COLORADO TOBACCO RESEARCH PROGRAM
2002 COMPENDIUM OF FUNDED PROJECTS

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INTRODUCTION

The Colorado Tobacco Research Program (CTRP) is pleased to announce the initiation of 16 research projects that will lead to more knowledge about the etiology, pathogenesis, diagnosis and treatment of tobacco- and addiction-related diseases and the development, implementation, evaluation, and dissemination of existing or novel approaches to tobacco control and substance abuse education. Individual investigators from five institutions from across the state, including Colorado affiliated colleges and universities (e.g., Colorado State University and the University of Colorado campuses) and non-profit hospitals (National Jewish Medical & Research Center) are embarking on research that will reduce the morbidity and mortality associated with tobacco use. By providing more than $6.5 million to fund these new awards, the State of Colorado has pledged its commitment to reducing the physical and mental health impact, and the corresponding economic burden, of tobacco-related diseases within the state.

BACKGROUND

Senate Bill 00-071

By creating the tobacco research fund, the Colorado State Legislature made optimal use of newly available monies to benefit Colorado citizens. Senate Bill 00-071 determined how the State of Colorado's share of the national tobacco settlement funds would be spent. The bill allocated up to 8% of the monies received annually for the establishment of a comprehensive clinical, basic science, mental health, and evaluative research grant program that would serve Colorado's tobacco- and substance-abuse-related health care needs.

Colorado Tobacco Research Program

To implement the research program, the State Legislature assigned the Office of the President of the University of Colorado (CU) the duty of administering the Colorado Tobacco Research Program. Within the CU Office of the President, the Vice President for Academic Affairs and Research thus created CTRP, with the charge to award research grants based on scientific merit and relevance to the Program's mission in an open, competitive manner. Research supported by CTRP is consistent with the intent of SB 00-071 in that all supported projects directly address the mental health, educational, cessation, prevention and illness-related needs caused by tobacco and substance abuse within the state.

Scientific Advisory Committee

SB 00-071 also directed the Governor of the State of Colorado to establish a Scientific Advisory Committee to counsel the University on the direction, scope and progress of CTRP. Appointed by the Governor, Committee members represent voluntary health organizations dedicated to the reduction of tobacco use, experts in the fields of biomedical or social/behavioral research, representatives from research universities and institutions focused on tobacco-related issues affecting children and youth, and members of medical or health organizations. The Scientific Advisory Committee primarily develops the strategic objectives and priorities of CTRP, facilitates coordinated efforts between the Program and other stakeholder entities focused on reducing tobacco use and tobacco-related disease in Colorado, participates in Program evaluation, and makes the final recommendations on which research applications should be funded.

RESEARCH PRIORITIES

CTRP supports both basic and applied research in social and behavioral sciences, biomedical sciences, and public health and policy. CTRP invites investigations into the etiology, pathogenesis, diagnosis and treatment of tobacco- and addiction-related diseases and the development, implementation, evaluation, and dissemination of existing or novel approaches to tobacco control and substance abuse education. The following is a list of the 2002-2003 CTRP Research Priorities:

Biobehavioral and Nicotine Addiction Treatment Research

CTRP seeks to fund basic biobehavioral investigations of the biological, psychological, sociocultural, and genetic factors that influence initiation of tobacco use, progression to nicotine addiction, smoking cessation, and relapse; the pharmacological basis of nicotine addiction, including, but not limited to, the role of nicotine receptors in addiction; the appropriate role of nicotine replacement therapies (NRT) in nicotine addiction; research that identifies, tests, and disseminates interventions to treat addicted tobacco users; studies that shed light on how nicotine addiction and disease develop; and explorations of applying the "harm-reduction" paradigm to tobacco use.

Biological Research

CTRP requests studies that strive to reduce the morbidity and mortality from tobacco-related diseases. Appropriate areas include basic disciplines-such as physiology, biochemistry, pathology-as well as translational and clinical investigations that focus on problems associated with tobacco use. CTRP encourages studies that identify and validate biomarkers of tobacco exposure and tobacco-induced cellular events that relate to the different stages of disease progression; define the mechanisms by which tobacco use contributes to disease progression and management; examine the effects of prenatal and postnatal exposure to parental tobacco use; contribute to the understanding of the effects of smoking on our physical and mental health, and discern how these effects may differ by age, ethnicity, race or gender.

Effects of Exposure to Secondhand Smoke

CTRP will fund research that focuses on the biological impact of exposure to secondhand smoke. In addition to research on chronic ailments directly associated with tobacco smoke exposure (e.g., atherosclerosis), studies into the mechanisms, diagnosis or treatment of pulmonary diseases associated with childhood exposure to secondhand smoke (e.g., chronic bronchitis) or exacerbated by secondhand smoke (e.g., asthma) are encouraged. Important in this regard are quantifying and understanding the chronic effects of exposure to secondhand smoke; and how the impact of exposure to secondhand smoke differs by age and by other demographic factors, emphasizing the need for appropriately designed studies to characterize potentially disproportionate exposures and sensitivities.

Epidemiological and Surveillance Research

CTRP is interested in funding studies that identify differences in host (inherited and acquired), environmental, and behavioral factors that may help elucidate unique contributors to tobacco use and tobacco-related disease. An important and emerging area of research in tobacco use and addiction control is genetic epidemiology. CTRP encourages investigations into the shifting patterns of tobacco use in youth and young adults, smokeless tobacco and cigar use among Colorado teens, and the relationships of illicit drugs to tobacco use. Surveillance and research is needed to monitor and evaluate trends in tobacco use and related disease risk factors, health services, and policy and environmental interventions to determine the influence of these factors on trends in tobacco-related disease incidence, morbidity, mortality, and survival. CTRP also encourages studies that use Colorado's data collections for secondary data analysis.

Prevention of Tobacco Use

CTRP seeks basic and applied social/behavioral research in the prevention of tobacco and substance use. Topics may include, but are not restricted to, tobacco use in schools and communities; experimentation and the casual use of nicotine products; exposure to secondhand smoke; and tobacco usage by mental health populations. Interventions in historically understudied communities or specific racial and ethnic groups to elucidate unique factors and forces shaping their tobacco consumption are invited. CTRP particularly encourages studies that illuminate the resiliency among subpopulations of youth, and that document trends and develop interventions to curb the rise in smoking among young women.

