TRDRP
Tobacco Related Disease Research Program
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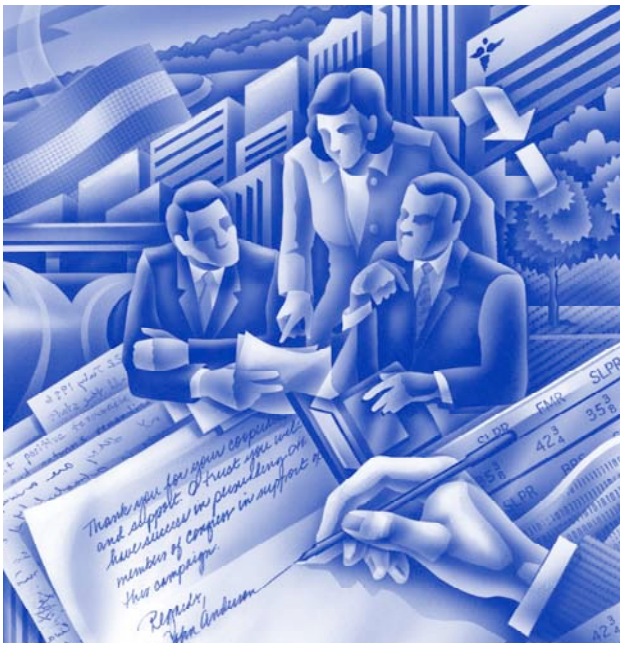
Research for a Healthier Tomorrow

Since its inception in 1989, the Tobacco-Related Disease Research Program (TRDRP) has become the premier program for state research funding on tobacco control and tobacco-related disease in the U.S. TRDRP's grant portfolio covers a broad range of scientific disciplines, diseases, and public health issues. TRDRP-funded research projects have made significant advances in our knowledge of cancer, cardiovascular and pulmonary disease, nicotine dependence, and tobacco control, as well as improvements in programs, policies, and interventions for the prevention and treatment of tobacco-related disease. Many studies have focused on California's diverse population, including ethnic and racial groups, low socioeconomic status, and sexual orienation. TRDRP has also played a key role in building a robust infrastructure for tobacco-related research comprised of exceptional scientists who have become international leaders in their respective fields. TRDRP is an integral component of California's comprehensive tobacco control effort. Other states and nations look to TRDRP as a model and partner.

Articles

Research is Vital to Tobacco Control



by Francisco O. Buchting, Ph.D.

The reality is tobacco-related research has been, and will continue to be, a key weapon in the battle against Big Tobacco. This fact was true before the release of the 1964 Surgeon General Report: Reducing the Health Consequences of Smoking, and research became even more prominent in the tobacco battlefield after the release of that report. In fact, research is just as imperative today in the post-MSA environment where the tobacco wars continue. In California, TRDRP has been the leader in funding credible and scientifically sound tobacco-related research that is vital for tobacco control efforts.

This article explains why and how research is a vital part of tobacco control, provides an example of how research has played and continues to play an important role in the issue of second hand smoke (SHS) exposure, and spells out the challenges for the future of TRDRP.

Why do we need a research program?

By the early 1950's, the tobacco industry (TI) was faced with an increase in published independent research linking tobacco use to lung cancer, a questioning of consumer confidence, and threats of litigation. Early research findings were the catalyst for the conversion of tobacco use into a public health issue as well as wake-up call to the TI that business as usual was not going to last forever. According to the TI's internal documents, the tobacco companies' strategy to snuff out this wildfire was to jointly conspire to misuse and manipulate scientific research to severely cripple any public health efforts addressing the effects and damage of tobacco use. Thus research became a very powerful weapon in the tobacco-control battles for over half a century. (See TRDRP Newsletter, March 2001, The Tobacco Industry as a Funder of Scientific Research).[1]

The manipulation of data and the creation of "tainted science" have been and continue to be a cornerstone in the TI's strategic public relations efforts to diminish, dismiss, or negate the health effects due to tobacco use and SHS exposure. "The most important type of story is that which casts doubt in the cause and effect theory of disease and smoking. Eye-grabbing headlines were needed and should strongly call out the point – Controversy! Contradiction! Other Factors! Unknowns!"[2] Even to this day, the TI continues to deny or call into question scientific findings and continues to fund and disseminate questionable research findings.[3] The production and use of "tainted science" has been an effective tool for the TI to delay and sometimes forestall tobacco control efforts in California, the US, and worldwide.

TRDRP has been an antidote to the TI's "tainted science" strategy by modeling its practices after the National Institutes of Health peer review and by building a distinguished record of funding high quality scientific work by reputable scientists, thus making TRDRP a credible and highly respected funder of research. Re-search findings from TRDRP-funded projects have been used in key state and national documents to create or support tobacco control policy and legislation, to highlight and discredit the TI's "tainted science", and to support tobacco control efforts.

It is not surprising that the TI had significant concerns when California voters, through the passage of Proposition 99, created a comprehensive tobacco control effort that included an aggressive tobacco control campaign and a tobacco specific research p r ogram. A 1989 TI document titled "Project California," and prepared by the State Activities Division of the Tobacco Institute proposed an all concerted effort to block the activities from two of the Proposition 99 programs it had classified as unacceptable: "Industry consultants have completed an initial assessment of proposals offered by the Governor and have identified "acceptable" and "unacceptable" programs listed for funding. Through industry efforts, a significant amount of Prop 99 revenues have been assigned in the Governor's budget, as noted above, to "acceptable" programs. There are two exceptions – University of California Research and Grants and Department of Health Services anti-smoking programs. A sound legislative tactical plan is presently underway to address concerns."[4] This document spells out the steps the TI would undertake to undermine or halt the work to be done by both programs. Evidently, the TI recognized and was concerned about the negative impact a legitimate state-specific funder of tobacco-related research would have on its pro-tobacco activities.

