PANEL DISCUSSION: SOURCES OF CARCINOGENS*

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DR. ROY E. ALBERT. Dr. Upton, are you prepared to speak on the current controversy about mammography for women under age 50? Does that fall into the risk-versus-benefit category you spoke of?

DR. ARTHUR C. UPTON. Yes it certainly does. I do not consider myself an authority on benefits, but I was deeply involved in helping to assess the presumptive risks.† The risk of breast cancer is very strongly age-dependent, so that as a woman passes from childhood, where the risk is almost zero, into early adult life, the risk begins to be appreciable. As she ages further, the risk becomes quite significant, so that the older a woman gets the greater is the likelihood that when one examines her an asymptomatic lesion will be found; in other words, the greater the possibility of benefit from screening such an asymptomatic woman.

At the same time, the data would argue that the older a woman is when her breast is irradiated, the smaller the risk of causing cancer in that irradiated breast. The data are not conclusive, but in the model we reported to the National Cancer Institute we suggested that a factor of two was well justified, and the risk may actually go down with age by much more than a factor or two. Clearly, of course, the risk will be zero if a woman fails to survive long enough to develop the disease, and the latent period for breast cancer following irradiation would appear to be 15 years or more. Hence, if a woman of 60 is irradiated, she may not live long enough to develop the lesion because of naturally limited life expectancy. This, then, would

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†Upton, A. C., Beebe, G. W., Brown, J. M., et al.: Report of NCI Ad Hoc Working Group on the risks associated with mammography in mass screening for the detection of breast cancer. *J. Nat. Cancer Inst. 59*:479-93, 1977.

indicate that the older the woman is at the time of screening the greater the benefit and the smaller the risk. The problem is, if you work backward the younger the woman is at the time of screening the smaller is her expected benefit and the larger is her expected risk. However, I do not think we have good enough information to determine whether the tradeoff becomes strongly positive at 50 or some younger age. I think that the group under Dr. Breslow* was satisfied that 50 was a reasonable age at which to make the procedure routine, but under age 50 they were not convinced about it. I must say I am not convinced either, but I do not think I can argue the case, because I do not know the benefit assessment well enough.

I think that this issue represents a paradigm for medical practice overall. Dr. Ernst Wynder sounded a clarion call here for more attention to prevention—more careful examination of procedures and priorities in health care—and I think that the question of benefit, or cost-effectiveness, from a given medical application is one that will receive more and more attention in the years ahead as resource limitations require us to look more closely at priorities.

DR. ALBERT. Dr. Carnow, when you referred to the increase in lung cancer of 5% per cigarette per day, you seemed to throw that out without distinguishing where the range would be. Should one infer from that a suggestion on your part of a fairly linear relation?

DR. BERTRAM W. CARNOW. I think if you look at some of E. C. Hammond's data[1] and of the other data in the literature there is a not quite linear relation, but I think you can assume that kind of relation. Again, as we look more and more at chemical carcinogenesis we are beginning to make such assumptions. The question of threshold, I think, has no meaning when speaking of cancer. A serious problem that we have not addressed has to do with the question of total body burden and target organ. You may have noticed that much of the material Dr. Herman Kraybill mentioned in relation to water was the same I mentioned as being in the air. It may also be in cigarettes and I think that when we talk about contribution we must consider multiple sources of single and multiple carcinogens impacting on single target organs. Many carcinogens have multiple sources and the big question is from what source can we remove it most easily and how much do we have to remove before it becomes

*Breslow, L., Henderson, B., Massey, F., Jr., et al.: Report of NCI Ad Hoc Working Group on the gross and net benefits of mammography in mass screening for the detection of breast cancer. *J. Nat. Cancer Inst.* 59:473-78, 1977.

prohibitive to society from a cost-benefit standpoint? I do not like to deal with the question of threshold because it does not really matter where you get the lead from—the air, the water, the cigarette, and so on. The body does not care about that; it experiences a total body burden of the material.

DR. UPTON. Another aspect of the same question is the nature of the effect itself, that is, does the increase that we produce with a carcinogen constitute an absolute number of additional cases per unit dose or some multiple of the natural risk per unit dose? Thus, the yield from a given dose of carcinogen may be equivalent either to the natural incidence plus some effect or to the natural incidence times this effect. Our existing data, by and large, do not permit us to distinguish between these alternatives in many instances. Clearly, however, if cofactors are involved one must deal with high-risk groups in which the effect of a carcinogen will be much larger than would otherwise be predicted. Over a large heterogenous population it may not affect the average risk greatly, but for individual groups it may make a lot of difference.

