

Materials

Tobacco - Program and Budget



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

July 11, 1997

TO: Harold Varmus, M.D.
Director, NIH

FROM: Director, NCI

SUBJECT: Tobacco-Related Biomedical Research Trust Fund

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Goal:

The goal of this research Trust Fund is to provide substantial funding to allow the Nation to make progress towards reducing the burden of tobacco and tobacco-related disease via:

- a) Research into the use and direct effects of tobacco and tobacco products
- b) Research into reducing the burdens of tobacco-related diseases

Size of the Trust Fund:

In order to make a significant and sustained impact towards reducing the terrible toll exacted by tobacco use and addiction, we need to provide an amount of research funding commensurate with the enormous burden of disease and disability that tobacco causes. If we assume that 20 to 25 percent of the death and disability in this country can be related to tobacco and that our current investment in research aimed at alleviating all disease is approximately \$13 billion. We estimate a need of approximately \$3 to \$3-1/2 billion per year.

Principles:

- a) This Trust Fund should provide for a stable source of funding over long periods of time. For that reason, we propose a mechanism whereby the principal of the Trust Fund is able to be invested so that the income on the investment grows in order to provide \$3+ billion a year in stable research funding. The stability for the long-term investment that will be required should entail a protection of the principal, once the fund reaches the capacity to sustain a steady state funding level. Details of the rate of growth and disbursement of funds will require further modelling to achieve the funding goals.

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- b) The Trust Fund should be used to address the full range of tobacco-related and tobacco-related disease research and the research must be of high quality. To optimize the assurance of high quality and so as to not reinvent funding mechanisms, the Trust Fund income should be funneled through the US Government to be further distributed among well established research structures within the government, including NIH, CDC, AHCPR, VA, etc.
- c) In order to assure that the funds are used to achieve an agreed upon program of tobacco-related and tobacco-related disease research activities, an independent periodic review and set of programmatic recommendations should be made by a disinterested body of experts convened by a neutral entity such as the National Academy of Sciences. A three-year review would provide an evaluation of the fund activities and recommend how the funds should be distributed across programs, scientific and medical needs and opportunities, as well as across agencies. Such a regular review should assure the public of the proper use of the funds.
- d) There should be a separate and distinct accounting of the Trust Fund monies to assure that they represent supplements to the Nation's investment in tobacco-related and tobacco-related disease research activities and that these supplements fulfill the special goals of the Trust Fund.
- e) An attempt should be made to formulate a mechanism to protect the appropriation process for PHS research agencies so that Trust Fund monies do not serve to replace appropriations. For example, no agency can receive monies from the fund in any fiscal year, if they do not receive an appropriation for research equal to or greater than the previous year's appropriation.
- f) A Presidentially-appointed Board of Trustees would oversee the investment and fund disbursement of the Trust Fund monies and assure that the quality control processes for independent review and program recommendations take place. This Board would be responsible for implementing the recommendations of the outside review panel, and charging that panel(s) with future review requirements.

Richard D. Klausner, M.D.

NIH Plans for the Public Health Trust Fund for Research on Tobacco Use and Tobacco-Related Diseases

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I. PREFACE

The NIH mission is to uncover new knowledge that will lead to better health for everyone. This knowledge is aimed at helping prevent, detect, diagnose, and treat disease and disability ranging from rare genetic disorders to the common cold. As part of the fulfillment of this important mission, the NIH conducts and supports a wide variety of research related to tobacco and the diseases to which tobacco contributes. Tobacco-related research is particularly relevant to the missions of certain of the individual Institutes that are components of the NIH. These Institutes are: the National Cancer Institute (NCI); the National Heart, Lung and Blood Institute (NHLBI); the National Institute of Child Health and Human Development (NICHD); the National Institute of Dental Research (NIDR); the National Institute of Drug Abuse (NIDA); and the National Institute of Environmental Health Sciences (NIEHS). The relevance of tobacco to the missions of these Institutes is self-evident given that: 1) tobacco is a major causal factor in the four leading causes of death in the US (heart disease, cancer, stroke, and chronic obstructive pulmonary disease); 2) approximately 90% of adult smokers begin smoking as children, adolescents, or teens; 3) tobacco can have very deleterious effects on children passively exposed in utero and during infancy; 4) tobacco is a contributing factor to several serious oral conditions including cancers; 5) nicotine is a highly addictive drug; and 6) smoke from tobacco is a serious environmental hazard.

Representatives from each of the above Institutes and from the Office of the Director, NIH have contributed to the formulation of this document, which has a three-fold purpose. Firstly, the impact of tobacco on the health of the Nation and the consequent costs will be described. Secondly, the tobacco-related research within the portfolios of each of the Institutes will be briefly summarized. Finally, an attempt will be made to describe the vision of each of the Institutes regarding plans for the utilization of a Public Health Trust Fund (PHTF) that has been proposed as part of the recently announced Tobacco Settlement Agreement. Specifically, examples of the types of expansions of effort that could be enabled by the establishment of the PHTF will be provided in the context of their impact on the ability of the NIH collectively to combat tobacco-related diseases.

While the programs of each of the Institutes will be considered separately in this document, it should be stressed from the outset that tobacco use and tobacco-related disease are considered to be common enemies. While there may be some areas of overlap in the efforts of the individual Institutes to reduce tobacco use and the burden of tobacco-related disease, these are not seen as areas of competition but rather as opportunities for cooperation and collaboration. All of the Institutes that comprise the NIH are firmly committed to improving the health of the Nation. Perhaps nowhere is this resolve more pronounced than in the battle against tobacco use and tobacco-related diseases. The motivational basis of this mutual commitment is summarized in the next section of this document that describes the havoc that tobacco wreaks upon the health of the American people.

II. THE IMPACT OF TOBACCO USE ON THE NATION

This section is arranged as a series of bullet points that describe in various ways the impact of tobacco first in terms of morbidity/mortality and then in terms of the economic costs of tobacco to our society. Individuals are affected variably by these illustrations finding one or another of them to be either shocking or astonishing. Indeed, these descriptions of the impact of tobacco are intended to shock and astonish, because the devastation of tobacco is truly shocking and astonishing.

A. The National morbidity/mortality burden of tobacco use

- Tobacco kills over 430,000 of the US population each year, more than alcohol, cocaine, heroin, homicide, suicide, car accidents, fire, and AIDS combined. This death toll is about equivalent to a no-survivors plane crash with 200 persons on board occurring every 4 hours around the clock every day of the year.
- Tobacco annually kills more Americans than died in all of World War II, 8 times more Americans than died in the entire Vietnam war, 6 times more than die annually in accidents, and 20 times more than are murdered each year.
- During the 1990's tobacco will kill more than 4.5 million American—the equivalent of to losing every man, woman, and child in Portland, OR; Fargo, ND; Flint, MI; Buffalo, NY; Greensboro, NC; Miami, FL; Baton Rouge, LA; Austin, TX; Denver, CO; Berkeley, CA; Salt Lake City, UT; and Cleveland, OH, combined.
- Each day in the US, nearly 3,000 persons under age 18 start smoking. About 18 will someday die from homicide and 35 in car accidents, but 1,000 will die from a tobacco-related disease.
- 5 Million children alive today will die prematurely because of the decision to start smoking as adolescents, and on average, each would live 15 years longer if a nonsmoker.
- Smoking is a major contributor to the top four leading causes of death in the US [Heart Disease, Cancer, Stroke, and Chronic Obstructive Pulmonary Disease (emphysema + chronic bronchitis)].
- Of the smoking-associated mortality each year, approximately 180,000 deaths are from cardiovascular disease, approximately 150,000 deaths are from cancer, approximately 85,000 deaths are from respiratory diseases, nearly 2,000 are deaths among infants, and another nearly 1,400 people die in fires started by smoking.
- Lung cancer is the number one cancer killer in both men and women with over 150,000 in the US expected to die this year alone. Lung cancer kills more than twice as many men as prostate cancer, the number two killer in men and about the same as prostate, colorectal, pancreas, and lymphoma combined. Since 1987, more women have died each year of lung cancer than breast cancer, which for over 40 years, was the major cause of cancer death in women. In 1997, it is estimated that approximately 22,000 more women will die of lung cancer than of breast cancer. Within 5 years, twice as many women will die of lung cancer than of breast cancer.

- Use of smokeless tobacco (spit tobacco) is increasing especially among male adolescents and young male adults with as many as 20% of male high school students having used smokeless tobacco and 6% of males 18 years and older being regular users of snuff or chewing tobacco. In some populations, spit tobacco use is as high as 40%. Smokeless tobacco can cause cancer and a number of other oral conditions with nearly a 50-fold excess risk of cancer of the cheek and gum among long-time users. Smokeless tobacco also contributes to nicotine addiction that may manifest itself in smoking in addition to smokeless tobacco use.

- 9 out of 10 nonsmokers have a detectable nicotine metabolite in their blood indicating recent exposure to cigarette smoke; ~37,000 heart disease deaths and ~3,000 lung cancer deaths each year are due to second-hand smoke; one study indicates that being around people who are smoking, even as little as one hour a day, nearly triples a woman's risk of contracting breast cancer.

- Over 40% of children age 2 mo. to 11 yr. live in a home with at least one smoker; some estimates attribute 10% of all infant deaths to smoking by others; in infants under age 18 months, secondhand smoke is associated with as many as 300,000 cases of bronchitis and pneumonia; as many as 15,000 infant hospitalizations may be linked to second-hand smoke.

B. The National economic burden of tobacco use

- Smoking is responsible for approximately 7 percent of total US health-care costs
- For each of the ~24 billion packs of cigarettes sold each year, over \$2 are spent on avoidable medical-care costs (nearly \$50 Billion in total).
- Between 1987 and 1993, the direct costs of medical care attributable to smoking doubled.
- ~\$27 Billion of these smoking-attributable costs were for hospital expenditures, ~\$15 Billion for physician expenses, ~\$5 Billion for nursing-home expenditures, and ~\$1 Billion for home health-care expenditures.
- Of these costs, over 40% (~ \$20 Billion/year) are from public funds (i.e., Medicare, Medicaid, and other federal and state sources); for those over age 65, public funds accounted for more than 60% of the smoking-attributable medical-care costs.
- Even though they die at earlier ages than non-smokers, the current and former smokers generate an estimated \$500 Billion in excess health-care costs over their lifetimes.
- Each year, decisions by 1 million youth to become regular smokers commit the health care system to over \$8 Billion dollars in extra expenditures over their lifetimes.
- These cost estimates are underestimates in that they do not include burn care from smoking-related fires, perinatal care for low-birthweight infants of mothers who smoke, and medical-care costs associated with disease caused by second-hand smoke.
- Taken together direct and indirect costs of smoking is more than \$100 Billion/year or about \$4 for each pack sold in the US. Each minute, tobacco costs the American people about what we pay our President in salary for a year.

III. NATIONAL CANCER INSTITUTE (NCI)

The National Cancer Institute coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients. Tobacco use is responsible for approximately one-third of all cancers. Foremost among the cancers caused by tobacco is lung cancer, which is the number one cancer killer in both men and women. While certain other factors (e.g., radon and asbestos) have been linked to lung cancer, far-and-away the most significant risk factor is cigarette smoking, which has been linked to about 90% of lung cancer cases. Over 500,000 cases of lung cancer are anticipated in the US in 1997 with over 90,000 men and over 60,000 women expected to die of the disease in this year alone. Lung cancer is among the most tragic of cancers in that it is largely preventable, and once contracted, current interventions are of very limited efficacy with 5-year survival of all stages combined being only 14%. In addition to lung cancer, mortality attributable to current and past tobacco use has also been linked to cancers at other sites including lip, oral cavity, pharynx, esophagus, pancreas, larynx, trachea, cervix uteri, urinary bladder, and kidney. Cancers at several other sites have also been suggested to be linked to tobacco use and these putative associations are currently under study.

