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Tobacco: Nicotine [3]

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001. list	tobacco contacts (partial) (1 page)	nd	b(6)

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Clinton Presidential Records
Office of Science and Technology Policy
Jerold Mande
OA/Box Number: 13035

FOLDER TITLE:

Tobacco: Nicotine [3]

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RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

- P1 National Security Classified Information [(a)(1) of the PRA]
- P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
- P3 Release would violate a Federal statute [(a)(3) of the PRA]
- P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
- P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [(a)(5) of the PRA]
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- b(1) National security classified information [(b)(1) of the FOIA]
- b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
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- b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
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- b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

1 DR. SHIFFMAN: They don't have rights.

2 DR. GELLER: They have less rights. But they
3 can make an informed decision whether to enter a study or
4 not, if, say, it is a quit study, for instance. But it
5 need not be.

6 I think it is easy to follow them, because they
7 are extremely likely to buy their cigarettes at the PX,
8 because they are so much cheaper. So you can -- it is
9 just so much easier.

10 MR. SHOPLAND: What I am saying is that there
11 are all kinds of problems. I am thinking of those
12 prisoners who do smoke. If you were to find a way to
13 enroll them into a study, where you could give them free
14 cigarettes.

15 DR. GELLER: Offering them a study, I think, is
16 coercive, because offering the study ---

17 MR. SHOPLAND: No, no, we are talking about
18 existent smokers.

19 DR. GELLER: No, no, I think it coercive for
20 them to enter the study, because if they enter ---

21 MR. SHOPLAND: Why is it coercive?

22 DR. GELLER: -- they are good.

23 MR. SHOPLAND: I don't understand. I don't
24 understand the argument.

25 DR. GLYNN: Jack.

1 DR. HENNINGFIELD: This just gets into all kinds
2 of other issues. The Addiction Research Center moved to
3 Baltimore, because -- I think it was a 1976 ruling that
4 federal prisoners can't participate in research. I don't
5 know if there are any loopholes in that.

6 MR. SHOPLAND: They cannot?

7 DR. HENNINGFIELD: Cannot.

8 DR. HUGHES: Again, that is federal prisoners.
9 We have done studies in prisons in Vermont. They are not
10 in a federal prison. So you can do that.

11 DR. GLYNN: I think the take-home message is to
12 look for populations that we can work with.

13 DR. SHIFFMAN: But I think part of the point is
14 that the advantage of a prison or a PX on an isolated base
15 is not that you enroll volunteers, but that you have a
16 closed market. So I wouldn't give the cigarettes away
17 free.

18 The issue is what happens -- I mean, there would
19 be a very interesting study to get these cigarettes out
20 and manipulate the price and find out what point do people
21 select these cigarettes versus select the higher -- that
22 is not a volunteer study. That is a closed market
23 economic ---

24 DR. PERKINS: That is just the problem. They
25 would become currency. They would become currency.

1 DR. SHIFFMAN: That is not a problem.

2 DR. PERKINS: They would be traded for different
3 commodities and whatever in the prison.

4 DR. KRASNEGOR: But that could yield value.

5 DR. PERKINS: But if you go to look at cotinine
6 and things like that -- if it has no relationship to
7 whatever they have earned, because they are trading them
8 for other things ---

9 DR. SHIFFMAN: Except in order for them to
10 become currency, they have to be of value, if not to the
11 purchaser, to the buyer.

12 DR. PERKINS: I am just looking at the
13 pharmacologic aspects.

14 DR. : How about a cruise ship?

15 (Laughter.)

16 DR. GLYNN: I want to spend five more minutes on
17 this topic -- a few minutes early.

18 MR. JARVIS: Coming back to the issue of
19 socioeconomic deprivation, there is very strong evidence
20 that deprived smokers are also more nicotine-dependent. I
21 think, that again raises serious questions about the
22 implications of reducing nicotine exposure across the
23 whole population.

24 It would differentially bear on the more
25 deprived groups in society and might again give rise to

1 especial difficulties.

2 DR. GLYNN: Okay. Is there any other issue
3 dealing with this, or with this particular question -- any
4 other question that we need to ---

5 DR. HOFFMAN: Should -- make groups, for
6 example. Older men, at least at our institute, a large-
7 scale study, are more likely to be ex-smokers than
8 20-year olds.

9 Isn't there -- can one not incorporate this in a
10 study to see if this group is easier to get ex-smokers?
11 They are anyway at high risk, the older ones. They are
12 more -- disease -- incorporate this in a single focus in
13 this group.

14 DR. GLYNN: Can certainly be included. Okay. I
15 cavalierly earlier said, oh, 3:30 is fine for people with
16 five o'clock flights, but I wanted to make sure that
17 neither Martin nor Michael was among those -- is yours a
18 five o'clock flight?

19 DR. RUSSELL: It is 6:45.

20 DR. GLYNN: Okay. That is fine. I just wanted
21 to make sure -- if it is international, it will take you a
22 little bit longer going out of Dulles, and I just wanted
23 to make sure I wasn't consigning you to staying overnight
24 at Dulles.

25 DR. RUSSELL: (Inaudible.)

1 MR. JARVIS: I think they were talking about
2 3:15, a bit early.

3 DR. GLYNN: I am going to try and get us
4 finished by 3:15, so the five o'clock people can get in
5 cabs at 3:30. So that is why I am accelerating a little
6 bit. Harry.

7 DR. LANDO: This has been a relatively short
8 session on this topic. I guess I would just like to
9 reiterate the point that to look creatively at some of the
10 existing data sets. I have not read everything that is in
11 COMMIT, but there is a lot there. I believe there are
12 some others that, I think, will bear on some of these
13 issues.

14 DR. GLYNN: Yes, I think that is something that
15 has to come out in any recommendations that come from this
16 is to try and make use of existing data sets as they
17 exist, or as much as possible, because it does fulfill two
18 of the criteria that we set out earlier, quick turn-around
19 and reasonably inexpensive.

20 DR. LANDO: If anybody has any exciting ideas
21 for things we can incorporate on a low budget to an Air
22 Force study, I am all ears.

23 DR. GLYNN: Then going on to the last question,
24 and this one, I think, does turn a little bit more than
25 the second and third questions, which were similar -- this

1 does introduce some new issues in terms of compensation,
2 as well as the idea of continuing to smoke even without
3 nicotine, and what the effects of that intake of that
4 smoke are.

5 Neal agreed to lead that final conversation.

6 AMONG ADDICTED SMOKERS, IF THE NICOTINE CONTENT OF
7 TOBACCO IS REDUCED OVER TIME, WILL THERE BE A
8 COMPENSATORY INCREASE IN CIGARETTE CONSUMPTION?

9 DR. BENOWITZ: As was brought up earlier, we
10 have to consider: Is there any harm that might result
11 from a policy, as we are talking about?

12 And there are a few types of harm. We talked
13 about black market before. But I think the harm that most
14 people are concerned about is whether low nicotine content
15 cigarettes will be more hazardous to smokers, and that
16 really becomes a critical issue to try to get a handle on,
17 although we may not have a final answer before such a
18 policy became implemented and would clearly have to be
19 monitored during implementation.

20 (Slide.)

21 The question is really: Among addicted smokers
22 -- this is not for the youth -- among addicted smokers, if
23 there is a reduction in nicotine content, will
24 compensatory smoking result in harm to those smokers?
25 That is really the question. Not is there any

1 compensation, but is there likelihood of harm?

2 You all know about nicotine regulation. There
3 are really three types of data available that address the
4 question.

5 The largest group of data are on self-selected
6 brands, and there, I think, many, many studies have shown
7 -- all except for one from R. J. Reynolds -- that there is
8 very little relationship between currently marketed yields
9 of cigarettes and nicotine consumption, as measured by
10 cotinine levels.

11 So, clearly, there is very good regulation based
12 on what is available. And that is no surprise, because
13 there is plenty of nicotine in the tobacco.

14 There are also many experimental switching
15 short-term studies, indicating people do over-compensate.
16 So they may increase their carbon monoxide exposure and s
17 smoke more cigarettes and take more puffs.

18 There is only one experimental long-term study
19 that I am aware of, and I think that is three or four
20 months. It is in the U.K. I don't know if you were
21 involved, Mike or Martin.

22 But there is one study which is sort of
23 equivocal in terms of whether there is any over-
24 compensation when you look at several months of switching.
25 Clearly, what we are talking about here is not acute

1 short-term switching. We are talking about long-term
2 switching.

3 So there are no decent studies available to date
4 to make any judgment about compensation with long-term
5 switching.

6 DR. RUSSELL: We had one with 10 weeks.

7 MR. JARVIS: Are you thinking of the Frost and
8 Wald study that came out in *Thorax* recently, because that
9 is actually very big, and it is randomized allocation to
10 brand switching.

11 They actually interpreted it as showing
12 compensation, but some substantial downregulation. But if
13 you look at their actual cotinine, there is very little
14 reduction in people who are changing. I don't know if you
15 have seen that one. It is very recent.

16 DR. BENOWITZ: Who was the first author?

17 MR. JARVIS: The first author was a chap called
18 Frost, but Nick Wald was the main person running that
19 study.

20 DR. BENOWITZ: So it sounds like there may be
21 something there ---

22 MR. JARVIS: It is very questionable whether it
23 shows other than fairly complete compensation.

24 DR. BENOWITZ: Okay.

25 (Slide.)

1 So some issues that are relevant to what this
2 measures, the first one is how does compensation occur?

3 Certainly, in short-term studies, it occurs by
4 smoking more cigarettes and more intense smoking, which is
5 translated into either taking more puffs and/or larger
6 puffs and/or blocking ventilation holes. Clearly, all of
7 these issues are relevant to compensation if one switches
8 to different kinds of cigarettes.

9 Then the next question is: If there
10 compensation, is compensation harmful? Well, if nicotine
11 is a concern, that would not be harmful, because you were
12 not taking more nicotine.

13 Carbon monoxide is a combustion product, and so
14 virtually any nicotine compensation would be expected to
15 be associated with higher CO exposure. So CO definitely
16 would be a concern in terms of harm.

17 The tar exposure and other toxins is really
18 unresolved, because many manipulations that have changed
19 nicotine delivery also have changed tar delivery. So we
20 don't really know what to expect in terms of exposure to
21 larger amounts of other potential toxins.

22 And I think one question that would need to be
23 addressed is: How do we get handle on measuring exposure
24 to toxins other than carbon monoxide and nicotine.

25 I think the American Health Foundation studies

1 and studies like that are really critical to try to figure
2 out what else should we be measuring.

3 (Slide.)

4 So the research questions that I think are
5 important to address here is basically: With reduced
6 nicotine cigarettes, will there be greater exposure to
7 carbon monoxide, tar, and other toxins?

8 The second one is: Is compensatory smoking, if
9 it occurs, temporary or persistent? Because we don't know
10 that question.

11 A third one is: Are there some dose reduction
12 schedules that are associated with less over-compensation?
13 So if we reduced nicotine content gradually, will that be
14 associated with less over-compensation than if we do it
15 more quickly?

16 And then something which came up from other
17 speakers before: Is there a particular level of nicotine,
18 below which over-compensation will extinguish, because it
19 is just not reinforcing or just takes too much smoking,
20 too much work, to achieve compensation?

21 But these are all unresolved questions, but I
22 think researchable questions

23 (Slide.)

24 The last points I would like to make are some
25 research design issues relevant to compensation studies.

1 The first is selection of subjects is clearly important.
2 We need to look at people with different levels of
3 dependence. As mentioned before, compensation may be
4 quite different in people with high levels versus low
5 levels of dependence.

6 We need to study people who are interested and
7 not interested in quitting. And then also the ones who
8 are not interested in quitting now, but actually would
9 like to quit sooner or later, because I think their
10 compensation responses may be quite different.

11 There was one study that I was involved with
12 Lynch many years ago. It was actually a retrospective
13 study looking at people who had spontaneously quit five
14 years later, and then getting a cotinine level, and
15 getting cigarette consumption.

16 What we found is that people who shifted to low
17 yield cigarettes had lower cotinine consumption, but it
18 was because they smoked fewer cigarettes. Presumably,
19 this was part of an attempt to reduce health consequences.
20 They didn't reduce cotinine per cigarette, but they didn't
21 increase it either. It stayed about the same.

22 So I think we need to have information up-front
23 about what a person really expects to do in terms of
24 smoking in the next few years.

25 In any design that looks at successively lower

1 levels of nicotine, I think we have to ask: What are the
2 effects of different decrements, and that is why I thought
3 before when Jack raised the question, what cigarettes are
4 needed, we need to have the possibility of different
5 decremental reductions, 20 percent reduction, 10 percent,
6 40 percent. I think we need to explore some of those
7 things.

8 And different rates of tapering. In our
9 proposed, we talked about 10 or 15 years, which we felt
10 was relatively painless for most smokers to do it that
11 way. But that is a totally arbitrary number really. It
12 is just something which sounded reasonable.

13 And then outcome measures. Clearly, cigarettes
14 per day are outcome measures. Nicotine and cotinine
15 levels in plasma or saliva are measures. Carbon monoxides
16 levels are measures. And I think we really need to try to
17 get some handle on tar exposure or other toxin exposures
18 as well, because carbon monoxide may not be the whole
19 picture.

20 (Slide.)

21 And now the final issues regarding research
22 design. In studies like these that are within subject
23 studies, the number of subjects can be relatively small,
24 because you are following individuals. So you don't need
25 to have huge population studies.

1 A second thing is we could probably get pretty
2 good answers over six months, I would think, at least in
3 terms of the first few stages. So these don't necessarily
4 need to be five-year studies.

5 The last issue -- Dr. Geller brought this up,
6 and I have to say that this has been a very difficult one
7 for me to deal with, too, is how do you ever assess
8 compliance. Because there is no way I know of, with the
9 sort of cigarettes we are talking about, to tell if you
10 just go out and buy a regular cigarette, because you are
11 not getting enough nicotine.

12 I think that is a very perplexing problem, and
13 one which has to be dealt with. So those are my comments.

14 DR. GLYNN: Thank you, Neal. This is actually
15 one of the good parts about a meeting like this is you get
16 to raise all the questions, and you don't have to do the
17 answers right now.

18 Clearly, some of the questions are going to be
19 very difficult to address, but I think they are questions
20 we need to get out on the table.

21 So why don't we start? Let's go right up the
22 road to Jed, Dietrich, and Terry.

23 DR. ROSE: Just two quick points, Neal. First,
24 I am not quite sure why you were as hesitant to expect an
25 increase in tar, given people compensate, because the

1 technology that we are talking about, presumably
2 extracting nicotine from the cigarette, so tar and CO are
3 going to go together very closely.

4 DR. BENOWITZ: Well, I actually -- that would be
5 an important observation to make, and that could probably
6 be done with a smoking machine paradigm to show that that
7 is true. Yes, I agree with that. That could be dealt
8 with that way.

9 DR. ROSE: Okay. And the other thing, just some
10 data that we actually have and recently published, shows
11 the short-term compensation -- I agree, the important
12 issue is the long-term -- but we did a study where we had
13 people wearing an active nicotine patch or a placebo skin
14 patch and then smoking denicotinized cigarettes.

15 We found that if they weren't getting nicotine
16 from the patch, they over-smoked the denics by a factor of
17 two. Their CO boost was twice as high. So there seems to
18 be short-term compensation. My guess is that it will
19 extinguish, but the study needs to look at long-term ---

20 DR. BENOWITZ: Almost every study has shown
21 short-term compensation like you found. But ---

22 DR. ROSE: Well, most studies haven't used
23 denics.

24 DR. HOFFMAN: There is a large number of (?)
25 studies that show that during the last 10-15 years there

1 has been shifting of squamous cell carcinoma --
2 predominant lung cancer type -- adenocarcinoma of the
3 lung.

4 The largest study was by (?) and compared the
5 incidence rates '70-'71 compared to '84-'85, one-seventh
6 of the U.S. population. They found a significant increase
7 in -- a higher increase in adenocarcinoma in women, (?),
8 in men, in all four groups.

9 Now you may ask, so what does that mean? You
10 could say this because of smoker compensation to inhale
11 deeper in order to get the higher -- (inaudible).

12 In addition, our laboratory studies, have shown
13 that those carcinomas -- laboratory animals get
14 adenocarcinoma are significantly increased when you
15 compensate. So there is some indication that you may, by
16 compensation, induce one new factor.

17 DR. ROSE: Which is worse? Which kind of cancer
18 is worse?

19 DR. HOFFMAN: You die with both.

20 DR. GLYNN: Terry.

21 DR. HOFFMAN: -- cancer, the cure rate is 5
22 percent.

23 DR. GLYNN: Terry.

24 DR. PECHACEK: Just a quick comment. I would
25 hope that it might be possible to look into some type of

1 additive to the research cigarette that could be tracked
2 onto the amount of nicotine so you would have some type of
3 a marker that could be used as compliance.

4 DR. BENOWITZ: Well, the problem is not
5 compliance with the research cigarette. The problem is
6 whether you are smoking something else as well.

7 DR. GELLER: It is the others you want to mark.

8 DR. PECHACEK: -- look at that ratio.

9 DR. BENOWITZ: Oh, I see. If NCI had a lot of,
10 lot of money, they could manufacture cigarettes that
11 labeled nicotine, and all of our assays would involve
12 labeled -- and we could look at the presence of unlabeled.
13 That is certainly doable, but at a price.

14 DR. GLYNN: John.

15 DR. HUGHES: (Inaudible) -- the reason being is
16 I think we ought to use the lab to model the population so
17 we can actually get some parameters for the population.

18 Because what happens across drugs of abuse, if
19 this is a dose, and this is intake, is as you decrease
20 dose, the animals "depend," if you will, their dose of the
21 drug. Then it falls off. If you look at the vehicle, how
22 much of the vehicle do they use, it goes like that. It
23 goes up to a point, and at this dose, then it starts to
24 drop off. Okay?

