with an overall rate of 48 percent; the same rate was observed across placebo conditions. High attrition rates are also common in psychosocial cocaine treatments (Gottheil, Sterling, and Weinstein, 1995; Siqueland et al., 1998; Van Horn and Frank, 1998; White, Winn, and Young, 1998).

TABLE H-1 Dropout Rates in Pharmacological Treatment Trials for Cocaine Dependence

		Active Drug Condition			Placebo Condition			
Active Drug	No. of Studies	Drop-outs	*N*	Rate (%)	Drop-outs	*N*	Rate (%)	Relative Risk
Bupropion	1	11	74	15	13	75	17	0.86
Desipramine	8	72	185	39	39	136	29	1.36
Fluoxetine	1	8	16	50	15	16	94	0.53
Gepirone	1	9	20	45	11	21	52	0.86
Imipramine	1	24	59	41	27	54	50	0.81
Ritanserin	1	11	40	28	13	40	33	0.85
Amantadine	6	68	144	47	55	140	39	1.20
Bromocriptine	3	32	70	46	31	72	43	1.06
Pergolide	1	111	156	71	89	153	58	1.22
Carbamzaepine	4	92	152	61	110	161	68	0.89
Disulfiram	2	14	47	30	6	40	15	1.99
Mazindol	2	10	40	25	12	40	30	0.83
Naltrexone	1	18	24	75	15	22	68	1.10
Phenytoin	1	23	29	79	25	31	81	0.98
Risperidone	1	23	30	77	42	45	93	0.82
TOTAL		526	1,086	48	503	1,046	48	1.01

SOURCE: Adapted from Silva de Lima et al. (2002).

Methadone Maintenance

One might hope participation rates would be higher for a more effective pharmacological intervention. But dropout rates computed from data on 22 controlled methadone maintenance trials (reported in Farré et al., 2002) range from 13 to 80 percent, with a mean of 43 percent and a median of 46 percent. As might be expected, dropout rates are lower in programs with higher daily methadone doses (see Figure H-4), but even at the highest studied doses (100 mg/day), one-quarter of participants dropped out. (Participants receiving a placebo or another treatment are excluded from this analysis.)

Drug Court Graduation Rates

One might also assume that participation rates might be higher in mandatory, court-administered programs, where clients face possible criminal sanctions for noncompliance. But the drug court literature suggests that as many as half of assigned participants fail to "graduate" (averaging 47 percent in studies reviewed by Belenko, 2001). This low rate may seem to contradict the notion of a "mandatory" program, but Belenko (1998, p. 25) notes that in a recent Department of Justice survey "only 25 percent of probationers reported that they were required to undergo drug testing" and "one quarter of felony probationers had had no contact of any type with their probation officer during the past month."[8]

Disease Vaccine Programs

Finally, nonparticipation is a serious problem in vaccination programs for many serious diseases (Szilagyi et al., 2000). For example, Carter, Beach, and Inui (1986) found that only one-quarter to one-third of high-risk patients who were actively urged to get influenza shots actually did so. Moore-Caldwell et al. (1997) report that compliance with a hepatitis B vaccine series was reduced because "most teens perceived their risk of acquiring hepatitis B infection as slight or none," yet Lawrence and Goldstein (1995) report that the hepatitis B immunization has been hampered by the inability of medical providers to identify high-risk individuals. On the other hand, in a recent intervention targeting over a thousand heroin addicts in Italy, 88 percent completed a full hepatitis B vaccine series (Quaglio et al., 2002). So high compliance is possible even in heavy drug-using populations.

[8]Perhaps unsurprisingly, mandatory treatment compliance is much higher in in-patient psychiatric institutions (Zito, Craig, and Wanderling, 1991).

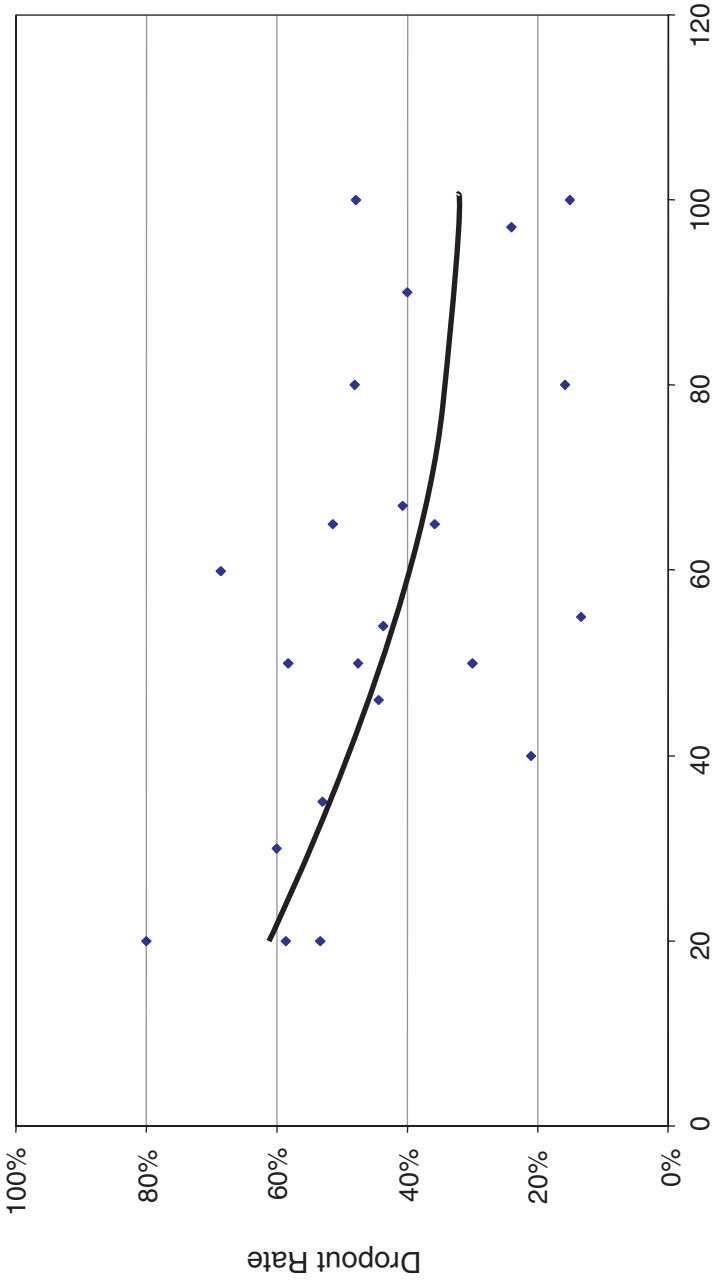

FIGURE H-4 Declining dropout rates as a function of increased doses in methadone trials (data reported in Farré et al., 2002).

Conclusion

Neither a voluntary nor a compulsory vaccination program can be expected to achieve high rates of compliance without aggressive recruitment and follow-up. Among a variety of roughly comparable interventions each routinely loses about one-half of its clients. Perhaps if I/DM programs were perceived to be less onerous (or more efficacious) than traditional substance abuse treatments, they might fare better—but not necessarily. High treatment dropout rates probably have less to do with treatment management than with the inherent difficulty of changing addictive behaviors (De Leon, 1998; Joe et al., 1998). Most addiction treatment clients are at best ambivalent about the prospect of total abstinence, and for that reason these interventions may be both encouraging and somewhat threatening. Indeed, addicts at risk of coerced treatment may even volunteer for traditional psychosocial programs to avoid participating in pharmacological programs.

Program designers will have to attend to a variety of factors that might increase participation:

- confronting fear and distrust of a novel and intrusive medical technology that has both medical and social control objectives,
- minimizing logistical barriers to participation (location, hours, etc.),
- carefully crafted persuasive appeals and outreach for voluntary programs, and
- monitoring and clear sanctioning of court-mandated clients (see Kleiman, 1997a, 1997b).

INCREASED CONSUMPTION TO "SWAMP" THE TREATMENT

The previous section examined incomplete participation—an across-client effect. This section considers the effects of an only partially effective intervention—a within-client effect. Thus, rather than (or in addition to) only a fraction of targeted people participating, this section considers what would happen if participating clients experience no reduction, or only a partial reduction, in drug craving and/or participating clients are able to produce the same subjective drug effects by significantly increasing their consumption (frequency and/or quantity)—in essence, "swamping" the treatment.[9]

The results of such a scenario are potentially quite serious. The down-

[9]Pentel (this volume) uses the label "compensation" for this effect, but that term is avoided in this appendix chapter because of potential confusion with a different behavioral mechanism discussed below that is called "compensatory behavioral response" in the risk literature.

ward shift in the demand curve plotted in Figure H-2 might not be expected. Users who maintain their previous level of consumption will experience fewer drug effects. From a clinical perspective this may produce a significant improvement in functioning, but from a market perspective there may be no observable behavioral change. This is particularly troubling for an illicit drug like cocaine because many of the harms associated with illicit drug use are primarily attributable to illicit markets rather than the effects of the drug per se (MacCoun et al., 1996; MacCoun and Reuter, 2001). Worse yet, participating users might simply increase their consumption of their drug of dependency in an attempt to achieve the same subjective effects. To the extent that this happened it would reduce the magnitude of reduction in demand and in theory could even produce a net increase in demand.

Although the analogies are not perfect, experiences with existing pharmacological treatments for addiction are not comforting. Positive urine tests for illicit opiates are found in methadone maintenance clinical trials in anywhere from 16 to 71 percent of the clients, with a median rate of 53 percent (Farre et al., 2002). Figure H-4 plots the results of 15 such trials as a function of experimentally assigned methadone dose. As might be expected, illicit opiate use declines with increasing maintenance dose, but even at the highest observed dose, 100 mg per day, over one-fourth of all clients continued using street opiates. Similarly, clinical trials for pharmacological treatment of tobacco dependence—bupropion SR and nicotine gums, inhalers, nasal sprays, and patches—routinely find that a majority of clients continue smoking (see Fiore et al., 1994; Fiore et al., 2000).

Of course, studies of these interventions provide no indication that users actually *increase* their consumption. And the immunotherapies and depot medications under consideration here surely differ from other interventions in important ways. But some of the differences could make the picture less encouraging rather than more.

A key consideration is the extent to which these interventions *reduce the motivation to use the targeted drug*, rather than (or in addition to) simply blocking the physical and/or subjective effects of the drug. Methadone and nicotine treatments do so, but the proposed I/DM interventions do not, at least not directly. They do not provide a substitute or maintainence substance, nor do they directly alter the brain mechanisms thought to be responsible for cravings and/or withdrawal.

Still, Pentel (this volume) suggests that "the hope in using this strategy is to reduce the rewarding effects of the drug that lead to and sustain addiction. For example, a cocaine addict who is vaccinated and then takes a puff of crack cocaine would feel little effect and therefore have little reason to continue using it." One way to characterize this argument is in terms of what behavior analysts call "extinction." In classical conditioning, extinction occurs when a conditioned stimulus is no longer paired

with unconditioned stimuli. In operant conditioning, extinction occurs when a learned behavior no longer receives a positive reinforcement. Treatments that prevent an addictive drug from crossing the blood-brain barrier are likely to produce both types of extinction.[10]

Extinction can produce lasting behavioral changes, but it has other predictable consequences as well (Azrin, Hutchinson, and Hake, 1966; Neuringer, Kornell, and Olufs, 2001; Skinner, 1953; Sulzer-Azaroff and Mayer, 1977):

- The target behavior does not cease immediately; responding may temporarily increase in frequency and variability.
- Occasional repairing behavior and the reinforcer change the extinction noncontingency to an intermittent schedule of reinforcement, which can encourage persistent responding.
- During extinction, conditioned associations are not unlearned so much as they are "forgotten," or put into competition with newly learned alternative contingencies, which means that even in the absense of further reinforcement the response can "spontaneously recover" (Bouton, 1994).
- Increased responding may be accompanied by aggressive behavior—the so-called vending machine phenomenon (Sulzer-Azaroff and Mayer, 1977).
- Ceteris paribus, extinction produces a net reduction in positive reinforcement, which if not replaced by substitute rewards can produce lethargy, apathy, and depression.

Moreover, a traditional extinction account may fail to capture important subtleties of addictive drug use. Both classical conditioning and operant conditioning have long been implicated in drug addiction, but they do not account for many aspects of the phenomenon (Robinson and Berridge, 2003). There is increasing evidence that chronic drug use can produce enduring changes in the brain's sensitivity to drug-related cues, producing a heightened motivational state that may persist long after drug use has been stopped (see Gardner and David, 1999; Robinson and Berridge, 2003).[11] Gardner and David (1999, p. 117) suggest that "strong

[10]Very similar predictions are made based on different arguments and evidence in the reactance theory and control theory literatures (see Carver and Scheier, 1998).

[11]Time-discounting accounts of addiction (see Elster and Skog, 1999, and Vuchinich and Heather, in press) also predict that I/DM treatments should reduce drug use, by eliminating, at least temporarily, the temptation posed by immediate reinforcers and encouraging the user to invest in alternative behaviors with larger but more delayed payoffs (work, sports, family, etc.).

and persistent drug craving may outlast drug detoxification and withdrawal by months or years."

Thus, there are reasons to be concerned that these new interventions will fail to fully block drug taking. Users may attempt to "swamp" the treatment by increasing their consumption. These effects may be temporary, but they could be extremely serious. For example, the immunotherapeutic effects are expected to dissipate between treatments (Pentel, this volume). If so, the effects of a given dose of the targeted drug will vary over time; a dose that produces no response or a mild response soon after a treatment may produce a very large response if attempted some weeks later. It seems unlikely that users will be able to accurately anticipate such effects and titrate their doses accordingly. Thus, users who attempt to overcome the I/DM blocking effect will be at serious risk of extreme psychiatric reactions, cardiac failure, respiratory failure, or other reactions to toxicity.

Consider also the implications if the user's previous consumption level was already at the outer limits of what he or she could afford. (This is more plausible for cocaine than tobacco.) If so, efforts to swamp the treatment with high doses could motivate increased income-generating "economic compulsive" criminal behavior.

For all these reasons, *it is crucial to use monitoring and counseling to discourage users from attempting to swamp the treatment by increasing their consumption*. I/DM treatments should not be viewed as a cure for addiction but rather a prolonged respite from it—an opportunity for the addict to regain control of his or her life and invest in a repertoire of alternative activities.

Later in this chapter, another mechanism is identified that might produce heightened risky behavior in response to a vaccine (Blower and McLean, 1994). The mechanism there is somewhat different, involving compensatory responses to perceived risk reduction.

DRUG SUBSTITUTION

Another major concern is whether a pharmacological relapse prevention or addiction protection program would inadvertently motivate participants to increase their use of *other* drugs—a substitution effect. Note that the substitute drug may have either more or less harmful physical and behavioral effects than the targeted drug.

Psychopharmacological researchers often study drug substitution using a drug discrimination paradigm (Kamien et al., 1993), which is useful for studying agonist and antogonist mechanisms. But while a client in a cocaine relapse prevention program may substitute another drug based on its similar pharmacological properties, the choice might be influenced

as much or more by situational factors—availability, price, peer use, etc. Moreover, the closer two drugs are in pharmacology, the more likely it is that I/DM treatments may at least partially block the effects of the substitute (Pentel, this volume). Thus, it is worthwhile to construe the notion of a "substitute" more broadly rather than in the drug discrimination tradition.

Economists have a purely behavioral way of operationalizing substitutes and complements that has been adapted by the behavioral economic research community in psychology (e.g., Petry and Bickel, 1998). Two goods are considered *substitutes* if an increase in the price of the first good leads to an increase in demand for the second good—a positive cross-price elasticity. Two goods are considered *complements* if an increase in the price of the first good leads to a decrease in demand for both goods—negative price and cross-price elasticities.

One might reasonably ask whether evidence on cross-price elasticities is relevant for understanding I/DM effects. Is an increase in the preferred drug's price analogous to decreases in the preferred drug's effects on the brain? Several arguments suggest the answer is probably *yes*. First, laboratory experiments have established that manipulations of effort, price, available income, and reinforcement magnitude have roughly equivalent effects on the rates of drug consumption (e.g., DeGrandpre and Bickel, 1995). Second, some of the econometric studies of substitution operationalize "price" using proxies like drug enforcement risk, marijuana eradication, and variations in state drinking ages, all of which involve reduced availability to the consumer.

In econometric studies, substitution and complementarity can be estimated in situ, capturing actual behavior outside the laboratory, though the relevant data are often sparse and poor, and there are serious concerns about endogeneity and spurious correlation (National Research Council, 2001). Bickel and colleagues (DeGrandpre and Bickel, 1995; Petry and Bickel, 1998) have developed a laboratory paradigm that avoids these problems by manipulating prices in a simulated market, but their participants, though experienced addicts, are nevertheless "behaving" in an artificial setting that may distort their choices. Because there are inevitable tradeoffs between experimental control and realism, both approaches seem necessary (see Mook, 1983).

