

According to the Institute of Medicine, health policy can do more than counsel to discourage smoking; it can promote the use of low-risk tobacco products for smokers unwilling or unable to quit.

Less Hazardous Smokes?

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CURRENTLY, SOME 50 MILLION AMERICANS, and perhaps over a billion people worldwide, smoke cigarettes. Of those, nearly 10 million may die prematurely each year and for decades to come because of the effects of smoking. The abolition or a worldwide decline in the use of cigarettes is not in the cards for the foreseeable future. One-fifth of humanity smokes with little indication they might soon quit, too many public and private interests benefit handsomely from the trade, and an illegal market stands eager to fill an uncontrollable demand should taxes and prices be set too high or should cigarettes be made illegal. Hence, the sensible and ethical public health policy would be to continue efforts to persuade smokers to quit, and to consider ways to reduce the risks for those who keep on smoking.

Toward the latter end, in September of 2001 the Institute of Medicine (IOM) of the U.S. National Academy of Sciences released a report asserting that reduced-risk tobacco products, and especially cigarettes, are feasible and within technical reach. The report, entitled *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*, calls for an official agency to regulate the manufacture and advertising of reduced-risk products. The report shines with much confidence in the public health and rational soundness of reducing the harm of tobacco use.

It is undeniable that progressively less hazardous cigarettes (LHCs) can be produced, and the IOM report is confident enough to venture that “regression of risk... might eventual-

ly bring a smoker to a risk equal to some lower level of lifetime exposure to conventional products.” Even before reaching that point, the potential public health gains could be magnificent.

LHCs attain special interest in light of the 1998 settlement between the tobacco industry and the states’ attorneys general, which counts on many decades of continuing cigarette consumption to sustain expectations of massive annual payments. The pooled revenue from those expectations and from long-standing federal, state, and local levies on cigarettes approached \$30 billion in 2001, as compared to \$9 billion in pretax profit for the entire U.S. tobacco industry in the same year. Inevitably, those combined expectations adduce a conflict of interest for the beneficiary governments, especially because the proceeds are mostly handled as general revenue funds and are minimally directed at controlling the risks of tobacco. A determined effort toward less hazardous cigarettes would offer an obvious remedy to a discernible ethical conundrum.

Why are LHCs not the mainstay of the market today? Their absence has been imputed to manufacturers’ inertia, but it could be linked more directly to stern U.S. prohibitionist policies of the past quarter-century. Partially effective in persuading many smokers to quit according to the IOM report, those policies have relentlessly opposed the promotion and thus the development of LHCs. The assumption has been that LHCs might tempt some to become smokers. Yet the IOM report finds that such a hypothetical may not hold against the certainty that LHCs will save lives, just as no serious argument could be raised to abolish seat belts on the theory they could induce some to drive faster.

Over 20 years ago, the same misguided concern suppressed virtually the same recommendations and science that now support the IOM’s conclusions, as reported in 1979 by the Smoking and Health Program of the National Cancer Institute and

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National Heart, Lung, and Blood Institute. Considering the human costs of having denied the development of LHCs for more than 20 years, the present implication of the IOM report is that a continuing opposition to LHCs would not be an ethically defensible, humane, or realistic public health policy.

EPIDEMIOLOGIC EVIDENCE

The IOM report finds that “for many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is feasible.” That conclusion is justified because “current knowledge of the dose-response relationship is sufficient to support risk reduction through exposure reduction.” The report also concludes that lung cancer is the disease most associated with cigarette smoking, and that the evidence of a dose/risk gradient of that association is the extreme paradigm for other smoking-related diseases.

The evidence is summarized in the Surgeon General’s “Smoking and Health” report of 1979, which lists several major studies showing that smokers of a half-pack of cigarettes per day have about one-quarter the lung cancer risk of two-pack-a-day smokers, making for a virtually direct proportional relationship. (See Figure 1.) In other words, the dose makes the poison in the case of smoking, just as for any other toxin. Moreover, LHCs could be made to lessen the risk not only by reducing the dose inhaled but also by changing the nature of the smoke itself.