25 If we are working our way down the scale, it

1 seems to me we want to get from here to here very quickly;
2 whereas, this part in here, which is the extra vehicle or
3 CO comes in, this is what we don't want. So we want to
4 maybe go slow here, speed up here, and then go fast here.

5 Now, that is very good, but the problem is this
6 is a -- where this point is that people fall off is a
7 population question. That is, if we could sample enough
8 of the population to find out where this point is, then
9 this is where we want to get to. Because after here, we
10 can go as slow as we want to. It doesn't matter, because
11 we won't be giving anybody harm.

12 So I like the idea, but I want to find out what
13 this point is so I know that is the point I have got to
14 get to as quick as I can.

15 DR. ROSE: Except that there could be an
16 interaction that -- as Neal was saying, it is conceivable
17 that people won't compensate if you move slowly, and they
18 will if you move fast. So that could reverse -- the
19 research issue should be to determine that.

20 MR. JARVIS: There is also a tension between
21 doing it on small numbers of smokers and having your
22 adequate representation of dependence levels, interest in
23 quitting socioeconomic categories, and so on. You can't
24 really have both.

25 DR. BENOWITZ: -- small numbers within special

1 groups, but obviously, each group has to be powered enough
2 to look at those changes. What I meant is that this
3 doesn't need to be done in a thousand people, I don't
4 think. Maybe it does.

5 DR. GLYNN: Mike.

6 DR. RUSSELL: I think you are recognizing the
7 importance of maintaining some nicotine delivery to avoid
8 the adverse effects of compensation.

9 That is fine for the early stages of your plan,
10 but I don't -- is the crunch, where it becomes difficult,
11 and you are going to have to -- or it look as though you
12 are going to have to sacrifice risk of taking in excessive
13 harmful products for reducing nicotine too much.

14 I just sort of wonder how you are going to go
15 about that. I think you could, provided you maintained a
16 certain amount of nicotine, you could work on -- an
17 maintain good ratios so that the intake of more harmful
18 products wasn't worse.

19 You could still gradually work on eliminating
20 smoking among those people as much as possible. But I
21 think if you go for the whole population too quickly,
22 in fact, you are going to then get into trouble of
23 having --

24 A lot of ongoing smokers are going to have to
25 take in far more harmful products just for you to sort of

1 forward the program fast enough to not -- to prevent
2 potentially new smokers from getting enough nicotine from
3 it.

4 DR. BENOWITZ: Well, I would strongly support
5 the idea, and actually it would go along with the adult
6 cessation, that any sort of policy like this would, at the
7 same time, be encouraging cessation and also educating
8 people about ways not to over-compensation, to try not to
9 smoke more cigarettes, not to puff more deeply, but do
10 those things in parallel.

11 I agree. Those would be important aspects of
12 maintaining safety.

13 DR. GLYNN: Dietrich.

14 DR. HOFFMAN: There is now a cigarette on the
15 market in which the pH has been raised -- the blended U.S.
16 cigarette has a pH up to 662, which does not contain any
17 uncotinated nicotine. You go higher, you have uncotinated
18 nicotine, which is primarily in the (?).

19 Therefore, when you smoke, it can be already
20 absorbed in the mucus membrane of the -- so they think
21 that when you increase the pH, you will have free nicotine
22 in the (?). You will not have to compensate by --
23 (inaudible) -- mucus membrane absorb, and you get your
24 nicotine kick, and you don't have to deep inhale.

25 DR. BENOWITZ: What cigarette brand is that?

1 DR. HOFFMAN: It is an U.S. brand.

2 DR. BENOWITZ: U.S. brand?

3 DR. HOFFMAN: I don't have -- advertise ---

4 DR. DJORDJEVIC: Just to address the comment
5 from John Hughes about compensation and getting exposed to
6 higher amounts of CO, maybe that solution is to make one
7 of the cigarettes with a type of charcoal filter, which
8 retains all volatile compounds and also carbon monoxide.

9 So that way, you wouldn't be exposed to higher
10 amounts of these when you compensate for nicotine --
11 (inaudible) -- nicotine type cigarette.

12 DR. BENOWITZ: Could I just ask, why are
13 cigarettes not manufactured now with carbon filters?

14 DR. DJORDJEVIC: Well, if you just look at the
15 epidemiology, epidemiologists find that cancer risk in
16 Japan is much lower than United States and they smoke
17 equal number of cigarettes, and there are more men than
18 smoke them here.

19 What is very interesting for the types of
20 cigarettes they smoke, there are 30 percent of cigarettes
21 with charcoal filter in Japan, and here it is only 1
22 percent. We don't know why.

23 But we think one of the companies is picking up
24 the rights, and they are coming on the market with one of
25 these designs. It was reported heavily at the Tobacco

1 Chemist Research Conference last year in Lexington,
2 Kentucky.

3 This type of cigarette reduces up to 80 percent
4 of everything, starting from free radicals to all volatile
5 (?), hydrogen cyanide, CO, mainly (?). That would be like
6 one way to go to keep the levels of nicotine but to reduce
7 other things by -- (inaudible).

8 DR. GELLER: I just would like to caution you
9 about saying that the study should be small and short. I
10 think that the underlying issue here is a long-term one,
11 if you are going to talk about tapering nicotine in
12 cigarettes by the FDA. That is a long-term study
13 inherently.

14 And I think by doing small and short studies,
15 you are not going to get any handle on that. You will get
16 handles on some things, of course. But I think some of
17 the studies just can't be short, small, and sweet.

18 DR. BENOWITZ: Yes, I think I was being over-
19 simplistic. At least if we could look some of the
20 -- in the first days -- may be able to do something that
21 can be done in stages.

22 Like you could look at tapering over six months
23 and see what happens. If there is over-compensation, then
24 one could look at a longer study, do things in stages.

25 DR. GLYNN: Dorothy.

1 DR. HATSUKAMI: Seems like this type of study
2 could also be considered in the context of the
3 availability of nicotine replacement, too.

4 So while they are reducing the whole harm
5 reduction, using nicotine replacement as a harm reduction
6 agent. If you have nicotine gum or nicotine patches in
7 place, you could get less compensation than if you didn't.

8 DR. GLYNN: Have we mined this issue? Someone
9 told me when we were planning this, they said that 75
10 percent of the questions -- the issues -- are going to be
11 covered in the first question; then it is going to be
12 about 15, then about 5; and you are going to get about
13 2 percent left over in the last one.

14 So your timing should be such that you go about
15 three hours for the first question, an hour-and-a-half for
16 the second, and so on.

17 DR. HOFFMAN: But we would have started --
18 (inaudible).

19 DR. GLYNN: Is there any other -- clearly, Neal
20 raised many of the questions, many or most of the
21 questions we need to deal with as far as the over-
22 compensation issue. But does anyone see anything else?

23 DR. HOFFMAN: We should have -- with
24 compensation, there is a concept that has not been
25 introduced. That when you draw too heavily, a second row

1 of perforation is covered by very thin paper, and you draw
2 too quick, this cover will blast and you get more -- you
3 cannot compensate. You understand?

4 That is an area -- we should not limit ourselves
5 that -- some of us -- not just limit ourselves to the
6 behavioral aspects. Also, there are technical aspects --
7 (inaudible) -- there must be approaches -- it was
8 mentioned before -- how can we avoid them -- construct a
9 cigarette where we avoid the compensation, the use of
10 compensation.

11 And there are technical feasibilities, and I am
12 sure when we check the patent literature, some smart aleck
13 from Philip Morris or Reynolds has already done that.

14 DR. ROSE: If you really have a lot of money, we
15 have published a technique which ---

16 DR. HOFFMAN: You have such a thing?

17 DR. ROSE: We have come up with some -- what we
18 thought is if you take smoked cigarettes and machine smoke
19 them, collect the condensate, discarding all the gases, so
20 you don't have any carbon monoxide or most of the hydrogen
21 cyanide and so forth. You take the condensate.

22 You can fractionate the condensate, extract,
23 your benzene, pyrene, and whatever you want to do. Take
24 the cleaned-up condensate, put it in a Premiere-like
25 device that heats but does not combust to pyrolyze new

1 material, and you get a smoke which is very low in
2 nicotine, low in nicotine.

3 So it is not like Premiere. But it is even
4 lower in tar. The nicotine to tar ratio is such it has a
5 lot of sensory impact, but it is low in everything
6 basically. People found it much more satisfying than
7 commercial low tar and nicotine ventilated cigarettes.

8 DR. HENNINGFIELD: I see Tom getting excited
9 about -- safer cigarettes ---

10 DR. GLYNN: I had a slide -- NCI research -- and
11 I called it the dark period in NCI's history.

12 DR. ROSE: I sense a certain skepticism.

13 DR. HOFFMAN: No. What is for sure -- done in
14 England -- in this country -- have come from the
15 scientific community a lot of ideas.

16 Industry has accepted some, but the progress is
17 not in changing the cigarette. Getting more knowledge
18 comes from the scientific community, not from the
19 industry.

20 So I think we should -- in the past, we have
21 done -- but don't expect the industry to come ever out
22 with -- they follow us -- but the ideas have to come from
23 the community. They have no idea. They will never come
24 out with anything. They live for nicotine. They will
25 never change nicotine.

1 DR. GLYNN: Harry.

2 DR. LANDO: I think this was really useful in
3 bringing together a number of us with rather diverse
4 research interests, and there are people, obviously, who
5 are not here who could have been.

6 It may be useful for an organization like SRNT
7 to -- assume will happen -- to continue some of this,
8 where we really are interacting across some of the
9 disciplines. I think we can further this.

10 DR. GLYNN: It is a good opportunity. SRNT
11 actually would be -- the diverse membership, I think,
12 gives it a good position to do that.

13 Let me do this. We are up to Conclusions and
14 Next Steps. Actually, people may get to the airport
15 without having to do quite as much of an O.J. routine.

16 I have some of the housekeeping things. First
17 of all, just things I have jotted down during the day.
18 Any corrections on titles, E-mail addresses and so on
19 needs to go to Pat Davenport before you leave.

20 Secondly, and this is important, as you are
21 leaving and sitting on the plane -- obviously, I want you
22 to pay attention to how to put your seatbelt on and what
23 to do if the mask comes down -- but after that, if you
24 have any other thoughts or something has occurred to you
25 in the interim, or over the next really couple of weeks on

1 this, of a particular research idea with any of the four
2 questions, or something that goes outside that, please
3 E-mail or fax it to me.

4 We want to get it incorporated into the whole
5 transcript. So it doesn't end just now. If it just all
6 of a sudden hits you, that is what -- there is a point you
7 wanted to get across, please do that.

8 Third: If either before you leave, or as soon
9 as you get back, Jack, Neal, Saul, and Harry, if we can
10 get your overheads or slides to make copies, particularly
11 the ones focusing when you posed the research questions.
12 So that is before -- Pat is going to make sure that you
13 don't get out the door without that promise.

14 Fourth: As far as next steps are concerned, the
15 first step really is for us to get the transcript.

16 Second, Jack and I briefly talked, and what we
17 probably will end up doing is having someone who is
18 knowledgeable in the field take the transcript and
19 anything that you have sent in in the interim and put this
20 into a format, which would read, here are the research
21 questions that have been identified.

22 Obviously, that is going to go on for a number
23 of pages. We will try and boil it down into topic areas,
24 maybe not following these questions as such. But let's
25 see how the transcript shows out.

1 And at that point, what we would be doing is
2 getting the Institutes involved in this together to try
3 and decide how we can promote research in this area.

4 Whether it would be through a Program
5 Announcement, more ideally through a Request for
6 Application, which means putting dollars up, which may be
7 somewhat more difficult, especially if there is no budget
8 to put dollars up.

9 At the NCI, we are assuming that we are going to
10 have a flat budget year. But, certainly, in a Program
11 Announcement, I think that we probably could come to some
12 agreement.

13 We will share all of this with the FDA, with the
14 acknowledgement again that this is not a policy issue
15 right now. It is a research issue that can inform policy,
16 but certainly, we want to make sure the FDA is aware of
17 what is going on. We had CDC reps here. So that is
18 certainly very helpful that we have been doing things
19 across the agencies.

20 What I hope would result is a very specific list
21 of research recommendations that people would be able to
22 respond to, not just in this room, obviously, but across
23 the board and actually address this question fairly
24 quickly and know whether we are in a position to use this
25 as a way of reducing tobacco use, which is the main issue

1 that we are about.

2 A very important person has just come into the
3 room, Cheryl Luck (?), who will raise her hand. Cheryl
4 has the professional service contracts for any of you that
5 traveled here, and you need to see here before you leave.
6 Hopefully, we can get that signed before you get out, so
7 that you might get the money next summer. Neal.

8 DR. BENOWITZ: Could I just make one comment?
9 Before we, as researchers, can do anything, we have to
10 have the cigarettes. So that happens to be the absolute
11 number one priority. That has got to be expedited before
12 anything else, even the transcripts.

13 DR. GLYNN: Do you want to talk about steps in
14 that ---

15 DR. HENNINGFIELD: Right now, the steps that
16 have been taken are just something I did in my own little
17 group. In fact, it got slowed by a few months, because I
18 didn't even have \$10,000 last fiscal year to do it, and I
19 had to break it up and do it later.

20 So that is a tiny little thing that I just did
21 just because it seemed so hard to even get something like
22 that rolling, and it has been useful already actually.

23 But the next step we can do within a couple of
24 weeks, which is develop a contract request, and anybody
25 that has your ideas, get them in really (?). Then it is

1 just a matter of little details like how much money there
2 is to work with.

3 We are going to run into walls and limits there
4 real quick, which is why it is important to prioritize.
5 Because even if Institutes could come up with money,
6 looking at a flat budget optimistically, or possibly now
7 they are thinking about -- depending on what comes out of
8 the budget deliberations -- or reduction. There is not
9 going to be lots of new money.

10 So we if we sink all the money into all of our
11 wish list of cigarettes, there is nothing for anything
12 else. So prioritization is real important.

13 As soon as I get my things, which are a separate
14 project, I will share with them anybody to see what you
15 think. Are we on the right track? Is it useful?

16 DR. GLYNN: With your recommendations to Jack on
17 specifications for cigarettes, clearly, keep in mind the
18 recommendations that were made here today to try and mesh
19 the types of research that we may see coming from this
20 with the cigarettes that he would contract for. So that
21 we do have a good fit there.

22 I agree. Without them, then anything else
23 doesn't happen. So the first step, besides writing down
24 any additional research thoughts, is get those specs to
25 Jack, and we are going to shake each other down -- each of

1 the Institutes down, including us, for dollars to see how
2 many cigarettes we can buy, which is an interesting ---

3 DR. HENNINGFIELD: There is something for staff
4 at NIDA, because NIDA has nicotine research going on, and
5 Alan and others have agreed that this makes sense. It is
6 important. It is crazy not to have a placebo --
7 (inaudible) -- placebo marijuana. So I think it is going
8 to happen -- (inaudible) -- we are trying to get --
9 willing to do this ourselves -- (inaudible).

10 DR. GLYNN: I see Norm saying that NICHD is in
11 for five cartons.

12 DR. KRASNEGOR: You got it. No, I have been,
13 through my career, involved with various and sundry
14 projects, one of which was the decade of the brain.

15 I just point this out, because we were trying in
16 that effort to become part of the President's Office of
17 Science and Technology and become involved in what is
18 called the FIXIT Committee, which I won't bore you with
19 what the initials mean.

20 But the point of it was -- is that several
21 different agencies across government worked together, and
22 they got new money. This is something that OMB and a
23 variety of other places look at with great favor. The
24 President currently is looking with great favor upon this.

25 It is a real opportunity, it seems to me, to

1 elevate this not to simply a research agenda that you are
2 talking about here. You will get as many cigarettes as
3 you want if you get onto the FIXIT Committee, and I will
4 be happy to work with you on that.

5 Because I think that there is a political will
6 now to do something different, particularly with kids, but
7 that will benefit the whole field. I think that,
8 initially, what we talked about today that has substantive
9 research questions is exactly the basis for now moving to
10 another level within the government to -- and if you could
11 get that on the agenda, you would be in really good shape.

12 DR. GLYNN: We should talk then about to get it
13 on there. Saul.

14 DR. SHIFFMAN: Really following on that, I just
15 want to thank a lot of people. It seems to me -- I mean,
16 this has been a very stimulating day. I don't know -- it
17 would be interesting to take bets around the room about
18 whether a policy like this will ever be implemented.

19 Be that as it may, in some ways, this is a
20 textbook example of what should happen; that is,
21 scientists make a policy recommendation out of scientific
22 literature.

23 A regulatory agency expresses interest; says,
24 wait a second, we need a scientific basis; goes to the
25 science agencies and says, can you develop them? And the

1 scientific agencies, lo and behold, cooperate and
2 collaborate and seek the input of scientists.

3 So it seems to me it has been an exemplary
4 process, and I really -- I want to thank Neal and Jack for
5 getting the ball rolling sometime ago and Tom and the
6 others from the other Institutes for bringing us together.

7 (Applause.)

8 DR. GLYNN: I will finish with the thank-yous.
9 First of all, thanking everyone. As I say, it has been a
10 long week for some people of travel and nicotine ad
11 nauseam.

12 But I particularly want to thank Jack, Neal,
13 Saul, and Harry for volunteering to do those presentations
14 on short notice and really to get the ball rolling; my NIH
15 colleagues, Mike Manley, who had to go to another meeting;
16 Peter Kaufmann, Norm Krasnegor, and John Boren for sitting
17 down and figuring out how to get this done and get it done
18 quickly; and finally Massey Max, Marilyn Massey and Pat
19 Davenport for actually making it happen.

20 Thank you and don't leave without seeing if we
21 traveled you here, Cheryl Luck before you go. We will be
22 around for a little while still. So we can talk. Thank
23 you very much.

24 (Whereupon, at 2:15 p.m., the meeting was
25 adjourned.)

A Cigarette Chemical Packed With Helpful Effects?

By JOHN SCHWARTZ
Washington Post Staff Writer

Everyone knows that smoking is bad for you. But not every component of a cigarette is harmful. Take nicotine, the chemical that makes smoking satisfying—and addictive.