The exposure to the cigarette smoke of others is also a significant issue. It has been estimated that 3,000 lung cancer deaths each year are attributable to exposure to the smoking of others (secondhand smoke). One recent study indicated that an exposure to even as little as one hour per day of secondhand smoke resulted in a nearly triple increase in a woman's risk of contracting breast cancer.

The NCI has been and will remain committed to reducing the burden of all cancers. In this document, the current portfolio of tobacco-related research supported by the NCI will be briefly summarized. In addition, examples of the types of research that could be enabled by the PHTF will be provided. The PHTF will represent a truly unique source of funding for cancer research. In planning for the use of these supplemental resources, the NCI believes that "big thinking" should prevail. Projects of a National scope whose sheer magnitude has previously taken them off our radar screens (because of funding limitations) ought now to be reconsidered. The NCI herein provides some examples of such projects. These include:

- Markedly increased funding for investigator-initiated tobacco-related research
- Expanded participation in clinical trials relevant to tobacco-related cancers
- Prevention of tobacco-related cancers for 45-50 million former smokers
- Development of preclinical models for tobacco-related cancers
- Exploration of cancer susceptibility and gene-tobacco interactions
- Improved early detection and diagnosis of tobacco-related cancers
- Improved National surveillance of tobacco-related cancers
- Improved communication about tobacco-related cancers and interventions

A. Tobacco-Related Research of the NCI

In FY96, the NCI supported a variety of research efforts related to tobacco and tobacco-related diseases. Smoking and health research totaled \$82M in FY96, which included behavioral research related to smoking, research related to smokeless tobacco, and the ASSIST program. Foremost among cancers caused by tobacco is lung cancer where

about 90% of cases are a result of exposure to primary or secondhand tobacco smoke. In FY96, the NCI sponsored over 500 grants with relevance to lung cancer (the actual degree of relevance to lung cancer varies from project to project as evaluated by the NCI), and the lung cancer portfolio of the NCI totaled approximately \$119M. In addition to lung cancer, mortality attributable to current and past tobacco use has also been linked to cancers at other sites including lip, oral cavity, pharynx, esophagus, pancreas, larynx, trachea, cervix uteri, urinary bladder, and kidney. In FY96, each of these cancer sites was the subject of NCI-sponsored research; research support for head and neck cancer totaled ~\$35M; bladder cancer studies totaled ~\$15M; kidney and urologic disorders totaled ~\$11M; esophageal cancer studies totaled ~\$7M; pancreatic cancer research totaled ~\$8.5M; larynx cancer research totaled ~\$1M; cervical cancer and uterine cancers research totaled ~\$60M. Cancers at several other sites have also been suggested to be linked to tobacco use and these putative associations are currently under study. The scope of NCI-sponsored projects in all of these cancers encompasses basic research at the molecular level, clinical and behavioral research, chemoprevention, surveillance and epidemiology, and applied research at the community level.

Categories of research supported, and examples of tobacco-related research within each category, include:

- Molecular/Genetic Studies (e.g., Carcinogen metabolizing enzymes and head and neck cancer; Molecular epidemiology of lung cancer; Genetic analysis of transformation of human fibroblasts; P53 marker for oral cavity premalignancy and cancer risk)
- Tobacco-Related Carcinogenesis Studies (e.g., Mechanisms of bladder tumorigenesis; Isothiocyanates and nitrosamine carcinogenesis; Experimental tobacco carcinogenesis; Dibenzo(A,1)pyrene - tumor initiation and promotion)
- Chemoprevention Studies (e.g., Chemoprevention of aerodigestive epithelial cancers; Phase II trial of Anetholtrithione (Sialor); Lung cancer chemoprevention program; Preclinical toxicology of chemopreventive agents; Chemoprevention of head and neck cancers)
- CARET - Carotene and Retinol Efficacy Trial
- Epidemiology Studies (e.g., Ecogenetic study of lung cancer in minorities; Genetic and environmental risk factors for bladder cancer; Epidemiology of glutathione transferase and lung cancer; Determinants of teenage smoking behavior; Occupation, ETS, and lung cancer in nonsmoking women)
- Clinical Intervention Studies (e.g. Smoking cessation, weight gain, and exercise in women; Indigent care hospital-based smoking cessation program; Smokeless tobacco - nicotine patch and self-help treatment; Reducing maternal smoking at the pediatric health visit; Interactive videodisc smoking cessation intervention; Effectiveness of nicotine patch adjuvants)
- Community Intervention Studies (e.g., Smoking prevention through a combined mass media and school program; Strategies for smoking cessation among low-income women; Legal interventions to reduce tobacco use; Mediators of worksite cancer prevention effectiveness; Tobacco farmers and tobacco control; Effectiveness of community initiatives to limit teenage access to tobacco)

- ASSIST - American Stop Smoking Intervention Study for Cancer Prevention (a trial of a protocol developed by NCI to reduce mortality from cancer caused by tobacco involving more than 6,200 organizations in 17 states)
- PLCO Screening Trial (a health study involving 150,000 Americans to determine whether screening tests for prostate, lung, colorectal and ovarian cancers will reduce the number of deaths from these cancers)

B. NCI Plans for Expanded Tobacco-Related Research

An especially exciting prospect of the establishment of the PHTF is the ability to reach significantly beyond the types of research efforts that are possible under current funding limitations. It is to this prospect that the remainder of this document will be addressed. Each of the sections that follow represent projects whose sheer magnitude has previously taken them off our radar screens because of funding limitations. If the PHTF materializes, these projects of truly National scope would be enabled. These include:

1. Markedly increased funding for tobacco-related research

The PHTF with an appropriate level of funding would enable significant expansion of the approaches already included in the NCI's portfolio. The NCI holds investigator-initiated research as one of its highest priorities. However, current funding limitations restrict the number of meritorious grant applications that can be funded. The NCI currently has a success rate for grant applications of approximately 25%, and has made as one of its goals to raise this success rate to at least 40%. It has been anticipated that the process of accomplishing this goal would take several years of incremental increases in Congressional appropriations. The PHTF would enable the NCI to more rapidly increase the success rate for tobacco-related research. This would be accomplished through a series of carefully considered Request For Applications (RFAs) and through increased funding levels of investigator-initiated grant applications in this area. An innovative tobacco control research program is essential to guide new policies, regulations, and programs supported by public and private funds. Research must address issues at the national, state, local, and individual level, and must include studies of adult tobacco use and its impact on youth. Of particular urgency is the need for science-based information to inform federal and state policies and programs that are under development. Research is also needed to guide the public education campaign, the use of smoking cessation trust funds, and required changes in the corporate culture of the tobacco industry. Studies that span the spectrum from basic through applied research are needed. A comprehensive tobacco control research portfolio will contribute to real reductions in tobacco use only if it is linked closely to ongoing and expanded intervention programs.

With resources from the PHTF, the NCI would immediately propose to institute an exceptions program for grant applications relevant to tobacco and tobacco-related diseases whereby applications outside the NCI payline would be eligible for funding if their peer review priority score were within the top 40th percentile (for R01 applications). Analogous increases via exception funding would be formulated for non-R01 granting mechanisms (e.g., P01). These increased resources would enable research that would include an increased investment in basic research aimed at understanding tobacco and the biological mechanisms underlying the cancers caused by tobacco. One of the metrics by which progress in the fight against cancer is measured is an increased knowledge about cancer. Common sense would

Indicate and experience has proven that knowing the enemy is a key feature of a successful engagement.

The PHTF could also fund increased investment in methodologic and behavioral research to clarify the most promising research designs and strategies for prevention and cessation of tobacco use, particularly in populations where tobacco use has remained high, e.g., adolescents, women, certain special populations, and among those with less education and income. A comprehensive program aimed at tobacco control research would include new research aimed at understanding the initiation of tobacco use and nicotine addiction. Studies must also address questions related to racial, cultural, and gender influences in youth tobacco use including the impact of new, proposed, and future tobacco product regulations. It will be critical to assess via research the impact of new tobacco products ("less hazardous tobacco products" on initiation and cessation rates prior to the marketing of these products). While many teenage smokers have tried to stop, most do not succeed. Research is desperately needed to guide interventions in this important field. Clinical studies are needed to develop new treatment regimens including pharmacological studies of nicotine delivery devices and other drugs either separately or in combination with a variety of behavioral interventions. It will also be critical to assess the success of intervention programs and to develop the methodologies for this assessment. Using methodology developed as part of the NCI's ASSIST program allows the relative contributions of regulatory and program interventions to changes in tobacco use to be assessed. As new interventions are developed, new assessment tools will need to be developed in concert.

2. Expanded participation in clinical trials relevant to tobacco-related cancers.

For more than 30 years the NCI has supported a successful cooperative multicenter trials program in treatment and, more recently, in prevention. Operating at hundreds of sites in North America, NCI's cooperative groups have generated much of the evidence on which the practice of oncology is now based. It is also currently the platform for two very large trials aimed at the prevention of breast cancer and prostate cancer, respectively. The clinical trials program has always paid close attention to tobacco-related cancers, and active programs for cancers of the lung, bladder, head and neck, esophagus, kidney, and pancreas have been in place for years.

Some of the anatomic sites at risk from tobacco present special opportunities for intervention. The bladder mucosa is an ideal site for regional therapy with chemicals or biologicals, and indeed topical therapy with chemotherapeutic agents or BCG has been the mainstay of therapy for bladder papillomas. It may be that antisense compounds mirroring the genetic sequence of certain key cancer-causing genes will be useful therapeutic agents here. Photodynamic therapy—a new way of sensitizing cells to visible light—has potential usefulness for thin layers of premalignant epithelial cells covering the surface of the mouth or esophagus.

For early diagnosis and detection, NCI is moving forward to establish a multicenter trials network for diagnostic imaging. This network will incorporate centers of excellence in imaging research and practice throughout the country and will collaborate with the imaging device industry and with third-party payers to accomplish the rigorous clinical assessment of technological innovation. We expect that anatomic sites affected by tobacco will receive significant emphasis.

To meet these challenges, we must have a clinical research base that can bring the best of

our emerging knowledge about tobacco-related cancers along with the best ideas, best technologies, and best people to the problems of prevention, detection, diagnosis, and treatment of these diseases. It is dismaying that only about 2% of adult cancer patients participate in clinical trials. The reasons for this low participation are complex including issues related to our society's health care system as well as issues related to the perception of the public regarding clinical research. The NCI would like to see all eligible cancer patients participating in clinical trials. Accomplishing this very ambitious goal will involve utilizing considerable resources to lower the barriers to participation. This will include "user-friendly" access to information about clinical trials as well as additional financial support for clinical trials. The resources of the PHTF would enable these barriers to be lowered on a time-scale that would otherwise be impossible.