DR. ALBERT. Dr. Carnow, you mentioned in passing that there still was considerable debate concerning the carcinogenic effect of urban air. Does a respected body of scientific opinion indicate that urban air really hurts us?

DR. CARNOW. Yes. Our work and the study of the National Academy of Sciences looked at Sir Richard Doll's data on gas retail workers and found a doubling of cancer among people exposed to about 2,000 ng. of benzopyrene and on that basis suggested that the amount in urban air was low enough to be negligible. What they failed to note, as somebody pointed out in a National Cancer Institute paper, is that workers are exposed only 22% of the time as adults. I think you cannot extrapolate that to anyone who has been exposed over a 70-year lifetime to a multiplicity of environmental stresses.

Part of the problem, also, is that a lot of these materials are synergistic. There is no question that asbestos is synergistic with cigarette smoke in causing lung cancer and there is no question that benzopyrene and particulate matter have a relation. If one accompanies the other the user effect is greater, so I do not agree with them. If one looks at some of the data that we have generated, for example Allegheny County or Lake County in Illinois, both downwind from coke ovens, and if one examines the benzopyrene concentration at the coke ovens and then looks at people living in those communities, one finds in some of those communities a 25% increase in lung cancer. Some or much of that may represent workers

dying as a result of exposure in the coke ovens, but it does not explain all of the deaths. Cancer is a 30-year disease and one may ask about the benzopyrene levels 30 years ago. Most of those coke ovens have been there for 60 or 70 years and we can make some estimates based on production, which we have done, to tell a little about how much benzopyrene was emanating from those coke ovens. They have not improved them in 70 years. Some people may argue against the air-pollution cancer factor because they feel that it takes away from the cigarette menace. I remember that in a courtroom once somebody suggested that the litigant's back was bad before the accident. The opposing lawyer asked the jury, "Have you ever been hit on the thumb with a hammer?" and the jurors winced and said, "Oh, yes," and he said, "Well, what if that thumb is swollen and infected and then you hit it with the hammer, is it better or worse?" A number of factors are involved: there's a swollen thumb and a hammer, and if cigarette smoking is the major carcinogen source then, with 70 million people at high risk because of cigarettes, they cannot afford having other factors imposed on them for a lifetime.

DR. ERNST L. WYNDER. In New York we are, indeed, surrounded by benzopyrene when we stand in Times Square and we certainly inhale particulate matter. We estimate that it would amount to about four cigarettes a day and we have found that in air pollution the carcinogens are almost exclusively polycyclic aromatic hydrocarbons, quite different from what we find in tobacco. We have produced cancer in animals with air-pollution condensates so there is no question that we are surrounded in our air by carcinogens. The question is whether it is below the threshold level.

The urban factor is very difficult to assess. First, nearly all cancers are reported commonly in cities. Second, more carcinogens related to lung cancer are present in cities than in rural areas, including exposure to asbestos-related working conditions. And, finally, cigarette smoking is quite different in cities than in rural areas. If you are a nonsmoker your chance of getting lung cancer, squamous or oat cell, is equally small in cities and in rural areas. I have only recently looked at 1,000 cases of lung cancer and can confirm this. Hammond and Horn's data show that histologically proved lung cancer, squamous type, has a death rate something like 3.4 per hundred thousand and the death rate for nonsmokers is 0.7 per hundred thousand. So there is no question that in the absence of cigarette smoking and certain occupational exposures, air pollution has no role in

lung cancer. The question remains whether it adds to the effects of smoking. The problem is that if cigarette smoking has an additive effect it becomes epidemiologically very difficult properly to determine and to standardize cigarette smoking.

I thought—having had some experience in asking questions on cigarette smoking which involves type of cigarette, inhalation, butt length, duration of smoking—that I knew something about the way people smoke, but recently we began to look at blood levels to reflect smoking habits and found that two people who claim that they smoke roughly the same amount have totally different concentrations of carbon monoxide and carboxyhemoglobin in the blood stream. It seems to me that only when metabolic studies show that two populations have exactly the same exposure to tobacco smoke can one say that air pollution adds an additional factor. Finally, it is obvious, as I have shown earlier, that cigarette smoking, particularly in the last 10 years, is particularly related to socioeconomic backgrounds and, consequently, if one lives downhill from a polluted factory it is likely that one has different smoking habits than the inhabitants of Scarsdale or Bronxville. The epidemiology of this is very crucial and, in agreement with Richard Doll, we can conclude that among nonsmokers, certainly, air pollution plays no role. Whether it plays a role in smokers remains to be determined. Independent of this, I am clearly in favor of cleaning up our cities as we have always said. Even if there were no evidence that air pollution relates to lung cancer in man, we certainly should do all we can to clean up our cities.