Nicotine serves as a natural insecticide in tobacco leaves. But the drug is relatively benign to humans in normal doses, especially when compared with the thousands of toxins in tobacco smoke.

In fact, nicotine has a wide array of potentially beneficial effects. As a result, today nicotine is being studied as a possible therapy for a broad range of ailments that includes Alzheimer's and Parkinson's diseases, schizophrenia, depression, adult attention deficit disorder, Tourette's syndrome and ulcerative colitis.

A second wave of research, meanwhile, is aimed at developing drugs that mimic nicotine's positive effects but don't produce its negative side effects. (Nicotine not only can cause nausea and rapid heartbeat, it actually tends to burn out the very receptors in the brain that it excites, forcing the brain to create more receptors to keep up.)

"There is a tremendous growth of interest in the nicotine field," said Jed Rose, a Duke University researcher who co-hosts an annual scientific conference devoted to the drug. "There's been a virtual explosion of new findings on every level."

This trend was on display yesterday, when several groups of researchers presented their latest work on nicotine and nicotine-like drugs at the annual Society for Neuroscience conference in Los Angeles. The presentations even included work by scientists at R.J. Reynolds Tobacco Co. on a drug designed to mimic nicotine's ability to improve memory and learning.

Research on nicotine as a possible treatment for disease got its start a decade ago, as researchers began to notice that smokers suffered less from certain diseases.

Nicotine, however, is not selective. It has many different, often contradictory, effects on the body—for example, it simultaneously calms smokers and speeds up their heartbeat.

"It's just what we would call a 'dirty drug,'" said Phyllis C. Pugh, a nicotine researcher at the Medical College of Ohio. "It has too many effects."

So researchers are looking beyond nicotine to try to come up with compounds that will act more specifically. Neuroscientist Edward Levin and colleagues at Duke University are working with a nicotine-like compound, ARR 17779, that appears to improve learn-

ing and memory in rats. Levin focuses on what are known as "alpha-7 nicotinic receptors," which are found in great concentrations in the hippocampus, part of the brain important to memory and learning.

Receptors are cellular locks that wait for a chemical with a specific shape to act like a key and trigger functions within the cell. In nicotinic receptors, nicotine fits the locks meant for acetylcholine (ACh), one of the body's natural receptor keys.

When Levin and his colleagues injected rats with the chemical, the rats were able to run mazes more effectively. The researchers then took the study a step further by giving the drug to rats whose memories had been impaired by damaging pathways to the hippocampus. Those rats improved as well—a hopeful sign for Alzheimer's research because the connection to the hippocampus is often damaged in victims of that disease.

Researchers at R.J. Reynolds have also been working with nicotine mimics, and have found similarly encouraging results. Two compounds, known as RJR-2557 and RJR-1734, also trigger the brain's ACh receptors. R.J. Reynolds researcher Patrick Lippiello gave the drugs to rats and found that the compounds boosted short-term and long-term memory. The effects last about 18 hours in rats, and the drugs can be taken orally.

The chemicals also seemed to protect rat brain cells from being destroyed by some toxins, which could point the way to a therapy that not only alleviates the symptoms of Alzheimer's but also prevents brain cell degeneration.

Of course, a drug that triggers receptors can work only if there are receptors to be triggered, and so the R.J. Reynolds researchers believe their drug, if effective in humans, will best be used if the disease can be caught in the early stages. "Early intervention in the disease would be a must," Lippiello said.

Any human therapies based on these drugs would be years away, Lippiello warned.

Seth Moskowitz, an R.J. Reynolds spokesman, said the company's venture into the drug business should not be taken as an admission that it is in the drug trade. "The work that we're doing in this area is totally separate and apart from our cigarette business," Moskowitz said. "It started about nine or 10 years ago with the realization that we have a lot of expertise and knowledge about nicotine." R.J. Reynolds is now planning to begin clinical trials on the drugs through a

partner in the pharmaceutical industry.

Along with the new nicotine mimics, many researchers believe that old-fashioned nicotine still has a role to play.

Paul R. Sanberg, professor and chair of neuroscience at the University of South Florida, said about 80 percent of his patients in a study of nicotine patches for Tourette's syndrome, a neurological disorder marked by uncontrollable tics, have "shown improvement in both decreasing the frequency and the intensity of the tics" with long-term effects. In a seeming paradox, giving patients drugs that block the action of nicotine also seems to lessen their Tourette's symptoms. No one yet knows why, but it may be because nicotine desensitizes receptors it works on—in effect making it its own blocker.

Other medical mysteries await researchers. The exceptionally high rates of smoking among people afflicted with Attention Deficit Hyperactivity Disorder (ADHD), depression and schizophrenia suggest that nicotine and similar chemicals might provide some relief. Studies have already shown an improvement in cognitive ability among schizophrenics and a greater ability to focus among ADHD patients who wear a nicotine patch.

Abbott Laboratories is working with researchers at the National Institutes of Health to study a nicotine-like drug from the skin of Amazonian frogs used for poison darts that is, in smaller doses, a highly effective painkiller. And Esther Sabban at New York University Medical College is exploring the role of nicotine in relieving the ill effects of stress on the body.

But what about addiction? Sanberg said he has given nicotine in patch form to children as young as 8 who suffer from Tourette's. "There were clearly people that didn't like the idea of giving their children nicotine and the thought that maybe they could get addicted or start smoking," he said. Nicotine in patch and gum form does not appear to carry the risk of addiction that smoking does, Sanberg said. In cigarettes, the first puff sends a potent jolt of the drug directly to the brain in about eight seconds, while patches and gum work far more slowly and consistently. "We haven't seen any addiction," Sanberg said.

Compared with the usual treatments for the disease, including potent antipsychotic drugs with side effects that can be severe, parents generally opt for the nicotine treatment, Sanberg said.

Scientists studying nicotine say that even if the drug can be addictive, that side effect is something that society will tolerate if the benefits outweigh the risks. Opiates, Levin noted, "can produce an awful addiction—but if you're in severe pain, it's a godsend."

The Washington Post

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Special Communication

The Emerging Market for Long-term Nicotine Maintenance

Kenneth E. Warner, PhD; John Slade, MD; David T. Sweanor, LLB

In increasing numbers, Americans will seek to satisfy nicotine addictions through the use of novel nicotine-delivery products devoid of several of the poisons that make cigarettes so deadly. In the vanguard are tobacco industry devices that heat tobacco derivatives rather than burn tobacco, and pharmaceutical industry nicotine-replacement products, with nicotine gum and the patch now available over the counter. Ostensibly, these 2 industries have diametrically opposed objectives, the tobacco industry striving to sustain nicotine addictions, the pharmaceutical industry to end them. However, a series of technological, economic, political, regulatory, and social developments augurs a strange-bedfellows competition in which these industries will vie for shares of a new multibillion dollar long-term nicotine-maintenance market. Regulatory options range from encouraging competition to banning all nicotine-delivery devices. A more realistic approach discourages use of the most dangerous products, while making less hazardous products readily available to adults.

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ACCOUNTING for a fifth of all deaths in America,¹ the toll of tobacco is all too familiar. So, too, is the ultimate source of tobacco's toxicity: the extraordinary grip that nicotine places on its users.² Although most smokers say they want to stop, for tens of millions, efforts to quit have failed, often despite frequent attempts.³

Recognition of the tenacity of smoking and its eventual deleterious consequences has led some health professionals to question continued, complete reliance on the traditional treatment paradigm, which has regarded abstinence as the only therapeutic goal. Instead, they are cautiously considering a harm-reduction strategy that envisions a role for long-term nicotine maintenance using products that deliver nicotine without the other toxic substances in tobacco products.⁴⁻⁸

At the heart of the nicotine-maintenance concept lies the belief that, although it is not risk free,⁹⁻¹² nicotine per se does not directly cause most of the enormous burden of tobacco-attributable disease. Rather, it is the tobacco products themselves (and their combustion products), the vehicles that deliver nicotine, that are "dirty" and dangerous.

The avoidance of tobacco use is thus considered far more important than kicking an addiction to nicotine. For those who cannot or will not stop using nicotine, might it not be prudent to offer an alternative to tobacco products, one that satisfies their addiction while dramatically reducing their risk of disease?

This question is actually quite complicated, requiring resolution of a myriad of issues. Can consumer-acceptable products be developed that will satisfy nicotine needs without subjecting consumers to substantial health risks? (What constitutes "substantial"? Would such products induce children who do not now use tobacco products to initiate nicotine addictions? Would they cause former smokers to relapse? To what effect? Would users of such products also use conventional tobacco products? Would the availability of alternative nicotine-

delivery devices substantially reduce the number of people who successfully become abstinent in the future? Again, to what effect? (Again, what is "substantial"? How would the nation's drug regulatory apparatus respond?

These are not merely abstract questions. A series of technological, economic, political, regulatory, and social developments has brought us to the brink of a new market for long-term nicotine maintenance. Whether or not the health community finds this desirable, these developments mean that tobacco users are likely to have growing numbers of nicotine-maintenance options available to them soon. Some will involve no tobacco; others will use tobacco in ways not previously imagined. There are numerous patents for such devices, including an electrically fired pseudo-cigarette.¹³

The options that will eventually be brought to market and the conditions of their availability remain to be defined. It is here that the health community can work with the larger society and its formal policymaking apparatus to shape the future of long-term nicotine maintenance. To broaden the debate, we describe developments that are forcing the issue and consider alternative approaches to defining and regulating a future market for nicotine-maintenance products, including those that use tobacco derivatives as the vehicle for delivering nicotine and those that do not. We derive salient lessons for the emerging environment of nicotine delivery from the history of innovation in the cigarette industry.

RECENT AND ANTICIPATED DEVELOPMENTS

New technology for delivering nicotine is evolving rapidly and dramatically. Some of the technology already commercially available is very familiar, such as

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2 nicotine replacement therapy (NRT) products: gum (nicotine polacrilex) and the patch.^{14,15} Some new technology has been introduced but is less familiar, including 2 cigarettelike devices from the R. J. Reynolds Tobacco Company, Premier and Eclipse.¹⁶⁻¹⁸ Finally, some of the new nicotine-delivery technology is quite unfamiliar. For example, nicotine nasal spray became available as a prescription drug only last year and a nicotine inhaler has recently been approved for marketing by the Food and Drug Administration (FDA).^{19,20}

In terms of their purposes, new products from the cigarette companies and nicotine-replacement pharmaceuticals appear to be worlds apart, the former dedicated to the perpetuation of nicotine dependence, the latter to its curtailment. However, plausible developments in both product categories and in the conditions of their availability could well make the cigarette and pharmaceutical companies the strangest of bedfellows, competing vigorously for a large market of long-term nicotine maintainers. The logic underlying this statement will emerge following consideration of each industry's innovations.

NEW-GENERATION CIGARETTELIKE DEVICES AND OLD-GENERATION EFFECTS ON HEALTH

Eclipse is being test marketed in Chattanooga, Tenn, Germany (under the name HI-Q), Sweden (Inside), and Japan (AIRS). Structurally, the device is dramatically different from the conventional cigarette, especially since it burns very little tobaccolike material. A carbon fuel element, insulated with a fiberglass jacket, heats a glycerin-laden charge of reconstituted tobacco. This vaporizes material that cools to condense into an aerosol largely made up of water and glycerin droplets that, in turn, carry nicotine and other volatiles. The consumer inhales an aerosol consisting largely of water, glycerin, nicotine, and the oxides of carbon. Nicotine is delivered at about the same rate and amount as a cigarette having a Federal Trade Commission-rated yield of 0.9 mg. Carbon monoxide yield is moderately higher than that delivered by such a cigarette. Carcinogens are much lower than in most conventional cigarettes.^{17,18,21,22}

The only similar device was Eclipse's immediate predecessor, Premier, a more radical innovation that produced an aerosol from glycerin and a tobacco extract adsorbed onto alumina beads just proximal to the carbon fuel element. Introduced in 1988, Premier failed market tests and was taken off the market amid mounting pressure on the FDA to regulate it under the Food, Drug and Cosmetic Act.²³

Both Premier and Eclipse seem designed to address 2 industry problems: smokers' concerns about the health effects of smoking, especially its carcinogenic potential, and nonsmokers' concerns about environmental tobacco smoke (neither product produces much visible smoke). Both of these industry problems have been addressed, largely without success, by earlier generations of product innovation. The environmental tobacco smoke issue is of more recent vintage, and relevant innovations are fewer in number. Two were cigarettes with built-in perfume and low-smoke cigarettes, designed with special papers resulting in less visible sidestream particulate matter.^{24,25}

Health concerns drove the 2 major previous paradigm shifts in cigarette architecture: filter-tipped cigarettes in the 1950s and low tar and nicotine (t&n) cigarettes at the end of the following decade, both presented to the public as radical design changes, much like the emerging generation of devices.

Filters were the industry's response to the then newly emerging public concern about smoking's relation to lung cancer.²⁶ The cigarette companies marketed filters as trapping the dangerous components of cigarette smoke but letting the "flavor" through.²⁴ Affording smokers an apparent alternative to quitting smoking, filters rapidly became the dominant product on the market. Their introduction and marketing were quickly followed by reversal of a 2-year decline in per capita cigarette consumption in 1953 and 1954 that had resulted from new evidence linking lung cancer to smoking, which then meant unfiltered cigarettes.²³ Ironically, the most successful early filter, touted quite explicitly for its health protection properties, the Kent Micronite filter, used crocidolite asbestos as the filtering agent.^{27,28} That filter cigarettes were introduced primarily as a public relations gambit, rather than as truly less dangerous products, is suggested by the fact that some early filtered cigarettes used harsher tobaccos, so that the filtered smoke would taste like the unfiltered smoke of old.²⁶

The industry's next technological "fix" was the low t&n cigarette, marketed, often explicitly, with the theme that health-conscious smokers had the choice of either quitting smoking or switching to low t&n brands.²⁹ By 1981, low t&n cigarettes had captured a majority of the market. Medical textbooks frequently recommended their use by patients unable or unwilling to stop smoking.^{30,31}

Since then, scientists have learned that smokers who switch from regular cigarettes to low t&n brands engage in

"nicotine regulation," compensatory behavioral changes that greatly narrow the supposed gap between high- and low-yielding cigarettes. Low t&n smokers may consume more cigarettes, take larger and more frequent puffs, inhale more deeply, smoke to a shorter butt length, and subvert the technologies that lower machine-measured t&n yields (by blocking ventilation holes in filters that, unoccluded, dilute smoke by mixing it with air).^{2,32,33}

The net effect is that, consistent with smoking being a drug dependence process, the variance in smokers' blood cotinine levels is significantly smaller than the variance of nicotine deliveries indicated in cigarette advertisements.³⁴ The public is generally unaware that t&n ratings are derived from standardized machine smoking of cigarettes, in which cigarettes are puffed at a constant volume (35 mL) and at a constant interval (60 seconds). As the data on nicotine regulation demonstrate, people do not usually smoke like machines.³⁵

Low t&n cigarettes could reduce health risks if smokers did not engage in nicotine regulation to a significant degree and if they would have continued to smoke even if low t&n cigarettes were not on the market. However, most smokers who "switch down" to low t&n cigarettes do engage in nicotine regulation.^{32,33,36} Further, the availability of low t&n cigarettes has probably substantially impeded smoking cessation.^{23,37-40} On balance, therefore, low t&n cigarettes may well have increased the aggregate societal burden of smoking, primarily by reducing the number of people who would have quit in the absence of their availability, and secondarily by switchers smoking more cigarettes.²³

Cigarette use likely would be much lower today if the only products for sale were 70-mm unfiltered smokes. The introduction and diffusion of filters and then low t&n cigarettes thus clearly benefitted the industry by maintaining or increasing sales. Industry documents show that at least some industry scientists regarded low-tar cigarettes as "health-image" products, public relations gimmicks, rather than truly "health-oriented" products.³⁸

The introduction of Eclipse thus follows a decades-old tradition of industry product innovation in response to public concern, with the industry's apparent intent being to reduce concern and thereby maintain or expand sales. "Concern," in this instance, has a social as well as a health connotation: emitting less visible smoke, Eclipse may be less objectionable to others around the smoker, thereby further reducing the smoker's incentive to quit. More similarly moti-

vated new-generation products will likely soon appear,^{13,17} especially if Eclipse is successfully introduced or if the national tobacco settlement proposed in June⁴¹ is enshrined in federal law. The proposal includes provisions that would encourage industry innovation leading to less hazardous products.

Whether past history is relevant to the new generation of tobacco company products remains to be seen. The promise of reduced risk for confirmed smokers may be genuine this time, especially with regard to cancer. If history repeats itself, however, this ostensibly less hazardous product might sustain high levels of nicotine addiction and, on balance, increase the aggregate disease toll.

One great risk specific to low-smoke devices is that they may be deemed acceptable for use in settings in which smoking is prohibited, such as workplaces. A plausible consequence would be regular cigarette smokers' consuming these devices during work hours, when at present they do not smoke, and then continuing to smoke their regular brands outside work. The net effect would be increased exposure to nicotine and carbon monoxide, since workplace smoking bans decrease daily cigarette consumption.⁴² For people who would have quit smoking in the absence of the daytime nicotine alternative, all the risks associated with smoking would be greatly increased.

Nicotine-Containing Pharmaceuticals

Nicotine gum introduced the era of NRT pharmaceuticals in the United States in 1984, followed by patches in 1991 and nicotine nasal spray last year, with the nicotine inhaler on the marketing horizon. A nicotine-containing lozenge on a stick (like a lollipop) is also being developed.⁴³ Researchers are investigating combination therapies as well, attempting to exploit the specific virtues of the different products.⁴⁴

A major change in product distribution may be as important as the development of NRT products: over-the-counter (OTC) sale, of nicotine gum and patches thus far. Although the quit rate will be lower than that associated with using NRT under the guidance of experienced clinicians, greater NRT accessibility could more than compensate, leading to more quitting in the aggregate.⁴⁵

Over-the-counter availability will also likely increase the use of nicotine-bearing products as partial or complete *ongoing* substitutes for cigarette smoking (and other tobacco product use). It will likely routinize the use of NRT products by smokers not trying to quit, to supply nicotine when they are not smoking, ei-

ther because they want to reduce their cigarette consumption or because law or custom precludes their smoking in certain locations (eg, workplaces or airplanes).^{8,46} For this use, NRT products should logically be called *nicotine-maintenance* products.