Relevant Evidence

Marijuana-Alcohol Link

The most studied linkage has been between marijuana and alcohol—a relationship that has little bearing for the interventions examined here.

Still, the literature illustrates the methodological challenges to correctly estimating the relationship. Some studies find a substitution relationship between marijuana and alcohol use (Chaloupka and Laixuthai, 1994; DiNardo and Lemieux, 1992), while others suggest the relationship is complementary (Pacula, 1998; Williams, Pacula, and Chaloupka, 2001). Chaloupka and Pacula (2000, p. 105) argue that "The mixed evidence with respect to alcohol and marijuana can be attributed to differences in the level of aggregation of the data as well as to differences in the populations being studied. When individual-level data are employed, and demand equations for marijuana can also be estimated, the findings are generally supportive of the complementary relationship between alcohol and marijuana. Until good measures of the money price of marijuana are obtained, however, this cannot be known with certainty."

Marijuana-Tobacco Link

Econometric studies of the relationship between marijuana and cigarette consumption suggest a complementary relationship (Cameron and Williams, 2001; Chaloupka et al., 1999; Farrelly et al., 1999; Pacula, 1998). If so, this implies that a successful pharmacological tobacco intervention ought to bring about some reduction in marijuana use.

Alcohol-Tobacco Link

The evidence on the alcohol-tobacco relationship is similarly ambiguous. Cameron and Williams et al. (2001) found an inverse association between the price of cigarettes and alcohol consumption, while alcohol prices are positively but insignificantly associated with cigarette consumption. Decker and Schwartz (2000) found that increases in the price of cigarettes are associated with increases in the prevalence of drinking and the amount consumed by drinkers.

Marijuana-Hard Drug Link

Model's (1993) analysis of Drug Abuse Warning Network emergency room data for the years 1975 to 1978 found higher rates of marijuana incidents and lower rates of hard drug incidents in states that had depenalized marijuana. Model interpreted this as evidence for a substitution effect, in which users shifted from harder drugs to marijuana after its legal risks decreased. A laboratory study of hypothetical drug purchase choices by heroin addicts also suggests that marijuana and heroin are substitutes (Petry and Bickel, 1998). On the other hand, Saffer and Chaloupka (1995) found that marijuana had a complementary relationship with cocaine and

heroin, but their data source (the National Household Survey on Drug Abuse) captures only a small and possibly unrepresentative fraction of cocaine and heroin users. The methodological differences across these studies are so great that the contradictory findings are difficult to resolve without more research.

Relationships Among Hard Drugs

It appears that only one econometric study has examined the cross-price elasticities between hard drugs, finding that cocaine and heroin were complements rather than substitutes (Saffer and Chaloupka, 1995). Again, the household sample may be quite unrepresentative of hard drug users. Petry and Bickel's (1998) simulation experiments using heroin addicts suggest that valium and cocaine substituted for heroin; mock "purchases" of these drugs rose with simulated rises in heroin prices. Heroin purchases were unresponsive to rises in the price of valium. Unfortunately for our purposes, cocaine prices were not manipulated. Despite the obvious limitations of the simulation (no legal risks, no actual consumption), a conceptual replication of this paradigm using cocaine addicts and manipulated cocaine prices might provide valuable insights into possible substitutes for cocaine.

In addition to these economic studies, there are large clinical literatures on cocaine-alcohol (Pennings, Leccese, and de Wolff, 2002) and cocaine-heroine (Leri, Bruneau, and Stewart, 2003) poly-drug use. Popular lore suggests that a cocaine-heroin mix (a speedball) has particularly attractive effects for addicts, which would suggest complementarity, but Leri et al. (2003, p. 7) argue that "clinical and preclinical experimental evidence indicates that the simultaneous administration . . . does not induce a novel set of subjective effects, nor is it more reinforcing than either drug alone."

Effects of Methadone Maintenance on Use of Other Drugs

Methadone maintenance provides a partial analogy to the pharmacological treatments at issue here. Methadone itself is a substitute for heroin in the empirical sense that it is inversely related to heroin use among former heroin users. Though methadone at adequate doses significantly reduces heroin use (e.g., Farre et al., 2002) (see Figure H-5), use of other street drugs is common among methadone clients (Leri et al., 2003; Preston et al., 1998). For example, one study reported that "more than half of the sample tested positive at least once for opiates (61 percent) other than methadone, almost half tested positive for cocaine (48 percent), almost half tested positive for benzodiazepines (46 percent), and more than three

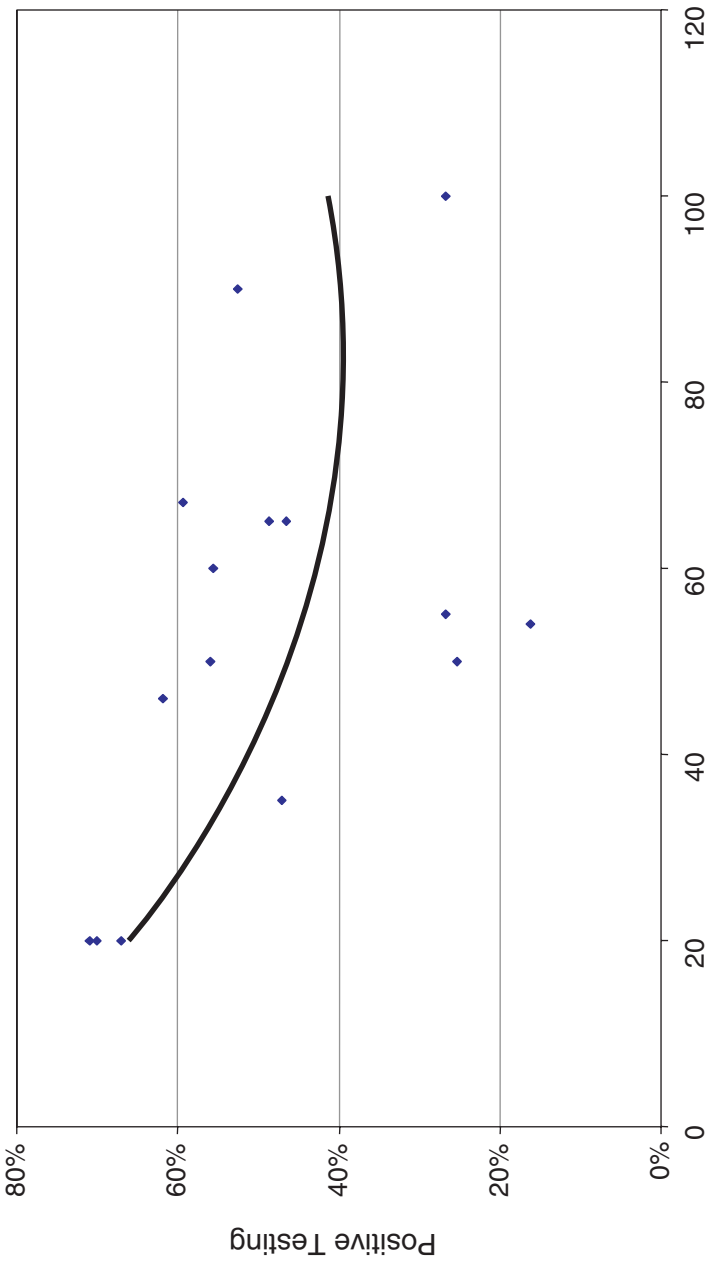

FIGURE H-5 Decreasing illicit opioid use with increases in methadone dose in methadone trials (data reported in Farré et al., 2002).

quarters tested positive for cannabis (78 percent)" (Nirenberg, Cellucci, Liepman, Swift, and Sirota, 1996, p. 225).

Naturally, there is a concern that use of these other drugs reflects a substitution effect of the methadone maintenance regimen. Clients do not appear to be substituting cocaine for heroin. Longitudinal studies suggest that many clients were already using cocaine prior to starting methadone and that participation in the maintenance program is associated with a decline in cocaine use (see Dunteman, Condelli, and Fairbank, 1992; Fairbank, Dunteman, and Condelli, 1993; Shaffer and LaSalvia, 1992; but see Compton et al., 1995, p. 109). Indeed, Kidorf and Stitzer (1993) were able to reduce cocaine use among clients by making methadone contingent on cocaine-free urine for 7 weeks (see also Caulkins and Satel, 1999).

Cigarette smoking is also common among methadone clients (Frosch et al., 2000), but experimental manipulations of methadone dose levels have produced inconsistent effects on smoking levels (Schmitz, Grabowski, and Rhoades, 1994; Stark and Campbell, 1993). On the other hand, buprenorphine maintenance appears to increase tobacco consumption, at least among concurrent opiate and cocaine users (Mutschler et al., 2002).

Conclusion

At present, the only substitution effect that can be predicted with any confidence for a tobacco relapse prevention or addiction prevention intervention involves *food*, as weight gain is a common consequence of smoking cessation (Cabanac and Frankham, 2002). Tobacco appears to have a complementary relationship with marijuana, but there is evidence for both complementarity and substitution between tobacco and alcohol. For cocaine cessation there is mixed evidence for a possible substitution effect involving marijuana and simply too little evidence to predict effects on the consumption of amphetamines, opiates, or alcohol. Pharmacologically, the use of stimulants seems plausible, but again, social and economic factors may be more determinative (price, availability, peer use).

It is apparent that additional research on drug substitution effects in natural, clinical, and experimental settings ought to be considered a high priority for the addiction research community. In the meantime, in the face of such scanty evidence, a conservative assumption would be that some sort of substitution is a plausible response to these interventions. Use of other drugs should be closely monitored, and appropriate preventive counseling should be provided.

COMPENSATORY RESPONSES TO RISK REDUCTION

Unlike the previously discussed mechanism, the remaining mechanisms suggest unintended effects on *drug use by those not receiving I/DM treatment*.

Risk analysts have learned that technological risk reduction often has the unintended consequence of increasing the prevalence and/or intensity of that behavior. According to MacCoun and Reuter (2001, p. 392):

> When technological innovations successfully reduce the probability of harm given unsafe conduct, they make that conduct less risky. And if the perceived risks were motivating actors to behave somewhat self-protectively, a reduction in risk should lead them to take fewer precautions than before, raising the probability of their unsafe conduct to a higher level. This notion has been variously labeled compensatory behavior, risk compensation, offsetting behavior, or in its most extreme form, risk homeostasis—a term that implies efforts to maintain a constant level of risk (Wilde, 1982).

Compensatory behavioral responses to risk reduction are now well established in a number of risk domains (see reviews in MacCoun, 1998b; Institute of Medicine, 2001). For example, people drive faster and more recklessly in cars with seat belts and air bags (Chirinko and Harper, 1993; Stetzer and Hofman, 1996). Similarly, smokers compensate for filters and low-tar tobacco by smoking more cigarettes, inhaling more deeply, or blocking the filter vents (Hughes, 1995; Institute of Medicine, 2001). In both domains, some of the safety gains brought about by a reduction in the probability of harm given unsafe conduct have been offset by increases in the probability of that conduct.

The total harm produced by a risky activity (e.g., addictive drug use) is a function of the average harm per incident, multiplied by the total amount of the activity (MacCoun, 1998b; MacCoun and Reuter, 2001). In theory, if a technological innovation reduces but does not eliminate the riskiness of an activity, and if the risk reduction motivates sufficiently large increases in the frequency or quantity of that activity, then average harm might fall, but total harm might increase.

In many settings, technological risk reduction provides little evidence that behavioral responses produce net increases in harm or even the constant level of harm predicted by Wilde's (1982) "homeostatic" version of the theory. Rather, such effects are sufficiently small relative to the benefits of the intervention they reduce but do not eliminate the gains in safety (Institute of Medicine, 2001; MacCoun, 1998a).

But there are some important cautionary tales. For example, in 1994, Blower and McLean published epidemiological simulations suggesting

that an HIV vaccine, unless perfectly prophylactic, could actually exacerbate the San Francisco AIDS epidemic. This would occur if individuals behaved less cautiously in response to their increased sense of safety.

In the decade that has followed, it has become increasingly clear that a similar scenario is playing out in response to highly active antiretroviral therapy (HAART; see Blower, 2001; Katz et al., 2002; Ostrow et al., 2002; Stolte, Dukers, de Wit, Fennema, and Coutinho, 2002). Katz et al. report that the percentage of San Francisco men who have reported unprotected anal sex increased from 24 to 45 percent between 1994 and 1999. The authors present correlational and anecdotal evidence linking this increase in risky sex to reduced fears of HIV since the advent of HAART. Survey results reported by Ostrow et al. (2002) also show a correlation between unsafe sex and perceptions that HAART reduces the harmful consequences of HIV infection.

Immunotherapies or depot medications for drug dependence are potentially vulnerable to compensatory behavioral responses. The decision to take risks is influenced by the expected outcome of an activity but also by perceived worst-case scenarios (March and Shapira, 1992; Slovic, Fischhoff, and Lichtenstein, 1979). Thus, the perceived *risk of becoming addicted* is an important predictor of the decision to initiate and/or escalate recreational drug use (e.g., Benthin, Slovic, and Severson, 1993; Goldberg and Fischhoff, 2000). As such, this risk is a major focus of the curriculum of primary drug prevention activities (National Research Council, 2001). An effective and accessible I/DM program may actually reduce the perceived risk of addiction.

Compensatory responses to I/DM might well be larger than those observed in studies of seat belts, needle exchanges, and other interventions. The reason is perceptual: Those other interventions are at best seen as ways to reduce the relevant risks at the margin. But the existence of an I/DM program for relapse prevention or addiction protection, if widely publicized, may convey—rightly or wrongly—a widespread belief that "addiction has been cured" (see MacCoun, 2003). Psychologically, the perceived elimination of a small risk has a much larger impact than perceived reductions of equivalent magnitude elsewhere in the risk distribution (Kahneman and Tversky, 1984). If so, current users who are not enrolled in a pharmacological program may increase their consumption. And current nonusers may, at the margin, be more willing to begin using the addictive substance.

The magnitude of such effects is unknown. There is no a priori reason to believe that such effects would be so large as to offset the benefits of reducing drug use among participants. But program designers should anticipate the possibility that an I/DM program might inadvertently encourage nonaddicts to risk becoming addicts.

SOCIAL NORM EFFECTS

Another way that I/DM programs might influence drug use by nonprogram participants is by altering networks of social influence. One such effect is beneficial. A reduction in use by light users could have "social multiplier" effects on nonusers and current light users (see Caulkins et al., 1999). This follows under the assumption that current users socially reinforce, encourage, and facilitate use among those around them. There is much correlational evidence for this assumption, at least among adolescents (e.g., Elliott, Huizinga, and Ageton, 1985), although the correlation conflates a social influence effect with a selection effect, since high-risk peers tend to select each other as friends (Bauman and Ennett, 1996; Kandel, 1996).

But it is possible that this social influence effect would be inverted in the case of hard-core dependent users.[12] Musto (1971/1987) and Johnston (1991) each offer versions of a "generational forgetting" model of drug epidemics, in which the increasing visibility of the deleterious effects of addiction triggers a reduction in initiation.[13] Behrens and colleagues (1999, 2000, 2002) have incorporated this process into Everingham and Rydell's (1994) model of the cocaine epidemic. Their analyses led to the disturbing prediction that if Musto and Johnston are correct, widespread drug treatment early in an epidemic could actually exacerbate it by slowing the social learning process. Similarly, if the generational forgetting model is correct, then ceteris paribus, reducing the visibility of the harms of addiction might reduce a social deterrent to drug use. This prediction is admittedly speculative. The generational forgetting model remains largely untested; there are simply too few "cycles" of data to test the cyclicity of drug epidemics. Still, this line of reasoning bolsters the concern that I/DMs might well encourage drug use by reducing the perceived risks.

UNINTENDED EFFECTS ON DRUG MARKETING

Putting aside the unintended consequences discussed thus far, assume again for the sake of argument that a successful pharmacological intervention is widely implemented and reduces the prevalence and

[12]Caulkins et al. (1999) included negative feedback from heavy use to initiation in their modeling of a social multiplier effect for primary prevention, but they concluded that the desirable multiplier effects would be larger than any negative effects.

[13]In Musto's account the predicted effect is cyclical because, as the number and visibility of users decline over time, initiation begins to rise again. The models developed by Behrens and colleagues (1999, 2000, 2002) allow for other possibilities (e.g., damped oscillation).

severity of tobacco or cocaine addiction. This would almost certainly threaten the profitability of tobacco or cocaine production and sales. Producers and sellers, whether licit or illicit, may well respond in a compensatory fashion.

