

Duquesne Law Review

Volume 34
Number 4 *Conference Proceedings: The
Duquesne University School of Law Institute for
Judicial Education's and the Supreme Court of
Pennsylvania Conference on Science and the
Law*

Article 6

1996

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Recommended Citation

Lewis Kuller, *Epidemiology Studies - Relevance and Significance in Litigation*, 34 Duq. L. Rev. 851 (1996).
Available at: <https://dsc.duq.edu/dlr/vol34/iss4/6>

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Epidemiology Studies—Relevance and Significance in Litigation

*Lewis Kuller**

I'm going to discuss some of the ways you can use epidemiology, how epidemiology evaluates a problem, and some of the nuances of epidemiology. I can start with a few commentaries about what epidemiology does and how it functions, and about some of the issues that are involved—especially at the present time. First of all, epidemiology is successful, as I like to point out to our students, in a situation which I call a chaos. An epidemiologist thrives on a chaotic situation and that is, if there's an earthquake, an epidemiologist can run out and study who got hurt, who didn't get hurt and why. If an epidemic occurs—suddenly a great number of cases occur and everybody runs around and screams and wonders what's going on. Epidemiologists do real well in those kinds of situations. A lot of epidemiologists make their living cleaning up the mess that is either created by the introduction of a new technology which hasn't been adequately tested, or in getting involved in issues related to medicine in which the introduction of a new drug or surgical procedure creates an epidemic. I know there's a lot of things that doctors are doing right now and I can guarantee that in a few years they're going to get sued like crazy, and if I tell them that they're doing it wrong now I'll become a leading expert witness. If I'm wrong, they'll just forget about it—if I'm right, I can have something to do when I feel like retiring. I say that facetiously, and I get some people extremely angry when I say that, but I do it as sort of a somewhat humorous comment, especially when I'm arguing with somebody about their treatment and the fact that they haven't tested it scientifically and about the fact that I don't have to worry anymore because I'll be able to testify when their treatment turns out to be a disaster.

It's very different than what you think about in physiology or

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in laboratory science. A laboratory scientist controls everything as best he can and tries to see what happens when he manipulates the system in one specific way. People who work in basic laboratory science sometimes get very confused about epidemiology. Epidemiology functions in the real world, and in the real world, everything is changing, so we have to use what exists around us and try to understand problems and as we see, have different methods of doing this.

The second issue in epidemiology is that there is considerable confusion these days between what I would consider to be societal problems and science and epidemiology—what I call a little bit of victim science. Some years ago I took a sabbatical leave and I worked with Claude Pepper in the early 1980's. He was a wonderful teacher and was very effective. He taught me right away how to successfully get societal legislation through. He pointed out that the way to do it is always have a victim. So when we wanted to get legislation passed to allow the government to pay for transplantation, all the scientists could come out there and say it's too expensive and it doesn't work this way or that way, and all they had to do was to bring a mother with a child who was jaundiced, yellow and have the television cameras focus on the child who was jaundiced, and we had the cameras focus on the scientific expert who was telling everybody about the health care cost, and you know who won. There was no chance in 100 years that Congress wasn't going to approve the money for transplantation when they had thousands or millions of people watching television and watching the mother with her child who obviously needed a liver transplant. That's not epidemiology, it was a way of getting legislation passed which is good for society. I worked in that area and I thought it was very important, but it certainly wasn't science.

I'll give you some examples which are fairly obvious in the area of the research related to breast implants. Most of the data on breast implants suggest that they are not related to any adverse affects to 99.9% of the people who are involved. The American Rheumatism Association, the Organization of Professional Physicians in the areas of arthritis and rheumatism, just came out with a blanket statement, which is unusual for any medical society, saying there was absolutely no evidence at all from the studies—and there were about twenty studies—and almost everyone totally negative. Now the problem is that if you come along and make this blanket statement several things happen. First, the obvious statement is that you are being paid by the company that's being sued—in this case, you're getting paid by Dow Chemical or some other chemical company, and

therefore you're a crook. So many of my colleagues who are honest and spent their lives in academia and have suddenly wound up doing studies are being tarnished or painted as being crooks because they came up with a negative study. When they started out they had no idea whether the study was going to be positive or negative. Second is that you don't like women because, in essence, you're doing something which is against women and against society. So even if you're a woman investigator, somebody will paint you that way.

Similarly, I was involved in the very first study in Vietnam of Agent Orange. I happened to be working with some colleagues who wanted to do a rather interesting study. They wanted to study identical twins, one twin who had gone to Vietnam and the other twin hadn't, and we were interested mainly in the psychological impact of the Vietnam experience. At that time nobody knew the first thing about Agent Orange. One day the Veterans Administration called and said that there's an Admiral who is terribly concerned, and Congress is concerned that there is some chemical that was sprayed in Vietnam that's killing everybody. They told us we had to do a big study to go prove what this is, and they increased the \$50,000 grant by millions and millions of dollars. No matter how much money was needed you could just go out and do the studies. Well, years later, after many studies, an advisory committee that looked at these studies with the Office of Technological Assistance, a group of mostly scientists and representatives of veterans organizations, concluded that the studies weren't going anywhere, and we weren't finding anything of any significance, and were unlikely to find anything. We recommended to the Center of Disease Control that the studies be stopped. The next day in the newspapers I saw a big article saying that Ronald Reagan had stopped all these studies, and that this was politically motivated. It was kind of interesting because I don't think Ronald Reagan or anybody in his office had the foggiest idea of what a bunch of academic scientists were doing in some little room somewhere, in making this decision, but it was kind of funny to see this because I had no idea and got very nervous about who the other people in the room were and whether some of my colleagues were really working for the CIA. These are the kinds of issues you sometimes get into in these types of studies.