Strange Bedfellows

Through product innovation by tobacco companies, pharmaceutical companies, and other consumer products companies, and through OTC distribution of NRT products, the lines distinguishing different types of new-generation nicotine-delivery devices could eventually become blurred. More or less intentionally, each company could find itself sustaining nicotine dependence among consumers whose choices would otherwise be limited to conventional tobacco products or abstinence. Ironically, tobacco companies and pharmaceutical companies, which approach nicotine addiction from diametrically opposite positions, could find themselves in direct competition for sales of nicotine-maintenance products among the same group of consumers.

The tobacco industry would clearly vie aggressively for such sales. With a potential market in the tens of millions of consumers in the United States alone, the pharmaceutical industry would also have to seriously consider aggressive involvement in a reconceptualized nicotine-maintenance market. Drug companies are competing now with advertising campaigns for OTC gum and patches exceeding \$100 million, which would certainly pay off more handsomely if consumers used these products over a long period.^{47,48} The relative ease of the transition from focusing exclusively on nicotine replacement to contemplating a much larger market for nicotine maintenance has been hinted at in advertisements promoting a non-nicotine smoking cessation aid, CigArrest, "for those times when you want to stop smoking, *for a moment*, or forever" (emphasis added).

What would be the health impact of such a market? As described above, the history of tobacco company innovation is not encouraging: previous generations of ostensibly "less hazardous" products may well have increased the aggregate harm caused by cigarettes by encouraging the maintenance of smoking rather than quitting. Still, some future mix of products could conceivably overcome enough of smoking's dangers that the cost of their substitution for cigarettes—continued dependence on nicotine—would be less than the benefit of the reduced exposure of the population to the other poisons associated with use of tobacco products.

ALTERNATIVE SCENARIOS FOR THE FUTURE AVAILABILITY OF NICOTINE

For many health professionals, contemplating competition between the tobacco and pharmaceutical industries for long-term nicotine users will generate a sense of moral repugnance. Like it or not, however, this competition will continue to develop, barring extraordinary regulatory measures (eg, the FDA's returning nicotine gum and patches to prescription-only distribution and prohibiting the marketing of any new tobacco industry products not demonstrated to be safe).

An optimal set of market and regulatory circumstances could conceivably create incentives that encourage the development of less hazardous methods of consuming nicotine. Note that we have had a market for long-term nicotine maintenance for decades: the tobacco market. Through strict regulation of nicotine in nontobacco products, and virtually no product regulation of tobacco to date, we have, essentially, granted the tobacco industry a monopoly in the nicotine-maintenance market. Reconceptualizing that market, opening it to innovative, less hazardous products introduced through competition between the tobacco and pharmaceutical industries, could conceivably satisfy the public's desire for nicotine without exacting the current enormous cost in ruined lives.

The creation and marketing of novel nicotine-delivery devices raise a myriad of possible scenarios concerning the future availability and use of both tobacco and nontobacco nicotine-bearing products. Here we summarize scenarios defined by the regulatory approach adopted. Product availability and use will also be defined by consumer demand. Without discussing this explicitly hereafter, we assume that many consumers will want to use nicotine devices characterized by convenience, reasonable price, social acceptability, and provision of a high degree of nicotine satisfaction.

Either consistently or idiosyncratically, each of the product categories—current tobacco products, new tobacco industry nicotine-delivery systems, and nicotine devices produced by the pharmaceutical (or other) industries—could be regulated according to the following options: (1) no regulation, (2) legal availability on a nonprescription basis, (3) availability by prescription only, and (4) not legally available. In addition, regulation could include limits on advertising, disclosure of information to consumers, and so on, such as the youth-oriented marketing and sales restric-

tions pertaining to cigarettes and smokeless tobacco imposed last year by the FDA.⁴⁹

Although a court has recently affirmed the FDA's authority to regulate conventional tobacco products,⁵⁰ they are currently subject to no health and safety regulation. In contrast, all pharmaceutical company innovations have been submitted to and regulated by the FDA, with efficacious nicotine-replacement products first permitted for prescription sale and then OTC, if their abuse liability is deemed low. The FDA has also asserted its authority over other nicotine-delivery devices not submitted to the agency for approval. Favor, a precursor to the new inhaler, was prohibited as an untested drug-delivery system. Similarly, the FDA determined that Masterpiece Tobacs, a chewing gum containing shredded tobacco leaf intended for use "Anytime, when you can't smoke," was a food product adulterated with an unapproved additive, tobacco.⁵¹

The regulatory status quo is thus well defined, with 1 critical exception: innovative tobacco industry products. To date, no major tobacco company has submitted an innovation for FDA approval, and the agency has not asserted its regulatory authority when confronted with a product from a major producer. However, the FDA has been petitioned to regulate Eclipse.⁵¹ The agency was considering claiming regulatory jurisdiction over Premier before R. J. Reynolds removed it from the market.⁵² The proposed national tobacco settlement would accord the FDA regulatory authority over such devices.

A future regulatory structure for nicotine-delivery devices could continue current policy, with new tobacco industry products treated either more like conventional tobacco products or more like conventional pharmaceutical products. Alternatively, it could treat all nicotine-yielding products identically, regulating them as either prescription or nonprescription drug-delivery devices. In theory, a decision could be reached to keep government out of the nicotine market altogether, allowing a free enterprise shoot-out between the tobacco and pharmaceutical giants. As unlikely as that seems, another possibility, banning all nicotine-yielding products, is even less conceivable.

A more rational regulatory approach might be to advantage less toxic products, instead of honoring accidents of history, as at present. All currently available nicotine-delivery devices would continue to be sold, but the least toxic would be the most easily available and attractively presented, as discussed below. Such an approach could also provide

incentives, or requirements, for incremental improvements in conventional products, for instance by requiring that cigarettes be fire safe.⁵³

A more radical differential regulatory strategy would require reduction of the nicotine content of conventional tobacco products over several years to levels unlikely to cause or sustain addiction.⁵² This would afford current users ample opportunity to wean themselves off of tobacco products, while simultaneously reducing the ability of tobacco products to addict future generations of children. All other nicotine-yielding products, regardless of industry of origin, would be evaluated as drug-delivery devices by the FDA, permitting only those that met a relative harm standard on the market. The harm threshold might (for example) tolerate nicotine addiction, but prohibit any other substances known or believed dangerous to health.

Under this policy, despite their delivery of toxic compounds, tobacco products could be freely sold once they were denicotined (possibly subject to age restrictions, as at present). If people really smoke for "flavor" or "taste"—the predominant tobacco industry claim—sales of tobacco products should not be affected. If, in fact, people smoke primarily to satisfy nicotine addictions, few if any consumers likely would choose to use denicotined products on a regular or even frequent basis. This may have been the experience with Next, a denicotined brand introduced by Philip Morris in the late 1980s that failed its market tests.⁵³

In addition to determining legal availability, regulatory agencies frequently regulate circumstances of manufacture, marketing, time and location of sale, and age of purchase. Current FDA regulation of cigarettes and smokeless tobacco, to protect children, focuses exclusively on just such conditions of marketing and sale.⁴⁹

Future nicotine-delivery device regulation could rely heavily on differential marketing and sale conditions to reduce the attractiveness of the most hazardous products and increase that of the least hazardous. For example, firms might be permitted to advertise, without restrictions, products that the FDA found minimally dangerous. In contrast, if permitted at all, cigarette advertisements might be limited to black-and-white block-letter factual text. Similar distinctions could be made with regard to packaging, with plain packaging required for the most dangerous products, such as cigarettes, with warning labels consuming a third to a half of the front panel of the package.^{54,55} Differential rates of excise taxation might be used to encourage consumer use of the less hazardous products.

Regardless of which of the diverse regulatory scenarios might be adopted, there is no reason to delay marketing, packaging, and sales restrictions to reduce the glamorous imagery associated with tobacco use or incremental product design changes helpful to the public's health (eg, fire safety).

TOWARD DEVELOPMENT OF A NICOTINE POLICY

The intent of a rational nicotine policy must be to deal realistically and constructively with the public health disaster wrought by the widespread use of tobacco products. An underlying premise, supported by a wealth of evidence, is that because of addiction, tobacco products exact their toll predominantly involuntarily on the part of consumers. With rare exceptions, nicotine addiction begins during childhood and adolescence; despite sincere desires to quit, many simply find the chore too difficult.

The primary goal of a new nicotine policy should remain to help everyone who wishes to be free from nicotine and tobacco to avoid addiction or achieve abstinence. Such a policy must recognize that people who are nicotine-dependent are victims of addiction and not social miscreants. They deserve a policy that acknowledges their individual dignity, the difficulty many would have in being forced to forgo nicotine, and the opportunity to continue consuming nicotine should they so desire. At the same time, children deserve the opportunity to grow up free of inducements to become addicted to nicotine. As such, the option of having minimally harmful nicotine products available to adults, in a social and policy environment that deglamorizes nicotine consumption, seems worthy of open-minded consideration.

The notion of nicotine maintenance in less harmful forms, rather than complete abstinence, is not new. Following the introduction of filtered and then low t&n cigarettes, numerous health professionals supported switching from the conventional product to the innovation.^{58,56} More recently, an oral pathologist has advocated the use of smokeless tobacco products as a less dangerous alternative for addicted cigarette smokers.⁵⁷

With hindsight, support of filtered and then low t&n cigarettes appears to have been misguided, quite possibly the cause of more rather than less disease caused by tobacco. Similarly, encouraging addicted smokers to switch to smokeless tobacco products appears shortsighted,⁵⁸ especially given the availability of the new NRT devices, the spray and the inhaler. These are far cleaner than smokeless tobacco and may satisfy nicotine needs at least as effectively.

The approach considered here—nicotine maintenance for some addicted consumers through the provision of less toxic nicotine-delivery devices—has been advocated for quite a while by a handful of prominent scientists.^{4,69,60} Nevertheless, nicotine maintenance is certain to be unpopular with many seasoned veterans of the tobacco wars. Acknowledgment of the possibility of a world in which nicotine addiction might be tolerated, and even encouraged, would be a bitter pill to swallow for many health professionals.

Stopping short of supporting a ban on cigarettes, universally recognized as implausible (and we believe undesirable), a prevalent "zero tolerance" philosophy derives in part from the accurate perception that, to date, ostensibly risk-reducing product innovations have typically had quite the opposite effect. For at least some members of the tobacco-control community, it also likely derives in part from a puritanical streak and a cynicism fed by decades of consistently dishonest and dangerous tobacco industry behavior.^{26,38,61} Such people may find completely unacceptable the tobacco industry's continuing to profit from the sale of any kind of product, especially one that perpetuates nicotine dependence.

Adoption of a nicotine maintenance policy is fraught with dangers, as well as opportunities; the 2 may occur together. For example, to compete successfully with cigarettes and other tobacco products, nicotine-only pharmaceuticals may need to be made more attractive to consumers. The current unappealing flavor of nicotine gum may have to be improved. Similarly, more efficient (rapid) means of getting nicotine into the brain may be required (eg, the new spray or inhaler). Therein lies the promise of consumer-driven shifts away from tobacco products; but the very process of making nicotine products competitive with tobacco products, from a consumer's perspective, will increase the abuse potential associated with the new products. This amplifies the need to ensure that any involved regulatory authority develops explicit objectives and criteria with both foresight and flexibility. Flexibility may prove essential to deal with failures in the domain of foresight: any regulatory system will need to make adjustments in light of actual experience.

The presence of alternatives to conventional tobacco products will influence the degree to which people seek abstinence, and there may be shifting back and forth among delivery devices. The risks faced by novices, the young, under various scenarios will have to be carefully considered as well. What may be

good policy for dealing with the current generation of tobacco users may not be so good for future generations. The opposite holds as well. For example, in the absence of consumer-acceptable alternative nicotine-delivery devices, a multi-year phaseout of nicotine in tobacco products could avoid future generations' addiction; however, it might do so at the expense of already addicted smokers ingesting more carcinogens, by smoking more low-nicotine cigarettes to satisfy their nicotine cravings. Clearly, it would be prudent for a national nicotine policy to be subject to periodic review and revision.

In any event, the absurd irony of the contemporary nicotine regulatory environment must be reversed: new pharmaceutical products currently face a long and expensive marketing approval process, while the most dangerous nicotine-delivery devices ever invented, tobacco products, are introduced and sold without regulatory impediments. In essence, the deck of competition has been stacked heavily in favor of conventional tobacco products. A manufacturer who wishes to introduce a new cherry-flavored smokeless tobacco product does so with no regulatory obstacles. If a pharmaceutical company wants to add mint flavoring to nicotine gum to make it more palatable as a nicotine-replacement product, the company must endure years of expensive regulatory hurdles. At a minimum, rationality recommends comparable treatment of the 2 situations. Certainly, the no-regulation tobacco product model is inappropriate. But the highly constrained, time-consuming, and expensive model for contemporary pharmaceuticals may be undesirable as well, effectively minimizing firms' attempts to be innovative in this challenging market environment.

A nicotine-maintenance market will emerge from the present ferment in device innovation. Its precise characteristics remain to be established. We urge the health community, and the broader public as well, to engage in thoughtful research and discussion on the nature of this market and on the characteristics it ought to have. The stakes are extraordinarily high.

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Lynn Kolowski

(b)(6)

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Industry should not be allowed to use right of attorney
 until shown to be less risky.

William F: 513-748-1659 direct 865-2166
 513-748-0445/415

Ricker - most concerned about toxicity - Dr
 Industry provide - Group assessment.

Oversight
 Monitor

Rpt on product modifications
 Identify research needs

Murray Kaiserman
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Ken Warner
 Univ. of Mich
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Amer. Psych Assoc.
 Withdrawal: APA practice guidelines

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Don Shapiro
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 Foul - Hoffman

Not for public NCI 214-592-2644

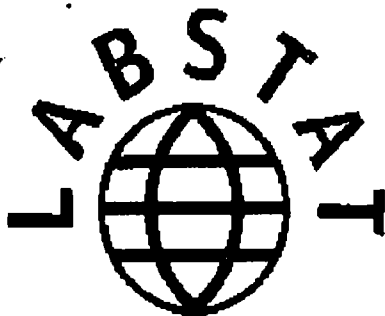
CW
 428-518-
 757

product use
 patterns

Oversight
 Monitor

Rpt on product modifications
 Identify research needs

Murray Kaiserman
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INC.

FAX COVER Sheet

To: Jerry Mande		From : Bill Rickert
Fax Number : 1-202-4566027		Company : Labstat Incorporated
Date : 7/22/97	Time : 13:15:00	For Information Call: 1-519-748-5409
Subject : White House Meeting		Fax Number : 1-519-748-1654

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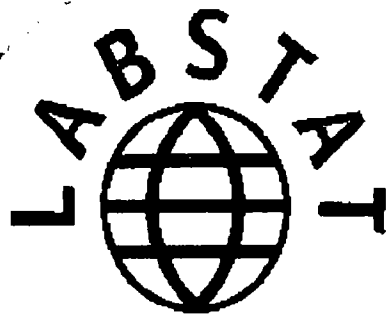
Good Afternoon Jerry

Thanks for giving me the opportunity of commenting on the potential "harm reduction" aspects of the tobacco settlement.

A one page description of my background and professional activities follows this coversheet.

Regards

Bill Rickert



INC.

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To: Jerry Mande		From : Bill Rickert
Fax Number : 1-202-4566027		Company : Labstat Incorporated
Date : 7/22/97	Time : 13:15:00	For Information Call: 1-519-748-5409
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Regards

Bill Rickert

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Special Communication

*Jerry -
With best regards.
(Don't forget this piece!)*
/Ger

The Emerging Market for Long-term Nicotine Maintenance

Kenneth E. Warner, PhD; John Slade, MD; David T. Swenor, LLB

In increasing numbers, Americans will seek to satisfy nicotine addictions through the use of novel nicotine-delivery products devoid of several of the poisons that make cigarettes so deadly. In the vanguard are tobacco industry devices that heat tobacco derivatives rather than burn tobacco, and pharmaceutical industry nicotine-replacement products, with nicotine gum and the patch now available over the counter. Ostensibly, these 2 industries have diametrically opposed objectives, the tobacco industry striving to sustain nicotine addictions, the pharmaceutical industry to end them. However, a series of technological, economic, political, regulatory, and social developments augurs a strange-bedfellows competition in which these industries will vie for shares of a new multibillion dollar long-term nicotine-maintenance market. Regulatory options range from encouraging competition to banning all nicotine-delivery devices. A more realistic approach discourages use of the most dangerous products, while making less hazardous products readily available to adults.

JAMA. 1997;278:1087-1092

ACCOUNTING for a fifth of all deaths in America,¹ the toll of tobacco is all too familiar. So, too, is the ultimate source of tobacco's toxicity: the extraordinary grip that nicotine places on its users.² Although most smokers say they want to stop, for tens of millions, efforts to quit have failed, often despite frequent attempts.³

Recognition of the tenacity of smoking and its eventual deleterious consequences has led some health professionals to question continued, complete reliance on the traditional treatment paradigm, which has regarded abstinence as the only therapeutic goal. Instead, they are cautiously considering a harm-reduction strategy that envisions a role for long-term nicotine maintenance using products that deliver nicotine without the other toxic substances in tobacco products.⁴⁻⁸

From the Department of Health Management and Policy, School of Public Health, University of Michigan, Ann Arbor (Dr Warner); Department of Medicine, University of Medicine and Dentistry of New Jersey, and St. Peter's Medical Center, New Brunswick, NJ (Dr Slade); and Non-Smokers' Rights Association, Ottawa, Ontario (Mr Swenor).