Clearly, any meaningful reduction of risk would result in massive health gains within 15 to 20 years, against the World Bank’s projection of some 10 million premature deaths per year from smoking by 2025 if there are no changes in current usage. Any forecast would be aleatory, but LHCs offering better than a 50 percent reduction of exposure and risk are with-

in technical reach and entirely feasible in much less than 10 years. (See Figure 2.)

NICOTINE

The IOM report notes the foregone premise that LHCs will have no significant health benefit unless they appeal to smokers, raising the need to recognize certain realities of why and how people smoke. To begin, the IOM report makes it clear that cigarettes without sufficient nicotine are not acceptable to smokers.

Nicotine safety As it happens, scientific evidence indicates that nicotine is not a perceptible health problem for smokers. That prompted the IOM report to affirm that the alleged risks of nicotine are biased by “misinformation,” because the substance is relatively safe. The report finds that “many studies of nicotine suggest that nicotine is unlikely to be a cancer-causing agent in humans,” that “high doses of nicotine do not seem to cause acute adverse events even among smokers who have experienced cardiovascular disease,” and that long-term nicotine replacement therapy has been “without an apparent cardiovascular hazard, not only in the general population... but also in patients with established cardiovascular disease.”

The safety of nicotine at the doses traditionally experienced by smokers was also recognized by the original Surgeon General’s report on smoking of 1964. It has been confirmed for nearly two decades by the Food and Drug Administration and regulators around the world who have permitted over-the-counter sales of nicotine patches and gums that contain nicotine equivalent to smoking several packs of cigarettes, and that are openly advertised, recommended, and used.

Nicotine and addiction The same Surgeon General’s report of 1964 concluded that smoking is a personally controllable habit, and official tallies show that over 50 million smokers have quit

on their own in the United States alone, in a social climate where cigarettes have been readily and legally available. Indeed, the IOM report implicitly agrees that nicotine cannot be compared to crack cocaine, a charge that has been made repeatedly but is inconsistent with reality and therefore not credible. Nicotine in smoking is not psychotoxic, does not lead to deranged and asocial behavior, nor to loss of personality control. On the contrary, the IOM report notes how nicotine and smoking enhance individual and social behavior, performance, learning abilities, and other improvements that together account for the persistent use of cigarettes despite severe warnings. Within a daily, monthly, or even a multi-annual cycle of smoking, the immediate behavioral benefits have virtually no perceptible negative counterpart, and they remain the likely reasons why increasing numbers of smokers decline to quit.

With this in mind, the IOM report concurs that a general strategy for reducing the harm of smoking is “retaining nicotine at pleasurable or addictive levels while reducing the more toxic components of tobacco.” In a nutshell, the core challenge of LHCs is to maintain a level of nicotine sufficient to meet smoker demand while reducing the dose of undesirable components of the particulate or liquid/solid components of smoke — hereafter identified as tar — and the gaseous components of smoke. Conveniently, there are many opportunities for cigarette modifications to attain those aims.

DESIGNING LHCs

Bottom-up and top-down approaches have been utilized in the development of lower-risk cigarettes. The former entails creating artificial smokes utilizing nicotine, buffers, and flavors, resulting in nicotine-carrying aerosols of sufficient density and with a range of particle sizes compatible with inhalation. In theory, that approach appears most desirable. Still, and although their future is promising, initial bottom-up models have gained only a small fraction of trade because of lingering technical difficulties and scarce acceptance, and because of official opposition to their promotion as being less hazardous.