3. Prevention of tobacco-related cancers for 45-50 million former smokers

About half of all living Americans who ever smoked have quit. Yet premature deaths from smoking will continue for many years to come, even if all smokers were to quit today. Heavy smokers retain some elevated risk for lung cancer when compared to never-smokers, even after 20 years of cessation. More than 50% of lung cancers diagnosed in the late 1990's occur in ex-smokers. Thus, the 45 to 50 million Americans who are former smokers are a population that could benefit greatly from chemoprevention research. They already have taken a major step toward improved health, but require new medical options to gain full advantage from this step.

Previous clinical studies have defined high-risk populations that should facilitate future detection and prevention trials. For example, lung cancer patients with completely resected stage I disease are at particularly high risk for second primary lung cancers. To a lesser degree, the 45-50 million ex-smokers represent a pool of high-risk individuals. The large population of former smokers in the Department of Defense, Veterans Administration and managed care systems makes access to individuals for clinical trials in prevention possible.

Promising preventative interventions (e.g., vitamin A analogs, selenium, non-steroidals and specific growth pathway inhibitors) are ready for testing. Prevention studies using aerosolized delivery of new targeted therapies including gene therapies, antisense therapeutics, and targeted small molecules will also need to be conducted. Key to these studies will be the identification and validation of intermediate biomarkers that will be used to define the activity of new preventative interventions. The research that underlies an undertaking of this magnitude is significant. The trials themselves will be massive and expensive to conduct. The PHTF offers the opportunity to move these efforts onto the fast track. Given current funding limitations, this would not be possible otherwise.

4. Development of preclinical models for tobacco-related cancers

For clinical trials to have a good chance of success, the interventions being tested in them should have to pass stringent tests in the laboratory that suggest they might work. For these laboratory tests to be valid predictors of what will happen in people, the laboratory models must be accurate mimics of human disease. For cancer this means that laboratory cancers should bear fairly close resemblance to human cancer in their molecular characteristics. The failure of some large clinical trials is attributable, in part, to the lack of predictive laboratory models for human cancer. Most current animal models have not proven of much utility in tobacco and smoking investigations, despite studies confirming the development of cancer in

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beagles chronically subjected to tobacco smoke. The use of dogs as routine models in cancer prevention studies (other than toxicity studies) has been very limited because of availability, and costs associated with purchase and maintenance. More recently, the exposure of certain rodents to specific tobacco smoke ingredients has resulted in lung cancer development. New animal models including an orthotopic lung cancer model which metastasizes in a pattern similar to that in humans may provide the means to study new preventative, diagnostic, and therapeutic approaches to lung cancer.

Biological advances have changed the prospects for developing such models, and it is now possible to engineer cells or even whole animals to have certain genetic properties that are desirable in cancer models. Much more work is needed to develop and refine preclinical models of the major tobacco-related cancers, so that clinical work in both prevention and treatment can proceed with a higher probability of success. The PHTF would allow for increased investment in the development of improved animal models for tobacco-related carcinogenesis including intermediate biomarkers for assessment of exposure to tobacco and the biological effects of such exposure with validation these models in parallel studies in animals and humans. It is also possible to use non-mammalian organisms to study the basis of tobacco-related carcinogenesis. The NCI would like to sponsor studies to determine whether metabolic pathways in "simple organisms" (e.g., *C. elegans*, *Drosophila*, *Xenopus*, Zebrafish, yeast, etc.) that are analogous to those involved in human cell transformation can be exploited in drug discovery for tobacco-related cancers. It may also be possible to study chemopreventative interventions at much higher efficiency once these models are developed. However, the research required to reach this goal is considerable. Without the resources provided by the PHTF, this important research would be delayed significantly, if in fact it could be done at all.

5. Exploration of cancer susceptibility and gene-tobacco interactions

It has become increasingly clear that a person's genetic makeup influences susceptibility to environmental agents such as tobacco smoke. Everyone knows individuals who have smoked for long periods of time without contracting cancer. What distinguishes these individuals from those who with the same tobacco exposure get lung cancer and die from the disease? The answer to this question resides in the understanding that cancer susceptibility is not a simple function of genes or environment but rather a function of the complex interplay of genes and environment. We need to identify the genes that influence susceptibility to tobacco and to understand how these genes function to modulate tobacco's carcinogenic potential. The identification of these genes will enable us to predict who is at the highest risk for cancer development allowing for better counseling, prognosis, and detection. This identification will also open research opportunities to develop therapies to counteract the high susceptibility to cancer development. The identification of these genes would only be possible within the foreseeable future through the increased investment afforded by the PHTF. The project is extremely costly involving years of case-control studies involving thousands if not tens of thousands of individuals. This project would entail the collection and maintenance of biological tissues and fluids from large population groups, the measurement of environmental exposure (e.g., through measurement of nicotine metabolites), development and use of a detailed questionnaire involving environment and behavior, and an informatics system capable of storing and analyzing the massive amounts of data generated in such a study.

Research enabled by the PHTF that is aimed at understanding the genetic predisposition to

tobacco-related cancers will include the development and expansion of biorepositories to provide access (with appropriate consent) to such materials as new hypotheses emerge. Such biorepositories also facilitate the identification of new molecular markers for cancer and precancerous lesions. Such markers are essential for the development of new early detection of tobacco-related cancers. Once such markers are found, they will require extensive clinical trials to assess their prospective value.

A significant fraction of what we know about carcinogenesis has its origins in studies of individuals with higher-than-average risk of cancer. The studies of rare hereditary disorders such as retinoblastoma and Li-Fraumeni syndrome have led to insights into cancers that are much less rare than these inherited diseases. The detailed examination of high risk individuals (i.e., individuals with current or past exposures to high levels of tobacco) will likely extend this paradigm. In fact, it seems very likely that benefits will accrue to non-smokers from the PHTF-sponsored research involving past or current smokers. This putative benefit is altogether fitting given that the entire society bears the cost of tobacco-related disease.

6. Improved early detection and diagnosis of tobacco-related cancers

Tobacco-related cancers present attractive opportunities for the development of much more accurate methods for earlier detection and better diagnosis. The population at risk is largely defined (i.e., current and past smokers), and many classes of tobacco-related cancers occur in anatomical locations accessible to biopsy or the obtaining of biological specimens (head and neck, esophagus, bladder) or radiological images (lung). It is a reasonable expectation that more sensitive diagnostic techniques will increase cure rates, since early cancers are, in general, more curable than advanced ones. Molecular techniques can now pinpoint cancer-causing mutations in the DNA of cells that appear in cells or cell debris from the mouth, aerodigestive tract, urine. More sensitive digital imaging and image-processing techniques are in development that should allow the detection of much smaller tumors in the lung, a notoriously difficult site for early detection. Emerging technologies related to high-throughput, cost-effective, comprehensive molecular analysis will soon allow a complete molecular profile of cancer cells and precancerous lesions. The translation of these emerging technologies to applications that benefit large number of patients is a daunting but necessary task. The PHTF could enable this to occur much more rapidly than would otherwise be possible.

Through the PHTF, the NCI could begin to fund testbeds for innovations in diagnosis emerging from either academia or industry (for example, new diagnostic devices based on molecular biology or imaging technology). Initial funding would probably involve the 55 existing NCI-designated Cancer Centers. These settings facilitate multidisciplinary collaboration between the sources of technological innovation and the scientists and physicians who can provide the necessary biomedical perspectives, tissue resources, and clinical setting for actual testing. Prototype devices could be subjected to pilot testing in these settings; these pilot tests may result in decisions to continue up the development ladder or may indicate the need for further refinement in the laboratory before broader testing. The fostering of collaborations between imaging scientists and investigators in other areas of biology and medicine will serve to hasten the development of non-invasive methods of tumor characterization important to foster improvements in diagnosis, prognosis, and treatment of tobacco-related cancers. The scale of this project requires resources such as those provided by the PHTF.

7. Improved National surveillance of tobacco-related cancers

The NCI desires to enhance our ability to gather more extensive and more intensive data on the burden of tobacco-related cancers throughout society, in order more readily to develop and test hypotheses about trends in the incidence and outcome of these cancers as patterns of tobacco usage change and as effective interventions are introduced on a large scale. The PHTF will enable this desire to become a reality.

The effects of changes in utilization of tobacco products by the American people, together with the results of implementing effective preventive or early diagnosis strategies nationally, when these become available, will be difficult to discern without adequately sensitive surveillance programs. NCI would like to reexamine its important databases such as the Surveillance Epidemiology and End-Results Reporting (SEER), which tracks the impact of cancer on the general population. The SEER database has proven to be of great utility to the scientific community but the SEER database contains only about 13% of the US population and representation of racial and ethnic groups within the database vary widely. There are also limitations to the depth of data collection and entry that is possible with the current level of funding. The PHTF would enable a significant enhancement of this database both quantitatively and qualitatively. We want to make sure that, to the maximum extent feasible, the SEER database not only tracks changes in cancer incidence and survival accurately, but also contains enough of the right kind of information to enable the generation of hypotheses about the basis for any observed changes in trends over time. New initiatives will be developed to expand surveillance research to allow more complete collection of information on risk factors, including exposure to tobacco. Emphasis on underserved or special populations at high risk (e.g. age, race/ethnicity) will be a key component of the program.

Establishing new linkages between databases containing different kinds of health-related information on populations is a very powerful tool for certain kinds of analyses. Advances in information technology will enable linkages like these to be established much more easily than in the past and, in time, will facilitate the creation of databases through electronic transfer of information from electronic source documents. The ease of long-distance communication made possible by the World Wide Web and other features of the Internet will create opportunities for collaboration and data sharing across national borders and oceans that have never before been a practical reality.

8. Improved communication about tobacco-related cancers and interventions

The power of computer-based communications and the capabilities of the World Wide Web will make possible new levels of cooperation in research on patients and populations. With funding from the PHTF, the NCI would embark on the implementation of an ambitious series of information networks to serve a needs of cancer research nationwide. Slow and cumbersome paper-based systems of data collection for multicenter studies will give way to electronic communication, facilitated by enhanced links between sources of data at points of care delivery (hospitals, offices, clinics) and the research database on which analysis of results is based. In collaboration with other Federal agencies, and with the participation of many external scientists and clinicians, NCI will modernize information links with its investigators, in a manner that will be compatible with standards set by the International Committee on Harmonization for North America, Europe, and Japan. We would also revise our criteria and standards for reporting adverse drug reactions and treatment-related toxicity. The results will be a set of common reporting requirements and terminological standards that will greatly

Increase speed and efficiency in the reporting of clinical trials both to sponsors and to regulatory agencies. NCI's long-range plans are in early stages of formulation now, but will call for the development of informatics systems and architectures that assist clinicians participating in trials with many aspects of the data collection and treatment process; the aim here is to reduce or eliminate barriers to participation in trials and to reduce the gap, wherever it exists, between the requirements of routine care and care on clinical research studies.

The potential of the computer as an instructional tool is just beginning to be tapped. Instructional modules on computer tailored for individual needs (i.e., semi-personalized courses) are likely to be much more effective than currently standard techniques for teaching people about concepts like the risk of getting a disease given a certain genetic predisposition, lifestyle characteristic, or environmental exposure. In the form of kiosks in public places like libraries or malls, computers can inform people about research results or studies of possible interest and relevance to them. NCI is already exploring this possibility in collaboration with the State of Maryland as a pilot study. The PHTF would enable this pilot to fly nationwide. With the active collaboration of several patient advocate groups, NCI beginning an ambitious effort to create a "patient-friendly" database, containing information on cancer and on clinical research protocols in nontechnical language. This will provide for enhancement of NCI's current large-scale efforts to provide the general public with access to up-to-date information about new research results, available clinical trials in diagnosis, treatment, and prevention, and contact points for additional information. This is a very large and ambitious project. The nationwide dissemination of this information system would not be possible without significant funds outside the current NCI appropriation. Without an external source of funding like the PHTF, it will be years before substantial headway can be made on this project. It is believed that this way of publicly disseminating information via computer will be of particular appeal to the current generation of adolescents who are as a group more "computer-literate" than previous generations. Public libraries also provide access to underserved populations.