Reprints: Kenneth E. Warner, PhD, Department of Health Management and Policy, School of Public Health, University of Michigan, 109 S Observatory, Ann Arbor, MI 48109-2029 (e-mail: kwarner@umich.edu).

At the heart of the nicotine-maintenance concept lies the belief that, although it is not risk free,⁹⁻¹² nicotine per se does not directly cause most of the enormous burden of tobacco-attributable disease. Rather, it is the tobacco products themselves (and their combustion products), the vehicles that deliver nicotine, that are "dirty" and dangerous.

The avoidance of tobacco use is thus considered far more important than kicking an addiction to nicotine. For those who cannot or will not stop using nicotine, might it not be prudent to offer an alternative to tobacco products, one that satisfies their addiction while dramatically reducing their risk of disease?

This question is actually quite complicated, requiring resolution of a myriad of issues. Can consumer-acceptable products be developed that will satisfy nicotine needs without subjecting consumers to substantial health risks? (What constitutes "substantial"?) Would such products induce children who do not now use tobacco products to initiate nicotine addictions? Would they cause former smokers to relapse? To what effect? Would users of such products also use conventional tobacco products? Would the availability of alternative nicotine-

delivery devices substantially reduce the number of people who successfully become abstinent in the future? Again, to what effect? (Again, what is "substantial"?) How would the nation's drug regulatory apparatus respond?

These are not merely abstract questions. A series of technological, economic, political, regulatory, and social developments has brought us to the brink of a new market for long-term nicotine maintenance. Whether or not the health community finds this desirable, these developments mean that tobacco users are likely to have growing numbers of nicotine-maintenance options available to them soon. Some will involve no tobacco; others will use tobacco in ways not previously imagined. There are numerous patents for such devices, including an electrically fired pseudo-cigarette.¹³

The options that will eventually be brought to market and the conditions of their availability remain to be defined. It is here that the health community can work with the larger society and its formal policymaking apparatus to shape the future of long-term nicotine maintenance. To broaden the debate, we describe developments that are forcing the issue and consider alternative approaches to defining and regulating a future market for nicotine-maintenance products, including those that use tobacco derivatives as the vehicle for delivering nicotine and those that do not. We derive salient lessons for the emerging environment of nicotine delivery from the history of innovation in the cigarette industry.

RECENT AND ANTICIPATED DEVELOPMENTS

New technology for delivering nicotine is evolving rapidly and dramatically. Some of the technology already commercially available is very familiar, such as

SOCIETY for RESEARCH on NICOTINE and TOBACCO

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September 12, 1997

Mr. Jerold Mande

Senior Advisor to the Director

Office of Science and Technology Policy

Old Executive Office Building, Room 346

17th Street and Pennsylvania Avenue, NW

Washington, DC 20502

Dear Mr. Mande:

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David KL Balfour, PhD

Scientific Liaison

John R Hughes, MD

Public Policy

The Society for Research on Nicotine and Tobacco (SRNT) is the only scientific organization in the world focused solely on research related to nicotine and tobacco dependence. We are writing today for two reasons: first, to offer you staff the services and expertise of SRNT members as you review the proposed tobacco settlement; and second, to register our concerns about the importance of research dollars for ongoing study of nicotine addiction.

The SRNT membership includes a broad range of experts whose research efforts have helped lay the scientific foundation for the proposed settlement and whose counsel has been called on in the past. For example, all of the scientific editors of the Surgeon General's Report on Nicotine Addiction are members of SRNT and several key members worked closely with the FDA to formulate the policy classifying nicotine in cigarettes as a drug and the restrictions on cigarette advertising and promotion. SRNT can contribute in very constructive ways to the discussion and decision-making process in which you are engaged. For your use, we have enclosed a brief description of our views and concerns regarding the potential settlement.

We recognize that there are many important components of the tobacco settlement with serious health and political implications, and the enormity and complexity of these issues at times encourages all of us to view the nicotine addiction problem from a short-term perspective. Notwithstanding some of the excellent provisions in the settlement, tobacco addiction, and its related health, social, and economic effects, are not going to disappear within the foreseeable future.

We do not know nearly enough about nicotine addiction and smoking behavior to be able to prevent or effectively treat nicotine addiction; and with our current knowledge base, we cannot confidently predict a smoke-free society in the future. SRNT was pleased to see that the proposed settlement provides for increased research and we fully support this provision. However, in all the public discourse to this point, the importance of research dollars dedicated to studying nicotine and tobacco addiction has been virtually ignored. The amount of research dollars as well as how those dollars would be administered, should a settlement be reached, must not be left to last-minute decision-making. We believe that the decisions made about these research issues will have a major, and possibly decisive, impact on the extent of the tobacco problem in the future.

COMMITTEES

Raymond Niaura, PhD

Finance

Neal Benowitz, MD

Long Range Planning

Martin Jarvis, MPhil

Nominating

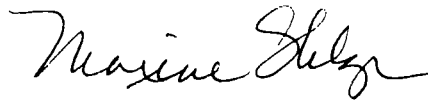
EXECUTIVE DIRECTOR

Judith C Woodward, CAE

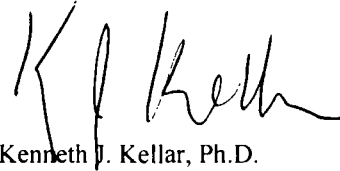
Mr. Jerold Mande
September 12, 1997
Page Two

As the issues of nicotine, smoking, and tobacco use come before you, SRNT is an important resource that you can call on. We can be contacted through Judith C. Woodward, SRNT Executive Director, at our national headquarters in Rockville, Maryland. Our phone number is 301/251-9133. Or, if you prefer, you may call us directly at the numbers listed below. Thank you for your attention to this important issue.

Sincerely yours,



Maxine L. Stitzer, Ph.D.
SRNT President
Bayview Medical Center
Johns Hopkins University
410/550-0042



Kenneth J. Kellar, Ph.D.
SRNT Policy Committee
Professor of Pharmacology
Georgetown University School of Medicine
202/687-1032

MLS/KJK/jb
Enclosures

The Importance of Research in the Development of National Tobacco Control Efforts

SRNT POLICY STATEMENT

July, 1997

The Society for Research on Nicotine and Tobacco was founded in 1994 to foster the exchange of information on the entire spectrum of research concerning nicotine use and tobacco dependence and to stimulate a generation of new knowledge concerning nicotine in all its manifestations.

1. *Scientific research findings have been a major driving force in recent advances in tobacco control, including the proposed tobacco settlement in the United States.*

Tobacco policy, prevention, treatment, and medication development have been a model of science aiding the public welfare. For example, consider the impact of the following research findings:

- ⇒ nicotine meets all the standard criteria as an addictive drug;
- ⇒ the brain has specialized receptors that bind nicotine. Nicotine and smoking causes changes in these receptors which may be directly related to the addictive properties of nicotine;
- ⇒ brain systems activated by nicotine are the same ones activated by cocaine;
- ⇒ tobacco advertisements influence smoking initiation in children;
- ⇒ increasing the price of cigarettes decreases initiation of smoking.

All of these findings have influenced the direction of tobacco control efforts. In the next several weeks, when major discussions are taking place about tobacco policy and control, it is essential that decision-makers consult those most familiar with nicotine addiction and smoking cessation — research scientists who can help clarify the public health issues and provide the foundation for rational policy development.

2. *Nicotine and tobacco addiction research must be substantially expanded to ensure progress in our ability to curtail the development of nicotine addiction and to effectively treat a broader range of nicotine-addicted people. This includes research ranging from the molecular basis of nicotine's action to genetic influences on the vulnerability to addiction, and the chemical, behavioral, and social modulators of the addictive process.*

Continuing research is essential to successful tobacco control and the viability of the tobacco settlement. The population of smokers remaining over the next 5 to 50 years will require new and innovative approaches to cessation. For example:

- ⇒ nicotine replacement therapies have been effective for millions of smokers to date; however, there are 40 million smokers who have not tried or who have failed on these therapies. Many long-term smokers today are those most highly addicted or have additional problems such as psychiatric disease or substance abuse;
- ⇒ two-thirds of all smokers are using what they think are low-tar/low-nicotine cigarettes. Yet, 20 years after their introduction, the data suggest that the health benefits of smoking such cigarettes may be negligible. In fact, low-yield cigarettes may be undermining cessation efforts.

3. *Effective treatments must be made easily accessible and, at the same time, new treatments for highly-addicted smokers need to be developed.*

Although prevention has been the positive focus of many efforts, pursuing prevention alone abandons the 40 million smokers who want to quit but are unable to do so. We also need to develop and implement a treatment and delivery system to provide scientifically-based interventions to smokers who either are more highly addicted or who for other reasons have been unable to stop smoking. It is worth noting that:

- ⇒ benefits of effective prevention programs are not realized for 20-30 years, whereas treatments that produce cessation and smoking reduction in current smokers provide quality-of-life benefits to the individual and economic benefits to the country which are realized within as few as 5 years;
- ⇒ as Agency for Health Care Policy and Research (AHCPR) guidelines have documented, effective scientifically-based treatments are available and increased access to these could benefit millions of smokers over the next several years;
- ⇒ there is a clear need for development and evaluation of treatments for lower income populations who are least able to afford the most effective treatments.

4. *The FDA must have the same authority to regulate the nicotine in tobacco as it does for nicotine in medications, and it must have the financial and administrative resources to do so.*

Nicotine is the addictive agent in cigarettes. Therefore, we believe that:

- ⇒ adding **unique** additional constraints to the FDA's ability to regulate the nicotine in tobacco would exacerbate the weaknesses in the present system: the most dangerous and addictive forms of nicotine delivery (i.e., tobacco) would be subject to less meaningful regulatory control than are nicotine replacement medications;
- ⇒ all nicotine products must be regulated in such a way as to maximize the public health benefit. To do this, the FDA will need to launch a major effort to develop a scientifically-based, long-term plan to approve medications for reducing smoking and its risks.

5. *Settlement provisions must include methods to systematically evaluate the effects of all aspects of the agreement and subsequent regulatory actions by the government to ensure that the policies implemented are achieving the intended health goals.*

Regular scientific review and progress reports on the effects of the settlement will be essential to guide the national policy on tobacco. In addition, these reports will provide important data for refining and adjusting national policy goals and/or provisions of the settlement. These reports would not take the place of ground-breaking HHS/Surgeon General reports but would supplement the literature and public information on a more frequent basis.

SRNT members include the world's leading nicotine and tobacco scientists, and we would be pleased to assist in the development of a research agenda that will ensure accelerated progress on the understanding, prevention, and treatment of nicotine addiction and its health consequences.

The Society for Research on Nicotine and Tobacco 401 East Jefferson Street, Suite 205 Rockville, MD 20850-2617 Tel: 301/251-9133 Fax: 301/279-6749 Eml: geninfo@srnt.org

Jack Henningfield -- former research scientist at NIDA whose work focuses on addictive drugs such as cocaine and nicotine. With Neil Benowitz, Henningfield wrote article in JAMA last year suggesting that levels of nicotine in cigarettes might be reduced to a non-addicting level. Now a private consultant.

John Slade -- a clinician who treats addicted patients at St. Peters Hospital (Rutgers) in New Jersey, he is former president of American Society of Addiction Medicine. Slade is also well known for his research into the industry's marketing practices and has recently become interested in the concept of whether it's possible to develop a "safer" cigarette.

Ken Warner -- economist from the University of Michigan. He was principal editor on a number of Surgeon General's reports on tobacco and his speciality is health economics. Widely regarded as one of the best strategic thinkers on health policies relating to tobacco

Lynn Kozlowski -- Penn State researcher who was an expert at FDA's advisory committee on nicotine in August 1994. Like Henningfield and Benowitz, he is interested in the concept of reducing nicotine levels in cigarettes to non-addicting levels. Kozlowski also has done much research on the issue of low tar in cigarettes and seems inclined to believe that a "safer" cigarette is an illusion.

Bill Ryckert -- Canadian expert whose company does testing on smoke, the constituent elements in cigarettes and has worked with Kozlowski extensively on the issue of low tar and whether it is possible to create "safer" cigarettes in this regard.

Saul Shiffman - Univ. of Pitt. National expert on "chippers" and youth cessation.



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Jerry Mande
Senior Advisor to the Director
Office of Science and Technology Policy
Old Executive Office Building, rm. 436
17th and Pennsylvania Aves., NW
Washington DC 20502

August 5, 1997

Dear Jerry:

I am racing around trying to get ready to leave for China next Monday (a bit of family vacation prior to the 10th World Conference on Tobacco or Health in Beijing August 24-28). As such, I am afraid that this must be brief.

I have read repeatedly that the President is likely to support the tobacco deal, with some revisions. I urge you, in the name of public health, to do all within your power to discourage this outcome. Only if the revisions are substantial and truly non-negotiable (i.e., he will veto any exceptions to the revisions) would his endorsement be acceptable. Much as I respect President Clinton, his record of compromise is too substantial to believe that he would adopt such a stance. Yet short of it, I am convinced that the deal that will eventually be passed is likely to be a big win for the tobacco industry (and a number of attorneys), with only a few bones thrown to public health.

Much as I have viewed the evolution of the deal with optimism until recently, it has become abundantly clear to me that Congress will do the industry's bidding, and that in this instance that means supporting the deal. Speaker Gingrich's naming Rep. Bliley to oversee the deal in the House is a flagrant case of appointing the fox to guard the chicken coop. The fact that Congress would not accept a modest 20-cent increase in the excise tax, after all that has been going on the past year, was doubly discouraging. And now the third strike: the provision inserted in the budget balancing act that credits the industry for the 15-cent tax increase. Even if the President could overcome this specific measure, the writing on the walls of Congress could not be more conspicuous: Congress will do whatever the industry wants it to do. And the industry very much wants it to legislate the deal, for good reason.

President Clinton has shown enormous courage as the first president in history to take on the tobacco industry. What he does here and now will have ramifications for years, likely decades, to come. If he succumbs to political pressure to accept a deal, the legacy of his contribution to public health will be in serious jeopardy. He may have the trappings; but we won't have made significant inroads against the public health disaster that is tobacco.

Jerry Mande
August 5, 1997 - Page 2

I am certain that the political pressures to support the deal are enormous. Unfortunately, the voice of public health is unlikely to be able to compete with those pressures. I can only hope that you will make a conscientious effort to encourage the President to put principles in front of politics on this most critical occasion for public health.

Thanks for hearing me out, Jerry.

Sincerely,

A handwritten signature in black ink, appearing to read 'Ken', with a stylized flourish extending from the end.

Kenneth E. Warner
Richard D. Remington Collegiate
Professor of Public Health

THE UNIVERSITY OF VERMONT

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38 Fletcher Place - Ira Allen School
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FAX COVER SHEET

DATE: 7/3/97

TO: Jerry Monde

FIRM: _____

FAX NUMBER: _____

FROM: John Hughes, MD

NOTES:

This message contains 7 page(s) including this cover sheet.

F-II
John Hughes [2594]*Addiction* (1996) 91(12), 1797-1802**REVIEW****The future of smoking cessation therapy in the United States****JOHN R. HUGHES***Human Behavioral Pharmacology Laboratory, University of Vermont, USA***Abstract**

Six trends that are likely to influence the future content, format, delivery and reach of smoking cessation therapy in the United States are discussed: (1) changing characteristics of smokers (e.g. more likely to be poor, have psychiatric co-morbidity and be more nicotine dependent), (2) health care reform demands for cost-effectiveness, (3) development of guidelines/algorithms that recommend stepped-care approaches, (4) continued emphasis on smoking as a form of drug dependence requiring intensive pharmacological and behavior therapy for some smokers, (5) interest in harm-reduction strategies for smokers unable or unwilling to quit (and 6) smoking cessation therapies become reimbursable on par with other drug dependencies.

Introduction

Twenty meta-analyses¹⁻²⁰ of over 300 studies have concluded that behavioral and pharmacological treatment for smoking cessation works. Typically, these reviews indicate brief advice, behavior therapy and nicotine replacement increase quit rates by a factor of 1.5-2.5.^{14,15,21}

Despite this wealth of empirical data, treatment for smoking has had an uphill battle for acceptance. For example, most primary care physicians fail to treat smoking because they receive little training and see smoking as requiring complex counseling, etc.^{22,23} Chemical dependency clinicians and psychiatrists also ignore smoking, in part because nicotine dependence does not cause immediate adverse psychosocial consequences or severe intoxication or withdrawal as do alcohol and illicit drugs. Finally, most smoking cessation therapies are run by voluntary organizations rather than being an integral part of medical services.²⁴

Possible reasons for the reluctance to accept treatment of smoking cessation as a legitimate medical or public health activity include historical precedence, the belief that most smokers voluntarily chose to quit on their own and are successful, denial that smoking is due to nicotine dependence, financial pressures to treat only acute illnesses, etc. As a result of these biases, treatment for nicotine dependence has no academic home and thus few champions.²² To add insult to injury, although treatment for smoking cessation has been shown to be the most cost-effective activity a physician can undertake,²⁵ this treatment continues to be denied in the developed countries due to the "no new expenditures" dictum of health care reform of the 1980s and 1990s.

These non-scientific biases will continue to influence the content, format, delivery and reach of smoking cessation therapy in the developed world.²⁶ The remainder of this paper suggests

Correspondence: John R. Hughes, MD, University of Vermont, Department of Psychiatry, 38 Fletcher Place, Burlington, VT 05401-1419, USA. Tel: 802-660-3060; Fax: 802-660-3064; e-mail: john.hughes@uvm.edu

Submitted 6th December 1995; initial review completed 27th March 1996; final version accepted 23rd May 1996.

1798 John R. Hughes

other demographic, social and institutional trends that may influence the future of smoking cessation treatment (defined as face-to-face interventions). Recognition of such trends should help administrators, clinicians and researchers develop and implement future treatments for smoking.