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Legitimate science vs. TI "tainted science" in the SHS battles

The TI used the same public relations strategy of systematic manipulation and adulteration of the scientific process and record with the issue of SHS just like they have used with any other tobacco issue that might lead to a tobacco control policy. The use of this strategy by the TI was spelled out very clearly in a 1978 report prepared for the US Tobacco Institute by the Roper Organization: "what the smoker does to himself may be his business, but what the smoker does to the non-smoker is quite a different matter … This we see as the most dangerous development yet to the viability of the tobacco industry that has yet occurred ... The strategic and long run antidote to the passive smoking issue is, as we see it, developing and widely publicising clear-cut, credible, medical evidence that passive smoking is not harmful to the non-smoker's health."[5] Even to this date, this is the strategy still being used by the TI in order to thwart attempts by the tobacco control community and health policy makers to deal with SHS. Why is the tobacco industry wedded to this type of strategy? Because it makes sense and it works, although not as well anymore.

Just as studies linking smoking and lung cancer began to show up in the scientific literature, so did the findings of health effects associated with SHS exposure begin to make a significant presence. The scientific evidence began to confirm what the public health community long suspected: that SHS is more than just an "irritant." A long battle ensued in the scientific literature and the public health arena over the health effects caused by SHS exposure. While the scientific community and the public health community used legitimate science and public health tools to bring light to the dangers of SHS exposure, the TI continued their public relations campaign of creating controversy and contradiction through "tainted science". The TI's need to obfuscate the legitimate scientific findings in the literature was so pressing that they jointly funded the Center of Indoor Air Research to mass produce their SHS "tainted science."[6] Nevertheless, epidemiological studies of health consequences due to SHS exposure continued to be published, making the case to create and support tobacco control policy to address SHS exposure.

In California, the clash of legitimate science and "tainted science" began to be played out in front of town hall meetings, city councils, legislation, and the courts. The success of local action in passing local ordinances to minimize the exposure to SHS rose to state level attention when AB13 was introduced and subsequently passed and when the California EPA classified environmental tobacco smoke as a Class A carcinogen. In the battles leading up to these two turning-point events, as well as in subsequent battles, the role of scientific evidence has played center stage.

Legitimate research findings, including research funded by TRDRP, produced the evidence needed to overwhelmingly dismiss the claims made by the strategic public relations "tainted science" campaign launched in California by the TI and the unsupported declarations from the TI's front groups. These legitimate research findings strengthened the arguments for SHS public policies, such as AB13, made by California's tobacco control community and public health agencies. For example:

♦ Research funded by TRDRP has shown that ventilation does not work when it comes to SHS. In addition, recent research findings are beginning to model how toxins from SHS can be deposited on the furniture and carpet in a room only to be later absorbed through the skin.

♦ TRDRP studies the chemical composition of tobacco smoke have identified a host of toxins and carcinogens associated with a variety of TRD and health effect effects.

♦ At the same time, TRDRP epidemiological studies have reported significant associations between SHS exposure, tobacco related diseases and health effects, while biomedical research has provided the causal evidence by identifying biological mechanisms by which SHS causes disease. For example, different types of cancer, decrease in lung functioning, cardiovascular disease, reproductive and developmental health effects including SIDS and inner ear infection can all be caused by SHS.

♦ Projects funded by TRDRP that looked at the TI documents revealed that the research funded by the TI in the area of SHS was of consistently lower quality than comparable legitimate research reported in the peer-reviewed literature. The findings from these studies helped bolster the 1996 US EPA findings on the danger of SHS when the industry tried to use its "tainted science" to discredit the report. Results from TRDRP-funded studies also played a role in the California EPA report, in which SHS is classified as a Class A carcinogen.

Ongoing TRDRP research into SHS will continue to produce critical findings that will be important for new public health initiatives in this area. Findings from TRDRP projects looking at home smoking bans across different ethnicities and other priority populations in California and research analyzing the best public health models for increasing success in this area will enhance tobacco control efforts. Likewise, TRDRP studies are also testing different SHS exposure prevention models with children and adolescents in California schools. Currently, TRDRP-funded research is being used by the California Air Resource Board to support their work on classifying SHS as an environmental toxin. TRDRP will continue to make research into SHS a priority, especially when this area is under-funded across all the sciences at the federal level.

What lies ahead?

Imagine a tobacco control effort in California without high quality tobacco-related research. Imagine the TI parading their "tainted science" in front of city councils and state legislature without

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being challenged by legitimate research. Imagine the TI or their front groups using this "tainted science" to overturn or weaken existing tobacco control policy or to stall proposed tobacco control and health policy. The TI's ability to delay, weaken or overturn tobacco control policy and health policy has been documented numerous times.

Research funded by the federal government will continue to have a significant role in tobacco control. But in California, a significant amount of the much needed research funded by TRDRP would not be funded by the federal government due to different priorities or political interests. For example, research on lung cancer, COPD, health effects associated with SHS exposure, and California policy specific research has not been historically funded by the federal government at the same level as other research topics. In addition, research that focuses on California's diverse population and on gender differences will not receive the same amount of attention as it does today, due in part to TRDRP. The synergistic relationship between federal research and California specific targeted research that exists today would also be lost. The reality is that public health policy is influenced by research or is supported by research, and sometimes it is a direct result of research. In the tobacco wars, this has been the case, but even more so now since the TI continues to manipulate science for its own purposes and not for public health. Thus, more legitimate California specific targeted tobacco-related research is needed.

The TRDRP finds itself at crossroads due to the recent budget reductions and the increasing appropriation to the California Cancer Registry. The staff at TRDRP is committed to ensuring that the will of the voters of California is carried out and the directions set forth by the legislation for Proposition 99 are followed as closely as possible. The mandate is broad, the challenge is welcome and the need to act is great – 42,000 Californians will die this year of a tobacco related disease. The TI will continue to addict the next generation of replacement smokers in order to maintain their profit margin. "Tainted science" will continue to be funded by the TI to derail tobacco control policy and efforts. The reality is that the science funded by TRDRP does make a difference, it has an impact, and it is one of the powerful weapons we have to combat an industry that knowingly disables and kills the people who use their product and those exposed to SHS.

More research is needed. TRDRP is committed to continue funding the best science and playing a key role in tobacco control in California. TRDRP will have to change in order to maximize the impact of our efforts as the budget situation continues to decline due to a misappropriation of funds from the research account. The minimum amount of funding needed by TRDRP in order for tobacco-related research to, in part, continue to have a significant impact in California is unknown at this time. What is known is that a strong and adequately funded TRDRP equals Research for a Healthier California.