Another issue that's important is that many of the companies have paid employees who are scientists, but in essence are employees, and you have to recognize that their job is to protect the company. If you understand that, at least you're on a level playing field. I worked on Reye's Syndrome and the problem with

aspirin, and did a study with the most skeptical people in the United States. In other words, we got the investigators who were convinced that aspirin had nothing to do with Reye's Syndrome and designed a study with them which was supposed to last three years. After it went six months, it was obvious that aspirin was the major cause of Reye's Syndrome and we stopped the study on ethical grounds. The study was being run out of Yale and we told the Yale Human Use Committee that the study had to stop. Well, I thought everything was finished and we went to present this to the companies. There are a lot of people from the companies who gave us fifty different reasons why the study couldn't be true. It was so obvious that even the most skeptical people were convinced. I said: "Fine. You can go tell the FDA and other people that aspirin isn't related to Reye's Syndrome, but the evidence is so overwhelming that there's no question."

Another very important problem is the concept that we live in a risk-free society and we're all immortal and that in essence, if we behave ourselves we'll live forever. I can tell you right now that sitting in this room you are increasing your risk of something. There is either something coming out of the carpet, there is something coming out of the lights, there is something coming out of the coffee you drank, or maybe there's something that you ate today. If I look hard enough, I could find that every one of you has something wrong with you. There is no question that if I examined every one of you the amount of the disease in the population is infinite. The only thing that is not infinite is how much disease I find and how much people are willing to let me subject themselves to my search for their disease. New techniques that we had developed to find people who had very early vascular disease predicted the likelihood of developing clinical heart attacks, strokes, etc. One thing we found is that in our studies of people sixty-five and over, is that 2/3 of the people had fairly significant vascular disease and didn't even know it, and yet they were at an increased risk of developing clinical disease and we have good therapies to prevent subsequent clinical disease. But the reality is that I have newer and newer tests which find more and more people with disease. We don't live in a risk-free society and it never will happen. When we talk about cancer risk of one in one million. We talk about the fact that everything is risk free. It just won't work in the sense that we will always find certain risks.

In relationship to that, we're always going to find an association, whether we like it or not, between some adverse health behavior an individual has and health. In the past we burned

witches in the 17th and 18th centuries. We burned women we thought were witches and men we thought were witches because people got certain diseases. The Bible is loaded with health regulations—what you can't do, what you can do, what you can eat and where you can sleep. What is the rationale behind burial practices in different religions? Why do you bury people? Why do Orthodox Jews bury people within twenty-four hours? Why do you have the burial and the services outside of the home? It's very obvious—somebody had a contagious, infectious disease, and the body had the likelihood to transmit the disease if you brought it to the house and kept it there for a few days—everybody in the family and everybody around the body got sick and also died. The argument was that God, or a supernatural being, was causing everybody to get sick. So you solved the problem when you took the body and put it out of the house and buried it very quickly because the disease no longer occurred and you made an assumption that you were doing the right thing.

We have the same problems now. We have people who try to relate behavior or exposure to a disease or behavior that another individual has. So we have people who try to understand why people have arthritis or joint pains or muscle pains or headaches or depression. Most of the people who have Gulf War Syndrome have a lot of symptoms, which are very common. That symptomatology makes them sick. They really are sick, but they attribute that sickness to some chemical exposure or some supernatural phenomenon which they don't understand. All of us have periods of depression, headaches, weakness, or fatigue. We know that symptomatology can also lead to weight loss, loss of hair, changes in immune function, and endocrine changes which one could measure. We are trying to find out whether chemical x causes migraines, chronic fatigue, arthritis, weakness, dizziness, and headaches and relating them to particular exposures. Some of that is right, some of it is wrong. But in essence we have a tremendous problem right now. The problem is that we try to prove that society is risk-free and that every problem in society can be related to some type of an exposure other than our own way of living, and we don't want to be the victim, we want to find somebody else to be the victim for our problems.

Now I'm going to try to look at epidemiology and how we go about doing it from a fairly conservative viewpoint, because I think you have to be conservative when you look at some of the studies.