Illicit Drug Sellers

Sellers of cocaine or other targeted street drugs may respond in various ways. Drug sellers might move into the production and/or sales of other psychoactive drugs (e.g., Constantine, 1995; Thompson, 2002) or develop new synthetics that mimic the targeted drug without being blocked by I/DM pharmacologies. At least in the short run, dealers may act more aggressively to protect and expand their share of the diminishing market. There might be (at least temporarily) an upsurge in violence as sellers compete for a shrinking pool of addicts. Drug-selling organizations might also attempt to expand into regions where the relevant I/DM interventions are less available or less widely used. It has long been rumored that urban cocaine-trafficking organizations expanded into rural areas as urban drug enforcement became more aggressive in the 1990s (Butterfield, 2002; Johnson, 2003; National Alliance of Gang Investigators Associations, 2000; cf. Maxson, 1998).

The Tobacco Industry

If I/DM interventions against tobacco addiction were to become popular, the tobacco industry might also seek new users who are not currently targeted for these interventions (e.g., young people, rural communities, other nations) and seek to establish or strengthen these alternative markets. For example, as U.S. tobacco consumption has declined, tobacco companies have become more aggressive in international markets, especially in developing nations (World Health Organization, 2001). There might be new forms of advertising, perhaps subtly hinting that tobacco addiction is now a more manageable risk of their product.

The Pharmaceutical Industry

For manufacturers of immunotherapeuties or depot medications, the largest market will involve addiction protection rather than relapse prevention simply because the population of potential clients is so much larger. There are many more potential addicts than actual addicts, especially if "at risk" is defined broadly. (This is especially likely to be true for the tobacco market, which is roughly an order of magnitude larger than

the market for illicit drugs other than marijuana.[14]) Many parents may feel a moral (or perhaps social) obligation to protect their children against the risk of future addiction. The industry might market the treatments in a manner that reinforces or amplifies this sense of responsibility.

Much may depend on the decision by public and private health insurance providers about whether to reimburse I/DM addiction protection and by any professional guidelines for off-label use established by professional medical societies (e.g., the American Medical Association). Broad coverage of youth addiction protection is likely to be socially inefficient. If parents and physicians define "addiction risk" too broadly, there will be a "moral hazard" problem of excessive utilization of the intervention. On the other hand, if insurers set strict limits on coverage (ex ante), they may face lawsuits if some youth who were denied coverage later became addicted.

UNINTENDED SOCIAL AND POLITICAL CONSEQUENCES

Again, assuming that a pharmacological intervention is widely implemented and is at least perceived to be successful in reducing addiction, other actors might also respond in unintended ways:

- Nonusers may further stigmatize or ostracize smokers and drug users who have not availed themselves of a pharmacological relapse intervention. While this stigma may help to discourage initiation and escalation by casual users, the labeling theory tradition in sociology suggests that it could actually intensify the drug involvement of heavy users (MacCoun, 1993).
- Law enforcement officials may demote cocaine offenses as an enforcement priority, increasingly viewing cocaine as a medical problem rather than a social control problem. This would be particularly troubling if these officials overestimated the actual "capture" or effectiveness rates of the pharmacological intervention.
- Politicians and the general public may be less willing to actively support more traditional forms of treatment, primary prevention, and law enforcement. This would be particularly troubling if in fact a large fraction of existing users were ineligible for such a pharmacological intervention. Also, a reduction in support could have pernicious effects on substance abuse control efforts involving drugs for which no pharmacological intervention is available.

[14]According to the National Household Survey on Drug Abuse, in 2001 there were 7 million current users of illicit drugs other than marijuana versus 66.5 million current users of a tobacco product. See http://www.samhsa.gov/oas/nhsda.htm#NHSDAinfo.

- There may be a political backlash against the coercive use (by legal authorities or parents) of this invasive technology. This seems particularly likely if mandated clients are disproportionately drawn from ethnic and racial minority groups, which is not implausible given the disproportionately high rates at which those groups are apprehended for drug use (MacCoun and Reuter, 2001).

CONCLUSIONS

This appendix raises a number of potential unintended consequences of a depot medication or immunotherapy program for addiction, including increased use of the target drug by some program clients (if the treatment is only partially effective and fails to reduce drug motivation, increased use of other drugs by program clients (a substitution effect), increased use of the target drug by those not in the program (through reductions in the perceived riskiness of the drug, and increased dealer violence (through increased competition for fewer customers and/or effects of the program on prices). There is little basis for estimating the likelihood of these potential outcomes other than to suggest that their probabilities are nontrivial (i.e., below 1.0 but closer to 0.50 than to 0).

Of course, these effects are not the only factors to consider when evaluating such a program. Even if all these consequences occurred, they may well be completely offset by the program's benefits. A full analysis of the desirability of an I/DM program should consider other factors assessed elsewhere in this volume, including the ethical obligation to treat drug dependence if possible; the ethical, legal, and political objections to the intervention; the administrative and medical costs of the program; the cost effectiveness of the program relative to other interventions; and the program's cost-benefit ratio. Nevertheless, the scenarios considered here are not implausible on their face. Each is based on familiar theoretical mechanisms, evidence from at least partially analogous interventions, or both. Program designers have an obligation to take these risks seriously and to minimize them through careful program implementation, monitoring, and evaluation.

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REFERENCES

Anglin, M.D., and Hser, Y.I. (1990). Treatment of drug abuse. In M. Tonry and J.Q. Wilson (Eds.), *Drugs and crime (Crime and justice): A review of research, Vol. 13* (pp. 393-460). Chicago: University of Chicago Press.

Azrin, N.H., Hutchinson, R.R., and Hake, D.J. (1966). Extinction-induced aggression. *Journal of the Experimental Analysis of Behavior, 9*, 191-204.

Bauman, K.E., and Ennett, S.T. (1996). On the importance of peer influence for adolescent drug use: Commonly neglected considerations. *Addiction, 91,* 185-198.

Behrens, D.A., Caulkins, J.P., Tragler, G., Haunschmied, J.L., and Feichtinger, G. (1999). A dynamic model of drug initiation: Implications for treatment and drug control. *Mathematical Biosciences, 159*, 1-20.

Behrens, D.A., Caulkins, J.P., Tragler, G., and Feichtinger, G. (2000). Optimal control of drug epidemics: Prevent and treat—but not at the same time. *Management Science, 46,* 333-347.

Behrens, D.A., Caulkins, J.P., Tragler, G., and Feichtinger, G. (2002). Why present-oriented societies undergo cycles of drug epidemics. *Journal of Economic Dynamics and Control, 26,* 919-936.

Belenko, S. (1998). *Research on drug courts: A critical review*. New York: National Center on Addiction and Substance Abuse, Columbia University.

Belenko, S. (2001). *Research on drug courts: A critical review, 2001 update*. New York: National Center on Addiction and Substance Abuse, Columbia University.

Benthin, A., Slovic, P., and Severson, H. (1993). A psychometric study of adolescent risk perception. *Journal of Adolescence, 16,* 153-168.

Blower, S. (2001). Calculating the consequences: HAART and risky sex. *AIDS, 15,* 1309-1310.

Blower, S.M., and McLean, A.R. (1994). Prophylactic vaccines, risk behavior change, and the probability of eradicating HIV in San Francisco. *Science, 265,* 1451-1454.

Borelli, B., Hogan, J.W., Bock, B., Pinto, B., Roberts, M., and Marcus, B. (2002). Predictors of quitting and dropout among women in a clinic-based smoking cessation program. *Psychology of Addictive Behaviors, 16,* 22-27.

Bouton, M.E. (1994). Conditioning, remembering, and forgetting. *Journal of Experimental Psychology: Animal Behavior Processes, 20,* 219-231.

Butterfield, F. (2002). As drug use drops in big cities, small towns confront upsurge. *The New York Times*, February 11.

Cabanac, M., and Frankham, P. (2002). Evidence that transient nicotine lowers the body weight set point. *Physiology and Behavior, 76*(4-5), 539-542.

Cameron, L., and Williams, J. (2001). Cannabis, alcohol, and cigarettes: Substitutes or complements? *The Economic Record*, *77*, 19-34.

Carter, W.B., Beach, L.R., and Inui, T.S. (1986). The flu shot study: Using multiattribute utility theory to design a vaccination intervention. *Organizational Behavior and Human Decision Processes, 38*(3), 378-391.

Carver, C.S., and Scheier, M.F. (1998). *On the self-regulation of behavior*. New York: Cambridge University Press.

Caulkins, J.P. (2001). Drug prices and emergency department mentions for cocaine and heroin. *American Journal of Public Health, 91,* 1446-1448.

Caulkins, J.P., and Reuter, P. (1996). The meaning and utility of drug prices. *Addiction, 91,* 1261-1264.

Caulkins, J.P., and Satel, S.L. (1999). Methadone patients should not be allowed to persist in cocaine use. *Drug Policy Analysis Bulletin, January*(6), 1-2.

Caulkins, J.P., Rydell, C.P., Everingham, S.S., Chiesa, J., and Bushway, S. (1999). *An ounce of prevention, a pound of uncertainty.* Santa Monica, CA: RAND Corporation.

Caulkins, J.P., Chiesa, J.R., and Everingham, S.S. (2000). *Response to the National Research Council's assessment of RAND's "Controlling Cocaine" study.* Santa Monica, CA: RAND Corporation.

Cepeda-Benito, A. (1993). A meta analytical review of the efficacy of nicotine chewing gum in smoking treatment programs. *Journal of Consulting and Clinical Psychology, 61*, 822-830.

Chaloupka, F., and Laixuthai, A. (1994). *Do youths substitute alcohol and marijuana? Some econometric evidence*. National Bureau of Economic Research Working Paper w4662. Available: http://www.nber.org/papers/w4662 [November 26, 2003].

Chaloupka, F., and Pacula, R. (2000). Economics and antihealth beahavior: The economic analysis of substance use and misuse. In W. Bickel and R. Vuchinich (Eds.), *Reframing health behaviour change with behavioural economics* (pp. 89-111). Mahwah, NJ: Lawrence Erlbaum.

Chaloupka, F., Pacula, R., Farrelly, M., Johnston, L., O'Malley, P., and Bray, J. (1999). *Do higher cigarette prices encourage youth to use marijuana*? Cambridge, MA: National Bureau of Economic Research.

Chirinko, R.S., and Harper, E.P. (1993). Buckle up or slow down? New estimates of offsetting behavior and their implications for automobile safety regulation. *Journal of Policy Analysis and Management, 12,* 270-296.

Compton, P.A., Ling, W., Charuvastra, V.C., and Wesson, D.R. (1995). Buprenorphine as a pharmacology for cocaine abuse: A review of the evidence. *Journal of the Addictive Diseases, 14,* 97-113.

Constantine, T.A. (1995). *International drug trafficking organizations in Mexico*. Testimony before the Senate Foreign Relations Committee, August 8.

Decker, S.L., and Schwartz, A.E. (2000). *Cigarettes and alcohol: Substitutes or complements?* National Bureau of Economic Research Working Paper 7535. Available: http://ideas.repec.org/p/nbr/nberwo/7535.html [November 26, 2003].

DeGrandpre, R.J., and Bickel, W.K. (1995). Human drug self-administration in a medium of exchange. *Experimental and Clinical Psychopharmacology, 3,* 349-357.

DeLeon, G. (1998). Reconsidering the self-selection factor in addiction treatment research. *Psychology of Addictive Behaviors, 12,* 71-77.

DiNardo, J., and Lemieux, T. (1992). *Alcohol, marijuana, and American youth: The unintended consequences of government regulation.* (Working draft WD-59220-DPRC). Santa Monica, CA: RAND Corporation.

Dunteman, G.H., Condelli, W.S., and Fairbank, J.A. (1992). Predicting cocaine use among methadone patients: Analysis of findings from a national study. *Hospital and Community Psychiatry, 43*(6) 608-611.

Edwards, G., Anderson, P., Babor, T.F., Casswell, S., Ferrence, R., Giesbrecht, N., Godfrey, C., Holder, H.D., Lemmens, P., Mäkelä, K., Midanik, L.T., Norström, T., Österberg, E., Romesljö, A., Room, R., Simpura, J., and Skog, O.-J. (1994). *Alcohol policy and the public good.* Oxford, England: Oxford University Press.

Elliot, D.S., Huizinga, D., and Ageton, S.S. (1985). *Explaining delinquency and drug use.* Thousand Oaks, CA: Sage.

Elster, J., and Skog, O.-J. (Ed.). (1999). *Getting hooked: Rationality and addiction*. Cambridge, MA: Cambridge University Press.

Everingham, S.S., and Rydell, C.P. (1994). *Modeling the demand for cocaine.* Santa Monica, CA: RAND Corporation.

Fairbank, J.A., Dunteman, G.H., and Condelli, W.S. (1993). Do methadone patients substitute other drugs for heroin? Predicting substance use at 1-year follow-up. *American Journal of Drug and Alcohol Abuse, 19*, 465-474.

Farabee, D., Prendergast, M., and Anglin, M.D. (1998). The effectiveness of coerced treatment for drug-abusing offenders. *Federal Probation, 62*, 3-10.

Farre, M., Mas, A., Torrens, M., Moreno, V., and Cami, J. (2002). Retention rate and illicit opioid use during methadone maintenance interventions: A meta-analysis. *Drug and Alcohol Dependence, 65*, 283-290.

Farrelly, M., Bray, J.W., Zarkin, G.A., Wendling, B.W., and Pacula, R.L. (1999). *The effects of prices and policies on the demand for marijuana: Evidence from the National Household Surveys on Drug Abuse*. Cambridge, MA: National Bureau of Economic Research.

Fiore, M.C., Smith, S.S., Jorenby, D.E., and Baker, T.B. (1994). The effectiveness of the nicotine patch for smoking cessation: A meta-analysis. *Journal of the American Medical Association, 271*(24), 1940-1947.

Fiore, M.C., Bailey, W.C., Cohen, S.J., Dorfman, S.F., Goldstein, M.G., Gritz, E.R., Heyman, R.B., Jaen, C.R., Kottke, T.E., Lando, H.A., Mecklenburg, R.E., Mullen, P.D., Nett, L.M., Robinson, L., Stitzer, M.L., Tommasello, A.C., Villejo, L., and Wewers, M.E. (2000). *Treating tobacco use and dependence: Clinical practice guideline*. Rockville, MD: U.S. Department of Health and H uman Services.

Frosch, D.L., Shoptaw, S., Nahom, D., and Jarvik, M.E. (2000). Associations between tobacco smoking and illicit drug use among methadone-maintained opiate-dependent individuals. *Experimental and Clinical Psychopharmacology, 8*, 97-103.

Gardner, E.L., and David, J. (1999). The neurobiology of chemical addiction. In J. Elster and O.-J. Skog (Eds.), *Getting hooked: Rationality and addiction* (pp. 93-136). Cambridge, England: Cambridge University Press.

Goldberg, J., and Fischhoff, B. (2000). The long-term risks in the short-term benefits: Perceptions of potentially addictive activities. *Health Psychology, 19,* 299-303.

Goldstein, P. (1985). The drug/violence nexus: A tripartite conceptual framework. *Journal of Drug Issues*, *14*, 493-506.

Gottheil, E., Sterling, R.C., and Weinstein, S.P. (1995). Generalizing from controlled treatment outcome studies: Sample data from a cocaine treatment program. *American Journal on Addictions, 4*, 331-338.

Hughes, J.R. (1995). Applying harm reduction to smoking. *Tobacco Control, 4,* S33-S38.

Inciardi, J.A., Martin, S.S., Butzin, C.A., Hooper, R.M., and Harrison, L.D. (1997). An effective model of prison-based treatment for drug-involved offenders. *Journal of Drug Issues, 27*, 261-278.

Institute of Medicine. (2001). *Clearing the smoke: Assessing the science base for tobacco harm reduction*. Committee to Assess the Science Base for Tobacco Harm Reduction, K. Stratton, P. Shetty, R. Wallace, and S. Bondurant (Eds.). Board on Health Promotion and Disease Prevention. Washington, DC: National Academy Press.

Janis, I. (1983). *Groupthink,* 2nd rev. ed. Boston: Houghton Mifflin.

Joe, G.W., Simpson, D.D., and Broome, K.M. (1998). Effects of readiness for drug abuse treatment on client retention and assessment of process. *Addiction, 93*, 1177-1190.

Johnson, A. (2003). Yardie drug gangs expanding to suburbs and villages, say police. *The Independent,* June 15.

Johnston, L.D. (1991). Toward a theory of drug epidemics. In L. Donohew and H.E. Sypher (Eds.), *Persuasive communication and drug abuse prevention* (pp. 93-131). Mahwah, NJ: Lawrence Erlbaum.

Kahneman, D., and Tversky, A. (1984). Choices, values, and frames. *American Psychologist, 39*, 341-350.

Kamien, J.B., Bickel, W.K., Hughes, J.R., Higgins, S.T., and Smith, B. (1993). Drug discrimination by humans compared to nonhumans: Current status and future directions. *Psychopharmacology, 111,* 259-270.

Kandel, D.B. (1996). The parental and peer contexts of adolescent deviance: An algebra of interpersonal influences. *Journal of Drug Issues, 26,* 289-315.