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TRDRP's Genesis and Work

The enabling legislation for Proposition 99 provided the framework for research to play a role in California's tobacco control efforts and in mitigating the health effects and diseases associated with tobacco use and SHS exposure. Health & Safety Code, Section 104370 states, "The department (of Health Services) and the California Department of Education shall apply the most current findings and recommendations of research including research funded by the Research Account (TRDRP) of the Cigarette and Tobacco Products Surtax Fund created by Section 30122 of the Revenue and Taxation Code." This tobacco control framework has been a three-pronged approach for California's tobacco control efforts where research (TRDRP), education and intervention (Tobacco Control Section and California Department of Education), and policy (local and state) inform and influence each other. The legislative charge to the University of California, per Health & Safety Code, Section 104530, was to create and manage a comprehensive tobacco-related research program. The scientific charge was broad in scope: "tobacco-related disease research includes, but is not limited to, research in the fields of biomedical science, the social and behavioral sciences, public policy, epidemiology, and public health."[7]

A comprehensive and searchable database of TRDRP research portfolios can be found at www.trdrp.org. In addition, highlights of the first ten years of research funded by TRDRP can also be downloaded.

Lung Cancer
The Case for Research Funding

by M.F. Bowen. Ph.D.

Absent thee from felicity awhile,
And in this harsh world draw thy
breath in pain, To tell my story.
William Shakespeare [Hamlet, V.ii.360]

Lung Cancer – An Overview

Lung cancer is the uncontrolled proliferation of non-differentiated, non-functional epithelial cells in the airways. There are several different types of lung cancer, depending on the type of epithelial cell which succumbs to carcinogenic damage and the histological appearance of the transformed cells. Smoking is responsible for 87% of all lung cancers [1] and is strongly associated with all histological classes.[2] The most common outcome for all types of lung cancer is the same: death due to loss of pulmonary function and/or complications due to metastasis to other sites, most commonly bone, liver, lymph nodes or brain. At initial diagnosis cancer patients most often present clinically with cough, blood expectoration, shortness of breath, chest pain and recurring pneumonia or bronchitis.[3] These symptoms are commonly associated with other, less deadly, conditions and by the time a diagnosis of lung cancer is made, it is usually too late: The disease has spread and treatment in such cases is more invasive, more difficult and less effective. If detected early enough, surgery is the treatment of choice. However, because early diagnosis is so problematic, radiation and chemotherapy are usually required in conjunction with surgery. The survival rate is 49% in those cases where the tumor is detected early but only 15% of lung cancers are detected early enough for patients to qualify for this relatively sanguine prognosis. The 5-year survival rate for all stages of lung cancer progression combined is only 14%.[4]

Lung cancer is now the leading cause of cancer mortality in both men and women in the US. An estimated 157,400 people died of lung cancer in the US in 2001, a figure which represents 28% of all cancer deaths that year.[4] Lung cancer annually kills more women than breast cancer and more men than prostate cancer. In California, for example, an estimated 13,200 people died of cancer of the lung or bronchus in 2001, 25.8% of all cancers in California; 2,800 died of prostate cancer or 5.5% and 3,900 of breast cancer or 7.6% of all cancers.[4]

There are at least two bright spots in this otherwise gloomy picture. For one thing, lung cancer rates between 1988 and 1997 dropped twice as rapidly in California as in the rest of the country,[5] due at least in part to California's aggressive anti-smoking campaign initiated in 1988. Secondly, long-term lung cancer survivors have recently been found to have a better quality of life than expected.[6] Nonetheless, recent incidence and mortality statistics remain dismal.

Lung cancer incidence and mortality rates display striking and largely unexplained racial/ethnic differences.[4] Among men reported lung cancer incidence rates (per 100,000) are highest in African Americans (117), followed by Caucasians (71.9), Asian/Pacific Islanders (51.9), Hispanic (38.0) and American Indians (25.1). Mortality rates follow this same trends. The underlying causes of these discrepancies are likely complex but at least part of the reason for the disparities in mortality may reside in the fact that race and ethnicity influence access to appropriate and aggressive cancer care and treatment post-diagnosis.[7] Biologic differences may also play a role as susceptibility to certain, possibly more deadly, histological types of lung cancer are higher in African Americans as compared to Caucasians even after adjustment for smoking.[8] Racial/ethnic differences in the metabolism and detoxification of tobacco smoke components, including carcinogens, may be another factor for the higher incidence of lung cancer in African American men.[9,10,11] The preference of African-American smokers for mentholated cigarettes[12] may be yet another factor in the increased cancer incidence seen in this population: Menthol may enhance

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exposure to carcinogenic smoke components, possibly through its action as a bronchial dilator.[12] Lung cancer rates among men are 2-3 times higher than those in women in all ethnic categories; however, there is compelling evidence that women are more susceptible to lung cancer given the same amount of smoke exposure.[13] As in the case of ethnic differences, the reasons for this disparity are largely unexplored and unexplained.

The Debate That Shouldn't Have Been

That lung cancer is caused by smoking is a fact so well-known, established, and incontrovertible that it is difficult to imagine a time when it was a subject of debate. Nonetheless it was. The controversy was fueled by the tobacco industry, which spent a considerable amount of time and money disputing the facts and clouding the issue.

Before the invention of cigarettes lung cancer was extremely rare. People started smoking in large numbers during World War I when tobacco companies distributed free cigarettes to members of the armed services.[14] By the 1930's the health effects of this largesse were evident. Physicians noticed a large number of lung cancer cases in men and lung cancer rates in this group rose rapidly thereafter from approximately 10 (per 100,000) in 1940 to approximately 75 in the mid-1980's.[2] Lung cancer incidence in women lagged behind that in men, but, following a steep increase beginning in the early 1960's, lung cancer surpassed breast cancer as the leading cause of cancer mortality in women in 1987. These patterns closely tracked trends in cigarette smoking. In fact the epidemiological association between smoking and lung cancer was so pronounced, so strong, and so consistent and the association between lung cancer and smoking history in patients so compelling, that the Royal College of Physicians in Britain issued a report in 1962 on the health hazards of smoking[15] which was followed shortly thereafter by the US Surgeon General's report on the same topic in 1964.[16] Nonetheless, smoking was so inculcated into American culture that the American Medical Association itself refused to endorse the Surgeon General's report. In fact, many medical doctors themselves were addicted to cigarettes. More ominously, the AMA continued to accept contributions from the tobacco industry.