Policy Research

CTRP is interested in funding evaluative research that examines the impact of public policies and program on smoking rates and practices. Included are studies of regulatory policies that limit or discourage access to tobacco products; studies which look at how safety claims for new projects developed by the tobacco industry will be evaluated; research into health care policies and the medical sector's actual and potential role in reducing tobacco in Colorado; and evaluation of efforts to eliminate the tobacco industry's promotions of tobacco products. CTRP also encourages research that documents the role of anti- and pro- tobacco forces in shaping Colorado tobacco policies (e.g. smoke-free bar issues); assessing the impact of the Master Settlement Agreement (MSA) on state and local anti-smoking policies.

TYPES OF PROJECTS FUNDED (AWARD MECHANISMS)

Independent Investigator Awards

Research Project Awards

Investigator-initiated research projects. The proposals should be fully developed, scientifically rigorous, and include sound background information, hypotheses, and promising preliminary studies or supporting data.

Term: Maximum of 3 years.

Award: Average annual direct costs should not exceed $175,000. Indirect costs are paid at the federally determined rate for eligible institutions.

Innovative Development and Exploratory Awards (IDEAs)

IDEA grants are for exploratory research that is not yet sufficiently mature to compete successfully for a Research Project grant. Although the proposed research might lack adequate pilot data or proven methods, it should be creative, intellectually exciting, and show clear promise to yield findings that could serve as the basis for a well-defined future Research Project application.

Term: Maximum of 18 months.

Award: Total costs cannot exceed $75,000 in direct costs, including a maximum of $5,000 for equipment. Indirect costs are paid at the federally-determined rate for eligible institutions.

Career Development Awards

Postdoctoral Fellowship Awards

These are awards for individuals to obtain postdoctor al research training under a designated mentor (not intended for junior faculty members). Applications, which must be prepared and submitted by the fellows, must outline a separate research project and include letters of support. The fellow must commit to a minimum of 80 percent time to the research project.

Term: Maximum of 2 years.

Award: Maximum of $35,000 direct costs per year plus up to $10,000 for fringe benefits and health insurance, averaged over the duration of the award. The indirect cost rate is 8% for eligible institutions.

Dissertation Research Awards

These awards are provided to support the dissertation research of doctoral candidates who wish to pursue tobacco-related research. The awards are designed specifically for students who will have advanced to candidacy by the award start date and who are initiating their dissertation research. Applicants and their mentors must be affiliated with an academic institution in Colorado that grants doctoral degrees and the doctoral candidates must be directly supervised by a mentor who is eligible to be a principal investigator at the applicant's institution. The awardee must commit a minimum of 80 percent time to the research project.

Term: Maximum of 2 years.

Award: Maximum of $20,000 direct costs per year for stipend and supplies plus up to $10,000 for tuition remission, fringe benefits, and health insurance. No indirect costs will be paid.

CTRP AWARD PROCESS

Research funds are available to investigators at all universities, colleges, research institutes, and other nonprofit institutions in Colorado via a grant application process. Following the receipt of grant applications, and prior to the peer review process, all applications are screened for their direct relevance to tobacco or substance use or tobacco-related disease. Briefly, most of the proposals reviewed in the tobacco prevention, cessation, policy and epidemiological disciplines focus directly on human tobacco use and/or tobacco control issues, making their relevance to CTRP's mission apparent. Those applications that directly focus on the etiology, pathology, diagnosis or treatment of a specific tobacco-related disease, for which there is unequivocal epidemiological evidence, are also considered highly relevant to CTRP's mission. In contrast, those research proposals focused on basic biological phenomena must demonstrate how the research will yield insights into tobacco-specific health effects. Only those applications considered relevant to the goals of CTRP are forwarded for scientific peer review by an appropriate review panel or "study section".

In 2002, CTRP contracted with the University of California Tobacco-Related Disease Research Program (TRDRP) to review CTRP grant applications. Established in 1989, TRDRP operates a grant evaluation program modeled after that of the National Institutes of Health (NIH), utilizing expert reviewers from all states (including Colorado) but excluding California. Relevant applications submitted in response to the 2002 CTRP Call for Applications were assigned by TRDRP staff to a study section comprised of evaluators appropriate for the scientific discipline and subject matter. For further information on TRDRP please refer to the following website: www.ucop.edu/srphome/trdrp.

CTRP applications were reviewed in a two-tiered manner similar to the NIH peer review process. As part of the first tier (scientific merit evaluation), CTRP applications were reviewed in conjunction with TRDRP applications. In April and May of 2002, 143 reviewers evaluated 48 applications from CTRP (along with 221 applications from California) in the following 8 study sections:

1) Cancer
2) Cardiovascular Diseases
3) Epidemiology
4) General Biomedical Sciences
5) Nicotine Dependence
6) Public Health, Public Policy and Economics
7) Pulmonary Diseases
8) Social and Participatory Research

Rosters of the TRDRP 2002 study sections are provided on pages 23-31.

Once the peer reviews had been completed by the appropriate study section, CTRP applications were then ranked by scientific merit score and percentile. Each program's applications were subsequently disaggregated prior to developing the respective funding models. Applications scoring in roughly the upper half of the merit range within each study section were forwarded to the CTRP Scientific Advisory Committee (SAC), who made the final recommendations to the President of the University on which applications should be funded, based on the established Program priorities, the scientific merit of the proposals as determined by peer review, and the amount of funds available. SAC members and the organizations they represent are listed on page 22.

In response to the 2002 Call for Applications, the investigator-initiated research areas funded in the second cycle of awards drew from the broader research priorities set by CTRP. The research areas listed below do not define the parameters of the research to be funded in future cycles. In other words, the types of projects supported by CTRP in any given cycle will reflect the particular disciplines of applications submitted, their relative scientific excellence, and the amount of funds available to CTRP that year. Thus, the awards of any given cycle do not represent the definitive research portfolio supported by CTRP. Indeed, applications focused on those Research Priorities that have been underrepresented (e.g., policy and/or evaluative research; health effects of secondhand smoke) will be particularly encouraged in future cycles.

For 2002, CTRP has awarded a total of $6.57 million for 16 grants to individual investigators at 5 research organizations. This funding level represents a "payline" of 33% of all applications submitted last year. The second cycle of awards supported by CTRP fall into the following research areas:

Disease Diagnosis & Treatment
Nicotine Addiction
Prevention and Cessation
Mental Health

In other words, slightly more than one-third of the awarded funds will support seven studies that focus on tobacco-related disease processes, ranging from basic biological studies of the molecular and cellular changes that are critical to the initiation of disease, the development of new or refined diagnostic approaches to identify disease progression, and on potential therapies and/or novel drug delivery techniques. Approximately one third of the award monies support three projects that will investigate the underlying physiological mechanisms that may predispose individual susceptibility to nicotine or play key roles in the progression of addiction. About one-quarter of the awarded funds are dedicated to five projects that center on the social and biobehavioral factors underlying why individuals start to smoke, and on the development of interventions to counter youth susceptibility to tobacco imagery in popular media. Finally, one project will focus on nicotine addiction in mentally ill (e.g., schizophrenic) patients.