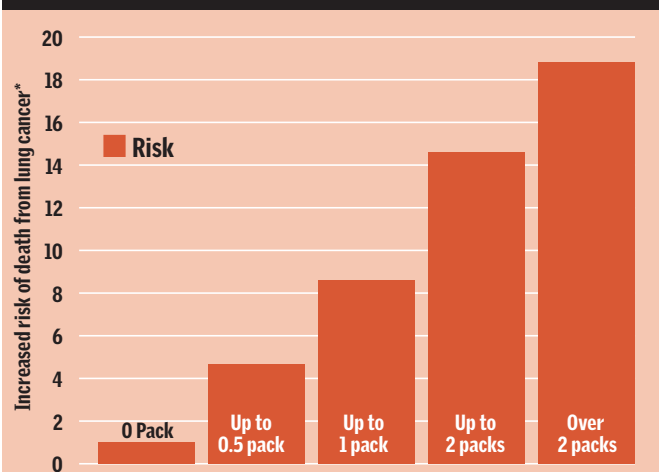
The top-down approach entails a progressive reduction of undesirable smoke components of traditional cigarettes. The Smoking and Health Program of the National Cancer Institute and the National Heart, Lung, and Blood Institute explored basic techniques to achieve that goal some 30 years ago. Some 150 experimental cigarettes were tested and many were successful in reducing the yields and carcinogenic potency of tars. The findings of that program, and the large number of patents in the hands of the cigarette industry and other inventors, tell of many feasible approaches to both the reduction of dose and of the intrinsic toxicity of smoke.

Gradual change The retaining of nicotine while lowering other smoke components will tend to reduce the amount of tobacco in cigarettes, the density of the tobacco-derived smoke, and the traditional tobacco flavor of smoke. Those changes will disturb smoker acceptance, raising the technical challenge of incorporating safe aerosol substitutes to restore sufficient smoke density to carry nicotine, buffers of nicotine harshness, and flavors. A likely corollary is that progressively less efficient filters will be

FIGURE 1

The Dose Makes the Poison

Typical epidemiologic dose/response gradient for cigarette smoking and lung cancer



* The risk is relative to the risk of nonsmokers, e.g. a value of 10 means 10 times the baseline risk for nonsmokers.

needed as the contribution of burnt tobacco to smoke density is reduced, while the demand of tobacco leaf also might decrease, signaling a probable contraction of tobacco farming.

In any event, the implication is that initial changes in taste and appearance should be introduced gradually if LHCs are to remain reasonable alternatives to traditional brands, which must continue to be available to smokers, lest an illegal market take over.

Need for nicotine Smoker preferences would have to be closely monitored. They begin with ease of draw and number of puffs obtained, and extend to flavors and fragrances, the mouth feel or “impact,” and the inhalability of smoke. The IOM report notes how those characteristics strongly depend on nicotine levels and

related products that purport to reduce one or more tobacco toxicants or to reduce the risk of disease.” With such regulation, the IOM report sustains, “manufacturers [will] have the necessary incentive to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease.” The report further completes those recommendations, expanding on plausible tests to assess the risk reduction of less hazardous smokes, and exploring the regulatory criteria that might follow.

TESTING LHCs

As we have seen, the need to secure smoker acceptability would require initial LHCs to deviate slowly from traditional ciga-

Smokers would be especially motivated to switch to LHCs that are marketed with explicit messages of health benefits based on credible tests of reduced risk.

the acidity of the smoke. Slightly acidic smokes reduce nicotine harshness and favor inhalation and the rapid onset of those psycho-motor effects of nicotine that are the ultimate rewards of smoking. Absent nicotine, all other rewards have proven insufficient to sustain the habit, and the IOM report observes that cigarettes without nicotine have not survived the market.

Regardless of brand and label, current cigarettes contain an average of 15 milligrams of nicotine, of which smokers obtain about one milligram per cigarette on a daily average, not to exceed a ceiling around two milligrams. Throughout the day, smokers carry out a minute-to-minute titration of nicotine intake to obtain momentarily desirable effects. Thus, nicotine intake is manifestly self-limiting not to exceed instantaneous thresholds, beyond which the effects of nicotine become immediately unpleasant and aversive. Overdosing on nicotine is virtually impossible, as the IOM report finds.