In such an atmosphere, the tobacco industry found it advantageous to mount a two-pronged attack on its public relations problem. On the one hand, it denied the association between lung cancer and smoking and on the other it began to market cigarettes with implied reduced health risks.

In 1954 the tobacco industry set the tone of the debate by publishing, under the dubious auspices of the Tobacco Industry Research Committee, the now-infamous "Frank Statement to Cigarette Smokers," which claimed that there were many possible causes of lung cancer and that there was no agreement among authorities that cigarette smoking was one of the causes. Thus began decades of refusal by the tobacco industry to recognize a cause and effect relationship between smoking and lung cancer. At the same time the tobacco industry capitalized on the growing public awareness that smoking was dangerous by promoting first filter then low-tar cigarettes starting in the 1950's and 1960's. Advertising "tar wars" ensued between competing tobacco companies (the tar derby), which fueled the consumers' misperception that these products were low-risk.[17] By the 1970s and 1980s the tobacco industry had introduced numerous low tar, "light" cigarette brands. However, subsequent research has shown that these products are anything but safe for human consumption and have not appreciably reduced the risk of lung cancer. This may be due to the fact that smokers compensate for reduced nicotine levels by inhaling more deeply and because levels of carcinogenic nitrosamines in such products have actually increased over time.[18]

The cause and effect relationship between cigarette smoke and lung cancer has of course, since been abundantly and irrefutably demonstrated. The first evidence that a tobacco com-

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Did you know that:

Nat King Cole	Lon Chaney
Carl Wilson	Wayne McLaren
Joe DiMaggio	(The Marlboro Man)
Roger Maris	Eddie Rabbit
Jimmy Dorsey	Lee Remick
Susan Hayward	Doug McClure
Betty Grable	Edward R. Murrow
Joe Higgs	Larry Linville
Gary Cooper	Chet Huntley
Cal Ripken Sr.	Franchot Tone
Walt Disney	Yul Brynner
George Peppard	Sarah Vaughan
Spencer Tracy	Mort Downey, Jr.
Harry Reasoner	Alan J. Lerner
Melina Mercouri	Desi Arnez
Audrey Meadows	Chuck Connors
Art Blakey	John Wayne
Ed Sullivan	Leonard Bernstein
Duke Ellington	Bert Parks
Jack Benny	Arthur Godfrey

all died of lung cancer?

(from: Smoke-Free Educational Services, Inc.)

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pound directly interacts with a DNA site known to be involved in cancer initiation was produced by a TRDRP-funded researcher.[19] As early as 1986 it was recognized that environmental tobacco smoke can cause lung cancer in adult non-smokers.[20, 21] It is no surprise that in 1993 the U.S. Environmental Protection Agency declared environmental tobacco smoke to be a Class A, or known, human carcinogen. Moreover, smoking has now been linked to many other types of cancer beside lung cancer.[22]

Chronic Underfunding

With lung cancer the leading cause of cancer mortality in the US, it is surprising that it is grossly underfunded as compared to other types of cancer. In 2001 approximately $900 per death was spent on lung cancer research; by (per death) comparison, $9,000 was spent on breast cancer research, $3,500 on prostate cancer, and $34,000 on HIV/AIDS.[23] All of these diseases richly deserve the funding support they receive. But given the high incidence and mortality of lung cancer and (because of the difficulty of early and accurate diagnosis) the costs of treating it,[24] lung cancer deserves much more funding than it presently receives. The fact that lung cancer is not a disease that is sexy or that garners much sympathy or empathy from potential donors does not help the situation. Nor does it help that lung cancer victims, once diagnosed, do not live long enough to become activists for their cause.

TRDRP has tried to rectify this situation for the California research community. Of the 962 grants funded by the TRDRP through 2001, 168 have involved research either directly related to lung cancer or research on basic biological phenomena common to many cancers, including lung cancer. This issue represents 89% of TRDRP's total biomedical portfolio. TRDRP has supported research on etiological mechanisms, new and improved diagnostics and innovative therapies. TRDRP researchers have provided evidence that tobacco smoke damages the p53 tumor suppressor gene,[25] developed sensitive tests for the detection of metastases[26] and for the early detection of transformed cells,[27] demonstrated that environmental tobacco smoke induces tumor development in an animal model,[28] developed an anti-angiogenic DNA vaccine[29] and developed a blood test for tobacco-specific carcinogenic nitrosamines.[30] These are only a few examples of accomplishments of TRDRP-funded researchers that address the inception, progression and devastating consequences of lung cancer.

Future Directions

Ongoing work to develop early diagnostics and to design more effective and less damaging treatments for lung cancer needs continued support. We also need to address recently-emerging areas of concern. New and diverse biomarkers are needed to assess lung cancer risk from the new generation of "harm-reduction" tobacco products.[31] We need to assess the extent of exposure reduction and the impact of these products, if any, on public health.[32] History tells us that we cannot expect accurate answers from the tobacco industry in response to questions about their new and "improved" products. Such an assessment must be conducted independently. The biological mechanisms underlying ethnic and individual differences in lung cancer susceptibility and mortality need to be defined; in so doing, new ways to approach lung cancer diagnosis and treatment may be revealed. This approach also offers hope that treatment can be pharmacogenomically designed to fit each patient's specific needs, thus vastly improving clinical outcome.

Conclusion

Like AIDS, lung cancer is a stigmatized disease, with many non-smokers of the opinion that smokers "get what they asked for." This ignores several salient and incontrovertible facts: That nicotine is one of the most addictive substances known; that as long as it is sold to consumers in the form of cigarettes it is a legal substance; and, perhaps most frightening of all, that the tobacco companies have the financial and, by extension, political, power to influence marketing and legislation to their advantage. Lung cancer will continue to exact a high human toll on its victims and their families, as well as a financial drain on our health service systems. Lung cancer survival rates have changed little over the past 10 years. We have an opportunity to change that. New techniques in molecular biology, biochemistry, synthetic chemistry, and biomedical engineering provide unparalleled opportunities to uncover the mechanisms underlying lung cancer, develop innovative techniques for diagnosis, early detection and treatment, and unravel the mysteries underlying ethnic, sex-based, and individual differences in incidence and survival.