Award Distribution

Research Areas	Awards	Amount Funded (% of total)
Disease Diagnosis & Treatment	7	$2,470,020 (37)
Nicotine Addiction	3	$2,068,298 (32)
Prevention and Cessation	5	$1,536,615 (23)
Mental Health	1	$493,073 (8)
Total	**16**	**$6,568,006 (100)**

This compendium lists the 16 funded grants in two sections. First, projects are grouped within research areas by principal investigator (in alphabetical order); a brief summary of each project is provided. Following the next section, the lay abstracts of each project, composed by the investigators themselves, provide additional details; these are grouped by award type and again are arranged in alphabetical order of the principal investigator's name. The time frame of the project (duration of award) is provided along with the total award amount; dollar amounts for each award include direct and indirect costs.

Disease Diagnosis & Treatment

Glode, Michael L.
University of Colorado Health Sciences Center
Silibinin Treatment of Bladder Cancer
(Research Project: duration of 3 years, award amount = $713,751)
Will determine the efficacy of a natural compound (currently being tested for treatment of prostate cancer) in combating bladder cancer.

Hanneman, William H.
Colorado State University
Tobacco and Gene Expression
(IDEA Project: duration of 1.5 years, award amount = $103,178)
Seeks to identify heretofore unknown tobacco-sensitive genes so as to permit assessment of their relevance to tobacco-related disease.

Liu, Xuedong
University of Colorado at Boulder
Regulation of Tumor Suppression By TGF-beta in Lung Cancer
(Research Project, 3 year duration, award amount = $608,310)
Seeks to define the mechanism by which negative growth hormones and tumor suppressors control the proliferation of normal vs. lung cancer cells.

Mattison, Christopher P.
University of Colorado at Boulder
Regulation of Cell Division by mMps1/TTK in Lung Cancer
(Postdoctoral Fellowship: duration of 2 years, award amount = $86,400)
Will pursue the connection between key proteins involved in altered cell division and lung cancer.

Peebles, Katherine A.
University of Colorado Health Sciences Center
Biomarkers of Smoke-Induced Lung Cancer in a Mouse Model
(Dissertation Award: duration of 2 years; award amount = $48,320)
Seeks to determine if a specific protein can be used to detect the presence of lung cancer.

Rabinovitch, Nathan
National Jewish Medical and Research Center
Health Effects of ETS in Urban Minority Children with Asthma
(Research Project: 3 year duration, award amount = $796,690)
Will characterize how various smoking behaviors determine children's exposure to secondhand smoke and their corresponding severity of asthma and/or decreased lung function.

Stansbury, Jeffrey W.
University of Colorado Health Sciences Center
Novel Polymer-Drug Conjugates for COPD Therapies
(IDEA Project: duration of 1.5 years, award amount = $113,371)
Seeks to devise new organic molecules to facilitate delivery of drugs used in the treatment of lung diseases caused by tobacco use.

Nicotine Addiction

Adams, Catherine E.
University of Colorado Health Sciences Center
Alpha-7 Nicotinic Receptor Role in Hippocampal Development
(Research Project: duration of 3 years, award amount = $524,224)
Seeks to determine which developmental processes in a critical region of the brain are influenced by a key nicotinic receptor and its relationship to tobacco addiction.

Tanguay, Robert L.
University of Colorado Health Sciences Center
Zebrafish: A Model For Nicotine Developmental Toxicity
(Research Project: duration of 3 years, award amount = $772,324)
Seeks to develop an alternate vertebrate research model to define how nicotine modifies central nervous system development and function.

Wehner, Jeanne M.
University of Colorado at Boulder
Nicotinic Receptor Mediation of Anxiety and Cognition
(Research Project: duration of 3 years, award amount = $771,750)
Will define factors critical to the transition from tobacco experimentation to addiction by examining the effects of nicotine on emotional calming and its ability to enhance concentration.

Prevention & Cessation

Ehringer, Marissa A.
University of Colorado at Boulder
Candidate Genes for Tobacco Use And Nicotine Dependence
(IDEA Project: duration of 1.5 years, award amount = $110,250)
Seeks to identify presence and role of genes that may influence adolescents' risk for tobacco addiction.

Jessor, Richard
University of Colorado at Boulder
Tobacco and Alcohol Use in College: A CU Developmental Study
(Research Project: duration of 3 years, award amount = $691,581)
Seeks to advance our understanding of the personal and social characteristics that influence tobacco and alcohol use among male and female college students.

Perrine, Nicholas E.
Colorado State University
Motivational Orientations and the Smoking Cessation Process
(Dissertation Award: duration of 2 years; award amount = $48,034)
Will examine roles of incentives and rewards in enabling smokers to quit.

Peters, Annie R.
University of Colorado at Boulder
Combined Effects of Alcohol and Nicotine
(Dissertation Award: duration of 2 years; award amount = $49,036)
Will pursue connections between biological and psychological motivations influencing alcohol and tobacco use in humans.

Walkosz, Barbara J.
University of Colorado at Denver
MATE: Media and Tobacco Education
(Research Project: duration of 3 years, award amount = $637,714)
Seeks to develop, evaluate and test the efficacy of a theoretically-based media literacy intervention to help children counter the influence of smoking imagery found in popular culture.

Mental Health

Leonard, Sherry S.
University of Colorado Health Sciences Center
Nicotine Receptor Expression in Mentally Ill Smokers
(Research Project: duration of 3 years, award amount = $493,073)
Will determine if nicotinic receptor presence and function are altered in mentally ill patients and how this may contribute to the high prevalence of tobacco addiction in this population.