Katz, M.H., Schwarcz, S.K., Kellogg, T.A., Klausner, J.D., Dilley, J.W., Gibson, S., and McFarland, W. (2002). Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *American Journal of Public Health, 92,* 388-394.

Kidorf, M., and Stitzer, M.L. (1993). Contingent access to methadone maintenance treatment: Effects on cocaine use of mixed opiate-cocaine abusers. *Experimental and Clinical Psychopharmacology, 1*(1-4), 200-206.

Kleiman, M.A.R. (1993). Enforcement swamping: A positive-feedback mechanism in rates of illicit activity. *Mathematical and Computer Modeling, 17,* 65-75.

Kleiman, M.A.R. (1997a). Coerced abstinence: A neopaternalist drug policy punitiative. In L. Mead (Ed.), *The new paternalism: Supervisory approaches to poverty* (pp. 182-219). Washington, DC: Brookings Institution.

Kleiman, M.A.R. (1997b). The problem of replacement and the logic of drug law enforcement. *Drug Policy Analysis Bulletin, 3,* 8-10. Available: http://www.fas.org/drugs/issue3.htm [January 8, 2004].

Lawental, E., McLellan, A.T., Grissom, G.R., Brill, P., and O'Brien, C. (1996). Coerced treatment for substance abuse problems detected through workplace urine surveillance: Is it effective? *Journal of Substance Abuse, 8,* 115-128.

Lawrence, M.H., and Goldstein, M.A. (1995). Hepatitis B immunization in adolescents. *Journal of Adolescent Health, 17*(4), 234-243.

Leri, F., Bruneau, J., and Stewart, J. (2003). Understanding polydrug use: Review of heroin and cocaine co-use. *Addiction, 98,* 7-22.

MacCoun, R.J. (1993). Drugs and the law: A psychological analysis of drug prohibition. *Psychological Bulletin, 113,* 497-512.

MacCoun, R.J. (1998a). Biases in the interpretation and use of research results. *Annual Review of Psychology, 49,* 259-287.

MacCoun, R.J. (1998b). Toward a psychology of harm reduction. *American Psychologist, 53,* 1199-1208.

MacCoun, R.J. (2003). Is the addiction concept useful for drug policy? In R. Vuchinich and N. Heather (Eds.), *Choice, behavioural economics and addiction.* Oxford, England: Elsevier Science.

MacCoun, R.J., and Reuter, P. (2001). *Drug war heresies: Learning from other vices, times, and places.* Cambridge, England: Cambridge University Press.

MacCoun, R.J., Reuter, P., and Schelling, T. (1996). Assessing alternative drug control regimes. *Journal of Policy Analysis and Management, 15,* 1-23.

Manning, W., Keeler, E., Newhouse, J., Sloss, E., and Wasserman, J. (1991). *The costs of poor health habits.* Cambridge, MA: Harvard University Press.

March, J.G., and Shapira, Z. (1992). Variable risk preferences and the focus of attention. *Psychological Review, 99,* 172-183.

Maxson, C. (1998). *Gang members on the move.* Washington, DC: Office of Juvenile Justice and Delinquency Prevention, U.S. Department of Justice.

Maxwell, S.R. (2000). Sanction threats in court-ordered programs: Examining their effects on offenders mandated into drug treatment. *Crime and Delinquency, 46*(4), 542-563.

Miller, N.S., and Flaherty, J.A. (2000). Effectiveness of coerced addiction treatment (alternative consequences): A review of the clinical research. *Journal of Substance Abuse Treatment, 18*(1), 9-16.

Miron, J.A. (2003). *Do prohibitions raise prices? Evidence from the market for cocaine.* Unpublished manuscript, Boston University. Available: http://econ.bu.edu/miron/images/prices_submit.pdf [January 8, 2004].

Model, K.E. (1993). The effect of marijuana decriminalization on hospital emergency room drug episodes: 1975-1978. *Journal of the American Statistical Association, 88,* 737-747.

Mook, D.G. (1983). In defense of external invalidity. *American Psychologist, 38*, 379-387.

Moore-Caldwell, S.Y., Werner, M.J., Powell, L., and Greene, J.W. (1997). Hepatitis B vaccination in adolescents: Knowledge, perceived risk, and compliance. *Journal of Adolescent Health, 20*(4), 294-299.

Musto, D.F. (1971/1987). *The American disease: Origins of narcotic control.* New York: Oxford University Press.

Mutschler, N.H., Stephen, B.J., Teoh, S.K., Mendelson, J.H., and Mello, N.K. (2002). An inpatient study of the effects of buprenorphine on cigarette smoking in men concurrently dependent on cocaine and opioids. *Nicotine and Tobacco Research, 4*, 223-228.

National Alliance of Gang Investigators Associations. (2000). *Regional gang assessments.* Available: http://www.nagia.org/NGTASection_III.htm [January 8, 2004].

National Research Council. (1999). *Assessment of two cost-effectiveness studies on cocaine control policy.* Committee on Data and Research for Policy on Illegal Drugs. C.F. Mansiki, J.V. Pepper, and Y. Thomas (Eds.). Committee on Law and Justice and Committee on National Statistics. Commission on Behavioral and Social Sciences and Education. Washington, DC: National Academy Press.

National Research Council. (2001). *Informing America's policy on illegal drugs: What we don't know keeps hurting us.* Committee on Data and Research for Policy on Illegal Drugs, C.F. Mansiki, J.V. Pepper, and C.V. Petrie (Eds.). Committee on Law and Justice and Committee on National Statistics. Commission on Behavioral and Social Sciences and Education. Washington, DC: National Academy Press.

Neuringer, A., Kornell, N., and Olufs, M. (2001). Stability and variability in extinction. *Journal of Experimental Psychology: Animal Behavior Processes, 27*, 79-94.

Nirenberg, T.D., Cellucci, T., Liepman, M.R., Swift, R.M., and Sirota, A.D. (1996). Cannabis versus other illicit drug use among methadone maintenance patients. *Psychology of Addictive Behaviors, 10*(4), 222-227.

Nishimoto, R.H., and Roberts, A.C. (2001). Coercion and drug treatment for postpartum women. *American Journal of Drug and Alcohol Abuse, 27*(1), 161-181.

Ostrow, D.E., Fox, K.J., Chmiel, J.S., Silvestre, A., Visscher, B.R., Vanable, P.A., Jacobson, L.P., and Strathdee, S.A. (2002). Attitudes towards highly active antiretroviral therapy are associated with sexual risk taking among HIV-infected and uninfected homosexual men. *AIDS, 16*, 775-780.

Pacula, R. (1998). *Adolescent alcohol and marijuana consumption: Is there really a gateway effect?* Cambridge, MA: National Bureau of Economic Research.

Pennings, E.J.M., Leccese, A.P., and de Wolff, F.A. (2002). Effects of concurrent use of alcohol and cocaine. *Addiction, 97*, 773-783.

Pentel, P.R. (2004). Vaccines and depot medications for drug addiction: Rationale, mechanisms of action, and treatment implications. In H.J. Harwood and T.G. Myers (Eds.), *New treatments for addiction: Behavioral, ethical, legal, and social questions*. National Research Council and Institute of Medicine. Washington, DC: The National Academies Press.

Petry, N.M., and Bickel, W.K. (1998). Polydrug abuse in heroin addicts: A behavioral economic analysis. *Addiction, 93*, 321-335.

Preston, K.L., Silverman, K., Higgens, S.T., Brooner, R.K., Montoya, I., Schuster, C.R., and Cone, E.J. (1998). Cocaine use early in treatment predicts outcome in a behavioral treatment program. *Journal of Consulting and Clinical Psychology, 66*, 691-696.

Quaglio, G., Talamini, G., Lugoboni, F., Lechi, A., Venturini, L., Accordini, A., Bellio, G., Bossi, C., Cantiero, D., Ceravolo, R., Cicciu, G., Civitelli, P., Corso, F., Faccini, M., Forza, G., Manera, R., Manzato, E., Mecenero, V., Pajusco, B., Parolin, A., Residori, M., Sabbion, R., Saccardi, C., Schifano, F., Smacchia, C., Vendramin, A., Des Jarlais, D.C., and Mezzelani, P. (2002). Compliance with hepatitis B vaccination in 1175 heroin users and risk factors associated with lack of vaccine response. *Addiction, 97*(8), 985-992.

Reuter, P., and Kleiman, M. (1986). Risks and prices: An economic analysis of drug enforcement. In N. Morris and M. Tonry (Eds.), *Crime and justice: An annual review of research, vol. 7* (pp. 289-340). Chicago: University of Chicago Press.

Reuter, P., Crawford, G., and Cave, J. (1988). *Sealing the borders: The effects of increased military participation in drug interdiction*. Santa Monica, CA: RAND Corporation.

Robinson, T.E., and Berridge, K.C. (2003). Addiction. *Annual Review of Psychology, 54*, 25-53.

Rose, G. (1992). *The strategy of preventive medicine.* Oxford, England: Oxford University Press.

Rydell, C.P., and Everingham, S.S. (1994). *Controlling cocaine: Supply versus demand programs.* Santa Monica, CA: RAND Corpoation.

Saffer, H., and Chaloupka, F. (1995). *The demand for illicit drugs*. Cambridge, MA: National Bureau of Economic Research.

Schmitz, J.M., Grabowski, J., and Rhoades, H. (1994). The effects of high and low doses of methadone on cigarette smoking. *Drug and Alcohol Dependence, 34*(3), 237-242.

Shadish W.R., Hu, X., Glaser, R.R., Kownacki, R., and Wong, S. (1998). A method for exploring the effects of attrition in randomized experiments with dichotomous outcomes. *Psychological Methods, 3*, 3-22.

Shaffer, H.J., and LaSalvia, T.A. (1992). Patterns of substance use among methadone maintenance patients: Indicators of outcome. *Journal of Substance Abuse Treatment, 9*(2), 143-147.

Shrader-Frechette, K.S. (1991). *Risk and rationality.* Berkeley and Los Angeles: University of California Press.

Silva de Lima, M., Garcia de Oliveira Soares, B., Pereira Reisser, A.A., and Farrell, M. (2002). Pharmacological treatment of cocaine dependence: A systematic review. *Addiction, 97,* 931-949.

Simpson, D.D., Joe, G.W., and Brown, B.S. (1997). Treatment retention and follow-up outcomes in the Drug Abuse Treatment Outcome Study (DATOS). *Psychology of Addictive Behaviors, 11*, 294-307.

Siqueland, L., Crits-Christoph, P., Frank, A., Daley, D., Weiss, R., Chittams, J., Blaine, J., and Luborsky, L. (1998). Predictors of dropout from psychosocial treatment of cocaine dependence. *Drug and Alcohol Dependence, 52*, 1-13.

Skinner, B.F. (1953). *Science and human behavior.* New York: Free Press.

Skog, O.-J. (1993). The tail of the alcohol consumption distribution. *Addiction, 88,* 601-610.

Slovic, P., Fischhoff, B., and Lichtenstein, S. (1979). Rating the risks. *Environment, 21,* 14-20, 36-39.

Stark, M.J., and Campbell, B.K. (1993). Cigarette smoking and methadone dose levels. *American Journal of Drug and Alcohol Abuse, 19*(2), 209-217.

Stetzer, A., and Hofman, D.A. (1996). Risk compensation: Implications for safety interventions. *Organizational Behavior and Human Decision Processes, 66*, 73-88.

Stolte, I.G., Dukers, N.H., de Wit, J.B., Fennema, H., and Coutinho, R.A. (2002). A summary report from Amsterdam: Increase in sexually transmitted diseases and risky sexual behaviour among homosexual men in relation to the introduction of new anti-HIV drugs. *Eurosurveillance Monthly Archives, 7*(2), 19-22.

Sulzer-Azaroff, B., and Mayer, G.R. (1977). *Applying behavior-analysis procedures with children and youth.* New York: Holt, Rinehart, and Winston.

Szilagyi, P.G., Bordley, C., Vann, J.C., Chelminski, A., Kraus, R.M., Margolis, P.A., and Rodewald, L.E. (2000). Effect of patient reminder/recall interventions on immunization rates. *Journal of the American Medical Association, 284*(14), 1820-1827.

Tenner, E. (1996). *Why things bite back: Technology and the revenge of unintended consequences.* New York: Alfred A. Knopf.

Thompson, T. (2002). The dealers think they're untouchable now . . . *The Observer*, Feb. 24.

Van Horn, D.H.A., and Frank, A.F. (1998). Psychotherapy for cocaine addiction. *Psychology of Addictive Behaviors, 12*, 47-61.

Vaughan, D. (1996). *The Challenger launch decision: Risky technology, culture, and deviance at NASA.* Chicago: University of Chicago Press.

Viscusi, W.K. (1992). *Fatal tradeoffs: Public and private responsibilities for risk.* Oxford, England: Oxford University Press.

Viswesvaran, C., and Schmidt, F.L. (1992). A meta-analytic comparison of the effectiveness of smoking cessation methods. *Journal of Applied Psychology, 77*, 554-561.

Vuchinich, R., and Heather, N. (Eds.). (2003). *Choice, behavioural economics and addiction.* Oxford, England: Elsevier Science.

White, J.M., Winn, K.I., and Young, W. (1998). Predictors of attrition from an outpatient chemical dependency program. *Substance Abuse, 19*, 49-59.

Wilde, G.J.S. (1982). The theory of risk homeostasis: Implications for safety and health. *Risk Analysis, 2,* 209-255.

Williams, J., Pacula, R.L., Chaloupka, F.J., and Wechsler, H. (2001). *Alcohol and marijuana use among college students: Economic complements or substitutes?* Cambridge, MA: National Bureau of Economic Research.

World Health Organization. (2001). *Advancing knowledge on regulating tobacco products.* Geneva: World Health Organization.

Zito, J.M., Craig, T.J., and Wanderling, J. (1991). New York under the *Rivers* decision: An epidemiologic study of drug treatment refusal. *American Journal of Psychiatry, 148*(7), 904-909.

I

Vaccines and Immunotherapies to Control Addiction in Minors: The Legal Framework

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INTRODUCTION

Many sectors of society face the challenge of fighting substance addictions. Health and life insurance companies promote healthier life-styles by offering incentives for their subscribers to remain or become smoke-free. Individuals enter rehabilitation clinics every day hoping to fight their addictions for their own personal health and well-being. Federal and state governments attempt to curb addiction rates for public health reasons and to prevent patterns of crime and poverty. Prisons strive to rehabilitate addicted inmates, hoping to offer them a good shot at staying clean once they leave the prison walls, and schools fight for the drug-free environments needed for students to thrive.

Perhaps those most concerned about drug addiction, especially drug addiction among minors, are parents who struggle to keep their children resistant to the peer and other societal pressures influencing them to use addictive substances recreationally. Adolescence is a dangerous passage for children to navigate safely, and this appendix focuses on the legal problems associated with administering immunotherapies intended to control addiction in the young.

Background

Researchers have now developed drug addiction immunotherapies shown to curb the "high" of controlled substances such as PCP (phencyclidine), cocaine, alcohol, and nicotine. This appendix necessarily general-

izes the wide variety of these immunotherapies throughout much of the discussion, but social, legal, and ethical questions can obviously hinge on the nature, legality, and public consequences of the particular addiction.

Legal problems associated with immunizing human beings (including minors) against addictions generally fall into two broad categories, once the ethical, scientific, and policy hurdles of deciding whether these kinds of immunotherapies should be available at all have been cleared. The first grouping of issues involves the requirement for a patient's informed consent to any kind of treatment, including immunotherapy.[1] The second concerns liability for any injuries the patient sustains as a consequence of having been immunized.[2] This appendix concentrates on the consent problem presented when children are to be given immunotherapy, not the liability issue. More precisely, it deals with the subset of autonomy and consent issues that become relevant when authority figures seek to administer vaccines designed to prevent or control nicotine, alcohol, and drug abuse addiction in minors.

No constitutional or common law right to use addictive substances exists,[3] and such use may well be deemed illegal under state or federal law,[4] but individuals have constitutional and common law protections when it comes to others' attempts to interfere with their bodily integrity to circumvent addiction.[5] When anyone seeks to impose therapy on another regardless of consent in the name of public health, protection of third parties, crime prevention purposes—or indeed in that person's own purported best interests—the law will respect the targeted individual's right to refuse treatment unless very strong societal interests are found to justify trumping that person's autonomy.

This means that the law generally acknowledges a competent adult's right to decline therapy to treat an established addiction or to refuse vaccination to prevent one. But the legal situation is far more complicated when the patient is a minor, particularly one on whom the parent or another authority figure seeks to impose immunotherapy, as this appendix

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[1]On the history and development of the doctrine, see generally Katz (1984) and Waltz and Scheuneman (1970).

[2]See generally The National Childhood Vaccine Injury Compensation Act of 1986, 42 U.S.C. §§ 300aa-1 (2003), and Mariner (1995).