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Hooked on Hookah?
What You don't know can kill You

by Kamlesh Asotra, Ph.D.

"Harmful hookahs lure a young crowd"—announces the headline of a recent Contra Costa Times article. According to the article, public health professionals in California are very concerned about hookah smoking among our youth.[1] Researchers across the globe have echoed similar concerns.[2,3] A growing number of college students and others in the United States who have tried or now regularly participate in hookah smoking claim that they do not smoke cigarettes or use tobacco. Most of these individuals believe that hookah smoke is neither addictive nor as harmful as cigarette or cigar smoke.[4] This sense of false security may be perpetuated by the myth that the hookah smoke, after bubbling through water becomes devoid of the harmful elements that are present in cigarette smoke.

Among more than 1 billion smokers worldwide, 100 million people in Africa, Asia, and the Middle East use water pipe or hookah to smoke tobacco. Water pipe is variously known in different regions as hookah (Indian subcontinent and Africa), shisha, borry, goza (Egypt, Saudi Arabia), narghile, arghile (Jordan, Lebanon, Syria, and Israel), shui yan dai (China), or hubble-bubble. It's believed to have originated in India in the 16th century and found its way to Persia (Iran), Turkey, and the Eastern Mediterranean.[5] In the last 25 years, hookah smoking has become increasingly popular in Arab societies, Europe, and the United States due mainly to the cultural and social practices of new immigrants from countries where hookah smoking is an accepted tradition. Recently, hookah bars have mushroomed across California and in several other states with sizable Arab-American populations. More than 300 hookah bars are operating in the United States, with at least 50 in California. Many are located near colleges, universities, and shopping malls and are frequented by college students and locals. The bars offer an "exotic ambience" where customers can smoke a variety of fruit flavors and aromas in smoking sessions that last 45 to 60 minutes, for the cost of about $15.[4]

Is hookah smoke really so innocuous? This article describes hookah smoke chemistry and highlights facts related to hookah smoking and diseases that deserve attention and further scientific research.

Hookah tobacco combustion—"cool" burning

Hookah or water pipe is made of a clay bowl, body, water reservoir, and a stem or hose for inhalation of tobacco smoke. Hookah tobacco—mu'essel or maas-sel (assal means honey in Arabic)—is a moist, paste-like mixture of about 30% crude, cut tobacco, fermented with approximately 70% honey, molasses, and pulp of different fruits to create the fruity flavor and aroma of the smoke when subjected to slow combustion with burning charcoal. The combustion processes that produce cigarette smoke and hookah smoke are very different. Mainstream cigarette smoke is produced at 900°C. Hookah smoke is produced at nearly half that temperature at 450°C. Hookah smoke bubbles through water at the base reservoir. During a smoking session, more glowing charcoal is added to the partially consumed hookah tobacco once the original charcoal in the bowl is used up. As the hookah smoking session progresses, the reservoir water becomes increasingly brown in color on account of "tar," dissolved chemicals, and other particulates in the hookah tobacco aerosol. The chemical waste-laden water is discarded and the hookah reservoir is then replenished with fresh water for the next smoking session.

What is in hookah smoke?

During the last 40 years of research, nearly 4,800 chemical compounds have been identified in cigarette smoke, including 69 carcinogens.[6] In contrast, only five studies have been published in English on the chemical composition of hookah smoke, and those focused on only a relatively small number of chemical compounds.[7–11] Combustion chemistries in-volved in the production of mainstream cigarette smoke and mainstream hookah smoke differ due to widely different combustion temperatures and the dry or humid characteristics of tobacco. In both cases, plant-derived organic matter undergoes pyrolysis or volatilization, producing addictive nicotine as well as a number of the same toxicants from combustion. These include carbon monoxide (CO), "tar," and myriad carcinogenic polycyclic aromatic hydrocarbons (PAH). Also, hookah smoke contains significantly higher quantities of toxic heavy metals like arsenic, nickel, cobalt, chromium, lead,[10] and cadmium[12], as compared with cigarette smoke.[13] These facts about hookah smoke are a "screaming warning" that hookah smoking is harmful.

In a carefully designed recent study, researchers Shihadeh and Saleh used a smoking machine that replicated the puffing mechanics derived from precise measurements of 52 hookah smokers in Lebanon.[11] Shihadeh and Saleh carried out stringently controlled quantitative chemical analyses of hookah smoke. They found that hookah smoke produced nearly two orders of magnitude greater amount of "tar" from a single smoking session than that produced from a single cigarette. Simply put, hookah smoke produces nearly 100 times more "tar" than cigarette smoke, for each gram of the respective tobaccos. **Table A** shows that hookah smoke contains several-fold greater quantities of harmful chemicals thus far studied than found in cigarette smoke.

In light of these recent chemical data on selected constituents of hookah smoke as compared with those of mainstream cigarette smoke, hookah smoke of various fruity flavors, tastes, and aromas may be even more harmful than disease-causing cigarette tobacco smoke.

Who says hookah smoking isn't addictive?