Research Projects

Alpha-7 Nicotinic Receptor Role in Hippocampal Development

Adams, Catherine E.
University of Colorado Health Sciences Center

Despite educational efforts, approximately 25% of women in the United States still smoke while they are pregnant. Smoking during pregnancy causes greater rates of infant death as well as behavioral, learning and memory problems. Animal studies of fetal nicotine exposure have shown similar effects. An area of the brain that influences learning and memory is the hippocampus. The hippocampus is one of the brain regions that is damaged following fetal nicotine exposure. The hippocampal damage may be due to some extent to decreases in nutrition and oxygen supply associated with maternal cigarette smoking. However, the damage may also be due to the direct action of nicotine on specific nicotinic targets in the hippocampus known as α7 nicotinic receptors. The level of α7 receptors in the hippocampus is decreased after fetal nicotine exposure in some studies, but not in all. The first step towards determining whether the changes in hippocampus seen after fetal nicotine exposure are due to the action of nicotine on α7 receptors is to find out whether and how the α7 receptor influences normal hippocampal development. The α7 receptor is thought to influence several developmental processes, including the birth of neurons, movement of neurons from their place of birth to their final destination, organization of neuronal structure and neuronal death. Two different versions of the α7 receptor gene in two different mouse strains have been found to differentially affect the organization of both α7 receptors and interneurons in the hippocampus of the two strains. Mice without a functional α7 receptor gene (α7 knockout mice) also show differences in the organization of hippocampal interneurons. The interneuron differences in the three mouse strains could best be explained by different influences of the α7 receptor genes on hippocampal interneuron migration and/or death. The goals of the proposed studies are to determine whether the α7 receptor plays a role in hippocampal interneuron migration and/or death and to what extent allelic variations in the α7 receptor gene locus affects this role. Experiment 1 will examine the time course and pattern of α-BTX binding in C3H, DBA/2 and their congenic strains to determine when the α7 receptor initially appears in developing hippocampus, how the pattern of expression changes and whether the different α7 gene loci change the time course and/or pattern of α7 receptor development. Experiment 2 will examine whether the α7 receptor influences hippocampal interneuron migration and/or death in murine hippocampus and whether allelic variations in the α7 gene locus alters the influence of the receptor on these processes. Experiment 3 will examine whether a null mutation of the α7 receptor influences hippocampal interneuron migration and/or death in murine hippocampus.

Silibinin Treatment of Bladder Cancer

Glode, Michael L.
University of Colorado Health Sciences Center

Bladder cancer is the fourth most common cancer among men in the United States, and the 8th most common cancer among women. It is estimated that 39,200 men and 15,100 women will get bladder cancer in the U.S. in 2001, and more than 12,000 people in the U.S. die from bladder cancer each year. Smoking is responsible for 47% of bladder cancer deaths in men and 37% of bladder cancer deaths in women. The use of tobacco is thus a very major contributor to development of bladder cancer.

Standard treatment may include surgery, chemotherapy, radiation therapy, biological therapy, and combinations of these. However, the surgery has undesirable physical and psychological effects; metastases are difficult to treat, and recurrence is frequent. The current proposal deals with the use of a plant-derived chemical called silibinin from milk thistle. Milk thistle extract (MTE) already has widespread use and acceptance as a herbal supplement, and many cancer patients are already taking herbs to treat their cancer. Silibinin, the main active chemical in MTE, is well documented for its cancer preventative effects in many different animal and human systems, and its mechanism of action is fairly well understood.

As a traditional medicine, milk thistle seeds have been used continuously for 2000 years for liver conditions (first mentioned by Pliny in the 1st century). Historical references for MTE are particularly abundant in herbals of the Middle Ages, including the liver-protective activity. Eclectic physicians in 19th-century America extensively used milk thistle seeds for liver congestion. German physicians, in mid-19th-century revitalized the use of milk thistle seeds for the treatment of liver disease.

Recently, there has been a renewed public and scientific interest in the use of novel, less toxic preparations for treatment of cancer. We already have an ongoing clinical trial that uses silibinin to treat prostate cancer in men. Of particular importance to these studies is the documented safety of MTE and its main component silibinin. It is known to be well-tolerated and free of significant adverse effects. At different doses and modes of administration to mice, rats, rabbits, and dogs, silibinin has been shown to be nontoxic.

In the current proposal we will collect the necessary data to demonstrate the feasibility of developing silibinin as a potent alternative drug for bladder cancer. Based on our studies in other cancer types, we expect to find that

silibinin will be an effective anticancer drug for bladder cancer, either by itself and/or in a combination therapy with standard chemotherapy drugs (to be examined in the future). Successful completion of the studies we describe herein would allow us to proceed rapidly to clinical trials using silibinin, a novel and safe anticancer drug.

Tobacco and Alcohol Use in College: A CU Developmental Study

Jessor, Richard
University of Colorado at Boulder

The proposed research seeks to advance understanding of the personal and social characteristics that influence tobacco use and alcohol use among male and female college students. The research will examine the pattern of risk factors (such as having friends who smoke, and being under a lot of stress) and protective factors (such as believing that smoking is harmful to health; and having friends who exercise regularly, eat right, and have generally healthy habits or lifestyles) that, together, influence whether, and how much, college students smoke and drink. The proportion of college students who smoke cigarettes steadily rose in the latter half of the 1990s. The design of effective prevention programs depends on knowledge about factors that put students at greater risk for smoking and for heavier drinking, and about factors that protect students against becoming involved in these behaviors.

Approximately 1300 college students at the CU-Boulder and Denver campuses will take part in the proposed study. The study will begin in the fall of 2002, when the randomly selected participants (aged 18-19) are freshman and sophomore students. During that year and the next year, the students will fill out a questionnaire in the Fall and again in the Spring. They will answer questions about tobacco use; alcohol use; other risk behaviors, such as illicit drug use; health behaviors, such as diet and exercise; and socially positive behaviors, such as community service. They will also answer questions about personal and social risk and protective factors that may affect whether or not, and how much, they smoke and drink — including, among others, questions about personal beliefs and attitudes, health practices, church-going, life stress, and friends' and family's behaviors and attitudes.

Analyses of the data will focus on a number of specific questions about smoking and drinking among college students, including the following: Is higher risk associated with greater involvement in smoking and drinking? Is higher protection associated with lower involvement in smoking and drinking? Do protective factors buffer the impact of risk? Do more general protective factors, ones that are not obviously related to smoking and drinking (for example, involvement with religion, or intolerant attitudes about behaviors such as lying and cheating), have an influence on tobacco and alcohol use beyond that of more specific protective factors (for example, beliefs that smoking and drinking are harmful to health)? Is the same true for more general risk factors? Are the same risk and protection factors associated with both smoking and drinking, or are they different? Are students who are more involved in tobacco and alcohol use also more likely to be more involved in other risk behaviors, such as using illicit drugs, and engaging in unprotected sex? Are students who are more involved in tobacco and alcohol use also less likely to be involved in healthy and more socially positive behaviors, such as regular exercise, church-going, and volunteer work? Do antecedent levels of risk and protection influence subsequent involvement in smoking and drinking? Is the pattern of risk and protective factors that accounts for smoking and drinking similar for men and women, and for older and younger students? State-of-the-art statistical and analytic methods will be used to address these questions.