IV. NATIONAL HEART, LUNG AND BLOOD INSTITUTE (NHLBI)

The mission of the NHLBI is to provide leadership for a national program in diseases of the heart, blood vessels, lung, and blood. This year, about 430,000 Americans will die of smoking-related illnesses. More than 250,000 of these deaths are attributable to heart disease, stroke, or chronic obstructive pulmonary disease, all of which fall within the mandate of the National Heart, Lung, and Blood Institute (NHLBI), NIH. These diseases are worldwide problems that are rapidly overtaking mankind's traditional scourges—infections and malnutrition—as contributors to the global burden of disease.

Beginning with the famous Framingham Heart Study, initiated in 1948 by the NHLBI, research has systematically documented that smokers are particularly susceptible to developing heart attacks, strokes, and chronic lung diseases; that heavy smokers have a greater risk than light smokers; that smokers in their late teens and early twenties already show evidence of clogged arteries and symptoms of reduced lung function; that, among persons with high blood pressure or high cholesterol, smoking seriously magnifies the already increased risk of heart attack or stroke; and that quitting smoking at any age greatly reduces the likelihood that these catastrophic events will occur. These findings have formed the basis for educational campaigns to raise awareness among the public and health-care professionals that abstinence from smoking "makes the heart grow stronger" and to promote screening to identify smokers with early lung abnormalities.

These research efforts have been impressive, but much more needs to be done. Additional resources, such as those envisioned in the PHTF, would accelerate progress toward eliminating the burden of this public health threat. Research opportunities abound. For instance, our knowledge of the connection between smoking and disease has been based on probabilities calculated from observations of large populations. Thus, a given smoker can be advised that this habit increases the risk of developing an illness, but we cannot predict with any certainty whether he or she can expect to die of a heart attack, a stroke, chronic lung disease, or lung cancer or live to age 100 in the pink of health. Science has now reached the point where we may be able to discover the genes that govern individual susceptibility to the ill effects of smoking. This information will not only permit a personalized approach to preventive health counseling, but also open up new possibilities for treatment and cure based on a better understanding of how and why smoking-related diseases develop.

A. Tobacco-Related Research of NHLBI

Worldwide, tobacco smoking causes millions of deaths each year, many of them from cardiovascular diseases (coronary heart disease, peripheral vascular disease, stroke) and chronic lung diseases (chronic bronchitis, emphysema). Thus, research on the adverse health effects of cigarette smoking, the health benefits of cessation, and the impact of environmental tobacco smoke (passive smoking) on lung function impairment, atherosclerosis, hemostasis, and thrombosis in both adults and children is of high priority to the NIH.

In FY96, NHLBI expenditures for research related to smoking and health totaled ~\$26M. This figure included the Lung Health Study, a large-scale clinical trial of smoking cessation and pharmacologic therapy in smokers at high risk of developing chronic obstructive pulmonary disease; studies of smoking cessation strategies targeting men and women of a variety of ages, racial/ethnic backgrounds, and socioeconomic strata; research on prevention

of active and passive smoking in children; basic studies of the mechanisms by which smoking causes tissue damage; and epidemiologic observations of smoking as a risk factor for cardiovascular and lung diseases. The importance of tobacco avoidance is a key message of the Institute's educational programs, such as the National High Blood Pressure Education Program and the National Cholesterol Education Program. Because of the nature of the NHLBI's mission and the huge contribution of tobacco to diseases of the heart, lungs, and blood, much of the NHLBI's efforts are focused on tobacco-related diseases.

Innovative and exciting new directions in genetics and genetic epidemiology now have the potential to provide new information about the underlying biological mechanisms of injury caused by tobacco smoke and to identify the genes involved and determine how they work. Some of the multiple opportunities for smoking-related research and their potential impact on cardiovascular and pulmonary diseases are summarized below.

B. NHLBI Plans for Research on Tobacco-Related Diseases

1. Genetics of susceptibility to smoking-induced target-organ damage

Individuals with identical risk factor profiles vary considerably with respect to the course of a disease and the extent of damage it causes to target organs, such as the lungs and the cardiovascular system. For example, when people smoke or are exposed to tobacco smoke, some are susceptible to developing chronic lung or cardiovascular disease, while others seem to be protected. Evidence is emerging that there is a genetic basis for this variability in susceptibility to target organ damage. Identification of susceptibility/protection genes would provide innovative approaches for the development of new treatment and prevention strategies. Mapping, isolating, and characterizing these genes is complicated because multiple genetic and environmental factors interact in complex ways. However, information from the Human Genome Project, advances in analytical and statistical approaches, and new study designs now make it feasible to explore this promising research opportunity. The magnitude of this project would necessitate resources like those from the PHTF.

2. Families at risk of cardiovascular disease

Data suggest that a significant proportion of families afflicted by cardiovascular diseases may have cigarette smoking as their only identifiable risk factor. The existence of such families points to a genetic contribution to susceptibility to the specific effects of smoking on the cardiovascular system, but these genetic factors have not been well defined. This could occur via the PHTF. Targeted family-based studies of cardiovascular disease and its risk factors in both active and passive smokers would facilitate identification of genes and, thereby, enhance understanding of the mechanisms by which smoking increases risk for cardiovascular disease. Once identified, wide-scale screening for such genes in active smokers could enable identification of those most susceptible as candidates for intensive cessation efforts.

3. Genes that confer protection from smoking-induced diseases

Advances in molecular genetics make it possible not only to look for genetic factors that cause cardiovascular and lung diseases, but also to discern genetic factors that prevent or retard their progression. Just as susceptibility genes may predispose many to disease, "protective" genes may confer resistance. With support from the PHTF, NHLBI would seek to identify specific "protective" markers that may improve understanding of the etiology of these

common diseases and also assist in the development of new drugs or other therapies to treat them.

4. Identification of exposures that interact with smoking to induce disease

It has been reported that co-exposures, either biological or nonbiological, may interact with genetic factors to increase an individual's adverse response to tobacco smoke exposure. Co-exposures may trigger strong immune responses in certain individuals, thereby increasing susceptibility to smoke-induced damage. With currently available techniques in cellular and molecular biology, it is now possible to study mechanisms by which these co-exposures may contribute to the development of cardiovascular and pulmonary diseases. The PHTF could significantly speed this process.

5. Components of tobacco smoke that cause tissue damage

Nicotine stimulates the sympathetic nervous system and causes adrenal release of catecholamines, which increase heart rate, blood pressure, stroke volume, and cardiac output. Increased epinephrine and norepinephrine levels in the circulation affect various hematologic, metabolic, and endocrinologic processes and influence the development of atherosclerosis and its complications. In normal individuals, the increased work of the heart results in increased coronary blood flow. However, patients with compromised coronary and peripheral circulation may develop angina, heart attack, or sudden cardiac death. Other components of cigarette smoke (e.g., nitrogen oxides, carbon disulfide, cadmium, and possibly tar) may also contribute to cardiovascular pathology and merit detailed study. The comprehensive study of the many tobacco components and the interaction of each with tissue would require the resources of the PHTF.

6. Innovative investigations of the role of inflammation in smoking-related illness

Inflammation has recently been recognized as a key promoter of the atherogenic process, and smoking is known to be strongly related to inflammatory processes in the lung. The systemic effects of inflammation, such as elevated circulating levels of inflammatory mediators or enhanced thrombogenicity, have not been examined in relation to risk of atherosclerosis and endothelial dysfunction. These effects could readily be studied in smokers and persons exposed to environmental tobacco smoke, as well as in persons in smoking cessation programs whose exposure may have wide variations over time. Biological measures of direct smoke exposure and metabolism, coupled with serum markers of inflammation, should be correlated with noninvasive measures of atherosclerosis and endothelial function in population-based samples of persons free of known cardiovascular and pulmonary disease. Such large-scale studies could provide critical insights into the mechanisms by which smoking induces atherosclerosis and chronic lung disease but would require the resources of the PHTF.

7. Research on the interaction between smoking and therapeutic drugs

Cigarette smoking has been reported to interfere with the pharmacodynamic and pharmacokinetic profiles of certain drugs—including those utilized in the treatment of chronic conditions such as hypertension, angina, arrhythmia, dyslipidemia, asthma, and diabetes—thereby compromising drug efficacy. Possible mechanisms for these reported

cigarette smoking-drug interactions have been proposed, but little is known about their effects on patient outcomes or their underlying pharmacologic mechanisms. Both questions could be addressed with support from the PHTF.

8. Exploration of strategies to reverse tissue damage in emphysema

Although the lung tissue destruction that characterizes emphysema has always been thought of as irreversible, some evidence to the contrary has recently emerged. An interesting report indicated that in small animal models in which elastase was administered to produce emphysema-like changes in the lungs (larger airspaces and decreased number of alveoli), treatment with retinoic acid returned the lung alveoli to normal size and number. While these data suggest that emphysema may be reversible, this work must be substantiated in other animal models of smoking-induced emphysema before research in humans can even be contemplated. All animal model studies are costly and the validation in humans of findings from animals is even more costly. The PHTF could aid in these studies.

9. Surveillance of trends in smoking-related morbidity and mortality

Given the numerous serious chronic diseases related to smoking and the substantial shifts in smoking patterns (decreases in older and middle-aged men, increases in young women) that have occurred in recent decades, trends in morbidity and mortality can be expected to change dramatically in the next several years. Accurate information will be critical to guide future public health and research efforts in this area. National vital statistics are not sufficient for this purpose, because ascertainment of cause of death from death certificate data is problematic and mortality information fails to capture the majority of suffering and health care costs related to these illnesses. A broadly representative, community-based system for ascertaining and verifying incidence, prevalence, hospitalizations, and disability from the common serious illness caused by smoking is required to monitor future morbidity trends and focus efforts in research and prevention. As with any surveillance system, this one would require significant support not only for data collection but for the Informatics backbone that would be required for storage and analysis of the data. Such a system could be possible with resources from the PHTF.

10. New strategies to prevent smoking initiation in the young

Once initiated, smoking behavior is costly, and research consistently demonstrates that even effort-intensive approaches to smoking cessation often achieve relatively minor results. Because the majority of smokers (82 percent) began smoking daily before age 18 and 3,000 young persons take up the habit every day, tobacco prevention activities focused on school-age children and adolescents are an urgent priority. Prospective epidemiological studies are needed to understand the risk factors leading to the initiation of smoking behavior and patterns of tobacco use. Risk factors for smoking behavior—including accessibility, availability, attitudes, price, socio-cultural and religious beliefs, psychosocial variables, peer pressure, age, gender, minority status, parental smoking, and role models—need to be identified and classified. Research supported by resources from the PHTF should compare the effect of socioeconomic status on smoking behavior in various racial/ethnic groups in an effort to increase understanding of population needs and enable the design of cost-effective, culturally sensitive interventions.