Hookah smoking is an efficient nicotine delivery system. After a 45-minute hookah smoking session, the concentrations of nicotine and its longer-lived metabolic product, cotinine, become significantly elevated in saliva, plasma, and urine.[14] Comparison of urinary levels of cotinine between hookah smokers and cigarette smokers suggests that in a single hookah smoking session using 20 grams of hookah tobacco, the hookah smoker is exposed to several-fold greater quantities of the addictive stimulant nicotine for up to 45 to 60 minutes. That is equivalent to chain-smoking 15 cigarettes.[15] A cross sectional study on hookah smokers from 112 restaurants and cafes in Aleppo, Syria, reported that 96% of weekly hookah smokers and 50% of daily hookah smokers did not smoke cigarettes.[2] This survey found that 91% of weekly hookah smokers and 51% of daily hookah smokers did not have the will to quit, which highlights the addictive nature of hookah smoking[2] among myriad factors.[16]

TABLE A

Chemicals found in hookah smoke *versus* cigarette smoke. Adapted from Shihadeh and Saleh[11]

Chemical	Yield from 1 gm hookah tobacco	Yield from cigarette smoke, 1 gm tobacco	Multiple of average cigarette smoke value
"Tar," mg	802	Range:1-27 Average:11.2	100-fold
Nicotine, mg	2.96	Range: 0.1-2 Average: 0.77	4-fold
Carbon monoxide CO,mg	143	Range: 1-22 Average: 12.6	11-fold
PAH Phenanthrene, µg (co-carcinogen)	0.748	0.2-0.4	2.5-fold
Fluranthracene, µg (co-carcinogen)	0.221	0.009-0.099	4-fold
Chrysene, µg (tumor initiator)	0.112	0.004-0.041	5-fold

Carbon monoxide in hookah smoke: Effects on lungs, heart, and brain

Hookah smokers are exposed to three-fold greater amounts of CO—an odorless gas—than are cigarette smokers. Based on their chemical analysis, Shihadeh and Saleh[11] provide strong evidence that the CO-to-nicotine ratio in hookah smoke is 50:1, and that for cigarette smoke is 16:1. One of the reasons for the greater CO concentrations in Hookah smoke is the charcoal that is added to enhance the burning of the moist tobacco concoction. Hemoglobin, the iron-containing protein in blood that transports oxygen from lungs to all parts of the body in vertebrates, has extremely high affinity for CO, and forms carboxyhemoglobin (COHb), which can no longer serve as either the oxygen acceptor or as the oxygen carrier. Hookah smokers have significantly higher levels of COHb in their blood than heavy cigarette smokers who smoke 15 to 40 cigarettes.[17]

Because the duration of a single puff of hookah smoke is double that of a cigarette, and the suction pressure for inhalation of hookah smoke is four times that for a cigarette, the hookah smoke reaches deeper into lung tissue.[18] Consequently, hookah smoking may cause greater ventilatory incapacitation, especially in older individuals, than cigarette

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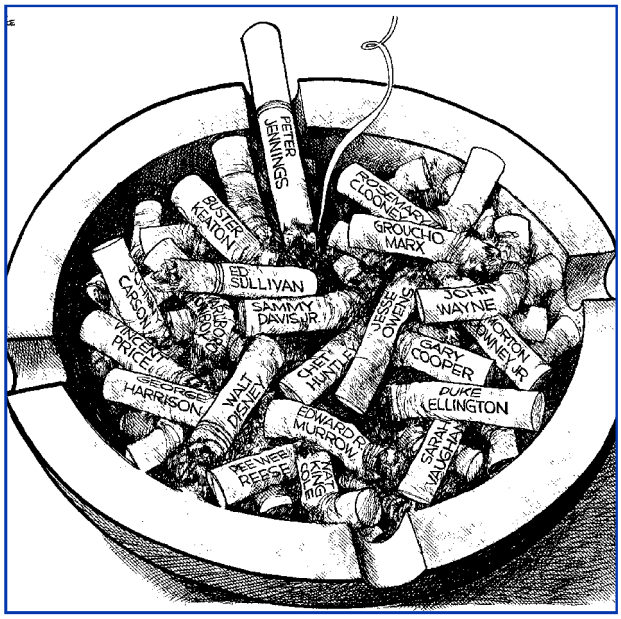
Nicotine Vaccines
Cessation Treatment of the Future?



by Phillip Gardiner, Dr.P.H.

On May 15, 2005, Cytos Biotechnology AG of Zurich reported that after four weeks, 40% of 341 heavy smokers using an experimental nicotine vaccine were abstinent compared with 31% who were taking a placebo. Even though this finding was not statistically significant, the real exciting news was that 57% of those receiving the vaccine developed a high antibody response and were abstinent for 24 continuous weeks.[1] Cytos CEO Wolfgang Renner said that if other trials go well, the product could hit the market as soon as 2010. The Cytos announcement followed the September 2004 report out of Nabi Biopharmaceuticals that their nicotine vaccine, NicVAX, had shown a 33% quit rate in smokers versus a 9% reduction in smoking among those smokers receiving a placebo.2 Xenova, another company in the hunt, stated that self-report data showed a 19% quit rate for smokers using their vaccine, TA-NIC, versus an 8% reduction in those smokers receiving a placebo.3 This burst of activity has buoyed the spirits of cessation researchers worldwide and of the Tobacco-Related Disease Research Program (TRDRP), since the development of nicotine dependence treatments is one of our priority research areas. Already, some California researchers are receiving TRDRP support to tackle the many thorny issues involved in the development of a nicotine vaccine. This quest for a 21st century solution to the alarming worldwide spread of nicotine addiction and tobacco-related diseases may have far reaching implications for researchers, tobacco users, and non-users alike.

Nicotine vaccine: The rationale

Tobacco use and all its attending diseases are the number one preventable cause of death in the world today. Indeed, it is estimated that if worldwide smoking patterns persist, about half a billion of the world's population alive today will be eventually killed by tobacco-related diseases.4 As incredible as this statistic seems, most people know that smoking is bad for them. Yet millions light-up everyday, a gruesome testament to the power of nicotine addiction. The current array of tobacco/nicotine cessation treatments, including nicotine replacement therapies (NRT) such as the transdermal nicotine patch, gum, lozenges, and sprays have only been moderately successful, at best. Bupropion and other monoamine oxidase inhibitors (MAOIs) likewise have had only limited success. Alternative therapies, including meditation, acupuncture, hypnosis, even though less studied, fall within the same modest range. All these regimens, even when coupled with counseling, on average show only a 30% quit rate at best.5, 6 Increasingly, scientists are turning to techniques that can block the uptake of nicotine, thus preventing the addiction in the first place. It is hypothesized that the development of nicotine vaccines will be much more efficacious than the c u r-rent cessation methods.