The population of smokers is changing

The first trend is that the population of smokers is changing in several ways. For example, the prevalence of smoking is declining little in less-educated²⁶⁻²⁸ and poor smokers.²⁹ This is due not only to continued high rates of initiation of smoking among the poor and uneducated, but also to a lower rate of smoking cessation in these groups.³⁰ Whether this lower cessation rate among the disadvantaged is due to more ongoing life stressors (e.g. poor health and one-parent families), lack of social support for cessation, lack of motivation, lack of coping skills or lack of resources for treatment is unclear.³¹

If the above-mentioned trends continue, then future smokers will more probably be composed of the poor and the uneducated. Given this, future therapies need to balance a focus on smoking cessation with addressing general life stressors. They will also need to be consistent with the media and reading preferences of the less educated and will need to be either inexpensive or reimbursed by third-party payors. Poor people are less likely to have a physician,³¹ so non-traditional methods of delivering treatment (e.g. via self-help groups) will be necessary. In addition, the poor and less-educated appear to prefer pharmacotherapies to psychological therapies for behavioral problems.³² Whether this is true for smoking cessation is unclear.

The prevalence of smoking is also declining little in psychiatric and alcohol/drug abuse patients.³³⁻³⁵ This also appears to be due both to higher initiation rates and to lower cessation rates.^{33,36,37} This selection should produce an increasing prevalence of psychiatric/alcohol/drug disorders among smokers, especially among smokers who have failed to stop on their own and are seeking treatment. Thus, in the future smoking cessation programs may need to screen for and be armed with programs to address these co-morbid problems.³⁸⁻⁴⁰ Research in this area has just begun; e.g. behavioral therapy focused on depression has been reported to increase quit

rates of depressed smokers.⁴¹ In fact, growing recognition of alcohol/psychiatric co-morbidity may portend the inclusion of smoking cessation research and services into alcohol/drug abuse or psychiatric institutions.

Finally, the prevalence of smoking appears to be declining less rapidly in smokers who are very nicotine dependent.^{26,42,43} The lower cessation rate of this group is thought to be due to increased withdrawal symptoms, long-term craving and retention of conditioned responses to cues for smoking. The results of the recent COMMIT trial^{44,45} and other studies^{43,46} indicate that traditional public health and psychosocial programs often do not help such smokers. Nicotine replacement therapy does help these smokers;⁴⁷⁻⁵¹ thus, as the remaining smokers are increasingly those highly dependent on nicotine, medications are likely to become an even more central part of future smoking cessation therapies.

Health care reform encourages cost-efficacy

A second major change that may influence smoking cessation treatment and research is health care reform. Although the high cost-efficacy of smoking cessation therapy might be expected to eventually win over insurers and governmental agencies to provide smoking cessation reimbursement,²⁵ three changes may be necessary to convince insurers and the government; i.e. (a) demonstrations that smoking cessation interventions in smokers who are heavy financial burdens on the health care system can produce decreases in health care utilization that are realized in a short period of time,⁴⁷ (b) evidence that cessation programs can *a priori* delineate those smokers who are not able to quit on their own and who would benefit from intensive treatment,^{47,48} and (c) the turnover in clients in HMOs, insurance plans, etc. decreases such that the insurer is responsible for the long-term health problems of a majority of its clientele.

Guidelines describe accepted treatments

A third trend is the advent of practice guidelines and algorithms.⁴⁹⁻⁵¹ Prior algorithms for smoking cessation,^{47,48,52-54} and the guidelines published by the Agency on Health Care Policy¹⁵ and other institutions¹⁴ will have a profound impact in codifying acceptable treatments. For example, transdermal nicotine has recently posed the dilemma of how third-party payors and HMOs

should handle a not-inexpensive, proven effective treatment for smoking cessation. The large majority of administrators, policy analysts, etc. have very little knowledge of the empirical basis for smoking cessation therapy. Thus, these groups will probably embrace expert guidelines in helping them allocate treatment for smoking cessation.

In all likelihood, these algorithms/guidelines will utilize a stepped care approach^{47,48} with minimal interventions early on. In addition, in an effort to save cost, most institutions will probably use non-physicians (e.g. nurses or pharmacists) to deliver smoking interventions.⁵⁵ The major issue will be when to undertake more intensive therapies.⁴⁷ The criteria will probably be a combination of having failed at minimal interventions and either currently having or being at high risk for an expensive smoking-induced disorder.⁴⁷

Smoking is more recognized as a drug dependence

A fourth trend that will change smoking cessation therapy is the continued recognition of smoking as a form of drug dependence⁵⁶ and pursuit of more pharmacotherapies for cessation.^{21,57} The recent interest in pharmacotherapies is due not only to the history of their efficacy in smoking,¹⁻¹³ but also to the possible large financial gain to pharmaceutical companies and the poor acceptability and availability of behavioral therapies.⁴² Development of medications will probably include two foci: (a) developing new nicotine agonists and antagonists^{58,59} and (b) identifying subsets of smokers with some characteristic (e.g. high anxiety) and treating them with the appropriate medication (e.g. buspirone).⁶⁰ This interest in medications and the selection biases mentioned above (i.e. future smokers will be those who are heavily dependent on nicotine and who have psychiatric/alcohol problems) may "medicalize" smoking control efforts even more than at present; however, several of these medications have become over-the-counter (OTC) medications, thus allowing smokers access to treatments without contacting the medical system.

Harm reduction is considered as a treatment goal

A fifth trend is that the combination of increased social pressure/restrictions on smoking and the

continuation of a group of "hard-core" smokers will produce renewed interest in harm reduction strategies for smokers who will not or are unable to stop smoking.⁴⁹ In response to this, as nicotine replacement medications go over-the-counter, many smokers may use such medications, not to stop, but rather to reduce or control their smoking.⁶¹ Similarly, nicotine-only delivery devices developed by the tobacco industry, such as Premier or Eclipse, may come to be marketed as safer alternatives to smoking.⁴⁹ Interestingly, this may mean that pharmaceutical and tobacco companies may become competitors or, even more interestingly, collaborators in the OTC market. Whether "harm reduction" strategies are desirable is debatable.⁴⁹

Cessation therapy is reimbursed

A sixth possibility is that, though it may be 10 years away, at some point governmental and private insurers will begin to reimburse smoking cessation. Besides physicians, two groups will probably then begin to market services. The first is the traditional private therapies such as SmokeEnders. The second is the chemical dependency community. In the United States, this latter group is much larger, already integrated into many health care organizations, and is adept at promotion and recruitment; thus, in all likelihood this group will become the major provider. This may produce a major problem as the practices of the chemical dependency community in the United States are based on treating alcohol dependence and may not readily translate to smoking (e.g. one has to overcome denial and one has to be totally drug-free) plus the chemical dependency community places much less emphasis on using only scientifically validated treatments than does the present smoking cessation community.⁶²

Conclusion

Many of these projected changes in smoking cessation therapy may not come to pass. In addition, other changes such as the systematic lowering of the nicotine content of cigarettes⁶³ or the changing racial composition of smokers⁶⁴⁻⁶⁶ could have a profound impact on treatments for smoking.

The present paper was written to help administrators, therapists and researchers consider

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non-scientific factors in planning the development and implementation of future smoking cessation interventions. The trends described above suggest several research areas; e.g. (a) longitudinal studies or a series of cross-sectional studies to examine whether the hypothesized selection biases are occurring, i.e. whether future smokers will more and more be the poor and uneducated, those with concomitant alcohol/drug abuse or psychiatric problems or those with severe nicotine dependence; (b) naturalistic studies of why smoking cessation is more difficult and treatment less accessible for poor smokers and those with alcohol/drug/psychiatric problems; (c) development of treatments tailored to smokers with the above problems; (d) demonstrations that smoking cessation therapy produces financial gain within a few years in those who use large amounts of health care; (e) studies of how to decide *a priori* which smokers will require more intensive treatments; (f) randomized trials of efficacy, effectiveness and cost-effectiveness of algorithms for smoking cessation versus usual care; (g) studies tailoring pharmacological and behavioral treatments to subsets of smokers; and (h) studies of the effects of "harm reduction" strategies not only on health benefits but also on whether such strategies undermine abstinence attempts.

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I enjoyed talking with you on Tues PM. In thinking more about the issues you raised, I came up with three major points that I would offer.

1. The major goal of the settlement should be on decreasing the morbidity and mortality from smoking. Obtaining money to punish the companies or to treat the consequences of smoking is very unsatisfying because the industry will find a way to survive and treatments for smoking-induced diseases are not very effective. In terms of decreasing mortality, we should focus not just on preventing initiation, but also on promoting cessation, offering better treatments and access to treatments and by engineering a safer tobacco product. These later goals are important because changes in initiation only accrue benefits 20+ yrs from now. Changes in smoking cessation, number of cigs/day and in safer cigarettes accrue benefits much sooner.

2. Ongoing research is essential because the settlement plans may not decrease smoking sufficiently and because smoking patterns will dramatically change in the future. In the 1950's, it was obvious that smoking is a habit not an addiction. Through systematic research, we have shown this belief was false and have suggested concrete methods based on addiction theory to deal with the smoking problem. In 1997, it appears obvious that the advertising restrictions and decreases in nicotine content in cigarettes proposed in the settlement will significantly decrease smoking. Again, it is imperative for research to evaluate whether such "obvious" solutions indeed work. In addition, since it is highly likely that some of our solutions will not work, we will need to fund both basic and applied research to have new strategies ready to supplement those proposed in the settlement. Finally, the pattern of smoking in the US will undergo drastic changes in the future that we cannot now anticipate (e.g. almost no one predicted the increase in smokeless tobacco in the 80s, the increase in smoking in teens in the 90s, or the popularity of cigars in the 90s). Long-term, ongoing research is essential to having information to discover such changes and to make plans how to deal with these.

3. There are well-documented effective smoking cessation treatments but very, very few therapists and no system to deliver the therapies. With the large amount of money being released for treatment, many vendors will appear to claim they have treatments

and expertise. The good news is that the two major treatment guidelines (sent by separate mail) are in good agreement about what has been shown to be effective and the data for effectiveness is overwhelming. The first bad news is that there is no accepted credentialling for smoking cessation therapists. In fact, the number of clinicians with any substantial knowledge of treating smoking is very small (probably < 5000 in the US). Thus, simply giving out money will result in giving money to have uninformed, previously uninterested therapists who will use treatments they are familiar with, regardless of whether they are efficacious for smoking or not. The second bad news is that there is no treatment delivery system. Most health care organizations would not know where to have smoking cessation services: e.g. in addiction services, in wellness programs, in preventive cardiology programs, in primary care clinics, etc? The important thing is that the personnel in each of these settings sees smoking very differently. In summary, the problem is not in the treatments but in delivering them.



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Jerry Mande
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July 28, 1997

Dear Jerry:

Once again, I want to thank you for including me in the White House meeting with the panel of scientists discussing nicotine regulation issues. It was a fascinating and, frankly, enjoyable experience. I've also enjoyed discussing the tobacco deal with you on the phone. You are in a position of truly incredible importance with regard to the future of public health in this country.

I don't recall whether Donna Shalala or Bruce Reed requested our new paper that projects future smoking prevalence. You said that you'd get copies to both of them. I'm enclosing three copies of that paper (Mendez, Warner, and Courant), as well as three copies of another paper on the market for alternative forms of nicotine delivery (Warner, Slade, and Sweanor). (One copy of each is for you.) Both papers are currently under consideration for publication by journals. As such, please treat them as confidential. (The Warner et al. paper is being revised as we speak for a resubmission requested by the journal. The revision will be tighter than this version; but you'll get all of our fundamental ideas from the enclosed version.) I hope you find these papers useful.

I do wish you all the best in your continuing deliberations. Needless to say, I'll be watching where the President comes out with more than the usual level of interest!

Sincerely,

A handwritten signature in dark ink, appearing to read 'Ken'.

Kenneth E. Warner
Richard D. Remington Collegiate
Professor of Public Health

DETERMINED TO BE AN
ADMINISTRATIVE MARKING
INITIALS: W DATE: 10/18/13

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**HAS SMOKING CESSATION CEASED? EXPECTED TRENDS
IN THE PREVALENCE OF SMOKING IN THE UNITED STATES**

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HAS SMOKING CESSATION CEASED? EXPECTED TRENDS IN THE PREVALENCE OF SMOKING IN THE UNITED STATES

ABSTRACT

From 1965 to 1990 the prevalence of cigarette smoking among U.S. adults fell steadily and substantially. Data for the 1990s suggest that the smoking initiation rate is increasing, and that the decline in smoking prevalence may have stalled, raising the fear that it will not continue its historic 25-year decline. In this paper, using a newly developed dynamic forecasting model, the authors show that although it is possible that the decline in smoking prevalence will slow down, the demographics of smoking imply that prevalence will inexorably continue to decline over the next several decades, even absent any intensified efforts at tobacco control. The authors estimated and validated the model using historical data on adult smoking prevalence. Their results indicate that the current rise in the smoking initiation rate partially explains the flattening of smoking prevalence, but even under the most grim assumptions about future initiation rates, adult smoking prevalence will continue to decline for several more decades. The authors predict that if current initiation and quitting behaviors persist, adult smoking prevalence will fall automatically from its current level of 25 percent to a value between 15 and 16 percent by the second quarter of the next century. Even so, smoking would remain the nation's leading cause of premature mortality.

Keywords: Forecasting; Prevalence; Smoking; Smoking cessation

HAS SMOKING CESSATION CEASED? EXPECTED TRENDS IN THE PREVALENCE OF SMOKING IN THE UNITED STATES

The prevalence of smoking among U.S. adults fell steadily and substantially for a quarter of a century following publication of the first Surgeon General's report on smoking and health in 1964 (1). In 1965, prevalence was 42 percent; by 1990 it had fallen to 25 percent (2). The decline was particularly notable among men, from 52 percent to 28 percent. Recent data suggest that the decline may have stalled, however. Government surveys through 1994 show adult prevalence holding steady at about 25 percent (3). Data on 30-day smoking prevalence among high school and junior high school students, the harbinger of future smoking patterns, show annual increases since the beginning of the decade (4). Health officials have expressed alarm at the apparent leveling off of smoking prevalence among adults and the potential for its future increase suggested by increasing smoking by teens.

We think the alarm is misplaced. Although it is certainly possible that the decline in smoking prevalence will slow down, the demographics of smoking imply that prevalence will inexorably continue to decline over the next several decades, even absent any intensified efforts at tobacco control. Indeed, assuming that nothing changes in terms of contemporary patterns of smoking initiation and quitting, we demonstrate in this paper that adult prevalence will automatically fall to about 16 percent by the end of the first quarter of the next century. This will be the inevitable result of the aging of the population and anticipated birth and mortality patterns, combined with cohort-specific rates of peak smoking prevalence, contemporary prevalence, and quitting rates. In this paper we describe the model used to derive this

conclusion and consider how robust our findings are with respect to plausible changes in smoking behavior on the part of young people and quitting behavior in older cohorts.

MATERIALS AND METHODS

Model

In this section, we describe a dynamic model to forecast future smoking prevalence among U.S. adults (≥ 18 years). The model computes prevalence over time by keeping track of the inflow of new smokers as well as the outflow caused by death or smoking cessation.

(See Figure 1.)

***** Insert Figure 1 about here *****

The mathematical specification of the model is as follows:

$$P_{a,t} = P_{a-1,t-1} \times (1 - \delta_{a-1,t-1}) \quad a = 1, \dots, 110 \quad (1)$$

$$P_{0,t} = \alpha_t \quad (2)$$

$$C_{a,t} = C_{a-1,t-1} \times (1 - \mu_{a-1,t-1}) \times (1 - \beta_{a-1,t-1}) \quad a = 19, \dots, 110 \quad (3)$$

$$C_{18,t} = \gamma_t \times P_{18,t} \quad (4)$$

$$R_{(a_i:a_f),t} = \frac{\sum_{a=a_i}^{a_f} C_{a,t}}{\sum_{a=a_i}^{a_f} P_{a,t}} \quad (5)$$

$$\mu_{a,t} = \begin{array}{c} \text{Age } (a) \\ \begin{array}{|c|c|c|c|} \hline & 18-30 & 31-50 & >50 \\ \hline \text{Year } (t) & 1970-1980 & v_1 & v_2 & v_3 \\ \hline & 1981- & v_4 & v_5 & v_6 \\ \hline \end{array} \end{array} \quad (6)$$

where:

$P_{a,t}$ = Size of cohort age a in year t

$C_{a,t}$ = Current smokers of age a in year t

$R_{(a_i:a_f),t}$ = Smoking prevalence between ages
 a_i and a_f in year t

$\delta_{a,t}$ = Death rate in year t for individuals of age a in the general population

$\beta_{a,t}$ = Death rate in year t for smokers of age a

$\mu_{a,t}$ = Smoking cessation rate in year t for smokers of age a

γ_t = Smoking prevalence for 18 year - olds in year t

α_t = Size of the birth cohort in year t

The number of people of age a in year t is computed by multiplying the number of people of age $a-1$ in year $t-1$ by the appropriate survival rate ($1 - \text{death rate}$). Birth cohort sizes are supplied exogenously to the model. The model ignores the effect of migration on future population size and smoking prevalence. The smoking patterns of future immigrants cannot be predicted. Given the small size of the immigration pool with respect to the domestic population, this omission is not likely to bias our results substantially.

Death rates are differentiated by year, age and smoking status. Current smokers in any given year are estimated as the number of current smokers in the previous year who survived to the current year and did not quit smoking. Smoking prevalence at age 18, supplied exogenously to the model for each cohort under study, is used to calculate the size of each year's cohort of new adult smokers. Smoking prevalence for any specific age group in a

specific year is computed by taking the ratio of current smokers to the total number of people within the group that year.

The model assumes that there is no more smoking initiation after age 18, when prevalence attains its peak value for the cohort. After age 18, smoking cessation drives the dynamics of the model. This is consistent with data that shows that by the 1980s almost all regular smoking began before the age of 20 years, and by 1991, the mean age of becoming a daily smoker was 17.7 years (5).

