between randomized "normal care" and "intervention" groups has been reported thus far. Rose *et al.* (10) recorded 19 cases of cancer other than lung cancer in the normal care group and 41 in the intervention, low-smoking, group; in a test of the null hypothesis they quoted $P = 0.003$. On a causal hypothesis the lower rate of smoking in the intervention group (a self-reported average of 7.6 cigarettes a day below the normal care group) ought to have produced some reduction in the incidence of cancers over the 10-year period of the trial, although we have no reliable way of estimating how much. Hence the causal hypothesis of the association between smoking and cancers other than lung cancer is rejected at an even higher, although not calculable, level. The trend in the MRFIT study (11) was in the same direction (47 deaths in the intervention group of 6428 men and 41 in the usual care group of 6438) but did not approach statistical significance.

A more useful test of the causal/constitutional interpretations would be to combine the data from the Whitehall and MRFIT studies and to analyze the deaths and registrations for all types of cancer that associate appreciably with smoking in case-control and prospective studies of males in the United States and United Kingdom. The log-rank test would probably afford the best discrimination. Perhaps the organizers of the two trials could be persuaded to perform such an analysis on their data.

In the meantime, those of us with an inborn tendency to scepticism, and with an understanding of methodology that differs from that of the Surgeon General, find the "evidence that tobacco smoking is the cause of 30 to 40% of deaths from cancer" to be less than overwhelming.

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Reply 1

We appreciate this opportunity to respond to Dr. Burch. We are gratified that he rejects his possible hypothesis 2, that cancer causes smoking. However, Burch still argues that the epidemiological data on smoking and cancer might be explained by hypothesis 1 (smoking causes cancer), hypothesis 3 (a third agent causes both smoking and cancer), or some combination of hypotheses 1 and 3.

We are gratified that Burch sees value in a temporal analysis of the effects of smoking on lung cancer. He cites his own work examining data from the United Kingdom (1) as evidence against hypothesis 1, that smoking causes cancer. Burch claims that the "synchronous" increase in lung cancer among both men and women, despite the temporal lag in tobacco smoking by women, suggests that these increases are due chiefly to improved diagnostic methods, not to smoking. Contrary to Burch's interpretation, a replot of his data on a linear scale shows more definitively that from 1930 to 1950, lung cancer rates among men rose more rapidly than rates among women. Moreover, Burch halted his analysis at 1955, just before lung cancer rates in men reached a plateau, while rates in women continue to rise to this day. If Burch is to argue that increases in lung cancer are due to improved methods of detection, he must assume that these methods contain a sex bias that decreases with time, a situation that strains credulity. Moreover, considering the rapid demise of patients with lung cancer, early detection is going to have little consequence on incidence. Thus, it appears that one of Burch's major reasons for rejecting hypothesis 1 crumbles quickly upon inspection.

With regard to the intervention trial studies, the following comments are relevant.

In the MRFIT study (3), subjects were placed into groups of "special intervention," who were advised to quit smoking and change diet; or "usual care," who received no such advice. However, all subjects were informed that they were considered "high-risk" for coronary heart disease. With time, both the "usual care" group and the "special intervention" group showed decreases in risk factors, such as serum cholesterol and cigarette smoking, and both groups experienced substantially lower mortality than had been anticipated. Thus, the information that they were considered "high risk" must have motivated some members of the "usual care" group to modify their habits. It therefore may be somewhat irrelevant to compare a group which was advised to stop smoking with a group that was not. More instructive is a comparison between those who continued to smoke with those who quit. Within both groups, "usual care" and "special intervention," coronary heart disease mortality rates were lower for quitters than for those who did not quit (lung cancer rates were not reported for smokers *versus* quitters).

Similar dynamics were observed in the study by Rose *et al.* (4). Smoking declined among the "usual care" group, perhaps due to notification of high risk, as well as among the "intervention" group. Within both groups, 10-year lung cancer mortality rates were lower for those who quit smoking after 1 year than those who continued smoking cigarettes. With regard to an observed higher number of non-lung cancers in the intervention group, the authors note that there was no site specificity and no relation to change in smoking habit; they thus consider the higher number "more likely to have been due to chance than to intervention." More important is the authors' concluding statement: "In our view the present policy of encouraging smokers

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to give up the habit should not be changed: stopping smoking benefits respiratory symptoms and cardiorespiratory disability, and it appears to reduce the risks of death from lung cancer and coronary heart disease."