Nicotine Receptor Expression in Mentally Ill Smokers

Leonard, Sherry S.
University of Colorado Health Sciences Center

Smoking is one of the leading causes of death from both heart disease and cancer in this country. The incidence of smoking among most age groups appears to be declining and approaches 25% of the general population. However, there is a large group of individuals in which the prevalence of tobacco use is extremely high and is not decreasing, the mentally ill. This group includes patients that suffer from schizophrenia, bipolar disorder and major depression. In this population, the incidence of smoking is greater than 50% and in schizophrenics may be as high as 90%! Smoking cessation programs for this group do not work effectively. As the total number of mentally ill individuals today is approximately 10% of the population and most of these subjects smoke, this group constitutes about 25% of all the smokers in the United States today, indeed a serious problem! What is the reason for smoking in the mentally ill? Is smoking in the mentally ill biologically the same as in a smoker with no mental illness? The biology of nicotine-induced responses in animal models suggests that levels of the receptors in the brain that respond to nicotine may be related to nicotine's effects. Nicotine binds directly to nicotinic receptors on the cell surface. Nicotinic receptors are one of the first targets in the body that respond when a person smokes a cigarette. The receptors then change their shape and this allows calcium to enter the cell, which turns on other transmitters to produce the effects of smoking. This laboratory has focused on the role of nicotinic receptors in both nicotine addiction and in the mentally ill, particularly in schizophrenia. We have shown that nicotinic receptor numbers are increased in smokers and levels are correlated with the number of cigarettes smoked per day. When a person quits smoking, their receptor numbers decline to their baseline level. A growing body of evidence suggests that nicotinic receptor levels are different in multiple brain regions of subjects with

schizophrenia, and further that smoking may not regulate them in the same manner as in normal subjects. Nicotinic receptors are formed from five protein subunits, which make a channel that lets the calcium into the cell. There are 11 different genes for nicotinic receptor subunits and the working receptor is formed from different combinations of 5 of these subunits. However, little is known concerning which of the multiple subunit proteins comprising the assembled nicotinic receptors are increased in normal smokers nor which might be affected in the mentally ill. We propose to investigate specific nicotinic receptor subunit expression in postmortem brain of normal smokers and non-smokers and in schizophrenic and bipolar smokers and non-smokers. We will also examine the relationship of expression between different receptor subunits to determine whether there are any regulatory effects of one receptor subunit on another receptor subunit. Our Specific Aims will, therefore, address the following questions: 1) What are the effects of smoking on nicotinic receptor subunit protein expression in postmortem brain of individuals with no history of mental illness? 2) What are the effects of smoking on nicotinic receptor subunit protein expression in postmortem brain of individuals with schizophrenia and bipolar disorder? 3) Are receptor subunit levels regulated coordinately in human brain? The results of the proposed research will provide important basic scientific information on any differences in nicotinic receptor composition in mentally ill subjects with the highest levels of smoking incidence. An understanding of this contribution to smoking in this group will further help in the design of appropriate smoking cessation protocols for the mentally ill.

Regulation of Tumor Suppression by TGF-beta in Lung Cancer

Liu, Xuedong
University of Colorado at Boulder

Cigarette smoking is the leading cause of lung cancer and is directly linked to many other types of cancer in our society. TGF-β is a negative growth hormone in mammalian epithelial cells and acts to prevent tumor formation in vivo. The vast majority of human lung cancer cell lines is refractory to TGF-β growth inhibition. They can proliferate even in the presence of TGF-β. Acquisition of TGF-β resistance appears to be a relatively late event in the progression to malignancy. Immortalized but nontumorigenic lung epithelial cells remain sensitive to TGF-β but tumorigenic cells usually overcome TGF-β growth restriction. P27Kip1 is another tumor suppressor. It functions as a break to halt the progression of the cell cycle. In tumor cells the levels of this inhibitor are usually deregulated. In lung cancer cells and samples from lung cancer patients, the levels of p27Kip1 are reliable indicators for tumor progression. In aggressive tumorigenic lung cancer cell lines or primary tumors from the patients, p27Kip1 is destabilized and the steady state levels of the protein are low. This configuration projects a poor survival rate for cancer patients. There appears to be a good correlation between TGF-β resistance and p27Kip1 levels. How these two physiological processes are linked has yet to be explored. In this proposal, we are going to study whether growth hormone TGF-β prevent tumor formation by setting a proper concentration of p27Kip. We want to understand how TGF-β achieves this function and apply the breaking mechanism to prevent runaway proliferation of normal cells. In addition, we want to know how this breaking mechanism was disabled in lung cancer cells. Understanding these connections and controlling mechanism will not only help us to achieve accurate prognosis of lung cancer but also may contribute to develop new therapeutics for treating lung cancers.

Health Effects of ETS in Urban Minority Children With Asthma

Rabinovitch, Nathan
National Jewish Medical and Research Center

One of the major triggers for asthma in school children is exposure to environmental tobacco smoke. This is a particularly important problem in the urban-poor population where asthma is more severe and smoking is more common than in the general population. Because nicotine-containing products are addictive, parents have difficulty with smoking cessation and try alternative strategies. These include smoking when the child is not home, smoking outdoors, and decreasing the number of cigarettes smoked per day. However, it is unclear whether any of these intermediate strategies truly have benefit and result in decreasing a child's asthma symptoms.

This study will assess the effect of smoking in a population of urban-poor mostly African-American children with difficult to control asthma. These children attend the Kunsberg School affiliated with National Jewish Medical and Research Center. This study will evaluate if decreasing, but not eliminating, tobacco smoke exposure has any impact on an asthmatic child's health. Using state of the art technology, which measures and monitors both the levels of tobacco smoke in the home and how much smoke is breathed by the child, the effects of changing smoking behavior will be evaluated.

In this study, we will characterize how various smoking behaviors affect tobacco smoke exposure levels. We will explore the mechanism by which ETS affects the airways in asthma and try to identify individuals with clinical sensitivity to the effects of ETS using markers of airway inflammation. Finally, we will attempt to quantify the acute and chronic health effects of acute ETS exposure on lung function and asthma severity. By implementing environmental measures to reduce ETS levels, we predict that we will decrease the frequency of exacerbations and reverse the known effects of ETS on asthma severity.