Smoking cessation rates are the parameters in the model to be estimated from historical data on smoking prevalence. The model recognizes that quit rates have changed historically with age and cohort. Existing data show that among cohorts born before 1935, cessation rates appear to be influenced primarily by calendar year, while the more recent cohorts appear to have cessation rates that are determined by age, with cessation rates generally higher at older ages (6). A preliminary analysis of the available data led to the age-group breakdown shown in expression 6 above. Additionally, it is particularly important to allow for different values of the cessation rate before and after 1980. Given that our observations consist of smoking prevalences, we are only able to estimate net rates of change in prevalence; that is, initiation and quitting rates are necessarily confounded in our estimates. Prior to 1980, a non-inconsequential proportion of individuals became regular smokers after age 20, particularly among women. As such, rates estimated for that period will not truly correspond to cessation rates, particularly those of the younger age-group. This is not the case for the period post-1980, when initiation has rarely occurred after age 20.

Parameter estimation

To use the model for forecasting, we first needed to estimate the smoking cessation rates used by the model to compute future smoking prevalence. The estimation procedure can also be used to test the validity of the model against past data. The procedure is described below.

Data. To estimate cessation rates, we collected data on past smoking prevalence. Specifically, we used smoking prevalence for the age-groups 18-24, 25-44, 45-64, and 65 and over, for the years 1970, 1974, 1978-1980, 1983, 1985, 1987-1988, 1990-1993. These prevalences were estimated by the Centers for Disease Control and Prevention (CDC) from the National Health Interview Surveys (NHIS) (2). The data are shown in Table 1.

***** Insert Table 1 about here *****

The National Health Interview Survey (NHIS) is a principal source of information on the health of the civilian noninstitutionalized population. The annual survey consists of a basic set of questions on health, socioeconomic and demographic items. To determine the prevalence of smoking among adults, the NHIS collects self-reported smoking information on cigarette smoking from adults, defined as individuals 18 years of age and older. Prior to 1992, the NHIS classified as current smokers those who answered “yes” to the following two questions: “Have you smoked at least 100 cigarettes in your entire life?” and “Do you smoke

cigarettes now?” Since 1992, the second question has been replaced by the following: “Do you smoke cigarettes every day, some days or not at all?” Current smokers are defined as those who have smoked 100 cigarettes and now smoke either every day or some days. According to the CDC, explicitly including some-day smoking in the definition of current smoking increases the overall smoking prevalence estimate by approximately 1 percentage point compared to the old definition (7). To make the reported CDC prevalence estimates comparable in our analysis, we subtracted one percentage point from the prevalence data reported in 1992 and 1993.

Data on age-specific death rates for the general population were obtained from the Statistical Abstracts of the U.S. for the years 1970 to 1990 (8). We assumed 1990 death rates for years after 1990. Death rates for current smokers were obtained from the 1986 NHIS National Mortality Followback Study (9), which estimated age-and gender-specific death rates for current smokers. To combine male and female death rates into a composite figure for the general population, we weighted the gender-specific death rates by the proportion of male to female current smokers at each age. We used these composite death rates to calculate the age-specific relative risk of death between current smokers and the general population in 1986. To calculate current smokers' death rates for years other than 1986, we multiplied each year's death rates for the general population by the age-specific relative risk between current smokers and the general population observed in 1986. We acknowledge that this is just an approximate procedure. As smoking prevalence changes, the death rates for the general population (which includes smokers) will change, and hence so will the relative risk between current smokers and the general population. However, this effect is not large enough to influence our results. We

performed a sensitivity analysis on this assumption by repeating the analysis conducted in this paper employing just the 1970 death rates for the general population (as opposed to the ones for the 1970-90 period) and obtained almost identical results.

Estimation procedure. The dynamic model specified in the previous section was implemented in an EXCEL spreadsheet. The unknown parameters of the model (the six cessation rates) were estimated by selecting the set of values that made the model conform as closely as possible to the past observations on smoking prevalence. Weighted Least Squares was chosen as a distance measure between model response and data. Weights were included in the estimation procedure because the observed smoking prevalences for the distinct age-groups have different variances, and therefore convey different amounts of information in the determination of the parameter values. Observed prevalences are the ratio of the number of smokers in the age group to total number of people within the age group. Because the age groups have different populations, and the sample sizes were not adjusted to reflect this, the observed prevalences are more "noisy" the smaller the population size (and hence the sample size) of the age group. The appropriate set of weights is one proportional to the inverse of the variance of the observations (10). Fortunately, along with the observed prevalence for the specific age groups, the data source included the maximum length for the 95 percent confidence intervals corresponding to those prevalences (See Table 1). Assuming that for a given sample size the prevalences are distributed normally, we used the lengths of the confidence intervals to obtain an estimate of the variance of the observed prevalence. The

calculated variances of the observations were used to weight the prevalence observations in the estimation process. (See Appendix for details.)

The Weighted Least Squares estimation was carried out by feeding the response of the dynamic model and the observed data to a minimization routine that controlled the changes in parameter values until the optimization criterion was satisfied. This combination of dynamic model and optimization routine for parameter estimation has been used previously. (See for example (11).) The optimization routine employed to estimate the parameters of our model was the Generalized Reduced Gradient (GRG) algorithm, an optimization technique for nonlinear problems. A current version of the algorithm, GRG2, is embedded in the "Solver" component of the Microsoft EXCEL spreadsheet software. Details on the GRG algorithm are provided by Lasdon et al. (12)

RESULTS

Estimation results

The estimated values and confidence intervals for the six cessation rates specified in the model are given in Table 2.

***** Insert Table 2 about here *****

The results show that the smoking cessation rate rises sharply with age and has increased from the 1970s to the 1980s, consistent with prior expectations. Coefficients for the rates corresponding to the two older age groups are significantly different from zero in the post 1980 time period. For the period 1970-80, just the coefficient for the older age group was

statistically significant. Again, it is important to note that particularly in the earlier time period, the estimates of the cessation rate are confounded by initiation rates. This confounding has the effect of downwardly biasing the estimates, and might partially account for the lack of significance in some of the coefficients.

The significance test was conducted by linearizing the model around the estimated values for the parameters and computing their asymptotic covariance matrix. Once the variances of the estimates have been calculated, a Z test can be readily performed to test the significance of the coefficients. (This procedure is discussed in detail in the Appendix.)

The model produced an extremely good fit for the data. The overall adjusted R^2 was 0.98. Figure 2 shows the fit of the model to data on overall adult prevalence (all four age groups combined).

***** Insert Figure 2 about here *****

Given that the observations for each specific age group constitute a time series of 18 elements, autocorrelation in the series could bias our estimates of the standard errors of the model parameters. To test for autocorrelation we assumed first that if it existed, it was defined by an autoregression process of order one (10). Furthermore, we assumed that the same autocorrelation structure held up among the four different age groups. Thus, we merely need to estimate the statistical significance of one correlation coefficient to determine the existence of autocorrelation in the data. Not all the data could be used for the determination of autocorrelation, because of gaps in the series. After the estimation was done, without

considering any autocorrelation structure, we computed one-year differences in the residuals and tested for first order autocorrelation according to the procedure described in (13). The null hypothesis that such autocorrelation did not exist could not be rejected at the 5 percent significance level. Details of the computations are presented in the Appendix.

The likelihood ratio test was used to test alternative model specifications. In particular, we tested the hypothesis that there was no statistically significant difference among the cessation rates post 1980 corresponding to the three age groups. We focus on the cessation rates post 1980 because they will be used to forecast future prevalence. Explicitly, the hypotheses tested were:

$$H_0^{(1)}: \nu_4 = \nu_5 \quad (7)$$

$$\text{and } H_0^{(2)}: \nu_5 = \nu_6 \quad (8)$$

against the alternative specification:

$$H_a: \nu_4 \neq \nu_5 \neq \nu_6 \quad (9)$$

The two hypotheses were rejected at the 5 percent significance level. Thus, we concluded that the three estimated cessation rates post-1980 were significantly different from each other.

Given the apparent stalling of smoking prevalence in recent years, it was particularly important to test the hypothesis that the quitting rates in the 1990s were not significantly different from the ones in the 1980s. To test this hypothesis we re-estimated the model, allowing for the cessation rates from 1990 and subsequent years to be different from the corresponding quitting rates in the 1980s. Employing the likelihood ratio test we did not

find a statistically significant difference between 1980s and 1990s quitting rates at the 5 percent significant level. We then concluded that there is no basis to assume that quitting rates in the 1990s are lower than the ones in the 1980s. (See Appendix for details.)

Forecasting Results

Using the estimated cessation rates for the post-1980 period, we forecasted future smoking prevalence in the U.S. to the year 2100, to give the model the opportunity to achieve a steady-state solution. The size of all future birth cohorts was held constant at the size of the average birth cohort for the period 1981-1990 (3,643,582). Sensitivity analysis was conducted on the future smoking prevalence of 18 year-olds. The smoking prevalence for the age group 18-24 year-olds in 1993 was 25.8 percent. This age group's smoking prevalence has been declining steadily for more than two decades now. Smoking prevalence for 18-24 year-olds has not reached 30 percent since 1985, nor 35 percent since about 1975. To forecast future prevalence, we examine the behavior of the model assuming that the smoking prevalence for 18 year-olds will remain constant at one of the following rates: 20, 25, 30, and 35 percent. At 27 percent, current prevalence for 18 year-olds lies between the two middle figures. The other two prevalences were selected as extreme cases for purposes of sensitivity analysis. In particular, 35 percent represents a worst-case scenario. Use of a 20 percent prevalence among youths indicates the potential impact on eventual adult smoking prevalence of modestly successful policies directed towards the reduction of smoking among youths.

Figure 3 shows the forecasted smoking prevalence for the adult population of the U.S., given the four different selected values for smoking prevalence at age 18. If cessation rates do

not decrease from the values they exhibited during the 1980s, overall adult smoking prevalence in the U.S. will continue to fall, even under an unlikely extreme value of 35 percent for the smoking prevalence for 18 year-olds. The results show that if current quitting conditions persist, with a prevalence of 25 percent at age 18 adult smoking prevalence will decline from its current level of 25 percent to a steady state value of between 15 and 16 percent by the second quarter of the next century. Prevalence rates of 20, 30 and 35 percent will produce steady state adult smoking prevalence rates of 12.2 percent, 18.4 percent and 21.5 percent, respectively.

***** Insert Figure 3 about here *****

The nearly steady prevalence of smoking among adults observed in the U.S. during the 1990s (see Fig. 2) has led many to believe that, short of dramatic new smoking control policies, prevalence will no longer decline. We examined the necessary rise in initiation rate (peak prevalence at 18) to keep the smoking prevalence constant at the current level of 25 percent. We performed this experiment under two sets of cessation rates: the ones estimated for the post-1980 period and the lower limits of their corresponding 95 percent CI. Note that the second set of cessation rates corresponds to a very unlikely worst case scenario. We found that the 18 year-old prevalence necessary to maintain the current level of adult smoking prevalence (25 percent) is 41 percent, for the first set of cessation rates, and 35 percent for the second. Current levels of smoking initiation rates are about 27 percent; this implies that, unless initiation rates rise well above 35 percent, overall adult smoking prevalence will continue to decline, regardless of the adoption of significant new tobacco-control initiatives.

DISCUSSION

Observed smoking prevalence data in the 1990s suggest that adult prevalence has stalled, raising the fear that it will not renew its historic 30-year decline. Our results suggest otherwise. If age-specific smoking cessation rates remain stable at the levels exhibited during the 1980s, overall prevalence is likely to continue falling during the remainder of this decade and through the next. In fact, we predict that overall prevalence will continue to fall even if the initiation rate rises to 35 percent, a level not reached since 1975. Under current initiation rates, the decrease in cessation rates necessary to maintain current smoking prevalence is extremely unlikely.

It is important to emphasize that we are not implying that smoking prevalence will decline naturally down to zero. On the contrary, we predict that, if current conditions persist, smoking prevalence will eventually stabilize at a level between 12 percent and 22 percent. Today's higher smoking prevalence reflects the smoking (and quitting) histories of many cohorts of smokers who joined the pool at different (and, over time, decreasing) initiation rates. For example, the cohort of current (1997) 50 year-olds had a smoking prevalence of 46 percent when those individuals were 18. Such a high prevalence for people aged 18 to 24 has not been observed since then (i.e., since 1965.) Even the most grim assumptions for future initiation rates are far below 46 percent. Even though initiation rates may be rising at present, and may continue to rise in the near future, we are still likely to observe a decline in overall smoking prevalence because older smokers who joined the pool at extremely high prevalence rates continue to boost the aggregate rate of smoking. These smokers are rapidly disappearing

from the pool due to death and smoking cessation, and their disappearance will continue to reduce overall prevalence.

Several reasons may account for the current apparent stalling of adult smoking prevalence. First, even though prevalence is still decreasing, as indicated in Figure 2 our model suggests that the rate of decrease is slowing down. Given this flattening of the adult smoking prevalence, it is more difficult to estimate the slope of the series than, for instance, 10 years ago, given the same number of data points.

Second, the 1990s have been sampled for smoking prevalence far more frequently than any earlier period. An inference of trend based on observations that are clustered so closely together might be clouded by noise in the series.

Third, as discussed previously, the NHIS changed its definition of current smokers in 1992 to explicitly include some-day smokers, many of whom likely escaped categorization as smokers in prior years' surveys. CDC estimates that this has increased their measure of prevalence by about 1 percentage point compared to the old definition. This artificial increase in prevalence creates the impression that the trend has flattened when smoking prevalence values pre - and post - 1992 are compared. We have adjusted CDC's prevalence estimates for 1992 and 1993 downward by 1 percentage point. As seen in Figure 2, the adjustment suggests a continuing decline in prevalence.

Fourth, and finally, initiation rates among teens have been on the rise in the 1990s. As discussed before, these high initiation rates are not enough to stall the reduction in overall smoking prevalence, but they will definitely slow its decrease and they provide some explanation for the apparent flattening of the smoking trend. This surge in smoking among

teens may reflect a response to significant declines in the price of cigarettes. For several years now, lower-priced "generic" and discounted brand cigarettes have gained in popularity, to the point that they now account for over 40 percent of the entire cigarette market. In response to the growing popularity of discounted brands, the major cigarette producers dropped the price of their premium brands by 40 percent in April, 1992. The net effect is that the average retail price paid for cigarettes, adjusted for inflation, is lower today than it was in 1991. A wealth of evidence demonstrates that price significantly affects smoking rates (14).

Our analysis indicates that cessation rates have been reasonably stable for at least a decade and a half. This implies that if the observed flattening of the smoking prevalence is really due to changes in the population's smoking behavior, this modified behavior is more likely to correspond to initiation, rather than quitting rates. Although we anticipate that adult smoking prevalence will continue to decline even if initiation rates rise to 35 percent, the eventual decline will be modest, to a rate of about 21.5 percent. If, in contrast, youth initiation rates can be brought down to 20 percent from their current level of about 27 percent, adult prevalence will decline to a steady-state rate of just over 12 percent. The difference is substantial in terms of the burden that smoking will place on the health of Americans well into the next century.

Our intent has been to forecast the "natural history" of smoking prevalence into the next century, assuming that current trends in initiation and quitting persist. Just as there is nothing natural about inhaling 4,000 chemicals from burning plant material, however, there is no need for us to consider this "natural history" inevitable. Through aggressive educational and policy efforts, the toll of tobacco can be brought well below the course it is on at present. We

note, however, that even if our most optimistic assumption about smoking initiation is realized, nearly an eighth of Americans will be smokers in the middle of the next century. The health toll of smoking will remain extraordinarily high. The health of our children and their children will depend on our not resting on tobacco-control achievements realized today.

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Table 1. Proportion of Current Smokers by Age Group

Year	Age Group				
	18-24	25-44	45-64	65 & over	Overall
1970	0.380	0.446	0.386	0.161	0.374
1974	0.378	0.445	0.377	0.173	0.371
1978	0.344	0.393	0.367	0.163	0.341
1979	0.344	0.389	0.348	0.164	0.335
1980	0.333	0.378	0.356	0.172	0.332
1983	0.342	0.363	0.333	0.167	0.321
1985	0.293	0.348	0.316	0.160	0.301
1987	0.271	0.332	0.309	0.152	0.288
1988	0.259	0.329	0.294	0.149	0.281
1990	0.245	0.297	0.270	0.128	0.255
1991	0.229	0.304	0.269	0.133	0.257
1992	0.264	0.308	0.273	0.140	0.265
1993	0.258	0.292	0.260	0.118	0.250
95% CI ¹	0.024	0.018	0.018	0.025	0.012

¹ These figures represent the maximum length of the 95% CI for the age group.