11. Investigations of the health prognosis of ex-smokers

It is generally believed that the risk of smoking-related lung diseases, including cancer, in ex-smokers returns to the level of never-smokers only after 10-15 years of abstinence. A better understanding of the rates at which ex-smokers continue to lose lung function and/or regain their lost function is important to assess quality of life and disease susceptibility. The PHTF could enable these important parameters to be assessed. Specifically, studies are needed to delineate the time course of loss/recovery of lung function and the potential for developing lung disease among various populations of ex-smokers, with the ultimate goal of developing interventions to recover/repair/remodel tissue damage caused by smoking.

12. Improved understanding of the relationship between smoking and body weight

Weight gain is often an unfortunate consequence of smoking cessation, and overweight is, itself, a risk factor for cardiovascular disease. Research is needed to determine the mechanisms underlying the weight-suppressing effect of smoking and the weight-increasing effect of smoking cessation, so that interventions to counter them can be developed. This represents a question that may be extremely relevant to smoking cessation in adolescents and is the kind of large study that would benefit from PHTF resources.

13. Maternal smoking and fetal/child health

Maternal smoking adversely affects fetal growth, but the reasons for this phenomenon are not clear. Recent studies have suggested that in utero tobacco exposure increases the incidence of a specific cluster of congenital heart defects, cleft palate and other craniofacial abnormalities, and abnormal neurological development and also results in abnormal lung growth and function after birth. Infants and children who live in households with smokers experience increased rates of ear infections, sinus infections, upper respiratory infections, reactive airway disease, and pneumonia, and as a result are hospitalized more frequently. The incidence of these health burdens increases with the number of adults in the household who smoke. More research is needed to explore the effects of exposure to smoking on the maternal-fetal unit, childhood physical and mental health, and future health problems (e.g., increased risk of cancer), so that effective preventive measures can be developed. The PHTF could enable this research.

14. Tobacco exposure and asthma exacerbations

Tobacco smoke is a major precipitator of asthma symptoms in children and adults. Exposure by adults with asthma to environmental tobacco smoke is associated with decreased levels of pulmonary function, increased requirements for medication, and more frequent absences from work. Research into the mechanisms whereby smoking increases bronchoconstriction and mucus secretions in individuals with asthma will provide important insights into the progression of asthma severity and could greatly benefit from the resources of the PHTF.

15. Smoking, estrogen, and deep vein thrombosis

Deep vein thrombosis and pulmonary embolism have been reported in young women who smoke and use estrogen-containing contraceptives. Emerging data suggest that women who smoke and use postmenopausal hormone replacement therapy may also have suffer similar complications. Hormone replacement therapy is being widely recommended not only for

symptomatic relief of perimenopausal symptoms, but also for its potential benefits in reducing the risk of coronary heart disease and preventing osteoporosis. More research is needed to unravel the complex relationship between cigarettes, estrogen, and deep vein thrombosis, as well as to develop methods to identify women, particularly cigarette smokers, who are at high risk of developing deep vein thrombosis when using natural or synthetic estrogens for hormone replacement or contraception. The PHTF could enable this research to be performed.

16. Demonstration research on smoking prevention in the young

Demonstration research projects should carefully design and evaluate comprehensive interventions combining smoking prevention education at school, in pediatricians' offices, in dentists' offices, and at home. To move resulting research successes into practice, assessment of the degree of implementation of proven programs is needed, followed by research examining the effectiveness of approaches to disseminating the programs. This type of research is costly and time-consuming. The PHTF could facilitate its completion.

17. Interventions for populations of low socioeconomic status

Nationwide public health efforts at disease prevention have enjoyed much success, but their benefits have not been fully realized across all segments of society. Despite targeted attempts, participation in prevention programs by persons of low socioeconomic status continues to lag. In addition, cultural characteristics, economic status, language differences, inaccessibility of cessation programs, and targeted promotional activities by tobacco companies have placed the more disadvantaged members of our population at higher risk. Effective, culturally sensitive programs of prevention need to be developed and carefully evaluated for all populations at risk. Individuals of lower socioeconomic status appear to have been disproportionally harmed by tobacco. The PHTF could enable research aimed at remedying this situation.

IV. NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

The NICHD conducts and supports laboratory, clinical and epidemiological research on the reproductive, neurobiologic, developmental, social and behavioral processes that determine and maintain the health of children, adults, families and populations. With regard to the proposed tobacco settlement, the NICHD has a major role in research related to discouraging children and adolescents from starting to use tobacco and in helping these groups, as well as pregnant women, to stop smoking. In addition, the NICHD has a role in research on the tobacco-related medical conditions of low birth weight and sudden infant death syndrome (SIDS).

A. NICHD Research to Discourage Starting and to Assist Quitting Tobacco Use

1. Basic studies of behavioral development and change

Smokers begin smoking early with 16% of adult smokers having begun before age 12, 37% before age 14, 62% before age 16, and 89% before age 18. Given these statistics, it is not surprising that researchers acknowledge that programs to prevent the onset of smoking or other risky behaviors should start *before* adolescence, when children are still in their *middle childhood* years (between kindergarten through six grade). In FY96, NICHD funded studies in this area totaling ~\$5.5M.

The NICHD leads efforts to better understand the social, emotional, and intellectual patterns of growth and rapid change that characterize the middle childhood years, and to understand how children's changing relationship with their parents and widening exposure to their communities and a variety of peers influence their chance for adopting unhealthy behaviors. NICHD-supported researchers are also trying to develop predictive measures of risk in this younger population, and have already identified four "protective" factors that can be targeted when developing programs to prevent the onset of smoking. The NICHD has led another effort to identify developmental measures that are appropriate for minority populations. Other studies, involving ethnically diverse youth starting in middle childhood, are examining the development of risk perceptions.

2. Surveillance

Any successful smoking prevention program must be developed with a firm understanding of how smoking and related risk behaviors, as well as contributing risk-factors, are distributed in various populations and change over time. Surveillance and epidemiologic studies also help researchers understand the link between smoking and a range of adverse health outcomes. These areas of research were supported by NICHD in FY96 at a level of ~\$2.8M.

The NICHD supports a range of epidemiologic studies targeting the impact of maternal smoking and environmental exposure to smoke on pregnancy outcomes and on child development. In particular, a large study involving 8,000 women in prenatal care is examining tobacco smoke as a risk factor for premature rupture of membranes. Other studies concern spontaneous abortion and intrauterine growth retardation in women who smoke, as well as the health and development of children with prenatal exposure.

The NICHD has supported the Add Health Study, an unprecedented survey documenting the health and health behaviors of adolescents, as well as the factors that contribute to these

outcomes (which include smoking). Another study, using survey data on youth and their families, is helping to distinguish between the genetic and environmental influences that lead children to adopt high risk behaviors, including smoking.

3. Public Health and Community-Based Studies

The NICHD supports a range of community-based prevention and intervention studies to prevent youth from starting to smoke or adopting other high risk behaviors. These studies build on the surveillance and basic behavioral research mentioned above and in FY96 totaled ~\$1M.

NICHD intramural researchers have designed and implemented a study to test the efficacy of a school-based program in preventing problem behaviors. This study, which involves 3,000 middle school students in a three-year prevention program, targets the common factors that lead to smoking, as well as other risk behaviors. It has a unique education component to help parents increase the monitoring, involvement, and support of their middle-school child.

Another NICHD-supported community-based study brings researchers and community organizations together to develop, implement, and evaluate interventions, targeted to minority youth, to help them develop the skills necessary to avert and avoid risky behaviors, ranging from substance abuse (which often includes tobacco use) to other high risk behaviors.

B. NICHD Plans for Expansions of Tobacco-Related Prevention Research

1. Smoking prevention programs targeting middle childhood

Based on the observation that the longer health risk behaviors can be delayed, the less likely they are to start, the NICHD could expand its middle childhood initiative with resources from the PHTF. Starting with a conference addressing cigarette smoking and middle childhood, already scheduled for September 1997 with multiple Institutes participating, researchers will develop a multidisciplinary research agenda outlining the next generation of studies to help prevent children from starting to smoke. To conduct this research, four to six health risk prevention research centers would be established, combining the talents of researchers from the biological, behavioral, and social sciences. The centers would identify which of the "protective" factors identified to date are most important and amenable to the development of interventions, and employ longitudinal studies to test the effectiveness of different prevention approaches, as children make the difficult transition from elementary to middle- and high-school. The PHTF could enable this important research to go forward.

2. Helping adolescents to stop smoking

To date, researchers have focused on how to prevent teenagers from starting to smoke and helping adults learn how to stop smoking; few researchers have targeted the important issue of how to help adolescents stop smoking. With PHTF resources, the NICHD plans to expand its multidisciplinary research to better understand how many developmental factors—ranging from hormonal to other physical, cognitive and social changes—affect the ability of teens to stop smoking, and to develop and test interventions to do so. The Add Health study could also be extended to collect a new round of longitudinal follow-up data to see how teen behaviors actually change over time, integrating social, psychological, and biological perspectives. In addition, several of the intervention studies targeting minority youth and the

changing of high-risk behavior could be replicated in new sites and contain a smoking-cessation component. The NICHD intramural study to prevent problem behaviors in schools could be expanded to new sites with increased emphasis on reducing the onset of smoking by young adolescents.

3. Helping pregnant women to stop smoking

Given that smoking is significantly linked to adverse birth outcomes, effective behavioral modification programs must be developed for pregnant women. The NICHD has developed one approach, "Baby and Me, Smoke-Free," but has never had funds to test it. In addition, marketing approval has not been sought to use the "nicotine patch" during pregnancy. Priority must be given to completing pharmacokinetic studies, safety evaluations, and clinical trials to allow pregnant women to have access to this important means to stop smoking.

C. Research of NICHD on Tobacco-Related Conditions

The NICHD supports extensive research on pregnancy and maternal health, fetal growth and maturation, labor and delivery and infant well-being. These studies include elucidation of the normal and abnormal factors that influence the course and outcome of pregnancy, such as maternal physiology and environmental variables, and those events, conditions and treatments occurring during pregnancy which contribute to a low-birth-weight (LBW) infant or other adverse outcome. Basic and clinical studies on infant health include the etiology, pathophysiology, therapy and follow-up of conditions and syndromes affecting infants, including LBW and SIDS, key factors in infant mortality. Environmental factors are important, with maternal smoking alone accounting for as much as one-third of LBW incidence. Of all the things we know, stopping smoking during pregnancy would have the greatest effect on reducing LBW. Independently, prenatal and postnatal exposure to smoke each dramatically increases an infant's risk of SIDS, approximately threefold and twofold, respectively. Therefore, an understanding of the mechanisms by which this increased incidence of LBW and SIDS occurs would contribute to a major reduction in infant mortality and morbidity.

1. Low Birth Weight Infants

The NICHD has a substantial portfolio of research on LBW and preterm delivery totaling ~\$62M in FY96. Ongoing studies demonstrate that bacterial vaginosis (BV), a common vaginal condition, significantly increases a woman's risk of premature delivery of a LBW infant and that, in addition to BV, smoking increases the risk of preterm delivery by 40%. Other research attempts to identify new approaches to achieving fetal maturation when preterm birth is likely.

NICHD supports networks of Maternal Fetal Medicine Units (MFMUs) and Neonatal Intensive Care Units (NICUs), to conduct multicenter randomized clinical trials and other prospective clinical studies in obstetrics and neonatology, especially targeted to both the treatment and prevention of LBW. The multidisciplinary Perinatal Research Emphasis Centers (PERCs) fund basic, preclinical and clinical research addressing the complex problems of pregnancy and perinatology, including intrauterine growth retardation, fetal hypoxia, fetal maturation and initiation of preterm labor.