Zebrafish - A Model for Nicotine Developmental Toxicity

Tanguay, Robert L.
University of Colorado Health Sciences Center

A significant and increasing number of women smoke during pregnancy. Exposure of the developing fetus to nicotine from the maternal serum has been linked to a number of physical and abnormalities including; an increase in induced abortions, low infant birth weights, increased need for neonatal intensive care units, perinatal disorders and deaths. Furthermore, there is also increased concern that fetal exposure to nicotine is also associated with significant cognitive, intellectual and behavioral impairments. At this time there is a gap in our understanding of precisely how nicotine leads to these serious pregnancy complications. If we could determine the mechanisms by which nicotine causes toxicity, it may be possible to detect and prevent some of the effects of fetal nicotine exposure.

Developmental toxicology studies cannot be conducted in human subjects, and many of the common experimental models are hampered by overly complex central nervous systems making relevant whole animal toxicology experiments impossible. Zebrafish, a small fresh water fish, possess many unique characteristics allowing for rapid and informative whole animal studies. Although a fish, zebrafish share many cellular, anatomical and physiological characteristics with humans, making them an excellent alternative research animal. The goal of this project is to firmly establish zebrafish as a vertebrate model to understand the molecular mechanism of nicotine-mediated neural toxicity. It must be emphasized that individual genes and pathways are very well conserved between zebrafish and humans. As a first step, it is necessary to characterize the morphological and behavioral consequences of nicotine exposure during zebrafish embryonic development.

The goal of this study is to establish zebrafish as an alternative vertebrate research model to better understand how nicotine alters central nervous system development and function. Specifically, we propose to: 1) determine the stage of early development most sensitive to nicotine; 2) evaluate zebrafish behavior altered by nicotine, 3) characterize the impact of nicotine on early central nervous system development; and 4) investigate possible mechanisms to explain how nicotine causes behavior and nervous system deficits.

We believe that the results of these studies will firmly establish the zebrafish as an alternative research model to further our understanding of the molecular mechanism(s) and causes of nicotine-induced neuronal damage. Development of this research model will allow for rapid gene discovery that could lead to new insight about prevention and treatment of nicotine-induced neural injury in humans.

MATE: Media and Tobacco Education

Walkosz, Barbara J.
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Children today live in a media saturated environment spending an average of 6.5 hours per day or 40 hours per week, the equivalent of a full-time job, interacting with a wide range of media. The mass media play a significant role in the promotion of smoking to children. Today, smoking is prevalent in popular films and music videos, and exposure to these smoking images has been identified as a contributor to adolescent decisions to smoke. The power of smoking imagery in films comes from the fact that it occurs in a context that is not regulated and takes place in a setting in which actors, who are often powerful role models for young children, portray smoking as a normal part of their lives.

In order to help children learn strategies to counter the smoking images found in popular culture, Project MATE will develop, evaluate and test a theoretically-based media literacy program. Media literacy emphasizes the skills of analyzing, evaluating, and creating media messages. In the context of public health prevention programs, this approach is particularly salient because the opportunity exists to teach children critical thinking skills related to their health choices. Further, Project MATE addresses the cultural environment in which children spend large amount of their time and which can exert a strong influence on their lives.

A web-based interactive multimedia program, which has been found to be highly engaging and effective in educational settings, will be used to deliver the MATE curricula. The education modules are designed to help children: (1) understand the pervasive role of media in their lives; (2) recognize how persuasive messages about smoking imagery are presented in media narratives; (3) realize how film makes smoking look desirable; and, (4) understand media production choices and techniques.

Very few scientific, controlled studies exist to support the efficacy of media literacy programs. Thus, programs such as MATE can contribute to our understanding of how to address the influences on children's decisions to use tobacco.

Nicotinic Receptor Mediation of Anxiety and Cognition

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Recent data indicate that more than 70% of the young people in the United States experiment with tobacco (Kandel et al., 1997). Similar data were reported during the 1960's and 1970's when approximately 60% of "adult" males and 30% of adult females were smokers. In contrast, recent analyses indicate that less that 30% of adult Americans of both sexes use tobacco today. These findings indicate that the dramatic decrease in tobacco use seen in the last 30 years is largely due to an increase in the number of people who have stopped smoking

rather than to a decrease in the rate of initiation. Therefore, gaining an understanding of those factors that regulate the initiation of tobacco use may be of vital importance for making progress in minimizing tobacco-related health problems. One of the major problems that have kept us from understanding why tobacco is addicting is we do not have a clear understanding of why tobacco (nicotine) is reinforcing. Many drugs that are addicting, including nicotine, stimulate the release of the neurotransmitter, dopamine in brain. Nicotine, unlike other psychostimulants such as cocaine and the amphetamines does not induce euphoria, which is believed to be a consequence of increased dopamine release in brain areas such as the nucleus accumbens. Smokers rarely report a euphoric effect following tobacco use. Instead, they frequently claim that tobacco has emotional calming effects (witness the huge jump in tobacco sales in New York City in the weeks after 9-11-01) or that it helps them to concentrate (e.g. the increased use of tobacco by college students during final exams). The studies outlined in this grant proposal have as their major goals establishing whether nicotine does, indeed, have emotional calming effects (reduces anxiety) and whether it enhances concentration (increases attention, learning, memory, cognition). The studies will use several genetic strategies, in part because studies with humans indicate that genetic factors are of importance in regulating the transition from experimentation with tobacco to addiction to tobacco.