[3]See Employment Division, *Department of Human Resources of Oregon v. Smith*, 494 U.S. 872, reh'g denied, 496 U.S. 913 (1990) (holding that the state of Oregon could constitutionally ban the use of peyote and therefore could legitimately deny unemployment compensation to those who illegally use it for religious purposes).

[4]See id. (Oregon's prohibition of the use of peyote deemed constitutional). See generally Controlled Substances Act, 21 U.S.C.S. § 801 (2003).

[5]*Schloendorff v. Society of New York Hospital*, 211 N.Y. 125, 129 (1914) ("Every human being of adult years and sound mind has a right to determine what shall be done with his own body.")

will explore. Parents are generally deemed to be the appropriate medical decision makers for their minor children, although some state statutes specifically authorize adolescent consent to substance abuse treatment with or without parental concurrence.[6] Administering immunotherapy to a nonconsenting adolescent pits the autonomy interest of the minor against the parent's countervailing determination of that child's best interests. The reverse legal dilemma can also occur, as when a minor seeks therapy—such as birth control—but the adolescent does not want to inform the parent about his or her sexual activity or when the parent refuses to authorize the treatment.[7]

Whose interests will prevail in parent-child disagreements about undergoing immunotherapy cannot be predicted with certainty for, as with virtually all legal questions, the answer depends on the underlying facts of the particular situation. How old is the child? What has been the history of the parent-child or other relevant authority figure relationship? How imminent is the threatened harm? How well established is the proposed therapy? How invasive is it? How permanent are the effects of treatment and of nontreatment? All of these factors must be weighed in determining whether a parent or other party *in loco parentis* has legal authority to make decisions about immunotherapy "for" an individual child or whether indeed that child might have the legal capacity to make such decisions on his or her own.

Generally speaking, the younger the child, the more imminent the threatened harm, and the more short lived the effects of the vaccine, the more likely the courts will uphold parental choices about administering immunotherapy to their offspring, notwithstanding a child's lack of specific assent. Conversely, the older the adolescent, the more remote the perceived harm, and the longer lasting the effects of the treatment, the more likely it is that courts will give weight to a minor's refusal to assent to immunotherapy in the face of parental pressure to undergo it.

Types of Immunotherapy

At first glance, drug addiction vaccines seem promising and attractive for short-circuiting addictions in minors before they get the chance to take hold. The addictive nature of potentially harmful—if not deadly—substances diminishes significantly after this kind of immunotherapy takes effect. Addiction immunotherapies reduce chemical dependency on addictive substances and can be administered in two different ways: as either active or passive immunotherapy.

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[6]See statutes cited in Hartman (2002).

[7]Id. at note 38. See also Newcomer and Udry (1985).

Active immunization works like a vaccine by stimulating an antibody response from the recipient's own immune system (Pentel, this volume). Passive immunotherapies use animal antibodies and are administered via a two-step process. An animal is vaccinated to produce the relevant antibodies; those antibodies are extracted and purified and then administered to the target recipient. These addiction immunotherapies do not become effective instantaneously. They can require multiple injections over several weeks and several months to reach full strength.

Both active and passive immunotherapy typically last 3 to 6 months after achieving full efficacy, but booster shots can be administered to increase this duration (Pentel, this volume). In theory, addictions will not take hold so long as the vaccine remains effective. If the addiction is already established, cessation theoretically becomes exponentially easier for a vaccinated person. Once an addiction's hold no longer saps a person's will, the focus of substance abuse prevention can switch to peer pressure, social attitudes, lack of education, and other social factors that can promote substance abuse and antisocial behavior. Although these pressures are still daunting enough hurdles to surmount, especially for adolescents, who are more likely than adults to be influenced by their peers to use addictive substances, they pale in comparison with the gargantuan task of overcoming established addictions.

The relatively long-term effect of drug addiction immunotherapies presents a particularly appealing prospect. The need for ongoing patient compliance with addiction therapy—in populations that arguably pose a special challenge for conformity to treatment regimes[8]—and the financial cost of repetitive therapeutic services are reduced significantly as the duration of immunotherapy effectiveness increases. Recipients of active or passive immunotherapies have to see their caregivers less often than do recipients of more traditional addiction therapy.

In lay terms, active immunotherapies theoretically make it harder for a user to get a "buzz" from addictive substances. However, substance abusers may be able to override the therapeutic blockade by ingesting ever-larger doses of the agent against which they have been immunized. These megadoses can prove even more dangerous to abusers than taking the substance without medically induced immunity. This potential for "swamping" the blockade effect of immunotherapies by upping the amount

[8]Compliance poses a challenge in a variety of clinical settings. See, e.g., Chasnoff et al. (1989) (displaying problems with compliance in cocaine-addicted pregnant women); Kress (2000) (discussing the compliance challenges that the mentally ill face); Kuszler (1996) (explaining the difficulty of compliance with tuberculosis drug regimens); Ayers (2002) (addressing HIV-infected pregnant women's compliance with AZT, a treatment proven to reduce the likelihood of transmission to the baby).

ingested particularly troubles parents who might otherwise attempt to prevent addiction by immunizing their children.

For example, a heroin-immunized adolescent could seek to overcome the vaccine-created euphoria barrier by simply countering it with an even larger dose of heroin. So could adolescents unaware that they had been immunized. Moreover, although immunotherapy's current efficacy decreases within 3 to 6 months postvaccination (Pentel, this volume), previously immunized users whose efficacy has expired might nonetheless continue taking higher doses in the mistaken belief they were still necessary to achieve the desired euphoric effect. A user's ignorance about the dosage required to overcome the blocking effect, as well as uncertainty about the length of immunotherapy effectiveness, could lead to fatal consequences. In this respect, many immunotherapies pose merely an obstacle, not an insurmountable barrier, to addiction and could precipitate even more serious health problems—even death—for substance abusers.

When an authority figure seeks to impose immunotherapy on a minor, the potentially lengthy duration of its blockading effect presents serious ethical and legal questions related to the young person's autonomy and privacy. For example, many of these vaccines will leave permanent biological tracers in recipients' bodies that could be detectable years later by employers, medical providers, and insurance providers, to name a few. If employers can identify workers previously targeted as likely to become addicted to a controlled substance, the potential for workplace discrimination exists,[9] notwithstanding the medical privacy protections of the Health Insurance Portability and Accountability Act (HIPAA).[10] HIPAA's medical privacy requirements do not apply to employers and employment records per se, but they do apply to employers in their capacity as "covered entities" if they administer or maintain employer-sponsored health insurance programs within the meaning of the federal ERISA (Employee Retirement Income Security Act) legislation governing employer-sponsored "welfare benefit plans."[11] The Americans with Disabilities Act[12] and other antidiscrimination statutes presumptively offer after-the-fact remedies for workplace discrimination, but the uncertain-

[9]As employers gain more ability to test regarding particular health concerns, the potential for employee discrimination based on medical status—potential or actual—increases. See, e.g., *Norman-Bloodsaw v. Lawrence Berkeley Laboratory*, 135 F. 3d 1260 (9th Cir 1998) (employers tested certain employees' blood for syphilis, pregnancy, and sickle cell trait without their consent).

[10]P. L. No. 104-191, 110 Stat. 1936 (1996).

[11]45 C.F.R. 160.102, 160.103; see also http://www.cms.hhs.gov/hipaa/hipaa2/support/tools/ decisionsupport/default.asp.

[12]42 U.S.C.A. § 12101 (2003).

ties of litigation are a poor substitute for forestalling employment abuse in the first place.

Although drug addiction immunotherapies offer real promise for addiction prevention programs, their indiscriminate use has undeniable capacity to threaten personal autonomy and privacy.[13] Competent and fully informed adults who voluntarily seek to protect themselves from addiction by electing to undergo immunotherapy present society with few legal questions. The lawyer's antennae rise, however, when more vulnerable populations, such as prisoners, mental patients, or minors, are pressured to undergo immunotherapies with potentially long-lasting effects. Such "persuasion" is especially worrisome when the recipient is not currently in thrall to a deleterious substance but merely predicted to be at high risk for future addiction.

THE MEDICAL DECISION-MAKING PROCESS

Adults as Their Own Medical Decision Makers

To analyze the legal and ethical issues associated with giving minors immunotherapy to forestall addictive behavior, the way the law views the making of medical choices in general must be understood. Then special issues raised by medical decision making for minors can be examined in more detail. The common law's deep respect for personal autonomy remains the core principle underlying legal, ethical, and scholarly insistence that individuals should have the right to control what happens to their own bodies (Jones, 1990). U.S. jurisprudence proceeds from the assumption that individuals have the right to be left alone so long as their actions do not infringe on the rights of others. The law of informed consent on this side of the Atlantic (as contrasted with Continental jurisprudence, which is more deferential to the supremacy of the state) has consistently reflected the principle of personal autonomy throughout the course of its evolution during the 20th and 21st centuries.

This right of personal integrity and medical self-determination is near absolute in the eyes of the common law, and health lawyers and ethicists often assert—with strong legal justification—that an informed and competent person can voluntarily refuse consent to medical treatment for good reason, bad reason, or no reason at all. When competency or voluntariness is compromised, as can happen in circumstances ranging from minority

[13]Drug addiction prevention programs could target vulnerable populations, such as people in lower-income communities, minorities, people with a family history of drug abuse, and minors, among others.

to senility to incarceration,[14] or if the individual lacks material information at the time a medical decision is made,[15] the legal analysis gets trickier.[16] Nonetheless, the law's rock bottom respect for personal autonomy still dominates the legal discourse about informed consent in the United States.

An individual's right to self-determination with regard to medical treatment may be overridden only for the most compelling of circumstances, as can be the case when the public's health would otherwise be seriously jeopardized. Thus, for example, persons with infectious tuberculosis who are noncompliant with antibiotic therapy have been quarantined for the purpose of treatment,[17] and military service personnel slated to be deployed to Kuwait during Operation Desert Storm were threatened with court martial for refusing consent to be vaccinated against chemical and biological weapons.[18] Similarly, incarcerated prisoners are not permitted to manipulate prison discipline by threatening to refuse consent for life-saving treatment (e.g., renal dialysis) as a weapon to secure transfer to a less restrictive prison environment.[19] As a general rule, however, a competent individual cannot be compelled to undergo medical treatment against his or her wishes.

Involvement of Minors in Medical Decision Making

The law presumes that children under the age of 14 lack the capacity to give meaningful consent to medical treatment on their own because their judgment and ability to comprehend short-term implications and the long-range medical consequences of illness and therapy have not yet matured (Rosato, 2002). For adolescents—minors between the ages of 14 and 18—the legal situation is more complicated (Hartman, 2000; Hawkins, 1996; Scott, 2000). Their assent to treatment, notwithstanding any legal disability with respect to capacity, may be essential to accomplish any therapy that requires their cooperation. In one widely-reported case, Billy Best, a 16-year old Massachusetts boy diagnosed with Hodgkin's disease, ran away from home after five sessions of a projected longer course of chemotherapy at Boston's Dana Farber Cancer Center. He had pleaded with his parents to let him forego the incapacitating treatments, but

[14]See generally Addicott (1999) and Walter (1998). For a discussion of the ability of minors to provide informed consent, see generally Redding (1993).

[15]See, e.g., Macklin (1982).

[16]See infra Parts B, C, and D of this section.

[17]*City of New York v. Antoinette R.*, 630 N.Y.S. 2d 1008 (Supp. Ct. 1995).

[18]*Doe v. Sullivan*, 756 F. Supp. 12 (D.D.C. 1991).

[19]*Commissioner of Correction v. Myers*, 399 N.E. 2d 452 (MA 1979).

doctors had said that without the chemotherapy Billy would die in little more than a year. Fearful that their son would not survive without further chemotherapy, Billy's parents told him in essence that he had no choice in the matter—he had to submit.

Billy promptly went missing, until his increasingly frantic parents and his doctors pledged publicly that they would not force him to undergo further chemotherapy without his consent. He did finally come back home after spending more than 3 weeks in Texas and then worked with his parents and caregivers to devise an alternative course of therapy for his disease. Billy was included as a full participant in devising his medical protocol, and in due course assented to, and did, comply with it (Negri, 1995; Knox, 1995). Five years later, in 2001, he was reported to be healthy and cancer-free, "living the snowboarder's life" in Vail, Colorado (Lasalandra, 2001; Hart, 1999).

Billy Best's case is instructive because it illustrates graphically the dire consequences that can ensue if an adolescent's wishes are ignored in the consent process for medical procedures requiring their cooperation. The same ethical—and highly pragmatic—principle of respect for an adolescent's right to have a say in what happens to his or her body applies when it comes to securing his or her assent to *any* medical treatment.[20] Moreover, emancipated minors have the legal right to make their own medical decisions regardless of age,[21] the Supreme Court has recognized a minor's right to obtain contraceptives,[22] and in some states a young woman who meets the definition of a mature minor has a statutory right to undergo an abortion without parental consent using a judicial bypass procedure, notwithstanding her lack of either majority or emancipation.[23] These statutory exceptions to the common law rule that parents make medical decisions *for* children reinforce the point that an adolescent's rights are entitled to respect and that securing an adolescent's assent may be essential to effective medical treatment.

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[20]*In re Green*, 292 A. 2d 387 (Pa. 1972) (Jehovah's Witness mother of a 16-year-old boy with 94 percent curvature of the spine who was unable to stand or ambulate because his spine had collapsed refused consent for a spinal fusion operation for him).

[21]An emancipated minor is generally defined as one who has married, enlisted in the armed forces, or become self-supporting below the age of majority. Emancipation ends the parents' duty of support and confers on the minor those decision-making capabilities of adults. See, e.g., *Parker v. Stage,* 371 N.E. 2d 513 (N.Y. 1977).

[22]*Carey v. Population Services International,* 431 U.S. 678 (1977).

[23]*Wicklund v. Lambert,* 979 F. Supp. 1285 (D. Mont. 1997); Laws Requiring Parental Consent or Notification for Minors' Abortion, available at http://www.plannedparenthood.org/LIBRARY/ABORTION/StateLaws.html.

Parents as Medical Decision Makers for Their Children

The parent-child relationship has always been deemed near sacrosanct in the eyes of the law. In the words of the Supreme Court, "It is cardinal with us that the custody, care and nurture of the child reside first in the parents, whose primary function and freedom include preparations for obligations the state can neither supply nor hinder."[24] Parents are presumed to act in the best interests of their children, and the law interferes with their right to make decisions about their minor offspring only in the most compelling of circumstances. Thus the parent or parents with custody can generally dictate where, for example, their children live, what kind of food they will eat, what kind of discipline they will be subjected to,[25] what kind of education they will get,[26] and the religion—if any—in which their children will be raised (Dwyer, 1994). They can also make medical decisions for their children, usually free from state interference (Holder, 1985).[27]

When children are deemed in need of care and protection concerning the choices their parents (or others) make for them, however, the state can—and will—intervene in the parent-child relationship. Again in the words of the Supreme Court, parental power "may be subject to limitation . . . if it appears that parental decisions will jeopardize the health and safety of the child."[28] Feinberg (1980) eloquently states the rationale for state intervention as follows: "Children are not legally capable of defending their own future interest against present infringement by their parents, so that task must be performed for them, usually by the state" (p. 124).

The state intervenes in its *parens patriae* role when alerted to situations where the parents' medical decisions have potential to cause irreparable harm to children's health and welfare.[29] Thus when Jehovah's Witness parents refuse to consent to life-saving blood transfusions for their minor children, the state can petition for a court order permitting it to assume guardianship status for the limited purpose of consenting to medically urgent blood transfusions.[30] Similarly, when Massachusetts parents refused to authorize chemotherapy for their 2-year-old son suffering from

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[24]*Prince v. Massachusetts*, 321 U.S. 158 (1944).

[25]See generally 59 AM. JUR. 2D, *Parent and Child*, § 25 (2002).

[26]See generally *Pierce v. Society of Sisters of the Holy Name of Jesus*, 268 U.S. 510 (1925); *Meyer v. State of Nebraska*, 262 U.S. 390 (1923).

[27]See http://www.agi-usa.org/pubs/ib_minors_00.html.

[28]*Wisconsin v. Yoder*, 406 U.S. 205 (1971).

[29]Adults have mistreated children in many different ways all through the course of history. See generally Mason (1972).