DR. CARNOW. I agree that this is the controversy. Sir Richard and I and the other 12 people agreed that from 10 to 15 cases per 100,000 in Sweden might be caused by air pollution. Now, in a lot of cases cigarettes and pollution are certainly working together, but I disagree with your statement negating it as a factor at all. I think our data presents a formidable case.

DR. ALBERT. That is 10 to 15 cases per 100,000 in smokers additional?

DR. CARNOW. No, Ten or 15 cases per 100,000 increment in lung cancer. This is in males, but that this would represent an increase of 10 to 15 cases per 100,000 population in most cities in Europe.

DR. ALBERT. In nonsmokers?

DR. CARNOW. We did not differentiate. We just said increase in lung cancer. That is all we said and, of course, nonsmokers generally do not get lung cancer. I do not know how valid it is. I am not a pathologist, but Dr. David Spain, who did some studies in New York City, suggested that

there was a lot of squamous metaplasia in people who never smoked who were raised and died in New York City. Such pathologic data would add some credence to this. There is no question, however, that many of our contaminants have carcinogenic properties.

DR. WYNDER. Oscar Auerbach has done some very nice studies that showed that the nonsmoking population in Veterans Administration Hospitals had very minimal changes.[2] One other interesting point: women make a very useful point for studying epidemiology. At the very beginning, years ago, when we saw the differential in sex ratio in male and female lung-cancer rates, we said that this is unlikely to be explained by general air pollution because women certainly are exposed to the general air over New York City as much as are men. Years ago the sex ratio used to be 10 or 20 to one and now, as women are smoking more and more, the rates go up. The final point made by Richard Doll,[3] that the rate of lung cancer has precipitately dropped in British physicians, is another indication of the carcinogenic role of smoking.

DR. CARNOW. So has air pollution dropped in London.

DR. WYNDER. Yes, but during the same time the rate in the general population in England has increased 7%.

DR. UPTON. In this same context, I would like to ask some of the epidemiologists if they would comment on the graph that Richard Doll showed at the International Cancer Congress in Houston in 1970 relating cigarette smoking and lung-cancer risk. As I remember his graph, which plotted lung-cancer rates per 100,000 against the number of cigarettes smoked per day, the resulting curve was a perfect straight line, from something like less than five cigarettes a day up to 40. I do not recall that there were confidence limits on the plotted points, so that one could determine whether the same data would fit a threshold model, but the curve suggested that Doll did not think the points were consistent with a threshold model. If the linear model is considered a reasonable representation of the data, then it would argue against a threshold for cigarettes. Further, if what comes out of the cigarette in its smoke condensate also gets into urban air from other sources, one would not suppose there would be a threshold for the latter. I wonder whether epidemiologists who have looked at this problem would wish to comment on it?

DR. WYNDER. One cannot draw a curve that is better than the data on which it is based. We are currently conducting a study on interviewee bias and we are under the impression that particularly lung-cancer patients

today underestimate the number of cigarettes they have smoked and before one can say that one has a measurable risk, let us say with fewer than 10 cigarettes, I would like to be convinced that the information we receive from our patients is indeed true. We are currently involved in this study and, particularly in the last few years, there is a very strong bias in lung-cancer patients as to their smoking habits. Obviously, Richard Doll has pointed out that one of the problems in his earlier studies was inhalation. Another problem relating to the inhalation data he had was interview bias and all of us who have interviewed patients realize how careful we have got to be because sometimes we do very fancy statistical analysis and never realize that data we get from patients have a rather large magnitude of error.

DR. ALBERT. In closing, it is apparent that this has been a very thorough discussion of the state of the art and we undoubtedly will come away with the impression that we are dealing with the health problems of exposure to a sea of carcinogens in the sense that there are many of them and they come in all sizes, shapes, and modes of exposure and at all levels; there is no question that the cumulative impact of all these things on human health is substantial. Because there are so many of them, regulatory action is not going to be a simple matter.

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