IDEA Projects

Candidate Genes for Tobacco Use and Nicotine Dependence

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There is strong scientific evidence that patterns of tobacco use are due to a combination of environmental and heritable factors. This project is focused on finding genes that may contribute to risk factors for tobacco use and nicotine dependence. It will involve looking at differences in two genes in an older adolescent sample that has been interviewed about their smoking histories. These two genes have been studied in mouse models related to nicotine and it will be important to uncover whether they may be important in humans. In mice with mutations in one of the genes, the alpha 4 nicotinic receptor, the animals display more anxiety and are able to be settled more easily when given nicotine than are mice without the mutation. Different mice, that are missing a gene, protein kinase C gamma, exhibit more impulsive behaviors than mice that have the gene. In humans, impulsivity is thought to be one personality trait that may influence whether or not adolescents try tobacco, so it is possible that DNA variations in the protein kinase C gamma gene in people may be related to an adolescent starting smoking. Similarly, differences in the alpha 4 nicotinic receptor gene, believed to be important in the brain's responses to nicotine, may contribute to a person's risk for becoming addicted to nicotine. This study will look to see if there is a correlation between a specific form of the protein kinase C gene and the age at which kids start smoking. For example, if adolescents with form "A" of the gene are more likely to try smoking at a younger age than kids with a different form "B", this may indicate that the protein kinase C gene is contributing to an impulsive personality trait that leads to experimenting with cigarettes. Secondly, this project will also examine only adolescents who already smoke. Some of these smokers display symptoms of dependence on nicotine, while others do not. It is possible that differences in the alpha 4 nicotinic receptor gene may influence whether a smoker is easily addicted or not. Therefore, different forms of the alpha 4 nicotinic receptor gene will be examined to see if one form is highly correlated with nicotine dependence. The results from this study may help with the identification of kids who are at risk for smoking and subsequent dependence on nicotine, in addition to contributing to understanding of potential mechanisms of nicotine action in the brain, which may aid in the development of stop smoking treatments.

Tobacco and Gene Expression

Hanneman, William H.
Colorado State University

The Surgeon General of the United States has identified the consumption of tobacco products as the number one cause of preventable disease in America. The list of those diseases includes cancer, heart disease, lung disease and birth defects. Understanding how tobacco products cause disease and addiction is one of the most important current medical research challenges.

Cigarette smoke contains over 4,000 known chemical compounds. Because of this, it's no wonder that exact cause of disease and addiction has never been determined. Some of theses known compounds have been previously shown to cause cancer in laboratory animals at very low doses. Moreover, at least one of the known compounds (nicotine) is associated with addiction to tobacco products. The fact that not all tobacco users develop cancer or heart disease is most likely due to the genetic diversity of the general human population. That is to say, for the same reason that each person looks, talks or acts differently, each person may respond differently to the complex mixture of chemicals in cigarette smoke or tobacco extract. This underlying difference between people is most often attributed to "their genetic make up" and is stored in DNA. Since the exact information (genes) contained in DNA is what differs between people, this information in part is what governs how a person responds to tobacco products and other poisons.

In light of these facts, the goal of our research is to better understand how cigarette smoke alters gene expres-

sion and thus causes disease. Specifically we propose to monitor gene expression changes in a very specialized cell known as embryonic stem (ES) cells. These cells are unique in that they express not only those genes present during adulthood, but also those genes that may be transiently expressed during development. The basic idea of our research is to insert (transfect) these cells with a promoter-less reporter gene construct. Successful transfection of a cell will knockout the endogenous gene and the reporter gene will be activated and under the control of the "trapped" endogenous promoter. Utilizing this technique, large numbers of unique "gene-trapped" ES cell clones will be screened in the presence or absence of cigarette smoke condensate (CSC), and altered reporter gene expression will be identified. The reporter gene itself will then be used as the starting point for sequencing those endogenous genes. Sequences will be compared to those in public gene expression databases (i.e. the product of the complete sequencing of the human genome) to identify novel genes as well as previously known genes that were unknown to be altered/dysregulated by tobacco. Knowing what genes are affected by exposure to these chemical compounds is fundamentally important to human health. These studies will pave the way for a greater understanding of how tobacco products cause disease.

Novel Polymer-Drug Conjugates for COPD Therapies
Stansbury, Jeffrey W.
University of Colorado Health Sciences Center

In the U.S. alone, smoking related diseases such as emphysema and chronic asthma cause progressive deterioration of lung function in millions of patients and result in approximately 100,000 deaths each year. Respiratory tract diseases, such as inflammation of the airways (known as chronic obstructive pulmonary disease, COPD), are often difficult to treat since the ongoing nature of the symptoms requires continual administration of drug compounds designed to help open the airways and treat the problems associated with inflammation in the lungs. The drugs involved are not well tolerated when applied throughout the body, as is the case when the drug is taken in pill form. Efforts to introduce these drugs directly into the lungs by inhalation therapy have met with more success but there are complications here as well. The drugs are small molecules that are rapidly transported into the bloodstream when applied in the lungs. This aspect minimizes the selectivity of the inhalation-based drug delivery mode. Advantages in the use of polymeric matrices for the introduction of therapeutic agents in the body include the potential to target drug release sites and to provide sustained release of the required drugs. The investigation proposed here involves the development of a new polymer to carry the drugs to the lungs and then release them there at concentrations that would minimize their systemic presence. This requires the preparation of polymer particles that are small enough to be used in inhalation therapy but large enough not to pass into the bloodstream when introduced into the lungs. The novel approach here to be demonstrated is that the construction of the polymeric carrier and the attachment of the drug molecules to the polymer are both based on the use of linkages that will decompose under the conditions present in the lungs. Thus, in a controlled manner, the relatively large polymer particles will breakdown to much smaller segments that can be eliminated from the body. The release of the bound drug molecules will also coincide with this degradation process, which will provide a stable concentration of drug being delivered at the site it is required over a prolonged period. While polymers are often used in drug delivery applications, the proposed research will give access to a new and highly versatile class of polymers that can readily be tailored to meet specific property and performance needs.

Postdoctoral Fellowship

Regulation of Cell Division by mMps1/TTK in Lung Cancer
Mattison, Christopher P.
University of Colorado at Boulder

Every time a cell divides it must equally distribute exactly one copy of its DNA to each cell. Defects in the distribution of DNA during cell division are strongly correlated with the development of cancer. Therefore, investigating the mechanism by which cells ensure proper distribution of DNA during each round of cell division will help us to better understand how cancer arises.

The cellular structure that is used to equally distribute DNA to each cell during division is termed the mitotic spindle. Proper formation of the mitotic spindle and distribution of DNA requires the duplication and assembly of a set of proteins (collectively known as the centrosome) once and only once per round of cell division. Defects in the duplication of centrosomes lead to the uneven distribution of DNA to dividing cells, and this is a hallmark of cancer.

Several components of centrosomes have been identified and characterized. One of these, the Mps1 protein, is unique in that it functions to regulate centrosome duplication and can also act to halt cell division if the mitotic spindle is damaged or formed incorrectly. The Mps1 protein is found in many diverse organisms including yeast, mice, and humans, and has similar functions in these different organisms. One goal of my proposal is to better characterize the important features of the mouse and human Mps1 proteins, mMps1 and TTK, respectively. A second goal of my proposal is to identify human lung cancers that contain mutations in the TTK gene, and characterize the effect these mutations have on cell division and distribution of DNA. This work will allow a more thorough understanding of how this important pro-

tein functions to control centrosome duplication and regulates the ability of cells to sense and adjust to mitotic spindle damage. Both of these processes are linked to cancer, and therefore this study may allow us to better understand how lung cancer arises.