2. Sudden Infant Death Syndrome

Current research includes studies to determine the underlying mechanism of SIDS and its probable cause(s), and to develop preventive approaches. SIDS research totaled ~\$11.5M in FY96. Emphasis is placed on research concerning the identification of infants at risk of becoming SIDS victims. This includes both basic and clinical studies of the neurophysiologic, cardiorespiratory, metabolic, immunologic, genetic, pathologic, environmental and infectious disease aspects of the syndrome. Studies also try to determine the relationship between high-risk pregnancy, high-risk infancy, and SIDS.

D. NICHD Plans for Expansions of Research on Tobacco-Related Conditions

1. Low Birth Weight Infants

With the PHTF, research could be conducted including the role of tobacco as a maternal risk factor for LBW and preterm delivery. Increased investment via the PHTF in the PERCs, NICUs and MFMs could greatly enhance basic knowledge about the etiology of LBW, its prevention and its treatment. For example, additional funds would accelerate accrual for a clinical trial to determine if screening for and treating BV in the first trimester of pregnancy is safe and effective. Additional support for the intramural Perinatology Branch would expand studies on the precursors of and disorders associated with infant mortality. Additional funds from PHTF would expand the NIH-DC Infant Mortality Initiative, a trans-NIH study of the determinants of the high infant mortality rate in the District of Columbia.

2. Sudden Infant Death Syndrome

In addition to supplementing the ongoing basic and intervention studies related to SIDS, specific Initiatives are proposed using PHTF resources. Some scientists believe that smoking is part of the causal pathway to SIDS, possibly through intrauterine hypoxia. In trying to delineate the mechanisms for increased risk of SIDS, it is important to differentiate between direct biologic actions of components of cigarette smoking on the maternal-fetal unit or the infant, and the behavioral factors associated with cigarette smoking. Some fruitful areas of research would include studies to: differentiate between direct effects of smoking on SIDS risk versus factors like reduced nutrition, maternal depression and increased susceptibility to infection associated with cigarette smoking; develop animal models on how smoking could impair autonomic nervous system development and function in early infancy, and lead to sudden death; elucidate the sleep, cardiorespiratory and immune system physiology of infants exposed to large doses of cigarette smoke pre- and postnatally; and develop more effective interventions to reduce cigarette smoking in the fetal and infant environment.

VI. NATIONAL INSTITUTE OF DENTAL RESEARCH (NIDR)

The mission of the National Institute of Dental Research (NIDR) is to promote the general health of the American people by improving their oral, dental and craniofacial health. Through nurturing fundamental research and the development of researchers, the NIDR aims to promote health, to prevent diseases and conditions, and to develop new diagnostics and therapeutics. Knowledge acquisition through science and effective and efficient science transfer are the means used to contribute to improved quality of health. The National Institute of Dental Research (NIDR) spent approximately one-fourth of its \$187 million appropriation in FY96 on diseases related to tobacco including craniofacial, oral and dental disease research. The three primary program areas that comprise NIDR's tobacco-related research include oral, pharyngeal and nasopharyngeal cancer, periodontal diseases and craniofacial birth defects.

A. Tobacco's Impact on Oral Health

Tobacco product uses (e.g., smokeless chewing tobacco and snuff, and cigar, pipe and cigarette smoking) are the number one risk factor responsible for oral, pharyngeal and nasopharyngeal cancers; that claim over 8,000 lives each year. Another 4,250 lives are lost to cancer of the larynx. It is estimated that 82% of laryngeal cancers are due to cigarette smoking. The incidence of oral cancer among smokers ranges from 2- to 18-times that among nonsmokers. At least 28 tumorigenic agents have been isolated and identified in smokeless tobacco products, nicotine being just one of these.

Internationally, the incidence of oral cancer is increasing. Throughout the world, malignant neoplasms of the mouth and pharynx rate as the fifth most common cancer in men and the seventh in women. Excluding facial skin, the majority of malignant neoplasms (over 80%) in the oral and pharyngeal region are squamous cell carcinomas of the oral and pharyngeal mucosa, tongue and lips. In industrialized countries, men are affected twice as often as women; and African American males are affected at twice the rate of Caucasian males. In the United States, one American dies every hour of oral cancer. There are approximately 42,000 new cases of oral, pharyngeal, nasopharyngeal and laryngeal cancer reported each year. The prognosis after 5 years is essentially 50% with approximately 12,000 deaths each year. The highest incidence is reported for African American men over the age of 45 years. The major risk factors include tobacco products, and alcohol.

Smokeless tobacco use has a significant effect on children by inducing oral premalignant and malignant mucosal lesions, and localized gingivitis. In 1992, 32% of high school students in the United States have tried smokeless tobacco; most of these males. In 1993, a national survey of boys 9-12 years of age indicated, for example, that 40% used smokeless tobacco in West Virginia, 39% in Kentucky, 33.8 % in Tennessee, 26.2% in Arkansas and 16.2% in Illinois. The available evidence suggests that there is a continued increase in the use of smokeless tobacco products by adolescent children in this country. Contact carcinogenesis is the most likely mechanism that results in this type of oral cancer lesion; the smokeless tobacco constituents condense on the oral mucosal and gingival surfaces in those specific topographical regions where the tobacco product(s) is placed.

Tobacco is also the number one risk factor for periodontal diseases (e.g. gingival bleeding, acute necrotizing ulcerative gingivitis, and periodontitis) which afflict more than 50% of the adult US population. Periodontal disease is the primary cause of tooth loss; approximately

10% or 17 million American adults are edentulous. The burden of tooth loss and edentulism is greater than \$10 billion each year.

A recent study by the California Birth Defects Monitoring Program (1996) reported that mothers who smoked 20 or more cigarettes per day during the month before conception through the first three months of pregnancy were more than twice (2.6 times) as likely to have infants with cleft lip and palate. Those mothers who smoked less were about 1.5 times as likely to have infants with oral clefts. Cleft lip and palate costs are estimated to be \$1 billion per year in the US.

Scientific inquiry continues to identify additional diseases and disorders where tobacco products alone or in combination with other risk factors are implicated in a number of other diseases and disorders such as low birth weight and premature births, osteoporosis, oral candidiasis, aphthous ulcers, altered taste and smell acuity, and impaired soft and hard tissue wound healing.

Finally, a sound basis has been established for involving the oral health professions in addressing tobacco control programs and in documenting the use of tobacco products. One example of this collaborative effort is the partnership between NIDR and NCI, CDC, Robert Wood Johnson Foundation, Oral Health America, Major League Baseball in addressing the problems associated with "spit tobacco." These initial efforts indicate that there is a strong capacity to extend the educational programs required to realize public cessation of tobacco use in this country, especially among youth.

B. Tobacco-Related Research of NIDR

Current NIDR-sponsored research related to tobacco and tobacco-related diseases includes research on smokeless and smoking tobacco, nicotine and other ingredients or metabolites of cigarettes, and studies that collect information on tobacco use or smoking history for tabulation or analysis. Research on tobacco totaled about \$2.5M which was about equally divided between basic and clinical research.

1. NIDR-Sponsored Basic Research

NIDR-sponsored basic tobacco-related research includes molecular genetics and cell biology. Most of these projects address tobacco/smoking and oral cancers: mechanisms of tumorigenesis and cell injury, clonality studies, replication error and DNA repair mechanisms. Others examine the effects of nicotine/tobacco on inflammatory mediators and immune cell function in periodontitis. Two studies are molecular epidemiologic, and one study assesses the role of tobacco in *Candida albicans* drug resistance in AIDS patients.

NIDR-sponsored clinical tobacco-related research includes case-control and longitudinal studies in humans to ascertain risk factors (one of which is tobacco use/smoking history) for adverse medical outcomes. Outcomes (listed in frequency order) are: oral cancer, periodontitis, skeletal and alveolar bone loss, and candidiasis. One study examines immunoglobulin levels after smoking cessation in successful versus recidivistic patients.

2. NIDR-sponsored behavioral research

NIDR-sponsored behavioral tobacco-related research includes one study of validation of self-reporting methods (patient recall of tobacco use) for retrospective analysis of risk assessment. Behavioral research is defined to include studies that addressed issues of why people smoke and how can we get them to stop. The validity of reports/estimates of smoking history are also included in this category.

3. NIDR-sponsored epidemiology/surveillance research

NIDR-sponsored epidemiology/surveillance tobacco-related research includes Several studies. One assesses drug use (including tobacco) by dentists and dental students. The other is a descriptive epidemiology study of the oral health of a defined minority population in which tobacco use/smoking history is one factor tabulated. In addition, NIDR sponsors the oral health component of the National Health and Nutrition Examination Surveys that include assessment of tobacco use as well as assessment of tobacco-related health effects.

4. NIDR Activities in Prevention

An example of NIDR activity in prevention is our collaboration with NCI focusing on "spit tobacco" educational initiatives targeted at children, adolescents, and young adults. With the help of role models from Major League Baseball, the key educational messages are as follows: spit tobacco is not a safe form of tobacco, spit tobacco is addictive, and spit tobacco use can lead to cancer and other health problems. This collaboration has produced a variety of educational, informative and motivational materials as brochures, baseball player trading cards, posters, a video and a teacher's guide.

5. NIDR-Sponsored Research on Tobacco-Related Diseases

NIDR-sponsored research on diseases that are impacted by tobacco totaled about \$45M. Of this research, 82% was classified as basic research and 14% as clinical. The three primary program areas that comprise NIDR's tobacco-related disease research include oral, pharyngeal and nasopharyngeal cancer, periodontal diseases and craniofacial birth defects.

C. NIDR Plans for Expanded Tobacco-Related Research

There needs to be an extensive increase in basic, translational, patient-oriented and community-based research in each of the three major areas outlined above: oral cancer, periodontal diseases and craniofacial birth defects. The PHTF could enable this increase to occur. For example, the molecular mechanisms are not as yet known for how specific tobacco ingredients cause oral neoplastic lesions, effect opportunistic oral microbes associated with gingivitis and periodontal diseases, or produce cleft lip and/or palate during the first trimester of human pregnancy. Sensitive and specific diagnostics are not available to identify tobacco-induced premalignant oral, pharyngeal, nasopharyngeal or laryngeal lesions, or to identify individuals highly at risk for tobacco-induced destructive periodontal diseases or craniofacial birth defects.

A substantial expansion of the Centers of Oral Cancer (co-funded with NCI) as well as support for increased investigator-initiated research using the resources of the PHTF could significantly enhance scientific progress towards understanding the natural history, etiology, molecular pathogenesis, diagnostics, therapeutics and prevention of tobacco-induced oral and pharyngeal cancers. Preclinical and clinical research should be significantly expanded, along with a major expansion of human behavioral research targeted to children and adolescents.

Specific efforts to define how tobacco constituents influence opportunistic oral microbe (viral, bacterial and yeast) pathogenicity as well as the host immune response should be increased and could be with resources from the PHTF. In addition, the basic science studies of how tobacco constituents effect bone formation and bone resorption should be expanded since this knowledge base is essential for the development of diagnostics and therapeutics for tobacco-associated periodontal diseases.