[30]*In re Sampson*, 278 N.E. 2d 918 (N.Y. 1972); *Jehovah's Witnesses v. King County Hospital*, 278 F. Supp. 488 (W.D. Wash. 1967).

a highly curable form of Hodgkin's disease, opting for what they termed "quality over quantity" of life (and treatment with laetrile) for him, the state sought and received a care and protection order—albeit too late to prevent the parents from fleeing to Mexico, where the child died relatively soon thereafter.[31] Finally, when Christian Scientist parents have refused permission for life-saving medical treatment for their minor children, courts have permitted the state acting in *parens patriae* to order medically necessary therapy for the youngsters.[32] Moreover, the state has prosecuted Christian Scientist parents whose child died after their refusal to authorize medical care for him.[33]

Parental authority to make medical decisions for their minor offspring is not, however, necessarily limited to those choices that the state considers immediately life-threatening to the child. In a 1970 case a 15-year-old New York boy suffered from von Recklinghausen's disease, which had massively disfigured the side of his face and neck. The surgery his doctors advocated could have improved both his facial structure and appearance, and therefore his psyche, but it would have necessitated blood transfusions, which his mother's religious beliefs prohibited. She therefore refused consent for the son's operation. The New York Court of Appeals ruled that the state could intervene in such circumstances, acting in the child's best interests, notwithstanding that a child's life might *not* be in imminent danger were a particular procedure not performed at that time.[34] Most courts, however, have declined to intervene in nonlife-threatening cases, especially when a parent's idiosyncratic medical aversions have been so inculcated in his offspring as to promote the child's "distrust and dread of" the procedure."[35] In theory the child will be free to make his or her own medical decisions at the age of majority so long as no irreparable harm is sustained in the interim.

Three Kinds of Medical Decisions Parents Make for Children

Parents possess inherent authority to make three general types of medical decisions for their children: protective decisions, therapeutic ones, and medical choices intended to enhance the child's natural physical and mental capabilities or presumed attractiveness. Deciding to administer addiction immunotherapy to minors can be analyzed to fit into any of these categories.

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[31]*In re Custody of a Minor*, 375 Mass. 733 (1978).
[32]*Walker v. Superior Court*, 763 P. 2d 852 (Cal. 1988).
[33]Cf. *Commonwealth v. Twitchell*, 617 N. E. 2d 609 (Mass. 1993).
[34]*In re Sampson*, 317 N.Y.S. 2d 641.
[35]Matter of Seiferth, 127 N.E. 2d 820 (1955) (14-year-old boy with cleft palate and harelip).

"Protective" Medical Decisions

The first of these decisional categories encompasses parental control over those medical decisions related to routine—or even somewhat unusual—preventive or protective measures for the child. This permits parents to authorize medical personnel to administer the testing[36] and immunizations[37] generally deemed requisite for their offspring from a public health point of view.[38] It also allows them to choose relatively unorthodox diets or exercise programs for their children or to take them to routine chiropractor or acupuncture visits as preventive measures (DeMarco, 2002). Immunizing a child against addiction would not—at least not yet—qualify as such a routine protective measure because the therapies themselves are still in the experimental stages. If, however, their safety and efficacy were satisfactorily established for children and their use in adult populations became widespread, parents might well seek to protect their offspring by immunizing them.

Given the speed with which cigarette smoking has fallen from grace as an acceptable social activity now that it and a wide variety of life-threatening and other illnesses have been scientifically linked, one can well envision the day (assuming a permanent vaccine becomes available) when childhood vaccination against nicotine addiction could be as routine as vaccination against measles. Whether vaccination against, for example, alcohol addiction could achieve similar "routine" status raises other issues altogether. Since childhood immunotherapy with relatively permanent effects might preclude adult choices about experiencing the pleasurable aspects of moderate alcohol intake, the legal, ethical, and political calculus about condoning parental authority in this area is less certain. The case for parent's authority to give consent for their children's immunotherapy, which has a more or less long-term impact on the children's

[36]On mandatory PKU testing of newborns, see, for example, Ma. St. 111 § 110A, Tests of newborn children for treatable disorders or diseases. ("The physician attending a newborn child shall cause said child to be subjected to tests for phenylketonuria cretinism and such other specifically treatable genetic or biochemical disorders or treatable infectious diseases which may be determined by testing as specified by the commissioner. The commissioner may convene an advisory committee on newborn screening to assist him in determining which tests are necessary.")

[37]MGL c. 76 § 15, Vaccination and immunization ("No child shall . . . be admitted to school except upon presentation of a physician's certificate that the child has been successfully immunized against diphtheria, pertussis, tetanus, measles and poliomyelitis and such other communicable diseases as may be specified from time to time by the department of public health.")

[38]"All fifty states and the District of Columbia require children to be vaccinated for seven of the previously common childhood diseases—polio, measles, mumps, rubella, diptheria, tetanus and pertussis—before they are permitted to attend school" Steel (1994).

ability to experience the chemical high produced by controlled substances, lies somewhere in between those two situations.

"Therapeutic" Medical Decisions

Parents have authority to make decisions about testing and therapy for their children's existing medical problems as well. This enables parents to authorize treatment for such routine ailments as strep throat, broken limbs, and urinary tract infections.[39] In fact, should they fail to authorize treatment when their child's health is seriously threatened, the state would presumably intervene to exercise the consent prerogative in their place. This category would also encompass parental authorization for more unusual therapies, such as administering human growth hormone (hGH) to increase the height of hormone-deficient children who are regarded as abnormally short by the medical profession (American Academy of Pediatrics, 1997). Such treatment would presumptively be considered within the customary standard of care and thus medically necessary and so should constitute a reimbursable expenditure for health insurance purposes.[40] The Supreme Court has gone so far as to recognize the power of parents to commit their children to mental institutions for evaluation and treatment provided that appropriate statutory procedural safeguards for the minors have been observed.[41]

Immunotherapy falls into the category of parental decision making involved with shorter-term treatment for a child's already-diagnosed substance abuse, such as heroin or cocaine addiction. A child in the throes of addiction presents a legitimate case for medical intervention, and a parent's authority to consent to appropriate treatment—assuming that the immunotherapy in question has received approval by the Food and Drug Administration (FDA)—seems strong. Moreover, to the extent that immunotherapy becomes the medical standard of care for treating addiction among adolescents, one could envision the state intervening in its *parens patriae* role to protect a severely addicted child whose parents refused consent for the child receiving it, making analogies to the Christian Scientist parent cases discussed earlier. Whether a court would uphold such a request by the state would depend on the severity of the child's illness and the potential consequences to the child of not receiving the treatment.

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[39]Cf. ethical controversies concerning cochlear implants (Lane and Grodin, 1997).

[40]On "medical necessity" as a health insurance reimbursement concept, see *Katskee v. Blue Cross/Blue Shield of Nebraska*, 515 N.W. 2d 645 (Neb. 1994).

[41]*Parham v. J.R.*, 442 U.S. 584 (1979).

"Enhancement" Medical Decisions

In this final category the law generally permits parents latitude to make those medical choices they believe will improve the physical, intellectual, or emotional well-being and prowess of their offspring, even though many—and in some cases most—other members of society would not necessarily sanction their choices. Current controversies over the wisdom of surgically placing cochlear implants in the ears of deaf children (Lane and Grodin, 1997) and the practice of male circumcision (Provenmire, 1998/1999), illustrate this point. Critics argue that parental authorization for such functionally irrevocable medical procedures during childhood, when there is no medical necessity for the intervention, violates the child's constitutionally protected right to adult bodily integrity. They contend that performing these procedures during childhood precludes the possibility that the child might make a different choice in adulthood about how to experience critically important aspects of life and its attributes. So far those arguments do not seem to have been found convincing by the courts, however.

Some irrevocable parental choices, however, fall outside the range of what is deemed acceptable medical "enhancement" for children in Western—indeed in some cases global—cultures. The practice of female circumcision, or clitorectomy, falls within this category, not only because of its brutality but because it forecloses one source of sexual pleasure for women (Annas, 1996). Female genital mutilation is classified as a federal crime in this country,[42] so parents therefore have *no* authority to consent to it, whatever their reasons or beliefs. Further, female genital mutilation has been condemned as a human rights violation globally under a United Nations resolution.[43] Parental authorization for sterilizing minor incompetents "in their own best interests" has also generated stiff legal resistance under Constitutional principles, for reasons related to the child's fundamental rights concerning reproduction and sexual privacy.[44]

This final grouping of parental improvement choices includes a more controversial subcategory of elective medical enhancements for children whose parents simply seek to upgrade characteristics otherwise deemed by society to be well within the range of normal. This subcategory of parental treatment decisions includes authorization for such procedures as

[42]Criminalization of Female Genital Mutilation Act, P. L. 104-208, 645, 110 Stat. 3009-708 (1996) (codified as amended at 18 U.S.C. 116).

[43]Convention on the Elimination of All Forms of Discrimination Against Women, G.A. Res. 180, UN GAOR, 34th Sess., Item 75, U.N. Doc. A/RES/34/180 (1980).

[44]*Pierce v. Society of Sisters*, 268 U.S. 510 (1925); *Meyer v. Nebraska*, 262 U.S. 390 (1923); *Davis v. Beacon*, 133 U.S. 333 (1890); *Reynolds v. U.U.*, 98 U.S. 145 (1878).

elective cosmetic surgery (reshaping a nose, for example) for the child or treating a child with hGH simply to provide a relatively short, though well within normal size, youngster with what the parents consider a more imposing physical presence (Cuttler et al., 1996). Burgeoning research into genetic therapies multiplies exponentially the possibilities for future "medical enhancement" of children, raising for some the specter of "master race" genetic manipulation and a widening gulf between the world's haves (who could afford it) and its have-nots (who presumably could not).[45]

Immunotherapy with more or less long-term attributes could be categorized as an enhancing, rather than a merely protective, procedure for a child. Presumably this category would apply when a parent contemplates authorizing immunotherapy that is not otherwise widely available for children or acceptable as a general public health measure. Parental decision making in this circumstance would be subject to the same ethical and legal criticisms as have been leveled against other elective procedures on minors that are not otherwise deemed medically necessary and whose long-term effects could conceivably carry over into adulthood in ways that the child's adult persona might not choose.

EXPERIMENTAL USE OF IMMUNOTHERAPIES FOR ADDICTION

The legal status of administering addiction immunotherapies is even more complex at the present time than the law's approach to administering FDA-approved medications because many immunotherapies are still in experimental stages.[46] For example NicVax, an investigational vaccine to prevent and treat nicotine addiction, is currently the subject of European Phase I/II (preliminary safety and efficacy) clinical trials.[47] Children's participation in clinical trials of experimental drugs, of particular concern for the purposes of this appendix (Labson, 2002), has long been a hotbed of political debate (Grodin and Glantz, 1994; Ross et al., 2002). That controversy intensified after 1997 when Congress passed the Better Pharmaceuticals for Children Act.[48] Then 4 years later a decision of the Maryland Court of Appeals excoriated the exploitation of minor subjects of clinical research in a decision that sent shock waves through the

[45]On the use of genetic techniques to "enhance" children, see generally Mehlman (1999).

[46]These drugs have not yet received FDA approval for marketing in interstate commerce.

[47]See Nabi Biopharmaceuticals News Release, available at http://www.nabi.com/releases/021903A.html [February 19, 2003]. For an analysis of similar ethical and legal problems raised by behavioral genetics research concerning adolescents and smoking, see Wilford et al. (2002).

[48]The Better Pharmaceuticals for Children Act is a provision of the FDA Modernization Act of 1997 (FDAMA), P. L. No. 105-115, 111 Stat. 2296 (1997).

scientific research community.[49] That important opinion found in essence that neither parents, nor scientific researchers, nor the institutional review boards designed to protect the human subjects of medical research can be fully trusted to protect children who are the subjects of nontherapeutic clinical research (Hoffman and Rothenberg, 2002).

The Better Pharmaceuticals for Children Act was enacted in part to remedy the status of children as "therapeutic orphans," so described because most of the medications doctors prescribe for them have not been adequately studied in pediatric populations (Gregory, 1997; Shirkey, 1968). In 1998 the FDA issued what is popularly known as the Pediatric Rule designed to implement that legislation.[50] The Association of American Physicians and Surgeons et al. challenged the regulation as beyond the scope of the FDA's statutory authority because it would effectively constrict off-label drug prescribing. The District Court for the District of Columbia agreed, finding that Congress "would likely have spoken more clearly" if it intended to grant the FDA authority to require drug manufacturers to study their products for off-label uses, and enjoined its implementation.[51] The American Academy of Pediatrics et al. moved for expedited consideration of the appeal as intervenor defendants, stressing the overriding need to protect children, but its motion was denied in December 2002 by the D.C. Circuit.[52] Suffice it to say that the controversies surrounding using children as the subjects of clinical research are far from resolved.

Drugs and vaccines in preliminary clinical trial stages cannot be promoted as legitimate therapeutic options for anyone, let alone children (Glantz, 1998). The prospect of exposing minors to immunotherapy with the potential for unknown long-term effects, which has not yet been proven safe and effective enough to justify its therapeutic use among adults, raises the kind of daunting legal and ethical questions that should probably preclude *experimental* use of drugs to control addictions in all but the most compelling of circumstances (Grodin and Glantz, 1994). Whereas one might be able to make the case for administering an investigational vaccine to children in the midst of a life-threatening epidemic of, for example, anthrax poisoning or smallpox, one would be hard pressed to come up with a similarly compelling scenario to justify the administration of unproven anti-addiction immunotherapy to minors.

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[49]*Grimes v. Kennedy-Kreiger Institute*, 792 A.2d 807 (Md. 2001).

[50]Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 21 C.F.R. pts. 201, 312, 314 & 601 (1998). Cf. Stolberg (2002).

[51]*Association of American Physicians & Surgeons v. FDA*, 226 F. Supp. 2d 204, 214 (D.D.C. 2002).

[52]*Association of American Physicians & Surgeons v. FDA*, 2003 U.S. App. LEXIS 2079 (D.C. Cir, February 5, 2003).

GOVERNMENT IMPLEMENTATION OF ADDICTION PREVENTION PROGRAMS THAT COULD AFFECT MINORS

Public health improvement measures raise legal questions and charges of government paternalism when access and targeting of suspect populations become policy issues. In the case of drug addiction immunotherapies, the legal questions relevant to this appendix involve targeting more than they do access to therapy. If immunotherapies prove to curb rates of addiction significantly, entities such as the Center for Substance Abuse Prevention may be expected to focus on innovative ways to implement them through public health initiatives targeting high-risk individuals, including minors.

The task of defining high-risk populations has the inevitable potential to facilitate invidious discrimination. Some scientific studies indicate that drug abusers may possess a genetic predisposition to addiction, and the National Institute on Drug Abuse (NIDA) has launched an initiative to gather research on genetic factors that might create a susceptibility to drug addiction (Stocker, 1999). Environmental factors such as local rates of drug use and availability of family support can also contribute to the likelihood of addiction. These factors can help authorities identify who needs prevention and treatment most desperately, but this kind of social targeting can also trigger deliberate or inadvertent discrimination. It could precipitate advocating immunotherapy for people who might not have become addicted but who just happened to live in lower-income communities or who possess a genetic predisposition that would never have materialized in addiction.

At least one commentator has postulated that these immunotherapies could be administered to every citizen, regardless of the individual's personal propensity for addiction (Cohen, 1997). Peter J. Cohen, adjunct professor of law at Georgetown University Law Center, argues that universal vaccination would neatly eliminate the potential for discrimination when determining who should receive immunotherapy. Universal vaccination would also reduce the likelihood of long-term discrimination against those in whom the vaccine can be easily traced. In order for the state to establish a universal vaccination program, however, the state interest would need to be extremely strong in order to outweigh the autonomy rights of individual citizens.[53] For example, universal smallpox vaccination programs were condoned by the Supreme Court at the turn of the last

[53]*Jacobson v. Massachusetts*, 197 U.S. 11 (1905). For further discussion of the state's police power for the protection of public health, see generally *Powell v. Pennsylvania*, 127 U.S. 678, 683 (1888); *Mugler v. Kansas*, 123 U.S. 623, 663 (1887); *Butchers' Union Co. v. Crescent City Co.*, 111 U.S. 746, 751 (1884); *Barbier v. Connolly*, 113 U.S. 27 (1884); *Yick Wo v. Hopkins*, 118 U.S. 356 (1886).

century because the vaccination program had a "real and substantial relation" to "preserv(ing) and protect(ing) the public health."[54] One could question whether the court would rule the same way today, especially in light of the public's recent lukewarm response to smallpox vaccination regimens when faced with the threat of biological terrorism post-9/11.

Where drug addiction immunotherapies are concerned, the nature of the state's interest differs from its interest in traditional universal vaccination for public health reasons. Because drug addiction is not an infectious or a contagious disease like smallpox or hepatitis (at least not in the medical sense), the state's public health interest in preventing further substance abuse addiction is weaker. Mass vaccination against contagious diseases like smallpox is designed to eradicate the disease from the entire community so that compulsory vaccination becomes unnecessary in the future. Since people contract smallpox from others who already have the disease, eliminating it from an entire community eliminates the risk of contagion. Substance abuse, however, often stems from social contagion; it is more likely to "spread" when drug use rates in a community are high. An unvaccinated individual can nonetheless succumb to addiction regardless of addiction rates in the surrounding community.