Whether those who quit smoking in these somewhat inconclusive studies were "self-selected" or not, the decreased mortality rates among quitters lend further support for the idea that smoking cessation is beneficial to health. Since the authors of these reports clearly state the above observations, we are frankly surprised that Dr. Burch failed to mention them in his letter.

Chemical analysis of cigarette smoke reveals a multitude of known mutagens and carcinogens. These include both initiators, agents that irreversibly start the carcinogenic process, and tumor promoters, substances that accelerate malignant changes. It is not known which of the chemicals in cigarette smoke cause lung cancer. If a causative agent were an initiator, the cessation of smoking would not be expected to reduce the incidence of this disease. Thus, the fact that this decrease is observed has suggested that tumor promoters in cigarette smoke are major causal factors. If this decreased incidence in quitters were not observed it would not detract from the arguments for cigarette smoke as a cause of lung cancer. The fact that cessation of smoking results in a decreased incidence of lung cancer need not have been expected but should surely provide strong motivation to stop smoking.

Finally, our position paper was not produced in a vacuum. Arrayed against the opinions of Dr. Burch is an overwhelming body of evidence, much of which has been reported in Surgeon General reports since 1964. Cigarette smoke contains numerous carcinogens, tumor initiators, tumor promoters, cocarcinogens, and mutagens. Successive Surgeon General reports have identified the association between cigarette smoking and lung cancer among men (5) and women (6), cancers at other sites (7), heart disease (8), and chronic obstructive lung disease (9) and have reported growing evidence for the deleterious health effects of passive smoking (7). The scientific debate on smoking and health was over long ago, and the tobacco industry lost. Discussion should now turn to the best methods of reducing the preventable epidemic of smoking-related diseases.

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Reply 2

The evidence implicating cigarette smoking as the cause of 75 to 90% of lung cancer in the United States comes from a wide variety of sources, including numerous case-control and cohort studies that demonstrate a clear dose-response relationship (1). Internationally, populations with low smoking prevalence generally have low rates of lung cancer. Parallels between increases in smoking prevalence and subsequent increases in lung cancer rates have been seen throughout the world (2). That smoking cessation is effective is suggested by studies that have shown that people who quit smoking subsequently have lower risks of cancer and heart disease than people who continue to smoke, as well as by studies showing that marked reductions in cigarette smoking among British physicians and among young American men have been followed by marked declines in lung cancer rates (3, 4).

The vast majority of scientists and medical societies find that the reported associations between smoking and lung cancer enjoy a consistency with few, if any, parallels in the history of disease etiology. Variation in the strength of associations or any anomalies in the temporal relationship of smoking with lung cancer reported across studies predominantly reflect differing smoking patterns of the populations studied, providing further support for a causal interpretation. Although specificity of the association of smoking with lung cancer is a criterion difficult to satisfy, this is largely because of the myriad of diseases in which smoking is implicated.

The Advisory Committee to the Surgeon General in 1964 and the authors of subsequent reports on smoking and health from the Surgeon General have made it clear that their use of the term "causal" has not been intended to exclude other agents in the etiology of lung cancer. The scientific community has seriously considered and acknowledged the role of other environmental pollutants (notably occupational exposures), and careful multivariate analyses have been published on this subject. None has exonerated the key contribution of cigarette smoking to lung cancer. In fact, these investigations have served to underscore the role that smoking plays in compounding risks associated with other exposures. There is strong consensus that cigarette smoking is the overwhelming cause of lung cancer in the general population.

Burch's statements about "synchronous" changes in lung cancer mortality for men and women in Britain between 1901 and 1955 are untrue. The rates in British men increased faster and more dramatically than the rates in British women, who started smoking later (5). These dysynchronous changes are illustrated in Cairns' graph of sex-specific smoking prevalence and lung cancer mortality rates (6), which is reproduced in our paper. The statement that "Any increases that might reasonably be attributed to smoking would have been much too small to be detected against the overwhelming background of synchro-

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