Specific efforts are needed to define how specific tobacco products effect maternal physiology associated with premature and low birth weight babies as well as craniofacial birth defects. In addition, high risk individuals need to be identified to enhance counseling efforts to reduce the burden of tobacco-associated birth defects. These approaches will require large and well-defined populations along with cost effective instrumentation and related technology for genotyping. The magnitude of this project will require funds such as those that could be made available from the PHTF.

Since monitoring of tobacco use is predominantly captured by self-report, the development of low cost and rapid salivary diagnostic tests to verify or validate use are needed. In addition, further development of salivary and other orally-related diagnostic tests for viral and other cofactors of diseases related to tobacco would permit more specific risk assessment of individuals and populations.

Behavioral and educational research efforts focused upon unique contributions to be made by health professions in tobacco control could further current efforts directed towards children. For example, 75% of children ages 3-17 years visit a dental office each year. Outreach of this magnitude would involve development, testing, production, storage, distribution, and assessment of interventions and/or educational material. Resources from the PHTF could enable this type of effort.

VII. NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

The mission of NIDA is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy. The use of tobacco products is by far the Nation's deadliest addiction. Research conducted by the NIH has contributed to the Nation's overall understanding of nicotine as an addictive drug. The NIDA has taken the lead in developing pharmacological and behavioral treatments for nicotine addiction. Nicotine addiction, like other drug addictions, is characterized by uncontrollable, compulsive drug seeking and use, even in the face of negative health consequences. A testimony to this is the fact that most smokers identify tobacco as harmful and express a desire to reduce or stop use, with nearly 20 million of them making a serious attempt to quit each year. Unfortunately, less than 7% of those attempting to quit achieve even one year of abstinence, with most relapsing within a few days of attempting to quit. This exemplifies the growing need to develop new and improved strategies and treatments for nicotine addicts that will not only contribute to improving the overall health of the nicotine addict, but lower the overall health cost of the Nation. Because of NIDA's understanding of addiction, it can play a pivotal role in preventing and treating nicotine addiction. Critical scientific opportunities for research are outlined below.

A. Basic Tobacco-Related Research of NIDA

Nicotine is the primary component in tobacco that acts on the brain. NIDA supports basic research on neurochemical and molecular approaches to nicotine addiction, nicotinic receptors in the brain and the pharmacologic basis of nicotine addiction. NIDA also supports projects examining genetic differences in nicotine sensitivity as well as behavioral genetic studies of smoking behavior. NIDA also supports research on the treatment of nicotine addiction by focusing on the development of nicotine and non-nicotine replacement medications in combination with behavioral strategies. NIDA also supports studies on craving and individual and gender differences in cigarette abstinence.

NIDA has an ongoing program of health services research looking at access to, effectiveness, and cost-effectiveness of drug abuse treatment services in improving the health and social functioning of persons addicted to illicit and licit drugs including tobacco. In addition, NIDA supports research to increase patient engagement in the treatment process that leads to improved retention rates and lower rates of relapse to drugs of abuse following treatment.

Cigarette smoking is a complex behavior. Recognizing that behavioral interventions are the cornerstone of nicotine addiction treatment, NIDA's behavioral research on nicotine and smoking focuses on an understanding of the antecedents of tobacco use, and changing behavior patterns.

One of NIDA's most important goals is to translate research findings, especially those about the actions of drugs on the brain, to help the public better understand the nature of addiction and the most effective strategies for its prevention and treatment. NIDA carries out a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice. It also develops and disseminates science-based prevention strategies to communities throughout the country.

Current NIDA-supported epidemiological studies monitor patterns of drug use including nicotine, such as The Monitoring the Future Study that the Nation relies on for examining current drug use and trends among our Nation's youth. These studies provide invaluable data to inform development of prevention and treatment strategies. NIDA also has a rich portfolio of research on risk and protective factors, as well as studies on the co-occurrence of nicotine with other drugs of abuse.

B. NIDA Plans for Expanded Nicotine-Related Research

1. Nicotine Addiction

With resources made available through the PHTF, NIDA intends to significantly expand its study of nicotine as an addictive drug. Emphasis will focus on a number of specific areas including

the brain regions that are involved in mediating the reward and reinforcing properties of nicotine. In addition, brain mechanisms of nicotine action will be explored with the goal of identifying specific brain receptor subtypes that mediate aspects of addiction and craving. It is clear that susceptibility to nicotine addiction is variable in the population. Although undoubtedly a complex phenomenon, it is likely the genetic differences play a role. The genetics of complex behaviors is beginning to be unraveled in a number of instances. It is the goal of NIDA to map and identify all of the genes contributing to vulnerability to nicotine addiction. While this is an ambitious goal, the PHTF could enable it to be realized.

2. Nicotine's Consequences

The interaction between nicotine and other drugs is also of interest to NIDA. With PHTF resources, NIDA will support research related to the "gateway hypothesis" that envisions the brain as being primed by one drug for other drugs. NIDA will support studies examining whether nicotine primes the brain for other drugs of abuse and the role that compounds such as caffeine play in priming individuals for nicotine addiction.

The developmental consequences of nicotine exposure are of profound importance given the significant degree of exposure that occurs in utero and during the critical developmental period following birth. Estimates are that greater than 40% of infants live with at least one smoker. The PHTF will enable large-scale studies needed to examine the peri- and prenatal effects of nicotine exposure, the long-term developmental consequences of nicotine on the brain, and vulnerability to subsequent nicotine addiction after exposure to nicotine in utero.

NIDA will also utilize PHTF resources to expand support for investigation of nicotine's effects on cognition and the effects of chronic nicotine exposure on brain function. The role that cognitive effects such as heightened alertness, sustained performance levels, and enhanced memory have in the development of dependence are complex and will require large-scale studies to unravel. Studies on observed changes in receptor function after chronic drug exposure are needed to understand the maintenance of smoking behavior.

C. NIDA Plans for Expanded Clinical and Treatment Research

NIDA currently supports research on the treatment of nicotine addiction by focusing on the development of nicotine and non-nicotine replacement medications in combination with behavioral strategies. Individual and gender differences in cigarette abstinence are being examined, but the PHTF could enable these efforts to be enhanced.

1. Medication Development

NIDA will employ PHTF resources to examine non-nicotine, non-addictive medications for nicotine addiction. Basic research is needed for the development of non-nicotine, non-addictive drugs that target molecular sites other than nicotine receptors (e.g., Wellbutrin®). NIDA will also expand research on nicotine replacement therapies focusing on novel nicotine-like compounds which act at nicotine cholinergic receptors and produce nicotine replacement as well as blockade.

Tobacco contains many chemicals in addition to nicotine. Recent neuroimaging studies have shown that smokers have significantly lower monamine oxygenase A and B (dopamine metabolic enzymes) levels than either ex-smokers or nonsmokers. It is critical to understand how components other than nicotine may contribute to the development of the addiction process, to sustained smoking behavior, and to develop treatments focusing on those components. The PHTF could enable a substantial enhancement of studies on the non-nicotine psychoactive components of tobacco.

2. Multicenter Clinical Treatment Trials

NIDA will utilize PHTF resources to enable multicenter clinical trials for the treatment of nicotine addiction. Interventions aimed at children and adolescents is crucial. An amazing 89% of all adult smokers began smoking before age 18. PHTF resources will enable research aimed at the development of efficacious treatments (both behavioral and pharmacological) specifically for children and adolescents early in the course of their nicotine use.

Expanded research on the most advantageous integration of pharmacological and behavioral treatments for all smokers is essential. It is likely that the optimal combination of pharmacological and behavioral interventions differs among different groups of smokers. NIDA will seek to explore these difference. In addition to children and adolescents, interventions for pregnant women and other special populations including specific ethnic/racial groups will be explored.

Another important issue that can only be addressed in large-scale clinical trials of the kind that could be enabled by the PHTF is that of comorbidity. NIDA desires to support the examination of the potential links between tobacco use and psychiatric disorders and to develop targeted treatments based on these trials.

D. NIDA Plans for Expanded Health Services Research

Health services research looking at access to, effectiveness, and cost-effectiveness of drug abuse treatment services in improving the health and social functioning of persons addicted to illicit and licit drugs including tobacco is extremely important. The best of interventions is worthless if it cannot be delivered to individuals addicted to nicotine. NIDA supports such research along with research aimed at increasing patient engagement in the treatment process. Such engagement is known to lead to improved retention rates and lower rates of

relapse to drugs of abuse following treatment.

NIDA will utilize PHTF resources to expand research that will increase the transportability of efficacious therapies to the community/private practitioners. Of particular interest is the use of new technologies to enhance access to interventions. Among the technologies that will be the subject of this research will be hand-held computers for delivery of smoking cessation interventions. NIDA will also support research aimed at the use of telephone interventions (e.g., hotlines) as well as Web-based interventions to advise those trying to quit on their own.

Additional research is needed to define the primary care needs of individuals with nicotine addiction. The PHTF will enable research on screening instruments that assess primary care needs among smokers aimed at matching patient needs with appropriate levels of care. It is also critical to recognize the barriers to treatment that exist within distinct population groups and to explore means for lowering these barriers. In the era of managed care, it is particularly necessary to identify the most cost-effective interventions in the context of a larger public health approach to nicotine addiction. To be cost-effective, treatments must be first and foremost be effective. Attempts simply to cut costs can result in inferior treatments if research is not conducted into the type of training and credentialing that is necessary in order to assure quality treatment. NIDA would conduct this type of research with resource from the PHTF.

E. NIDA Plans for Expanded Behavioral Research

Everyone agrees that cigarette smoking is a complex behavior and that behavioral research is a critical component of dealing with nicotine addiction. NIDA's behavioral research on nicotine and smoking will continue to focus on an understanding of the antecedents of tobacco use, and on means of changing behavior patterns. This research will explore the most effective images and communication modes for more strategic and effective antismoking media campaigns in children and adolescents.

While much research is dependent upon experimentation involving humans, NIDA will use PHTF resources to identify animal models that capture certain components of behavior related to tobacco use. These will include examinations of conditions under which stress causes nicotine tolerance and relapse to nicotine use.

Like all aspects of smoking, abstinence and withdrawal are complex. Because most smokers try to quit but fail, it is important to conduct research aimed at understanding the functional impairments such as psychomotor and cognitive functions that smokers experience during abstinence and withdrawal as primary factors in relapse. The PHTF could enable this critical research to be conducted quickly thereby increasing the success rate of smokers who are trying to deal with their addiction. Even among those who are not committed to quitting tobacco use, this research may influence levels of consumption. It will be important to assess craving levels in controlled and real life settings to develop better interventions.

F. NIDA Plans for Expanded Public Health and Community Research

One of NIDA's most important goals is to translate research findings, especially those about the actions of drugs on the brain, to help the public better understand the nature of

addiction and the most effective strategies for its prevention and treatment. This entails a large variety of programs to ensure the rapid dissemination of research information and its implementation in policy and practice.

In order to develop and disseminate high-quality, science-based prevention strategies to communities throughout the country, research is needed to guide the refocusing of current successful drug use prevention strategies on nicotine and to target interventions to particular populations including children and adolescents. The tobacco industry has spent billions of dollars on advertising to promote tobacco use, and these advertising campaigns were based on research. As the NIDA seeks to disseminate information regarding the kicking of the tobacco habit, it is no less important that these information campaigns be based on methodologies with demonstrated success. The PHTF would enable NIDA to pursue research that will aid in the development of materials that effectively focus on nicotine as an addictive substance and to develop effective media campaigns to foster the dissemination of information on the addictive nature of nicotine.