Law Enforcement

Prisoners' basic constitutional rights are restricted by the very nature of the incarceration that deprives them of their liberty. Their right to travel, which the Supreme Court has deemed a fundamental right,[55] is limited by their confinement (Mushlin, Kramer, and Gobert, 1993). Some religious practices that might enjoy constitutional protection in other circumstances may be stifled in order to protect the states' interest in general prison welfare and discipline.[56] Freedom of speech can be silenced by prison officials when there is a "clear and present danger that [the words or acts] will bring about substantive evil that Congress has a right to prevent."[57] On the other hand, prisoners have limited rights to receive rehabilitation services and in some cases a right to refuse rehabilitation altogether (Kerper and Kerper, 1974).

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[54]*Jacobson v. Massachusetts*, 197 U.S. 11 (holding that a Massachusetts smallpox vaccination program was constitutional because it had a "real and substantial relation to public health and safety").

[55]*Shapiro v. Thompson*, 394 U.S. 618 (1969).

[56]See, e.g., *Mayweathers v. Newland*, 314 F.3d 1062 (9th cir. 2002) (holding that prison penalties for attending Muslim religious services did not put a substantial burden on free exercise of religion).

[57]*Schench v. U.S.*, 249 U.S. 47 (1919).

Prisoners show a disproportionate rate of drug use,[58] which suggests that they could be targeted for drug addiction immunotherapies by enforcement authorities and others. Drug prevention and counseling efforts already focus on the inmate community in the hope that eliminating controlled substance abuse will reduce the likelihood of repeat criminal offenses upon release.[59] In particular, juvenile detention treatment programs are designed to attack the problem of drug use and addiction early, so that juvenile offenders do not become career criminals to support their addictions. Whether immunotherapies should be added to the list of prevention and treatment resources for incarcerated prisoners and juveniles is a rich subject for political and legal debate.

One area where prisoners (and others) have clear legal protections is in the field of medical research. The federal Common Rule, which mandates standards for human subject protection in medical research, demands that a prisoner's decision to participate in clinical research be free from coercion.[60] As a vulnerable population, prisoners (especially incarcerated juveniles) can be coerced into "volunteering" for research protocols when probation, parole, or other privileges are offered as inducements or threatened to be withdrawn. The voluntary nature of prisoner participation in clinical trials is thus by definition suspect.

Congress has intervened to protect the human subjects of clinical trials, and the Common Rule will clearly protect adult prisoners and incarcerated juveniles during the experimental phases of drug addiction immunotherapies. Although Congress has not acted in similar paternalistic fashion with regard to FDA-approved treatments in prison populations, the case for a protective approach to "mandatory" drug treatment for prisoners seems equally compelling. The same protective, autonomy-enhancing rationale that inspired these research protections could frame the administration of drug immunotherapies in the prison context. Requiring, or even suggesting, medical treatment as a condition of parole or probation can be characterized as coercive (Cohen, 1997). Under some circumstances such attempts at "persuasion" could conceivably exert pressure so overbearing as to approach the cruel and unusual punishment level forbidden by the Eighth Amendment.

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[58]See generally Bureau of Justice Statistics (2001), which reports that 11.96 percent of adult arrests are for drug abuse violations. Furthermore, 8.44 percent of juvenile arrests are for drug abuse violations.

[59]Drug treatment has been proven to reduce recidivism. See Hora, Schma, and Rosenthal (1999), reporting the results of a RAND study that found that the rate of recidivism among drug court participants was lower than for people in other tracks.

[60]45 C.F.R. § 46.305 (2003).

The Supreme Court has invalidated compulsory sterilization for those convicted of felonies involving moral turpitude,[61] citing the equal protection clause of the Fourteenth Amendment. As Justice Douglas, writing for the majority in *Skinner v. Oklahoma*, explained, there is no redemption for the individual whom the law touches. Any [medical] experiment which the State conducts is to his irreparable injury. He is forever deprived of a basic liberty."[62]

Controversy has also erupted over incorporating the birth control drug Norplant[63] into sentencing and parole incentives[64] and over programs that make the contraceptive more easily available to targeted sectors of society such as inner-city teenage girls. Soon after the FDA approved Norplant as a female contraceptive, the *Philadelphia Inquirer* published a highly controversial editorial suggesting that Norplant could be effective in "reducing the underclass" (Kimelman, 1990). Intense debate ensued, with the public strongly supporting not only making Norplant available to young women without parental consent but also making Norplant mandatory for drug-abusing women of child-bearing age.[65] Those who opposed the coercive use of Norplant argued that those in power wanted to use it to prevent poor minority women from "clutter(ing) up the gene pool" (Carrie Buck, 1991). There has not yet been a successful challenge—or seemingly *any* legal challenge, for that matter—to the constitutionality of Norplant use as a condition of parole (Stadler, 1997). Norplant apparently remains available as a sentencing component, although the political hullabaloo has quieted because of the drug's relatively infrequent use.

The male equivalent of the Norplant controversy has erupted over criminal punishment mandating medical procedures to alter the male sex drive chemically. In 1996, California enacted legislation permitting a

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[61]*Skinner v. Oklahoma*, 316 U.S. 535 (1942). See also Jeffrey F. Ghent , *Validity of Statutes Authorizing Asexualization or Sterilization of Criminals or Mental Defectives*, 54 A.L.R.3d 960 (1973).

[62]*Skinner v. Oklahoma*, 316 U.S. at 541.

[63]Norplant is a drug consisting of six silicone rubber capsules that slowly release pregnancy-preventing hormones. The capsules must be surgically inserted into a woman's upper arm and remain effective for 5 years unless surgically removed before then.

[64]See, e.g., Reporter's Transcript of Augmentation Proceedings at 4, *People v. Zaring* (Cal. Super. Ct., Tulare Cty 1990) (No. 29063); Reporter's Transcript of Judgment Proceedings at 10, *People v. Johnson* (Cal. Super Ct., Tulare Cty 1991) (No. 29390); Order of Probation at 2, *State v. Carlton* (Neb. Cty Ct., Lincoln Cty 1991) (No CR90-1937).

[65]Skelton and Weintraub (1991), reporting reporting that 31 percent of Californians approve of making Norplant available to teenage girls and 61 percent of Californians approve—and 46 percent strongly approve—of mandatory Norplant for drug-abusing women of child-bearing age). For general articles concerning the Norplant controversy, see Arthur (1992). See also Wattleton (1991); Segal (1991); Levin (1991); Kurtz (1990).

repeat child molester's punishment to include chemical castration,[66] a procedure through which offenders must undergo regular injections of Depo-Provera to control antisocial sexual urges. Judges can use chemical castration as a sentencing tool to reduce the likelihood that sex crimes will recur, and defendants can use chemical castration as a plea-bargaining tool to reduce incarceration periods or to speed up probation. With similar political support, a state could theoretically enact legislation that would require or induce criminals convicted of drug-related crimes to receive drug immunotherapy to curb the overall rates of drug addiction and to reduce recidivism (Cohen, 1997).

The ability to procreate arguably warrants a greater level of constitutional protection than does the ability to procure a chemical high from a controlled substance. However, the necessarily invasive nature of immunotherapies and their lengthy duration suggest that the courts might treat coerced administration of such immunotherapies in a similarly strict manner. When criminal defendants and prisoners are forced, or even strongly exhorted, to undergo sterilization, use contraceptives, or receive drug addiction immunotherapies as a condition for more lenient treatment, the voluntariness of an individual's informed consent is arguably compromised.[67]

Educational Institutions

Schools have obvious reasons for promoting drug-free environments. Drugs and the socially disruptive behaviors they tend to produce can cause virtually insurmountable obstacles to the educational experience. Since adolescents congregate at schools, drug prevention programs targeting kids naturally focus on implementation in schools. These programs have been implemented in many educational institutions to curb rates of drug use,[68] but they would undoubtedly have more impact if immunotherapy rendered adolescents incapable of experiencing the high that controlled substances offer.

Perplexing legal questions complicate the administration of drug addiction immunotherapies in schools. First, which students would be offered, exhorted, or even coerced to undergo the treatment? Would school administrators target only those students likely to become addicted?

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[66]Cal. Pen. Code § 645 (2003); Stadler (1997).

[67]Arthur (1992), suggesting that "a court order to use Norplant as a condition of probation may violate the doctrine of informed consent."

[68]For general programs promulgated by NIDA, see "NIDA Goes to School," available at www.nida.nih.gov/GoestoSchool/NIDAg2s.html [accessed February 22, 2003], detailing NIDA's current school-based drug prevention programs.

If so, how would they decide whom the population should include? Or would only those schools truly desperate to curb existing rates of drug use (perhaps schools for troubled adolescents or inner-city schools in high-crime neighborhoods) embrace immunotherapies? The potential answers to these questions suggest that discrimination and prejudice will surface if students' perceived likelihood of addiction becomes a determining factor in whether their school offers or mandates treatment for particular individuals or indeed to entire school populations.

Similar ethical and legal problems are raised when schools attempt to require children with attention-deficit hyperactivity disorder (ADHD) to take Ritalin, and the legal opinions on this subject may be instructive. As could be the case with immunotherapy, some teachers have sought to make taking Ritalin a precondition for staying in school, regardless of parental or the child's consent. While the law in this area is murky, many courts have found that educators cannot force children to take Ritalin without parental consent, although they have also confirmed that parents can legally administer it to children without the minor's assent (Komoroski, 2001). The take-home lesson is that parental rights with respect to medical decision making for their offspring usually trump those of educators.

The Supreme Court has recently upheld a school district's drug-testing program, required for participation in interscholastic activities, however.[69] The testing program survived a Fourth Amendment challenge because the defendant demonstrated "special needs" by showing the students' extraordinarily high rates of drug use. This defense to Fourth Amendment disputes applies when "special needs exist beyond the normal need for law enforcement, making the warrant and probable cause [Constitutional] requirement impracticable."[70] Drug testing as a component of a drug abuse prevention/intervention program is therefore constitutional if special needs are found to justify it. Although similarly coercive immunotherapy "requirements" would be considered more intrusive under the Fourth Amendment than mere drug testing and thus would less likely be deemed constitutional, the special needs analogy is instructive notwithstanding the outcome of the Ritalin cases.

Although certain schools may be targets for those seeking to administer drug addiction immunotherapies, the choice of who should actually receive immunotherapy in a school will most often be deferred to parents by analogy to the Ritalin cases, because—as previously discussed—minors are generally deemed legally incapable of giving their own informed consent to medical procedures.

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[69]*Vernonia School Disrict 475 v. Acton,* 515 U.S. (1995).

[70]*Skinner v. Ry Labor Executives' Association.*, 489 U.S. 602, 619 (1989) (quoting *Griffin v. Wisconsin*, 483 U.S. 868, 873 (1988)).

CONCLUSION

Addiction immunotherapies present intriguing potential for improving public health and personal well-being, but the question of whether, or how soon, they should be, or could be, administered to minors, particularly nonconsenting adolescents, is not a simple one. This appendix has attempted to flesh out the time-tested lawyer's answer (to queries highly dependent on factual context) of "that depends" with a structured legal and ethical analysis based on analogies to existing common and statutory law. By focusing on the particular kind of immunotherapy proposed to be administered to the child, the imminence of the threatened harm, the persistence of its effects, and by isolating the reason proffered for administering it—whether it be for the child's protection, treatment, or "improvement"—it is hoped that this appendix has contributed to this important dialogue.

REFERENCES

Addicott, D.C. (1999). Regulating research on the terminally ill: A proposal for heightened safeguards. *Journal of Contemporary Health Law and Policy, 15*(2), 479-524.

American Academy of Pediatrics. (1997). Considerations related to the use of recombinant human growth hormone in children. *Pediatrics, 99*(1), 122-129.

Annas, C.L. (1996). Irreversible error: The power and prejudice of female genital mutilation. *Journal of Contemporary Health Law and Policy, 12*(2), 325-353.

Arthur, S.L. (1992). The Norplant prescription: Birth control, woman control, or crime control? *UCLA Law Review, 40*(1), 1-101.

Ayers, L. (2002). Is mama a criminal? An analysis of potential criminal liability of HIV-infected pregnant women in the context of mandated drug therapy. *Drake Law Review, 50*(2), 293-314.

Barringer, F. (1990). Sentence for killing newborn: Jail term, then birth control. *New York Times*, November 18, p. A1.

Bureau of Justice Statistics. (2001). *Sourcebook of criminal justice statistics—2001.* Washington, DC: U.S. Department of Justice.

Carrie Buck, the 1991 version [Editorial]. *Washington Times*, (1991, January 10). p. G2.

Chasnoff, I.J., Griffith, D.R., MacGregor, S., Dirkes, K., and Burns, K.A. (1989). Temporal patterns of cocaine use in pregnancy: Prenatal outcome. *Journal of the American Medical Association, 261*(12), 1741.

Cohen, P.J. (1997). Immunization for prevention and treatment of cocaine abuse: Legal and ethical implications. *Drug and Alcohol Dependence, 48*(3), 167-174.

Cuttler, L., Silvers, J.B., Singh, J., Marrero, U., Finkelstein, B., Tannin, G., and Neuhauser, D. (1996). Short stature and growth hormone therapy: A national study of physician recommendations patterns. *Journal of the American Medical Association, 276*(7), 531-537.

DeMarco, P. (2002). Mommy, let's visit my chiropractor: Many parents say routine treatments can ward off kids' backaches. *Boston Globe,* June 10, p. 81.

Dwyer, J.G. (1994). Parents' religion and children's welfare. *California Law Review, 82*, 1371.

Feinberg, J. (1980). The child's right to an open future. In W. Aiken and H. LaFollette (Eds.), *Whose child? Children's rights, parental authority and state power.* Totowa, NJ: Rowman and Littlefield.

Glantz, L.H. (1998). Research with children. *American Journal of Law and Medicine, 24*(2-3), 213-244.

Gregory, A. (1997). Denying protection to those most in need: The FDA's unconstitutional treatment of children. *Albany Law Journal of Science and Technology, 121*, 134-147.

Grodin, M., and Glantz, L. (Eds.). (1994). Historical overview: Pediatric experimentation. In *Children as research subjects: Science, ethics, and law.* New York: Oxford University Press.

Hart, J. (1999). Cancer patient beating odds. *Boston Globe*, March 7, p. 82.

Hartman, R.G. (2000). Adolescent autonomy: Clarifying an ageless conundrum. *Hastings Law Journal*, *51*, 1265.

Hartman, R.G. (2002). Coming of age: Devising legislation for adolescent medical decision-making. *American Journal of Law and Medicine, 28*(4), 409-453.

Hawkins, S.D. (1996). The rights and interests of competent minors in litigated medical treatment disputes. *Fordham Law Review, 64*, 2075.

Hoffman, D.E., and Rothenberg, K.H. (2002). Whose duty is it anyway? The Kennedy Krieger opinion and its implications for public health research. *Journal of Health Care Law and Policy*, *6*, 109-147.

Holder, A.R. (1985). *Legal issues in pediatrics and adolescent medicine.* New Haven, CT: Yale University Press.

Hora, P.F., Schma, W.G., and Rosenthal, J.T.A. (1999). Therapeutic jurisprudence and the drug treatment court movement: Revolutionizing the criminal justice system's response to drug abuse and crime in America. *Notre Dame Law Review, 74*, 439-538.

Jones, C.J. (1990). Autonomy and informed consent in medical decisionmaking: Toward a new self-fulfilling prophecy. *Washington and Lee Law Review, 47*, 379-430.

Katz, J. (1984). *The silent world of doctor and patient.* New York: Free Press.

Kerper, H.B., and Kerper, J. (1974). *Legal rights of the convicted.* St. Paul, MN: West Publishing.

Kimelman, D. (1990). Norplant: Can contraception reduce the underclass? *Philadelphia. Inquirer*, December 12, p. A18.

Komoroski, A.L. (2001). Stimulant drug therapy for hyperactive children: Adjudicating disputes between parents and educators. *Boston University Public Interest Law Journal*, *11*, 97-122.

Kress, K. (2000). An argument for assisted outpatient treatment for persons with serious mental illness illustrated with reference to a proposed statute for Iowa. *Iowa Law Review*, *85*, 1269.

Kurtz, H. (1990). Inquirer birth control bomb: Staff uproar over editorial. *Washington Post*, December 18, p. B10.

Kuszler, P.C. (1996). Balancing the barriers: Exploiting and creating incentive to promote development of new tuberculosis treatments. *Washington Law Review, 71*(4), 919-967.

Labson, M.S. (2002). Pediatric priorities: Legislative and regulatory initiatives to expand research on the use of medicines in pediatric patients. *Journal of Health Care Law and Policy, 6*, 34.

Lane, H., and Grodin, M. (1997). Ethical issues in cochlear implant surgery: An exploration into disease, disability, and best interests of the child. *Kennedy Institute of Ethics Journal, 7*(3), 231-251.

Lasalandra, M. (2001). Government agrees to review treatment. *Boston Globe*, November 13, p. 1.