Those and other considerations suggest that acceptable LHCs would have to be capable of delivering 200 to 300 micrograms of nicotine per puff, and seven to eight puffs per cigarette. Again, that amount of nicotine is more than most smokers require and usually would not be inhaled and utilized, but would be sufficient to accommodate temporary peak demands.

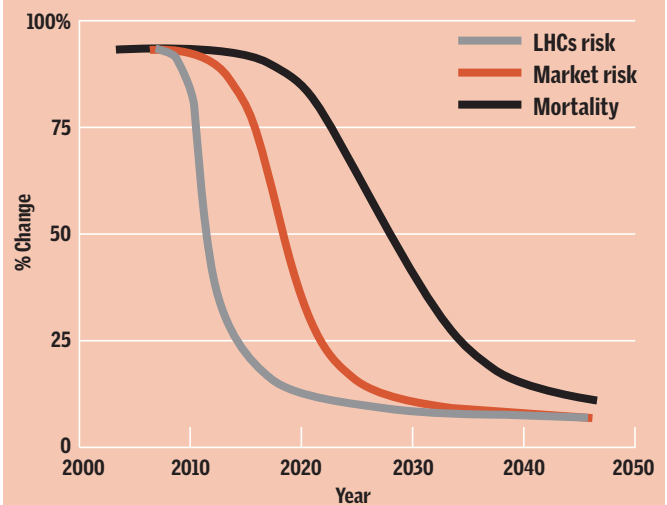
Regulating change In time, smoker expectations would change, as attested by today’s smokers who are satisfied with leading brands that would have been considered unacceptably weak some 10 or 15 years ago. Undoubtedly, smokers would be even more motivated to switch if LHCs were to be marketed with explicit messages of health benefits based on credible tests of reduced risk.

To that end, the IOM recommends that “Congress enact legislation enabling a suitable agency to regulate tobacco-

FIGURE 2

LHCs and Lower Mortality

Projections of the change in smoking-related mortality rates from the introduction of LHCs.



A plausible projection of a reduction trend of mortality attributable to tobacco use (black line), following a reduction of exposure/dose of tobacco smoke from the introduction of LHCs. The gray line indicates the likely sales-weighted reduction trend of exposure/dose attributable to LHCs alone. The red line indicates the possible sales-weighted reduction of exposure/dose from LHCs combined with the lingering risk of traditional cigarettes still on the market at any time. The mortality reduction curve (black) lags approximately 15-20 years after exposure/dose and risk reduction.

rettes. Still, the pace of change could be rapid, because market incentives would spur the industry and a host of inventors to intense activity. The likely outcome is a cascade of initial models, rapidly supplanted by superior improvements. Under that scenario, it would be impractical to ask for chronic testing of specific LHCs models, or for their specific post-marketing epidemiologic monitoring. In fact, the IOM report considers that such tests and monitoring might not be feasible, given the time requirements and the instability of epidemiologic settings.

The initial evaluation of risk reduction in cigarettes requires a frame of mind radically different from traditional regulatory approaches aimed at ensuring virtual safety. Here a reverse task is at hand, which is to estimate whether a well-known and high risk is reduced. Such an estimate is made intuitively much easier because it can be achieved straightforwardly by a measurement of dose reduction that directly translates into reduced risk. As mentioned, the IOM report

The lower the T/N ratio of a smoke, the lower its potential of risk.

In calculating T/N ratios, tar should be defined as the specific fraction of tar that is attributable to tobacco. That precaution considers, as just noted, that reducing tobacco tar in LHCs would result in a reduced tobacco smoke density, making it necessary to supplement smokes with non-toxic aerosol components. The weight of those supplements should be subtracted from the total smoke particulates collected by analytical smoking machines, thus yielding the specific tobacco tar fraction that is of concern in risk reduction. A T/N index so conceived would convey a proportional message and would be explicit in telling of the relative dose expectations from brand to brand.