Nicotine vaccine: what it does and doesn't do

Nicotine addiction is occasioned by nicotine binding to neuronal receptors in the brain, replacing acetylcholine and activating the dopaminergic system, the pleasure center of the brain. The repeated uptake of nicotine by the nicotinic receptors and the corresponding constant activation of the dopaminergic system through the release of dopamine is the basis for physical dependence. And since tobacco products are legal and heavily promoted, habits are relatively easily maintained. Moreover, unlike other drugs of abuse, cocaine and heroin, nicotine enables the users to be totally functional, indeed, in many cases more productive through increased alertness and improved cognition.[7] The paradox is this: a toxic, relatively inexpensive legal substance that is more addicting than many illegal substances is at the same time the most deadly, especially when packaged in a cigarette.

A nicotine vaccine consists of immunogenic compounds that are similar to nicotine in their molecular structure. When introduced into the body via the bloodstream, these molecules induce nicotine-specific antibodies. These antibodies prevent the nicotine from traveling to the brain and thus thwart the addictive process. Specifically, scientists are creating immunogenic molecules that will produce antibodies that bind to the nicotine molecule. Once these two molecules

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are joined, the resulting particle is much larger and unable to penetrate the blood-brain barrier. If the nicotine can not get to the brain, it cannot get to the neuronal receptors, and ergo, cannot activate the release of dopamine, the pleasure reinforcement center in the brain.

The trick is to successfully devise a substance that produces antibodies that specifically and effectively bind and stay bound to the nicotine. Initial clinical trials with immunogenic vaccines were more successful with cocaine, but not as successful with nicotine.[8] It subsequently has been discovered that co-caine is a relatively in-flexible molecule while nicotine has a flexibility that allows it to adopt multiple shapes. Hence, the chemical agents must be made in such a way to ensure the antibodies produced are flexible and bind better and longer to the nicotine (have a higher affinity). The biotech firms mentioned earlier are chemically altering viruses or other toxins that can be used as immunogenic material to induce the nicotine specific antibodies.[9]

Currently, vaccines are short-acting, only binding to the nicotine molecule and staying active in the bloodstream of the smokers for only a few weeks or months at a time.[9] These novel vaccines could be used in conjunction with existing behavioral modification regimens. Additionally, relapsed smokers could periodically get "booster" shots that ostensibly would return them to a smoke-free existence. The optimal strategy is to produce a vaccine that when injected into the body irrevocably alters the immune system, such that a smoker or a potential smoker will never be able to feel the pleasurable effects of nicotine nor experience the attending addiction and debilitating diseases.

While blocking the uptake of nicotine will prevent the pleasurable effects of smoking, those smokers taking the vaccine will still have to overcome the cravings, anxiety, and irritability that attend nicotine deprivation.

TRDRP's contribution

Even with clinical trials underway to test the efficacy of nicotine vaccines, scientists are still looking for better methods to develop and construct immunogenic agents. Kim Janda, Ph.D., research scientist at The Scripps Research Institute (TSRI) and currently funded by the TRDRP, is working on developing conformationally constrained nicotine vaccines.[10,11] Dr. Janda explained that "conformationally constrained nicotine vaccines are just big words for arranging the chemical structure of the nicotine antibodies in such a way that they more successfully bind to the nicotine molecule."[12] Dr. Janda explains that one of the reasons that previous vaccines had been only partially successful is because of the nature of the nicotine molecule itself; it is very small and mutable, continually changing. Thus, finding a method that will allow antibodies to change and adhere at the same time has been daunting.

Dr. Janda is using constrained haptens as a novel approach to vaccine development. Haptens are molecules that are chemically conjugated to an antigen to ensure an immune response; nicotine in and of itself does not generate antibodies. Janda and his colleagues at TSRI are using a different approach than the current vaccines being created by the pharmaceutical industry. Currently, most pharmaceutical companies are using well-known viral and toxin haptens that increase the number of antibodies but do not address the flexibility of the nicotine molecule, a property that seems very important in determining how tightly the antibodies bind nicotine. Janda believes that it is the reliance on these types of inflexible haptens, which have prevented the long-term adherence of the antibodies to nicotine and thus slowed the progress of the development of a long-term nicotine vaccine. Janda was cautiously optimistic about Cytos results: "hopefully the findings are true; however, I will wait to read their peer reviewed article on the subject and not rely solely on the press release."[12]

The future of tobacco cessation?

Fast forward to the year 2050, where a vaccine for nicotine (and other drugs of abuse) is commonplace. The tobacco industry and health groups have been locked in a fight for a decade over whether nicotine vaccines should be mandatory. The tobacco industry and its allies are arguing that people should have the individual right to choose whether they get vaccinated or not; it is their fourth amendment right. Health groups respond that nicotine addiction has killed and continues to kill more people than polio and influenza combined and people routinely get vaccinated for these maladies.

A shot to prevent tobacco addiction seems quite attractive on the surface and the futuristic standoff described above may be a bit far-fetched, but the truth of the matter is that the development of a nicotine vaccine raises many vexing ethical questions. Paramount among them is whether all children of a certain age should be inoculated with the nicotine vaccine? The logic being that if children already have the antibodies circulating in their system, their initial experimentations with tobacco products will not produce pleasurable effects and therefore not lead to a life-long addictive habit, which will, more often than not, make their lives less healthy and shorter. On the other hand, some authors have questioned whether parents have the ethical and moral right to have children vaccinated against smoking with statements such as: "altering the immune system of children in order to modify future behavior seems a major intrusion."[13] In between these two extremes stand those that advocate that only children at risk should be inoculated.[14] This position is no less ethically cumbersome. One might ask who are the children at risk? Is it those children with a genetic predisposition or those bombarded with advertisements, or those who are poor and statistically more likely to be smokers. Attending these ethical questions are the questions of insur-

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ance, liability, and societal cost (who is going to pay for the mass inoculation program anyway?)