Dissertation Awards

Biomarkers of Smoke-Induced Lung Cancer in a Mouse Model

Peebles, Katherine A.
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Lung cancer is a leading cause of death in the United States. The death rate due to this disease outstrips the combined rate due to pancreatic, breast, and prostate cancer. Efforts to discourage smoking, the major cause of lung cancer, have not been successful. Cancer is easier to cure at early stages of disease, but unfortunately lung cancer is only detected at very advanced stages. Finding a clinical test for early detection would increase survival.

To detect cancer in internal organs before large tumors develop, one needs a biomarker. A biomarker is a small molecule that is easily detectable in biological samples, like blood, that can be obtained without invasive procedures. Molecules can be considered useful biomarkers only when they are negligibly present if a person does not have cancer but present in high amounts at early stages of cancer. Upon detection of the biomarker, treatments would be initiated much sooner, greatly increasing the patient's chances of survival. Biomarkers for early detection of lung cancer do not exist.

Researchers are currently investigating a protein called heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNP A2/B1) for predicting lung cancer development when it is found in cells from phlegm recovered when a person coughs. Early work suggests that hnRNP A2/B1 may be an excellent biomarker for lung cancer. Its amount is increased and its cellular distribution changed only in people who will develop lung cancer. Little is known about how these changes occur. This knowledge would help researchers design more successful therapeutic strategies. If these changes are actually important in the development of lung cancer from normal tissue, researchers can develop drugs that interfere with A2/B1 activity. This will provide more targets for therapeutic intervention.

Many questions about A2/B1 cannot be answered by human studies. Using a mouse model of lung cancer, I will determine the basis of these A2/B1 changes. Proteins are produced by transcription, in which RNA is made, and translation, in which proteins are synthesized from the information coded in this RNA message. The amount of a protein that is present in a cell depends both on the amounts of RNA message and protein and how long each molecule exists before it is destroyed. This research will determine how these processes are altered for hnRNP A2/B1 in cancerous lung cells. Often cells that are mutated and dividing quickly, called hyperplastic lesions, disappear instead of becoming a tumor. I will determine whether hnRNP A2/B1 can predict which hyperplastic lesions develop into tumors and which regress. This work will help us to understand lung cancer and ultimately find a cure.

Motivational Orientations and the Smoking Cessation Process

Perrine, Nicholas E.
Colorado State University

Current formal smoking cessation programs (or treatment programs) use a "one size fits all" approach. This means that all smokers who seek treatment are assigned to the same type of treatment program. Health professionals and scientists have suggested that this "one size fits all" approach may limit the ability of some smokers to effectively quit. The current proposal plans to investigate how a smoker's personality (specifically their motivational orientation) influences the smoking cessation process. People who are motivated by challenging tasks that require large amounts of effort are considered to have a learning motivational goal orientation. Typically, learning-oriented people are driven to master tasks and find learning more about how to better complete a task to be rewarding. People who are motivated by proving to themselves and others that they can complete a task or challenge with very little effort are considered to have a performance motivational goal orientation. Performance-oriented people are motivated by favorable comments from others concerning their ability to perform well at a task without much effort and withdraw from tasks that require large amounts of effort (Button, Mathieu, & Zajac, 1996; Dweck & Legget, 1988). Results from the currently proposed study are expected to indicate whether smokers with different motivational goal orientations are better able to quit when operating in environments with different reward structures. The ability of performance-oriented smokers to quit is expected to be highest in the short-term when performance-oriented smokers receive constant tangible rewards from their environment (e.g., money, food, and verbal praise for quitting). The ability of learning-oriented smokers to quit is expected to be highest in the long-term when learning-oriented smokers receive feedback and rewards that they are indeed successfully learning to quit smoking. Further, motivational goal orientations are predicted to influence how a smoker responds to a lapse (e.g., smoking a cigarette after quitting). At least 80% of people who are attempting to quit smoking with the use of formal treatment programs experience a lapse within one year of quitting (Lando, 1993). Responses to lapses are so critical because the majority of smokers experience a slip when trying to quit. Learning-oriented smokers are predicted to respond more positively to a lapse when quitting (e.g., the slip was a learning experience). In general, after expe-

riencing a lapse learning-oriented smokers are expected to proceed to long-term abstinence (i.e., no longer use cigarettes), while performance-oriented smokers are expected to return to original rates of smoking prior to entering a formal treatment program. Results from the current proposal are expected to shed light in two specific ways as to how health professionals within the state of Colorado as well as across the nation may be better able to aid smokers in quitting. First, health professionals would be able to assign smokers to treatment programs that employ reward structures that are consistent with a smoker's motivational goal orientation. Effective treatment matching would increase the ability of health professionals to aid smokers in quitting. Second, health professionals would be able to more specifically target those quitting smokers who are at risk for negative responses to lapses.

Combined Effects of Alcohol and Nicotine

Peters, Annie R.
University of Colorado at Boulder

Alcohol and tobacco are very commonly used together, even by people who do not consider themselves to be regular smokers. The reasons for this phenomenon, however, have not been established. According to those who do smoke cigarettes when they drink alcohol, there is something particularly rewarding about using these two substances in combination. This study examines several possible hypotheses for this occurrence. First, both alcohol and smoking individually have been shown to improve mood, so the combination of these two substances may have an additive positive emotional effect. A second possible hypothesis for use of alcohol and tobacco together involves negative physical effects of alcohol. Smoking after drinking may reduce feelings of fatigue and sluggishness that frequently accompany alcohol use. Thus, these two substances may be used together so frequently because each drug counteracts the negative effects of the other, allowing only the positive effects of both drugs to be experienced. A third hypothesis is that smoking may improve clarity of thought that is impaired by drinking alcohol. Alcohol is known to reduce certain cognitive abilities, including memory and attention, while nicotine has been found to improve these abilities. Thus, smoking while drinking may serve to counteract cognitive impairment that may occur due to alcohol use. This study will examine all three of these hypotheses. Mood, physical stimulation, and certain thought processes will be measured before and after subjects drink alcohol and smoke a cigarette. Thus, we will obtain important information concerning possible biological and psychological motivations for the common use of these two substances together.

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