Levin, T. (1991). Implanted birth control device renews debate over forced contraception. *New York Times*, January 10, p. A20.

Macklin, R. (1982). Some problems in gaining informed consent from psychiatric patients. *Emory Law Journal, 31*, 345-374.

Mariner, W.K. (1995). Liability and compensation for adverse reactions to HIV vaccines. In *Adverse reactions to HIV vaccines: Medical, ethical, and legal issues.* Washington, DC: U.S. Government Printing Office.

Mason, T. (1972). Child abuse and neglect, part I: Historical overview, legal matrix, and social perspectives. *North Carolina Law Review, 50*, 293.

Mehlman, M.J. (1999). How will we regulate genetic enhancement? *Wake Forest Law Review, 34*, 671-714.

Mushlin, M., Kramer, D.T., and Gobert, J.J. (1993). *Rights of prisoners, 2nd ed*. Colorado Springs, CO: McGraw-Hill.

Negri, G. (1995). Youth seeks "alternative" cure. *Boston Globe*, February 5, p. 22.

Newcomer, S.F., and Udry, J.R. (1985). Parent-child communication and adolescent sexual behavior. *Family Planning Perspectives, 17*(4), 169-174.

Provenmire, R. (1998/1999). Do parents have the legal authority to consent to the surgical amputation of normal, healthy tissue from their infant children? *American University Journal of Gender, Social Policy, and the Law, 7*(1), 87-123.

Redding, R.E. (1993). Children's competence to provide informed consent for mental health treatment. *Washington and Lee Law Review, 50*(2), 695-753.

Rosato, J. (2002). Let's get real: Quilting a principled approach to adolescent empowerment in health care decision-making. *DePaul Law Review, 51*, 769.

Ross, L.F., Coffey, M.J., Labson, M.S., Wilfond, B.S., Geller, G., Audrain-McGovern, J., Lerman, C., Shields, A.E., Pollak, J., Hoffmann, D.E., and Rothenberg, K.H. (2002). Symposium: Research with children: The new legal and policy landscape. *Journal of Health Care Law and Policy, 6*, 1-193.

Scott, E.S. (2000). The legal construction of adolescence. *Hofstra Law Review, 29*, 547.

Segal, S.J. (1991). Norplant developed for all women, not just the well-to-do. *New York Times*, January 6, p. 18.

Shirkey, H. (1968). Therapeutic orphans. *Journal of Pediatrics, 72*(1), 119-120.

Skelton, G., and Weintraub, D.M. (1991). Most support Norplant for teens. *Los Angeles Times*, May 27, p. A1.

Stadler, A. (1997). Comment: California injects new life into an old idea: Taking a shot at recidivism, chemical castration, and the Constitution. *Emory Law Journal, 36*, 1285.

Steel, L.J. (1994). National Childhood Vaccine Injury Program: Is this the best we can do for our children? *George Washington Law Review, 63*, 144.

Stocker, S. (1999). New NIDA initiative focuses on vulnerability to drug addiction. *NIDA Notes, 13*(6). Available: http://www.drugabuse.gov/NIDA_Notes/NNVol13N6/Initiative.html [January 9, 2004].

Stolberg, S.G. (2002). Proposal to test smallpox vaccine in young children sets off ethics debate. *New York Times*, November 5, p. A14.

Walter, P. (1998). The mentally incompetent and medical/drug research experimentation: New York saves the day for the underdog. *Health Law Journal, 6*, 149-168.

Waltz, J.R., and Scheuneman, T.W. (1970). Informed consent to therapy. *Northwestern University Law Review, 64*(5), 628-650.

Wattleton, F. (1991). Perspective on race and poverty: Using birth control as coercion. *Los Angeles Times*, January 13, p. M7.

Wilford, B.S., Geller, G., Lerman, C., Audrain McGovern, J., and Shields, A. (2002). Ethical issues in conducting behavioral genetics research: The case of smoking prevention trials among adolescents. *Journal of Health Care Law and Policy, 6*(1), 73-88.

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Biographical Sketches of Committee Members and Staff

Henrick J. Harwood is a vice president with The Lewin Group. He has over 20 years of experience studying the economic impacts of alcohol and drug abuse. Mr. Harwood recently served as the chair of the "Treatment Gap" expert panel for the Center for Substance Abuse Treatment (CSAT) National Treatment Plan, is director of the CSAT funded practice research and evaluation network initiative for behavioral health professions, and served as the deputy director for the CSAT-funded National Evaluation, Data and Technical Assistance Center (NEDTAC). He has directed a number of studies examining the economic impacts of substance abuse and mental illness, including studies examining the relationship of substance use/abuse to labor market success (labor force participation, employment, wage rates), receipt of social welfare benefits, healthcare expenditures and other impacts (particularly impacts with externalities such as motor vehicle crashes and crime). Mr. Harwood has also managed several major evaluations of the costs and benefits of substance abuse treatment. Previously, he served as assistant deputy director for Treatment and Workplace Policy (Acting), and as senior policy analyst in the Office of National Drug Control Policy, Executive Office of the President. Mr. Harwood was on the Institute of Medicine staff where he was associate study director on the Substance Abuse Coverage Study and co-editor of Treating Drug Problems which is the most comprehensive analysis undertaken to date of the nation's drug treatment system. Mr. Harwood began his career at the Research Triangle Institute in North Carolina, where he was the principal author of Economic Costs of Alcohol and Drug Abuse and Mental Illness—1980.

Alexander M. Capron is the director of ethics and health for the World Health Organization. From 1985 to 2002, he served as professor of law and medicine, and co-director of the Pacific Center for Health Policy and Ethics at the University of Southern California. He specializes in legal-medical issues and biomedical ethics. Appointed by President Clinton, he served as a member of the National Bioethics Advisory Commission. Professor Capron was executive director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research and chair of the Biomedical Ethics Advisory Committee of the U.S. Congress. He also serves on the board of the Joint Commission on Accreditation of Healthcare Organizations. Professor Capron chaired the Board of Advisors of the American Board of Internal Medicine and served on the Recombinant DNA Advisory Committee at the National Institutes of Health and on various panels at the Institute of Medicine. His recent publications include Law, Science, and Medicine, "Stem Cells: Ethics, Law, and Politics," and Treatise on Health Care Law.

Jonathan P. Caulkins is professor of operations research and public policy at the Heinz School of Public Policy and Management of Carnegie Mellon University. His research focuses on modeling and analyzing problems pertaining to drugs, crime, and violence, and how policies affect those problems. He has testified before Congress and a variety of state legislatures on the effectiveness of various drug control programs and agencies and has briefed senior policy makers at the federal, state, and local level on issues pertaining to drug and crime control. Dr. Caulkins has served as a judge and a member of the advisory board of the International Mathematical Contest in Modeling; a member of the Society of Industrial and Applied Mathematicians' Visiting Lecturer Program. He earned a master's degree in electrical engineering and computer science and a doctorate in operations research at the Massachusetts Institute of Technology.

James W. Cornish is a psychiatrist at the Philadelphia Department of Veterans Affairs Medical Center and associate professor of psychiatry at the University of Pennsylvania. Since 1988, he has conducted numerous pharmacotherapy trials involving people dependent upon alcohol, cocaine, opioids and nicotine. He participated on the NIDA-sponored clinical trial of Depotrex® brand depot naltrexone for opioid dependent persons. Dr. Cornish also assisted with the planning of a phase II cocaine vaccine trial at Penn. He is the director for the Center's Pharmacotherapy Division and is the chairperson for the Research and Development Committee at the VA. Dr. Cornish his M.D. from Thomas Jefferson Medical College. He did residencies in general surgery at Bryn Mawr Hospital and psychiatry at Norristown State Hospital. He also completed a fellowship in adminis-

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Lewis E. Gallant is the executive director of the National Association of State Alcohol and Drug Abuse Directors, Inc. (NASADAD). He had served as president of NASADAD since 1999 and for the prior two years as first vice president. Dr. Gallant came to NASADAD from the Virginia Department of Mental Health, Mental Retardation and Substance Abuse Services (DMHMRSAS), where he held the position of director of the Office of Substance Abuse Services. He was responsible for promoting, monitoring and evaluating the office's service programs relating to the prevention and treatment of substance abuse problems, and for coordinating such programs within DMHMRSAS and with other public, private and community-based organizations. He earned a Ph.D. in social work, with an emphasis on human services administration at the University of Texas, Arlington.

Shirley Y. Hill is professor of psychiatry at the University of Pittsburgh School of Medicine, with a joint appointment in the departments of psychology and human genetics. Her career has been focused on etiological factors in addiction. Dr. Hill has been a consultant to the World Health Organization, Program on Substance Abuse, served as a consultant to the NIH Division of Research Grants Advisory Committee, and has served on a number of NIH Initial Review Groups (IRG). She has been a member of the Graduate Faculty University of Pittsburgh since 1990 and was a visiting professor (Spinoza Chair) at the University of Amsterdam, Faculty of Medicine in 1994. Dr. Hill serves on the editorial board of Journal of Studies on Alcohol and is a member of several research societies including American Psychopathological Association, International Society for Biomedical Research on Alcoholism, Research Society on Alcoholism, Sigma Xi Scientific Honorary, Society of Biological Psychiatry, Society for Psychophysiological Research and the American College of Neuropharmacology (ACNP). Currently, she is an ACNP Fellow and member of two ACNP committees, Education and Training, and Ethics. She obtained her early training in neurobiology, medicine, and research methodology at Washington University School of Medicine in St. Louis.

Martin Y. Iguchi is a senior behavioral scientist and director of the Drug Policy Research Center at RAND, located in Santa Monica, CA. Dr. Iguchi is a member of CSAT's National Advisory Council, NIDA's Center Grant Research Review Committee, the board of directors of the College on Problems of Drug Dependence, and of the editorial board for Drug and Alcohol Dependence. Currently, Dr. Iguchi is a principal investigator on three NIDA treatment research grants, an Robert Wood Johnson grant to examine the impact of Proposition 36 in Orange County, CA., a subcontract with UCLA to conduct a cost outcome analysis for a multi-site methamphetamine treatment study, and he also serves as principal investigator for the Ford Foundation grant that supports the RAND Drug Policy Research Center. Dr. Iguchi received his Ph.D. in Experimental Psychology from Boston University, and he completed 2 years of post-doctoral training in drug abuse and behavioral pharmacology at the Johns Hopkins University School of Medicine.

Thomas R. Kosten is a professor of psychiatry and medicine at Yale University Medical School and deputy chief of psychiatry at VA Connecticut. He has been supported by a research scientist award from the National Institute of Health since 1987 and directs the Yale Medications Development Center for substance abuse. He has served on national and international review groups for medications development in substance abuse. He is the vice chair for Added Qualifications in Addiction Psychiatry of the American Board of Psychiatry and Neurology. He is a fellow in the American Psychiatric Association and the American College of Neuropsychopharmacology, and past president of the American Academy of Addiction Psychiatry. He has several major awards for clinical research, and has been on the editorial boards of the major journals in substance abuse as well as the American Journal of Psychiatry. From his studies in substance dependence, post traumatic stress disorder, and neuroimaging he has published over 300 papers, books and reviews. Recent work includes developing a cocaine vaccine, buprenorphine for opioid dependence, and using combined medications with contingency management for opioid and cocaine dependence.

Joseph O. Merrill is an attending physician at Harborview Medical Center and associate professor of medicine at the University of Washington. His current research interest is with Methadone maintenance in primary care settings. Dr. Merrill is a member of the Society of General Internal Medicine and the American Society of Addiction Medicine. He has an M.D. from Yale University School of Medicine and an M.P.H. from the University of Washington, School of Public Health.

Tracy G. Myers serves as a Senior Project Officer with the Division of Behavioral and Social Sciences and Education with the National Research Council (NRC). Prior to joining the NRC, he worked at Westat, Inc., on experimental and quasi-experimental evaluations of human services programs targeted toward children and their families. His areas of interest include risk and protective factors that affect child and adolescent health and psychopathology, psychological assessment, minority mental health, and program evaluation. At the NRC, he is directing a study on behavioral, ethical, legal, and social issues associated with immunotherapies (e.g., vaccines and monoclonal antibodies) and sustained-release formulations for treating drug addiction; overseeing a workshop on the behavioral, ethical, legal and social issues associated with genetic information on who is and is not genetically susceptible to drug addiction; and directing a study to revamp the National Institute on Aging's research program in social psychology, adult development, and personality psychology. He has a PhD in clinical/community psychology from the University of Maryland, College Park.

Michael Owens is a professor of Pharmacology and Toxicology in the College of Medicine at the University of Arkansas for Medical Sciences (UAMS) in Little Rock, AR. He received his Ph.D. in experimental pathology from the University of North Carolina at Chapel Hill, and completed post-doctoral training in pharmacokinetics and therapeutics at the University of Arizona in Tucson. Since 1985, his medical research program has been continuously funded by the National Institute on Drug Abuse, and from 1986-1997 he was the recipient of a prestigious Research Career Development Award from the National Institute on Drug Abuse. From 2001-2002 he was the director of the Arkansas Biosciences Institute. His research interests are very broad including antibody-based medications development, experimental therapeutics, drug abuse and agrimedicine. He is currently developing monoclonal antibody-based medications for use in treating phencyclidine and methamphetamine abuse. In recognition of his research and academic accomplishments at UAMS, he was awarded a Wilbur D. Mills Endowed Chair in Alcohol and Drug Abuse Prevention in 2001.

Charles R. Schuster is an internationally recognized researcher on the psychopharmacology of drugs of abuse. From 1986-1992, Dr. Schuster served as the director of the National Institute on Drug Abuse (NIDA). In 1992, Dr. Schuster returned to his research career as a senior research scientist at the Addiction Research Center of NIDA. In 1995, he was appointed as a professor in the department of psychiatry and behavioral neurosciences at Wayne State University School of Medicine and the

director of the Clinical Research Division on Substance Abuse. He is currently director of the Addiction Research Institute at Wayne State University. Dr. Schuster has authored or co-authored over 200 scientific journal articles, as well as numerous book chapters and several books. He has served on the FDA Drug Abuse Advisory Committee and is also a member of the Expert Advisory Panel on Drug Dependence of the World Health Organization. Dr. Schuster's primary research interests include the development of medications and behavioral interventions for the treatment of tobacco, cocaine and heroin dependence; the laboratory evaluation of new medications for their abuse potential; the role of co-morbid psychiatric disorders in the etiology and maintenance of drug dependence; and the relationship between co-morbid psychiatric disorders and the nature and intensity of the cocaine withdrawal syndrome.

Zili Sloboda is currently an adjunct research professor in the department of sociology and senior research associate at the Institute for Health and Social Policy of the University of Akron. She was awarded a grant from the Robert Wood Johnson Foundation in November 1999 to review and enhance the middle and high school substance abuse prevention program being delivered through the Drug Abuse Resistance Education (D.A.R.E.) network and in February 2001, to conduct a national five-year evaluation of the combined effects of the new program. She also serves as a consultant to the United Nations Drug Policy Programme's Global Assessment Programme. From 1987 until 1998, Dr. Sloboda headed a program of research grants at the National Institute on Drug Abuse. She served as the director of the Division Epidemiology and Prevention Research from 1993 until 1998. She was trained as a medical sociologist at New York University and as an epidemiologist at the Johns Hopkins University School of Hygiene and Public Health. Her research has included epidemiological studies of drug abuse in New York City; evaluations of drug abuse treatment programs; health services research relative to the utilization of a geriatrics program, of dental services, and of a community-based hospital; and prevention research focusing on comprehensive community programs for sickle cell screening and for cancer. She has published in the areas of drug abuse, cancer prevention, and AIDS prevention.

Kathryn E. Stein is the vice president for product development and regulatory affairs at MacroGenics, Inc., in Rockville, Maryland. Prior to joining MacroGenics, she was the director of the Division of Monoclonal Antibodies (DMA), Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research (CBER), FDA and acting chief, Laboratory of Molecular and Developmental Immunology, DMA from 1992-2002. She joined CBER in 1980 as a senior staff fellow and became a senior

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Ellen M. Weber is an assistant professor of Law at the University of Maryland School of Law. Prior to joining the law school, Ms. Weber was an attorney with the Legal Action Center, a non-profit law and policy organization that specializes in drug, alcohol, AIDS and criminal justice issues. She worked as staff counsel and later started the Center's National Policy office in Washington, DC. Most recently, Ms. Weber served as the Center's Senior Vice President for Law. During her seventeen-year tenure with the Center, Ms. Weber developed and ran precedent-setting litigation protecting the civil rights and privacy of people with addiction and criminal justice histories and HIV disease and the agencies that serve them. She advised the Administration on drug, alcohol and AIDS policy, worked closely with congressional staff to shape legislation on appropriations, civil rights protections for individuals with disabilities, health care reform, confidentiality and other issues and testified extensively before Congress on these issues. Ms. Weber obtained her J.D. from New York University School of Law.