And while the futuristic example above might have been in jest, the tobacco industry in no way sees the potential development of a nicotine vaccine as a laughing matter. Tobacco control researchers combing through documents released as a result of the Master Settlement Agreement (MSA) have found that the tobacco industry was well aware of the possibility of developing a vaccine that would block the uptake of nicotine and ultimately threaten their livelihood.[15] In the early 1980s, industry researchers were already studying nicotine analogues and their partition coefficient properties, the attribute possessed by a chemical or molecule that allows it to cross biological membranes (e.g., the blood-brain barrier).[15] Indeed, by the 1990s, industry scientists had already identified specific immunogenic compounds that triggered the production of nicotine antibodies.[15] And as it was to be expected, the tobacco industry turned their attention and research toward how to construct compounds that could evade the newly developed vaccines![15]

Coda

Neither thorny ethical questions nor the tobacco industry's head-start should dissuade researchers from tackling the issue of blocking the uptake of nicotine as part of the fight to blunt the scourge of nicotine addiction and tobacco-related diseases. The construction and testing of immunogenic compounds that elicit antibodies that adhere, over the long-term, to nicotine molecules and thus stymie its pleasurable and reinforcing effects, is certainly a worthwhile research endeavor. The TRDRP welcomes all applications that seek to develop and explore the parameters of existing and novel nicotine vaccines. Along with this new and promising area of investigation, TRDRP continues to encourage cessation scientists to seek grant funding for strategies to increase the efficacy of pharmacological interventions, behavioral strategies, internet regimens, worksite programs, and the California Quitline.

(I would like to thank Dr. Kim Janda for his innovative research and review of this article.)

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* Page 6-7 Illustration by Michael Ramirez for the Los Angeles Times, represented by Copley News service.

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smoking causes.[19] Since smoking rates among 18 to 24 year-olds are the highest of any age group in California[20], the recent trend of hookah smoking among youth, unless checked, may exacerbate the future incidence of chronic obstructive pulmonary disease.

Blood pressure (systolic, diastolic, and mean), expired CO, and heart rate all increase upon hookah smoking.[21] Heart and brain have extremely critical requirements for a minimal threshold of oxygen. Episodes of sudden and short periods of oxygen deprivation can result in heart attack or brain stroke.[22] Chronic exposure to nicotine also has a direct effect on the heart, causing atrial flutter.[23] This exposure leaves h o o k a h smokers vulnerable to this debilitating condition.

How hookah smoke may affect fertility, virility and babies

It is becoming increasingly clear that, like tobacco smoking, mainstream hookah smoke and secondhand hookah smoke cause deleterious effects on reproductive systems in men and women and produce genotoxic[24], mutagenic, and teratogenic[25] effects on babies of smoking parents. These effects include infertility in females and sterility of males, and low birth weight [26, 27] and birth defects in babies born to smoking mothers.[28, 29] A recent study of 100 Egyptian infertile women determined that the couples' infertility was due to sterility of husbands who were hookah smokers.[30]

High concentration of CO is a major component of secondhand smoke from hookah. The contribution from burning charcoal in hookah may also have significant and deleterious effects on young babies that may be exposed to mild CO levels. Even at very low levels, such as 25 to 50 parts per million parts of air, CO can produce permanent damage to the inner ear in young babies and irreversible loss of hearing.[31-35]

TRDRP research on hookah smoking

TRDRP is at the forefront of recognizing and supporting innovative and novel ideas in a proactive manner. Keeping with its mandate, TRDRP funds innovative and high-quality biomedical, policy, and prevention research in California. This research aims to mitigate the suffering and economic burden due to myriad diseases caused by tobacco products.

This year, as over the past 15 years, TRDRP has once again distinguished itself among all federal and public funding agencies in leading the charge against tobacco by awarding the first ever research grant on hookah smoke. TRDRP has made a three-year new investigator grant award to Nada Kassem, Dr.P.H., M.S., R.N., C.H.E.S., to study "Water Pipe Use, ETS Exposure and Home Policies among Arab Americans." Dr. Kassem is currently a faculty research investigator at the Center for Behavioral Epidemiology and Community Health, Graduate School of Public Health, San Diego State University. This is the first tobacco-related research grant award to Dr. Kassem.

TRDRP invites research grant applications from California scientists on all aspects of hookah smoke for various funding mechanisms.

Dedicated to the fond memory of Surender S. Katoch, B.Sc., M.Sc., M.Phil., Ph.D. - a dear friend and scientific collabo - rator - who dedicated his life to mitigating cardiovascular disease, and suddenly died on May 14, 2005 due to a mas - sive heart attack. Dr. Katoch was Professor and Chairman, Department of Bio-Sciences, Himachal Pradesh University, Shimla, India. Surender will be sorely missed by family members and numerous friends all over the world.

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It is not surprising that in most of the great mystic and spiritual literatures of the world, the terms "breath" and "spirit" are synonymous. By finding a cure and by developing therapies and diagnostics that would mitigate the impact of this horrific disease, we would be doing nothing less than saving the victims of a vicious industry - not only in breath, but in spirit.

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Research for a Healthier Tomorrow

RESEARCH TOPICS: TRDRP awards research grants to scientists at nonprofit research institutions in California, including collaborations with community-based organizations in tobacco control. TRDRP has funded more than 1,100 multi-year research grants totaling approximately $365 million at 80 universities and research institutes. These projects investigate the causes and treatment of cancer, heart disease and stroke, lung disease, adverse effects on reproductive processes and outcomes, and nicotine addiction. Others investigate public health and public policy for tobacco control, the adverse health effects of secondhand smoke exposure, and social and behavioral science research on tobacco use cessation. A searchable database of grants is available at www.trdrp.org.

MISSION: TRDRP grants are designed to achieve the following goals:

- Improve the prevention and treatment of tobacco-related disease and tobacco control efforts by advancing scientific knowledge.
- Maintain and grow California's human and institutional research capacity by supporting the training of new researchers.
- Address community and school needs for tobacco control by funding participatory research projects, which are collaborations between university scientists, on the one hand, and either community-based organizations or schools, on the other hand, with an emphasis on improving tobacco control in California's diverse populations.

DISSEMINATION AND OUTREACH

"Investigator Conference" a biennial event highlighting research funded by TRDRP. The TRDRP Conference is attended by scientists, tobacco control professionals, health care providers, government representatives and elected public officials.
"*Compendium of Awards*" containing descriptions of new grants funded each year.
"*Annual Report to the Legislature*" containing summaries of grants that conclude each year and a status report on the program.
"*Burning Issues*" quarterly newsletter containing program updates and articles about TRDRP-funded research and timely and compelling topics in tobacco control and tobacco-related disease.