G. NIDA Plans for Expanded Surveillance/Epidemiology Research

NIDA-supported epidemiological studies monitor patterns of drug use including nicotine, such as The Monitoring the Future Study that the Nation relies upon for examining current drug use and trends among our Nation's youth. These and additional studies supported by the PHTF will provide invaluable data to inform development of prevention and treatment strategies. NIDA seeks to enhance its portfolio of research on risk and protective factors, as well as studies on the co-occurrence of nicotine with other drugs of abuse.

What are the risk factors that impact on tobacco use? The PHTF will enable research aimed at answering this complex question. Research will examine multiple levels of risk factors, including larger socio-environmental factors such as price, exposure to advertising, and promotional activities, ethnic influences, and affective states. Critical will be an expansion of surveillance systems to measure knowledge, attitudes, and behaviors regarding tobacco use among adolescents and adults. Large, population-based, longitudinal studies are needed to assess determinants of initiation and cessation of tobacco use. The PHTF could enable this research as well as provide the opportunity for epidemiological research on tobacco use as a comorbid disorder with mental disorders or as an antecedent to other drug use.

VIII. NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

The mission of the National Institute of Environmental Health Sciences (NIEHS) is to reduce the burden of human illness and dysfunction from environmental causes by understanding each of these elements and how they interrelate. The NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach.

A. Tobacco As An Environmental Hazard

Tobacco, particularly tobacco smoke, is a critical public and environmental health problem. Smoking is linked to cancers of the lung, esophagus, oral cavity, pancreas, kidney, and bladder, accounting for an estimated 30% of all cancer deaths. Smoking during pregnancy is linked to miscarriage and low birth weight in infants. Smoking contributes substantially to the risk of cardiovascular disease (coronary artery disease, stroke, and high blood pressure) and is the leading cause of chronic lung disease, responsible for 90% of deaths from chronic obstructive pulmonary disease (COPD). In addition, exposure to environmental tobacco smoke (second-hand smoke) is estimated to cause approximately 3,000 lung cancer deaths per year among nonsmokers and contribute to as many as 40,000 deaths related to cardiovascular disease.

This existing body of knowledge may be sufficient to drive a new wave of smoking cessation efforts, but there is still a great deal of research to be done which will ultimately shape our focus as public health practitioners, leading us to new prevention strategies, new target populations, and new interventions for tobacco-related morbidity and mortality. We need to understand better how tobacco and tobacco smoke exert their effects at the cellular and genomic level. We need to examine the effects of tobacco components on the endocrine and immune systems, with emphasis on developmental effects, effects of repeated exposures, and roles of inflammatory cells in generation of adverse health effects. We need a better understanding of susceptibility to tobacco smoke and its effects, including nicotine addiction. We need more research on the interactions of tobacco components and tobacco smoke with other environmental agents such as radon and air pollutants. Exposure to tobacco smoke in the home is already identified as a risk factor for development of asthma in children; continued study of tobacco smoke as an environmental factor in asthma and other multifactorial diseases may uncover additional, currently unsuspected health effects of tobacco that will drive our public health strategies in the future.

B. Tobacco-Related Basic Research of NIEHS

NIEHS has a long history of research on the numerous carcinogenic components of cigarette smoke such as benzo[a]pyrene and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, their metabolism and distribution in the body, and their ability to interact with, and damage DNA, leading to cancers. Building on this early body of work, NIEHS scientists are increasingly defining how genetic differences in the ability to metabolize cigarette smoke carcinogens confers individual risks to cancer. For example, NIEHS scientists showed that differences in the gene coding for the carcinogen metabolism enzyme glutathione S-transferase M1 could increase the risk of bladder cancer by 70% in smokers. These types of correlations between genetic differences in metabolizing enzymes and cancer risk are being attempted on a host of cancers, including those of the lung, prostate, breast, colon, and anogenital tract.

Cigarette smoke carcinogens operate in a multi-step process that involves interacting with, and damaging, critical strands of DNA. NIEHS has supported a number of studies that investigate this process, including the mechanisms by which the human body corrects any errors arising from carcinogen-DNA adducts, and the consequences when DNA repair mechanisms are unable to detect or repair damage. Important work in this area includes a recent study that identified the actual areas on the tumor suppressor gene, *p53*, that were preferentially attacked by the cigarette carcinogen benzo[a]pyrene. These sites were the exact areas that are found damaged in lung cancer patients, thus providing an early mutational "fingerprint" of subsequent lung cancer risk. Work of this nature gives valuable insight into the molecular mechanisms by which chemicals found in cigarette smoke can exert biological damage.

One of the greatest tragedies of cigarette smoking is that it can have adverse effects on children exposed to second-hand smoke. Maternal smoking is suspected of negatively affecting formation of the placenta and of causing premature separation of the placenta, resulting in perinatal morbidity and neonatal mortality. Pregnant women who smoke are twice as likely to give birth to infants with a harelip birth defect and their children are at greater risk of being born with low birth weight. The developing lungs and nervous system of the young are also suspected of being unusually vulnerable to even low levels of environmental tobacco smoke. The NIEHS is funding studies to investigate the impact of maternal smoking during pregnancy on the infant and child. In one study, rats are being used to determine if passive maternal smoking affects the neurobehavioral development of the fetus and subsequent cognitive development of the young animal. Of particular interest in this study are any structural and functional disruptions of the hippocampus. Such detailed study may in future lead to strategies by which these adverse effects could be circumvented or reversed.

C. Tobacco-Related Epidemiology/Surveillance Research of NIEHS

NIEHS researchers have long been interested in how tobacco smoke can potentiate the action of other known environmental carcinogens. For example early work on the fatal pulmonary cancer, mesothelioma, showed that it was caused by the insulating material, asbestos. When workers were exposed to both asbestos and tobacco smoke, their risk of developing mesothelioma was greatly enhanced. NIEHS epidemiologists are investigating whether concurrent exposure to tobacco smoke increases cancer risks from household radon exposures and other environmental exposures.

D. NIEHS Plans for Expanded Tobacco-Related Basic Research

The proposed Environmental Genome Project would provide a unique mechanism to increase our knowledge of specific genes affected by components of tobacco smoke and of the variability within the human population in susceptibility to these chemicals. This project will be a multicenter effort to obtain information on DNA sequence diversity for the U.S. population on genes currently recognized to affect susceptibility to environmental disease. This is an extremely ambitious but very doable project. The rapidity of its completion would be greatly enhanced by resources of the PHTF.

The effects of involuntary exposures to tobacco smoke on the fetus, infant, and child remains an important research area. It is particularly important to understand the vulnerability of the

developing lung and nervous system to tobacco smoke and the long-term consequence of these early exposures. Other important non-cancer endpoints include immune suppression and bone development. The PHTF could enable this important research.

The mechanisms by which tobacco smoke increases a woman's risk of the crippling bone disorder, osteoporosis, need to be defined. NIEHS-supported research suggests that cadmium delivered in the smoke stream might be the component most responsible for this disease. More research is needed.

Other important biological mechanisms to be explored include the effect of tobacco smoke on oxidative stress, inflammatory responses, immunosuppression, and disruption of hormonal homeostasis. Work also needs to be continued at the genomic level to identify mutational "hot spots" that are particularly vulnerable to attack by components of tobacco smoke. Study on the mechanistic components of tobacco exposure will provide insight into new health effects from tobacco smoke, into how tobacco smoke interacts with other environmental agents to potentiate adverse health effects, and into promising strategies for preventing, circumventing, or reversing these adverse effects. The PHTF could enable this research.

The PHTF could also support the identification of additional biomarkers of tobacco-related exposures and effects. These biomarkers could be used as "early warning systems" to alert individuals about impending disease development if they continue smoking. This might prove one of the most useful tools for encouraging smoking cessation since it would identify the actual risk that an individual has, rather than extrapolating from aggregated population studies.

E. NIEHS Plans for Expanded Tobacco-Related Epidemiology/Surveillance Research

With PHTF support, epidemiology studies could be expanded to investigate other disease endpoints for which concurrent exposure of tobacco smoke and environmental exposures confer greatly increased risk over single exposures. Additionally promising biomarkers of exposure and of genetic susceptibility could be incorporated into epidemiology studies to give a level of refinement and precision not previously possible in identifying health risks associated with tobacco smoke. The utility and precision of epidemiology studies on tobacco smoke could also be greatly enhanced by including markers of genetic susceptibility.

IX. SUMMATION OF THE PERSPECTIVE OF THE NIH ON THE PHTF

It should be abundantly clear from this document that there exists no shortage of worthy research projects aimed at reducing tobacco use and reducing the burden of tobacco-related diseases. Many of these research projects are of such a magnitude as to make them difficult to envision apart from additional resources. The Public Health Trust Fund could enable these projects to move from dreams to reality.

The millions of lives already lost to tobacco ought not to be followed by millions more. These deaths are largely preventable. The negative economic impact of tobacco that accompanies its wave of death and disability is also avoidable. There are things that can be done. Only some have been described in this document. The National Institutes of Health has been the leader in tobacco-relevant research and is positioned to continue to lead in the years ahead.

If the resources of the Public Health Trust Fund are large enough, if these resources are sustained, and if proper stewardship is exercised, its establishment may one day be viewed as among the most significant events in the history of public health.

PROGRAMS / FUNDS IN TOBACCO SETTLEMENT

UP-FRONT COMMITMENT (\$10 billion over 25 years)

- A one-time, \$10 billion payment would be required as of the date of enactment of the settlement. There is no dedicated use for these funds.

BASE PAYMENTS (\$333.5 billion over 25 years)

- **Federal and State Uses**

Reduction in Tobacco Usage (\$5.325 billion): For Secretary of HHS to encourage current tobacco users to quit through media-based and non-media based education, prevention and cessation campaigns.

FDA (\$7.5 billion): To the Food and Drug Administration (FDA) to enforce the terms of the settlement.

Programs like ASSIST (\$3.0 billion): For state and local tobacco control, similar to the community-based model of the ASSIST program

Research (\$2.5 billion): On the methods to prevent smoking and help individuals quit.

Education (\$12.5 billion): To fund an Independent, non-profit organization to run a multi-media campaign to discourage and de-glamorize tobacco use.

- **Cessation Fund (\$35.5 billion):** To create a trust fund to promote effective cessation programs and provide financial assistance to access such programs.
- **Teams' Fund (\$1.8 billion):** For 10 years, to compensate events, teams, or entries in such events who lose sponsorship by the tobacco industry as a result of the settlement. After 10 years, funds will be reallocated to education, enforcement of provisions, and community-based programs.
- **Health / Other (\$265.375 billion / possibly \$151.264 billion Federal):** Remainder of the Base Payments; no specified use.

PUBLIC HEALTH TRUST FUND (\$25 billion over 25 years)

- A Presidential Commission will be created to identify and fund specific tobacco-related medical research

Chris's Budget gap.

7/11/97

Issues - I funding flow will erode
→ new uses better?

— II Who should oversee? Change or priority change?
Tax revenue vs. specific spending.

— III tobacco-related only

Substitution — how to stop it? — Spend it on
new things; set up trust fund. 'But' ⇒
Things we're spending it on now are
not the highest value for marginal \$

INVESTMENTS

— Data / epi.

preventive / heal

— Screening — diabetes / for retinopathy

Assist → to the local level

Chris — We'll need \$ estimates; baseline state/fed spending.

Packaging

— Children's trust fund

— Health trust fund.