The meaning of T/N ratios could be refined by adjusting for brand-specific asymmetries in the relative delivery of tar and gaseous components. More complex schemes could be devised

Smoker acceptance of LHCs would likely increase significantly over time because market incentives would spur innovation within the industry.

concur that "current knowledge of the dose-response relationship is sufficient to support risk reduction through exposure reduction," which leads directly to the formulation of an index of exposure and risk.

Measuring risk reduction The assessment of a dose reduction index valid for all smokers is not as difficult as it may seem. By necessity, it could not tell of actual dose expectations because doses vary among smokers and even for the same smoker over time. Rather, a feasible index relies on the evidence that the extent of inhalation varies mainly in function of the limiting amount of nicotine that any smoker finds momentarily desirable and sufficient; an amount that, as noted, cannot be exceeded. According to the IOM report, "The smoker titrates nicotine delivery toward a range of convergence that is reflected by the measurement of nicotine delivery, which in turn may reflect the dose-dependent convergence of the delivery of additional toxic, but unmeasured, constituents of cigarette smoke." In plainer words, nicotine limits its own inhalation and therefore the inhalation of smoke. Hence, the higher the smoke concentration of nicotine, the sooner inhalation is inhibited, the lower the dose of whole smoke to the lungs, and the lower the risk to be expected.

It follows that different brands' smoke-to-nicotine ratios gives the relative scale of inhaled doses of tar. Because of the fair correlation between the yields of gaseous components and tar, the more readily determined tar-to-nicotine (T/N) ratios would be reasonable proxies for the ratios of whole smoke and nicotine, and would be a valid index of overall risk reduction.

by defining the chemical signature and T/N ratio of a standard reference cigarette, against which the parallel signatures and T/N ratios of candidate LHC models would be compared to yield a composite index of risk reduction. Other criteria could grant fractional risk reductions if selected components were removed preferentially, such as nitrosamines, polycyclic aromatic hydrocarbons, or other substances of interest, although the IOM report remains skeptical of the overall risk-abating effectiveness of such selective reductions.

In the end, however, it would not make much sense to report risk reduction on a scale measured in more than one or at most two digits. The obvious reasons are the uncertainties of measurement inherent in assessing risk reduction, as well as the uneven individual meaning and utilization of a risk reduction message within a congeries of smokers. The common message should remain simple.

The validity of assessing exposure and risk reduction by the T/N ratio of smokes would decline in time as the proportion of tobacco-generated smoke might decline in advancing LHC models. All the same, and until tobacco smoke remains a significant component of cigarettes, gravimetric yields and the T/N approach could remain the main determinants in assessing relative dose and risk reduction. Later on, other considerations and the adoption of yet unforeseeable formulas would become necessary as the composition of smoke may radically change.

T/N ratios have been falling over the last 30 years to a sales-weighted average of around 12 in the United States. Acceptable cigarettes with ratios of between 5 and 7 could become feasi-

ble in a few years utilizing readily available technology, for a credible exposure reduction of some 50 percent – potentially a most impressive reduction of risk for more than 1 billion smokers worldwide.

The IOM report also advocates the use of biological markers in assessing risk reduction, even though recognizing that most such markers are of unknown correspondence to human risk. In reality, their utility may be limited, and in that regard the IOM report itself concedes, “Any conclusion as to the relative harm [of LHCs] must necessarily be inferred from a base of indirect knowledge.” Still, the precariousness of such inferences is manifest in the case of markers, but not so for the unique direct evidence of reduced dose that the IOM report acknowledges – a direct evidence that T/N ratios would mirror. Indeed, biological markers in general may offer marginal improvements over the risk reduction estimate of T/N ratios, at least until tobacco tar remains a significant fraction of reduced risk smokes.