Table 2. Estimated Values for Annual Smoking Cessation Rates

Period	Age-group	Est. Value	95% C.I.	
			Lo-bound	Hi-bound
1970–1980	18–30	-0.00953	-0.02221	0.00315
	31–50	0.00718	-0.00125	0.01560
	51+	0.04528	0.03531	0.05525
1981–	18–30	0.00209	-0.00689	0.01107
	31–50	0.02147	0.01588	0.02706
	51+	0.05958	0.05441	0.06475

Figure 1. Overview of Forecasting Model

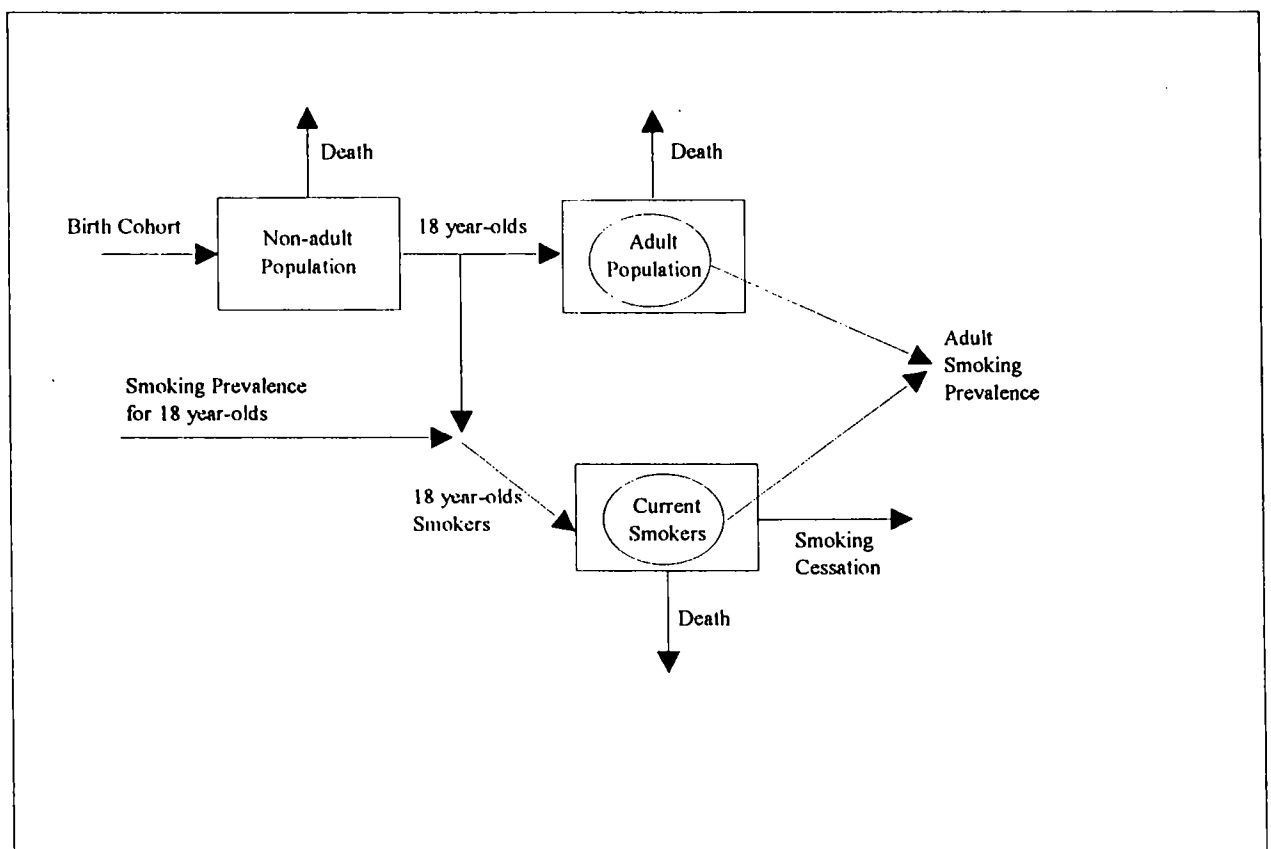
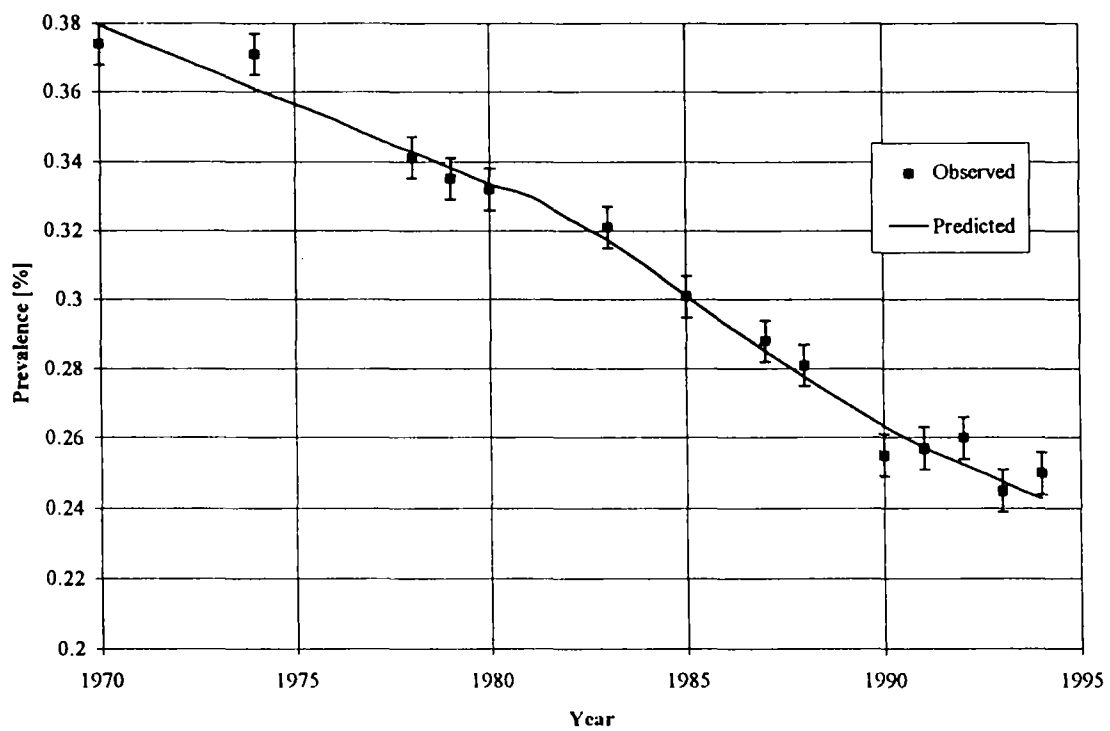
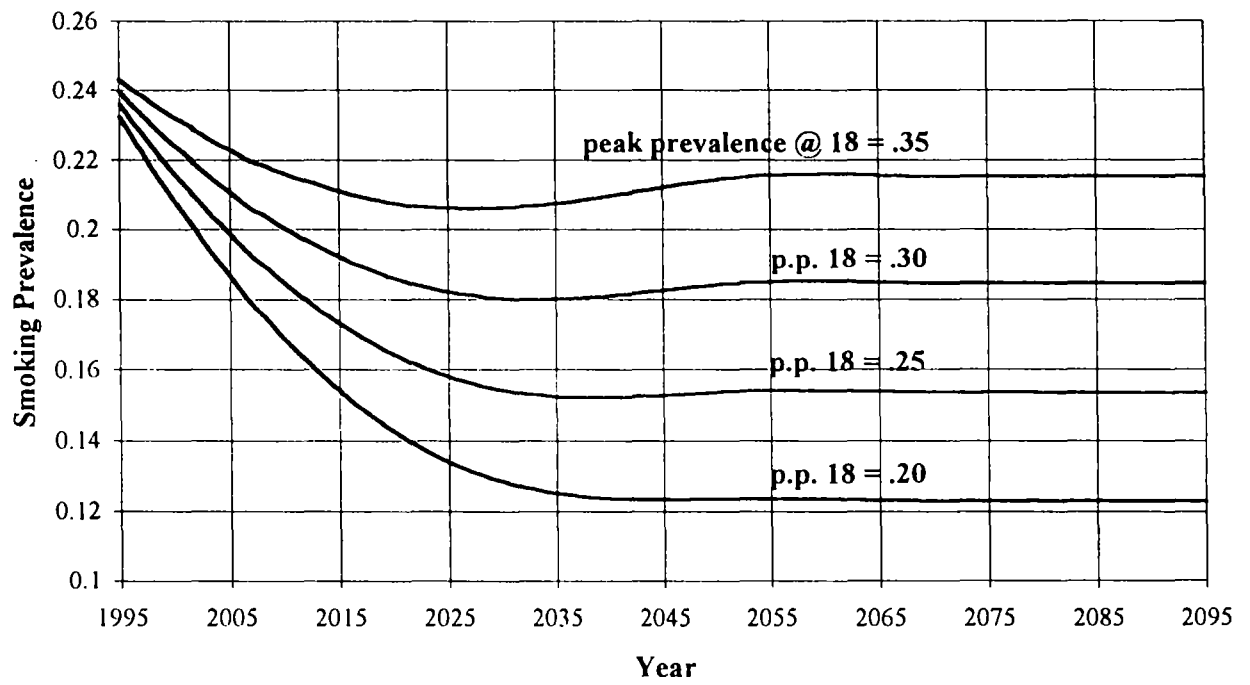


Figure 2. Observed vs. Predicted Smoking Prevalence



Observed values are shown with 95 percent confidence intervals.

**Figure 3. Forecasted Overall Smoking Prevalence by Different
Peak Prevalence at 18.**



TECHNICAL APPENDIX TO ACCOMPANY: HAS SMOKING CESSATION CEASED? EXPECTED TRENDS IN THE PREVALENCE OF SMOKING IN THE UNITED STATES

In this appendix we present and discuss in detail the data and analysis mentioned in the Materials and Methods section of the paper.

Model

The forecasting model employed in this paper is presented on page 3 in the text.

Data

Data from the National Health Interview Surveys on adult smoking prevalence were used to estimate parameters (cessation rates) for the model. These prevalences were available for selected years and the following age groups: 18-24, 25-44, 45-64, and 65 and over. These data are shown in Table 1 in the text.

Parameter Estimation

Nonlinear weighted least squares was used to estimate the model. A weighting matrix for the data was used to account for the fact that prevalences from different age groups are likely to exhibit unequal variances due to the difference in population sizes among the age groups. The weights for the data were selected to be proportional to the inverse of the data variances, to closely follow a Generalized Least Squares (GLS) estimation procedure (1). These variances were estimated from the reported maximum

lengths for the 95 percent confidence intervals for the data. Assuming a normal distribution for the data, the length of the 95 percent confidence interval is related to the variance by the following expression:

$$Var = \left(\frac{\text{Length of } 95\%CI}{2 \times 1.96} \right)^2$$

The reported 95 percent confidence intervals and the calculated variances for data in each of the four age groups are shown in Table A1.

Table A1. Variances for Data by Age Group

	Age Group			
	18-24	25-44	45-64	65 +
95% C.I.	2.4	1.8	1.8	2.5
Variance	0.3748	0.210	0.210	0.4067

For the implementation of the weighted non-linear least squares estimation, the following matrices/vectors were identified:

$$\bar{R}_{[52,1]} = \left(R_{(18-24),1970}, R_{(25-44),1970}, \dots, R_{(65+),1993} \right)' \quad \text{Observed prevalences}$$

$$\hat{R}_{[52,1]} = \left(\hat{R}_{(18-24),1970}, \hat{R}_{(25-44),1970}, \dots, \hat{R}_{(65+),1993} \right)' \quad \text{Calculated prevalences}$$

$$\Omega_{a[4,4]} = \begin{bmatrix} 0.3748 & & & \\ & 0.2109 & & \\ & & 0.2109 & \\ & & & 0.4067 \end{bmatrix} \quad \text{One-year weighting matrix}$$

$$\Omega_{[52,52]} = \begin{bmatrix} \Omega_a & & & & & \\ & \Omega_a & & & & \\ & & \cdot & & & \\ & & & \cdot & & \\ & & & & \cdot & \\ & & & & & \cdot \end{bmatrix} \text{ Weighting matrix}$$

$$\hat{N} = [\hat{\nu}_1 \quad \hat{\nu}_2 \quad \hat{\nu}_3 \quad \hat{\nu}_4 \quad \hat{\nu}_5 \quad \hat{\nu}_6]' \text{ Estimated cessation rates}$$

The vector of cessation rates was estimated by solving the following optimization problem:

$$\text{Min}_N \left(\left(\bar{R} - \hat{R}(N) \right)' \Omega^{-1} \left(\bar{R} - \hat{R}(N) \right) \right)$$

This minimization problem was solved with the Generalized Reduced Gradient algorithm, available in the Solver component of the Microsoft EXCEL spreadsheet program. The estimated values for the cessation rates are presented in Table 3 in the text.

Confidence Intervals

95 percent confidence intervals were developed for the estimated cessation rates.

The asymptotic covariance matrix of these estimated coefficients is (1):

$$\hat{\sigma}^2 \left(\left(\frac{\partial \hat{R}(N)}{\partial N'} \Big|_{\hat{N}} \right)' \Omega^{-1} \left(\frac{\partial \hat{R}(N)}{\partial N'} \Big|_{\hat{N}} \right) \right)$$

where the multiplicative scalar in the expression can be computed as:

$$\hat{\sigma}^2 = \frac{\left(\left(\bar{R} - \hat{R}(\hat{N}) \right)' \Omega^{-1} \left(\bar{R} - \hat{R}(\hat{N}) \right) \right)}{(52 - 6)}$$

Partial derivatives in the above expression were computed numerically in an EXCEL spreadsheet. Matrix computations were performed using the MATLAB software. The resulting asymptotic covariance matrix for the estimated cessation rates is:

$$0.001479 \times \begin{bmatrix} 0.0283 & 0.0005 & -0.0012 & -0.0032 & -0.0060 & 0.0008 \\ 0.0005 & 0.0125 & 0.0013 & 0.0019 & -0.0040 & -0.0023 \\ -0.0012 & 0.0013 & 0.0175 & -0.0002 & 0.0009 & -0.0062 \\ -0.0032 & 0.0019 & -0.0002 & 0.0142 & -0.0016 & 0.0000 \\ -0.0060 & -0.0040 & 0.0009 & -0.0016 & 0.0055 & -0.0003 \\ 0.0008 & -0.0023 & -0.0062 & 0.0000 & -0.0003 & 0.0047 \end{bmatrix}$$

The 95 percent confidence intervals for the cessation rates were obtained assuming that these parameters are asymptotically normally distributed. For instance, the 95 percent CI for v_1 is:

$$-0.00953 \pm 1.96 \times \sqrt{0.001479 \times 0.0283}$$

The 95 percent confidence intervals for the estimated cessation rates are shown in Table 2 in the text.

Alternative Models

Several alternative specifications for the cessation rates were formulated, to test whether the data supported a more parsimonious model. Since the post-1980 cessation rates are the ones that will be used for forecasting, the alternative specifications dealt with

imposing restrictions on such rates to simplify the model. Specifically, the following alternative models, identified by the restrictions on the v 's were proposed:

$$H_0^{(1)}: v_4 = v_5$$

$$H_0^{(2)}: v_5 = v_6$$

These two models were tested against the alternative specification:

$$H_a: v_4 \neq v_5 \neq v_6$$

which corresponds to the original (unrestricted) model estimated in the paper.

We tested the proposed restrictions on the model employing the likelihood ratio test (1). In order to describe the procedure, we introduce the following notation:

$$S(N) = \left((\bar{R} - \hat{R}(N))' \Omega^{-1} (\bar{R} - \hat{R}(N)) \right)$$

$\tilde{N}^{(i)}$ = Cessation rates estimated under model restriction (i)

$\hat{N}$ = As before, cessation rates estimated under 'full' model.

$$\lambda_{LR}^{(i)} = 52 \left[\ln(S(\tilde{N}^{(i)})) - \ln(S(\hat{N})) \right]$$

At the 5 percent significance level, the likelihood ratio test calls for the rejection of the proposed restricted model (i), in favor of the full model if $\lambda_{LR}^{(i)}$ exceeds $\chi^2(J, 0.05)$, where the number of degrees of freedom J is equal to the number of restrictions that the proposed model (i) imposes on the full model. The following table shows, for each of the proposed models, its calculated λ_{LR} and the critical value for rejecting the restrictions.

Table A1. Test of Alternative Models

Model (<i>i</i>)	$\lambda_{LR}^{(i)}$	<i>J</i>	$\chi^2(J, 0.05)$
1	4.61	1	3.84
2	21.16	1	3.84

The values in the table indicate that the two restricted models were rejected in favor of the unrestricted model.

We employed the likelihood ratio test to test the hypothesis that the cessation rates for the 1990s are not different from the ones in the 1980s. To test this hypothesis, we re-estimated the model allowing for the cessation rates from 1990 and after be different from the ones in the 1980s. By doing that, we added three new parameters to the model: v_7 , v_8 and v_9 , which represent the 1990's cessation rates corresponding to the age-groups 18-30, 31-50 and >50 respectively. Specifically, we tested the restrictions:

$$H_0: v_4 = v_7 \text{ and } v_5 = v_8 \text{ and } v_6 = v_9$$

versus a fully unrestricted model, where all the cessation rates are allowed to be different.

For this test, we obtained a $\lambda_{LR} = 2.60$. With 3 restrictions, at the 5 percent significance level, the critical value to reject the null hypothesis is $\chi^2(3, 0.05) = 7.81$.

Therefore cannot reject the restricted model and conclude that the cessation rates for the 1990s are no different from the ones in the 1980s. In fact, the p-value for this test is between 30 and 50 percent.

Autocorrelation

First order autocorrelation in the model was tested according to the procedure described in (2). Table 2 shows the residuals (e_i) of the model (observed minus predicted value) that correspond to contiguous observations.

Table A2. Model Residuals for Contiguous Observations

Year	Age Group			
	18-24	25-44	45-64	65 & Over
1978	-0.00514	-0.00266	0.00132	0.00146
1979	-0.00237	-0.00160	-0.01373	0.00859
1980	-0.00761	-0.00850	-0.00135	0.02198
1987	-0.00906	0.00243	0.00992	0.00214
1988	-0.00905	0.00667	0.00309	0.00250
1990	0.00116	-0.01214	-0.00628	-0.01028
1991	-0.00385	-0.00018	-0.00096	-0.00073
1992	0.01687	0.00458	0.00386	-0.00383
1993	0.00644	-0.00357	-0.00159	-0.02446

From (2) we have that under the null hypothesis that the first order autocorrelation in the residuals is equal to zero, the statistic $\sqrt{N} \times \frac{\sum e_i \times e_{i-1}}{\sum e_i^2}$ is asymptotically normally distributed with mean 0 and variance 1. At 5 percent significance level, we

would reject the null hypothesis if the absolute value of the statistic is greater than 1.96.

Evaluating the statistic with our data, we obtain:

$$\sqrt{36} \times \frac{0.000508}{0.002556} = 1.19 < 1.96$$

Therefore we do not reject the null hypothesis that there is no first order autocorrelation in the data, and our estimates of the standard errors are appropriate.

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