Southwest Foundation for Biomedical Research

Department of Physiology and Medicine

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Henry Blackburn, M.D.
Mayo Professor of Public Health (Emeritus)
University of Minnesota
1300 South Second St., Ste. 300
Minneapolis, MN 55454-1015

Dear Henry,

I enjoyed hearing from you after so long a time. I am officially retired from the Southwest Foundation as of 1 July 1996, but still have an office and am spending about 3-4 days a week writing, helping the younger people write grants and papers, reading, or whatever else I fancy. I am staying about as busy as ever but no more committee meetings, budgets, personnel actions, etc., none of which I miss in the slightest degree.

I spend most of my time working on the PDAY project. The collection phase closed about 2 years ago and the data files have been cleaned up. The Statistical Center is with Alex McMahan at the Medical School and I enjoy working with him very much. The results are relevant to the smoking question, as I will get to later.

We did conduct a cigarette smoking experiment with baboons. Enclosed are 2 reports from that project. In this experiment we learned about the "adaptation" to diet phenomenon, one which I believe also occurs in humans (but can't prove) and complicates the results of human feeding experiments. That is, some individuals who respond to a fat and cholesterol enriched diet with an elevation of plasma cholesterol during the first 4 to 20 weeks of exposure develop some mechanism while they are consuming the same diet that enables them to lower their cholesterol levels, sometimes back to baseline (chow, no cholesterol and 10% calories from polyunsaturated fat). I have never been able to get anyone else interested in this phenomenon but am firmly convinced that, if we could figure out *how* these individuals accomplish that feat, we would have an important bit of information about how the diet-sensitive persons might control their plasma cholesterol levels.

N. K.

The papers describe in detail the methods, the findings, and our interpretation of them at the time. We did achieve an increase in some of the markers for smoking but not for all of them. The intensity of smoking did not match that of "heavy" human smokers. The technology for training the animals to smoke was first-generation equipment and we did not have available the efficient microprocessors that are available today. Also, there was not available the marvelous array of molecular biology markers for gene expression, inflammatory mediators, enzyme activities, etc. that are

Mailing Address: P.O. Box 760549, San Antonio, Texas 78245-0549 ■ **Shipping Address:** 7620 NW Loop 410, San Antonio, Texas 78227-5301
Telephone: (210) 674-1410 ■ **FAX** (210) 670-3322

now available. Curiously, the only animals in which we observed any hint of "addiction" in the sense that they would smoke without water rewards were the females. In short, we really just learned how to do a proper experiment -- achieve high levels of smoking, and maintain human like high levels of plasma cholesterol (by using persistent high responders), and were unable to convince grant reviewers that we deserved a chance to keep on trying.

Perhaps more relevant to the immediate questions that you face are the results of the PDAY study that I mentioned above that I was working on. Enclosed is a JAMA reprint describing preliminary results, and a manuscript that has been accepted by *Arteriosclerosis Thrombosis and Vascular Biology* and should appear in print soon. As you can see in Figure 4, smoking, as measured by serum thiocyanate concentration, is associated with more extensive fatty streaks in the abdominal aorta in the 15-24 year age group; and it has a whopper effect on raised lesions (mostly fibrous plaques; very little calcification or other complicated lesions are present before age 35) in the abdominal aorta of the 25 to 34 year age group. This selective effect on the abdominal aorta is consistent with the very strong association of smoking with aortic aneurysms in middle aged and older adults. It is clear that the damage to the abdominal aorta from smoking begins *in the teen age years*.

Atherosclerosis of the coronary arteries as measured by extent of intimal surface involved shows no difference related to smoking up to age 35. However, smoking is associated with a higher prevalence of raised lesions occupying more than 5% of the intimal surface in the right coronary artery, a measure that seems to be more sensitive to small differences than the average total extent of surface involved (see results text section titled, "Risk level effects on raised lesion prevalence"). Results (as yet unpublished) of grading coronary lesions for microscopic characteristics (macrophages, lymphocytes, amount of lipid, etc.) indicate marked effects of smoking on lesions.

It is most gratifying to see the progress that is being made on the smoking front these days. Back in the '70's, I served on an NIH committee charged with advising on designing a less hazardous cigarette. This committee had on it research directors from the major tobacco companies. They insisted that cigarettes had to deliver nicotine to enhance the "flavor" and denied any addictive properties. Now we know that they knew all about addictiveness. The discouraging aspect is the frightening rate of smoking among young people (see the smoking prevalence data from the last PDAY paper). This prevalence is probably more accurate than self-reported smoking surveys. The "less hazardous" cigarette, I have concluded, is an oxymoron.

Good luck in Mississippi. Please let me know if I can give you any more ammunition of any kind.

Sincerely,

Henry C. McGill, Jr., M.D.
Senior Scientist Emeritus

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REVIEWER# 1

This is a study of gender differences in risk factors and their relationship to risk of myocardial infarction in a 12-year follow-up of the Finnmark Study of 11,843 men and women ages 35 to 52. It is based on 495 cases of first infarct among men and 103 among women. Heart attacks were 4.6 times higher for men than for women, and were strongly related to cigarette smoking, even more strongly in women than in men, after adjustment for other risk characteristics. Relative risk for men and women was similar for blood lipids and blood pressure levels, despite the large absolute difference in risk.
The strengths of this study include the fact that the men and women were derived from the same population, the "hard" endpoint of myocardial infarction was used, and that it is the only major prospective study since the Nurses Health Study to examine these relationships effectively in women.

Moreover, the population is representative and the response rate was 88%. Standardized measurements were used and ascertainment was good. The actual diagnostic criteria based on symptoms, enzymes, and ECG findings were not presented. Statistical analyses were appropriate to the design.

Body mass index was predictive only in men and body mass index and triglycerides became nonsignificant when adjusted for other risk factors.

The major conclusion from the study is that "smoking had a much larger relative detrimental impact on women" with a larger risk gradient per dose of daily cigarettes.

The discussion appropriately reviewed limitations in the study, including inadequate contact of out-migrants, with an estimated missed 15 cases of infarcts, not counting silent infarcts, and possibly biased misclassification of smoking status in women.

There is an extensive discussion of the possible mechanisms of gender differences in risk and in operation of the risk factors. No data were obtained on estrogen use or alcohol.