Whatever the misgivings, a judicious selection of markers would be deemed mandatory in complementing an assessment of risk reduction — a selection that would be all the more useful if it followed the IOM report’s advice that “public health is not well served by the...use of poorly defined terms...that imply a benefit when none has been proven to exist,” but “neither is public health served if smokers are discouraged by unduly cautionary language from using a new product with the potential for real risk reduction.” With that guidance, the report left the precise definition of regulatory criteria to the future deliberation of an official regulatory agency.

REGULATORY OPTIONS

Historically, alcohol and tobacco in the United States have been shielded from health and safety oversight. Undoubtedly that privilege reflects the political influence of the respective industries, which may not have been possible without a pervasive use and popularity of alcohol and tobacco. A few years back, the Food and Drug Administration sought to regulate cigarettes, but was confronted by a Supreme Court ruling that the agency lacks legal authority.

S. 2626 Some novel statutory language seems necessary. Last June, Sen. Edward Kennedy (D-Mass.) introduced Senate Bill 2626, which would authorize the FDA to regulate tobacco and cigarettes. Surprisingly, the bill appears unaware of the IOM report and carries no provisions for reduced-risk products. As the legislation moves through hearings in the Senate and House, that omission ought to be rectified based on the authority of what the IOM fervently addresses “to the FDA, FTC, other relevant federal and state regulatory and policy bodies, Congress, scientists and health care professionals, tobacco and pharmaceutical industries...” — a report that the FDA itself commissioned.

An effective statute will need to give the FDA the necessary instructions to enable reduced-risk tobacco products, including LHCs. In its premises, the statute needs to acknowledge the reality of millions of smokers who will be around for many decades to come. The statute should note that banning

cigarettes is impossible without facing the consequences of an uncontrollable black market. The law should explicitly recognize that regulating LHCs cannot aim at providing virtual safety, but rather is intended to assess the reduction of a known risk. It also must acknowledge that LHCs are meaningless unless used by smokers, and that they would challenge the acceptability of smokers to an extent likely proportional to the extent of risk reduction. It should follow that LHCs will not be successful unless they slowly challenge acceptability, lest smokers shun LHCs in favor of legal or smuggled traditional cigarettes. In that context, the law should recognize the IOM report finding that nicotine is safe at the doses experienced by smokers, that nicotine is necessary to smoker acceptance, and that it should not be denied to LHCs at levels acceptable to smokers.

A statute should recognize that acceptance of LHCs would improve if risk reduction could be credibly advertised. As the IOM recommends, the law should direct the FDA to evaluate LHCs on the basis of a quantitative scale of risk reduction, and to permit the advertising of cigarettes on that basis. An even faster acceptance of LHCs could be secured if the law were to grant tax, and thus price, advantages over traditional cigarettes.

It should be understood, overall, that the regulation of LHCs would affect one single product, or at least one narrow family of very similar products designed to achieve very similar effects. Until tobacco remains the main constituent of LHCs, the initial criteria and the scientific basis for regulation should be simple: the reduction of a well-known risk being objectively judged by the evidence of dose reduction.

To that end, and as long as tobacco remains a significant generator of cigarette smoke, the regulation of LHCs should be free of the inferential and extremely uncertain conjectures that are part of assessing potential but unknown risks. The IOM report implicitly allows that LHC brands could remain substantially tobacco-based for years to come, which should validate using T/N ratios as the simple and central criterion of risk reduction and regulatory decisions.

A regulatory agency would spell out the criteria for the evaluation and ranking of LHCs. It could also certify independent laboratories to conduct tests and analyses on LHCs, and could require substantial petitioner fees to defray the public costs of cigarette regulation. The IOM report considers that a regulatory agency might be expected to keep track of the eventual health benefits of LHCs. As noted, however, the post-marketing monitoring of specific LHC models would be extremely problematic, mainly because of the fast turnover of initial LHC models, the inconstancy of smoker choices, and the variable interference of confounding risk factors over the 15 years or more that would be needed to confirm epidemiologic trends. Public health improvements would be monitored more simply by the overall surveillance of morbidity and mortality that other government services provide routinely.

CONCLUSION

The IOM report acknowledges that many of the realities about tobacco and cigarettes have been obfuscated by policies that need to be amended on factual grounds, if rapid and sub-

stantial public health progress is to be made. Most difficulties are traceable at having approached tobacco and cigarettes as if they were a communicable disease problem. Indeed, infectious agents can be, and are, forcibly controlled and eradicated, but the case is much complicated when tinkering with people's behaviors and choices in the context of societies that are, in principle, free.

It has been a common experience that prohibitionist policies fail against substances and habits that too many people find interesting and rewarding, risky as they might be. The failure of alcohol prohibition in the United States early in the last century comes to mind, as should the constantly faltering war against drugs of abuse.

We live in a complex and imperfect world of imperfect peo-

ple who are not free. It is enormous to expect that progress to be made from smokers. At the same time, an implicit but clear premise of the IOM report is that smokers are entitled to compassionate public health services as others are, and should not be cast out, punished, and denied available help. In that light, the unavoidable implication is that a continuing reluctance to endorse the development of LHCs is not ethically tenable and would amount to a gross dereliction of public duty. A parallel implication of duty would force the cigarette industry to aggressively develop LHCs as an obligation of due diligence and to guard against likely successful legal challenges if it failed to develop LHCs along the IOM recommendations.

In reality, there are no difficult technological or scientific barriers, and initial criteria for the regulation of risk reduction would be limited to the simple objective evidence of dose

In today's climate of suffocating political correctness, the IOM report stands out as an example of intellectual and humane integrity.

ple whose free will is respected according to overriding principles of modern civility. It is only when mindful of such principles of individual liberty that public intervention could hope to be effective in promoting health in matters of personal choice.

Although the ethical and pragmatic injunctions of the IOM report are inescapable and merit immediate attention, they have gone largely unnoticed by mainstream public health organizations and publications. The reasons are complex, and mostly about appearances. The IOM recommendations compete head-on with the traditional goal of outright elimination of tobacco that has received exclusive, if utopian, public health attention for two decades. The prospect could be highly uncomfortable to many in top public health ranks who staked personal credibility on prohibition and have steadfastly opposed the concept of LHCs.

Adding umbrage, the IOM report adduces a palpable indictment of an opposition to LHCs that has endured for over 20 years. That is because the basic understanding and means to produce reduced-risk cigarettes had been made known long ago by the Smoking and Health Program of the National Cancer Institute and National Heart, Lung, and Blood Institute, as reported in a 1979 symposium held at Cold Spring Harbor Laboratories under the auspices of Dr. James Watson, Nobelist of DNA fame. Understandably, it would be uncomfortable to reflect on the staggering human costs of having denied for two decades the benefits of LHCs to a billion smokers worldwide. Yet, in a climate of suffocating political correctness, the IOM report stands out as an example of intellectual and humane integrity, to the point that neglecting its message would make things even more uncomfortable.

Presently, various governments in the United States have direct control over cigarette manufacturers and trade, and prof-

reduction. Public expenses would be minor, and the development, manufacturing, and marketing of improved cigarettes would be driven entirely by the very forces of demand that have sustained the tobacco culture against formidable efforts of suppression. In fact, once LHCs become officially regulated, a market rush to ever-improving models would be inevitable, self-sustained, and likely very rapid in the historical context.

The prospect of significantly reducing, in a few decades, the projected 10 million annual premature deaths linked to tobacco worldwide dwarfs most opportunities of saving lives and health. Beneath a veneer of technicalities and careful words, the IOM message counts as an anguished alert that ought to give the prospect of reduced-risk cigarettes an irresistible moral urgency to legislative and public health action. **R**

READINGS

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