We have exposure to a chemical which we might call x , increasing the risk of the disease y , in a population called z . This

is very common—we have a population of people who seem to have a higher frequency of contracting disease y and they claim it's due to the exposure to chemical x. Now, there are three things that happen. One, toxicologist reports that a specific chemical found in high concentrations—chemical x—maybe from the environment, maybe it's found in the food, water, air or soil, at least in an animal model, is related to a disease. The epidemiologist reports that there is a higher frequency of disease y occurring in the community population z. So the epidemiologist says that a lot of people seem to be getting the disease in the community in the population. What often happens is that individuals living in the community report that they are sick, that they have this disease y, because they have what we call a “cluster of disease”—there's a lot of people getting sick. I get calls constantly about people who tell me that everybody on their block has brain tumors, everybody has colon cancer, or everybody is dying of cancer. This is so common right now that the state health departments and most of the government agencies won't investigate these clusters unless certain criteria are met because the cost of doing these investigations is astronomical.

A toxicologist evaluates the effects of the chemicals, usually at high doses. A toxicologist will take a high dose of the chemical, test various routes of exposure in an animal model on specific tissues or cells, and relate the exposure to specific behaviors of the animal, which might include things like cancer. The animals can develop various diseases which mimic what they think is happening in humans. Toxicology attempts to relate the chemical characteristics of the agent to other structurally similar chemicals. Another approach—one of the areas we use computer science—is to say: “Does this chemical look like other chemicals which we know causes cancer? Does this look like benzene which we know is related to leukemia? Does this chemical have characteristics that might be associated with causing a cancer or disease?” Then we try to relate this in carefully controlled animal studies. The conclusion would be that chemical x causes disease y or a specific change in the structure of a tissue. It might change the DNA. It is important to note that often the route is not the human route. The interpretation is whether the animal model is related to risk in humans because the dose is different, and you have to extrapolate the exposure because there are differences in susceptibility. There are some animals that won't get cancer even though they are exposed to human carcinogens, and there are some animals that are very sensitive, especially to develop liver and thyroid cancers. If you expose an animal to enough of a chemical and you cause cells to divide and also to

cause some changes in the DNA, you'll get cancer in almost any animal model, at least at certain sites.

The epidemiologist essentially needs to find an epidemic. He or she has to find the place where there is exposure of a population to the chemical and where there is a natural experiment. That's why I say we operate in chaos. We have to go around and find either an occupation or community where there are people who are exposed to this potential chemical so that we can determine whether there is an unusual frequency of disease *y*. That is, it's increasing in frequency either in the population or in a subpopulation which might be defined on the basis of genetic susceptibility or co-exposures. For example, alcohol causes an increased risk of things like head and neck cancers, but it does so primarily in combination with exposure to cigarette smoking. There are chemicals like asbestos where the risk of lung cancer is relatively modest at lower doses. Asbestos is certainly bad, but if you add cigarette smoking to it, the risk goes up tenfold. The same thing is true of radon and cigarette smoking. Radon itself causes a slight increase in lung cancer that's hard to measure, but if you add cigarette smoking the risk goes up dramatically. So we want to see if there are co-exposures. And then you come to the conclusion that chemical *x* causes disease *y* only in a susceptible population of *z*, and that susceptible population *x* becomes very critical. Now where we get into trouble is the following: individuals in population *z* respond to newspaper articles that chemical *x* has caused disease *y* in population *z*. What often happens is that there is a claim made, often in a newspaper article or somewhere else, that this is proven, not that toxicology or epidemiology has proven that the disease *y* is being caused in population *z* by chemical *x*. It appears in the newspapers, it appears on television, radio, or 60 Minutes. One of the most hilarious parts of the whole Gulf War Syndrome was a presentation by prime time television that somebody with Gulf War Syndrome found what we call hydrocarbons in the blood of people who had been in the Gulf War, and that the hydrocarbons were all related to the symptomatology. The hydrocarbons in the blood have a half-life of about thirty minutes, and these people have been out of the Gulf War for a year and some bright chemist showed that when you put the blood into a tube with a rubber stopper the hydrocarbons came out from the rubber stopper and when he baked the rubber stopper, put the blood back in again and reran the test, there were no more hydrocarbons. They wrote to the television program and said they better tell people, but there was no way they were going to tell people how this guy screwed up.

What happens is that small but financially successful groups of epidemiologists, toxicologists, and lawyers get financial benefits. Unfortunately this is often the real situation and it's getting worse. Once the newspaper articles come in it's not hard to attract a pool of, as I pointed out this guy who did hydrocarbon testing and made a small fortune before somebody caught up with him, or even a group of epidemiologists who make a living doing this, and lawyers who join together. I did some work years ago in defending Conrail against claims that it was causing all kinds of diseases, and one of the most interesting things in giving the lawyers an education in epidemiology is that all the Conrail workers were being examined in a lawyer's office by a group of doctors in Buffalo and every single Conrail worker who they examined either had diabetes, hypertension or heart disease. These workers were men in their sixties, going in there with their blood pressure a little bit elevated because they were nervous.

The roots of environmental epidemiology are related to two things. That is what we call the investigation of traditional common source epidemics, and an investigation of occupational cohorts. Now what do I mean by that? Traditionally, epidemiology grew out of the investigation of people who went to a restaurant or who went to a party and ate some tuna fish or some egg salad which contained salmonella, staph, had some bacterial organism or some virus, and when they got home they had diarrhea or vomiting. People then called their friends and said they were all sick, called the Health Department, and the Health Department investigated and found out that somebody with dirty fingers got their fingers into the tuna fish or the egg salad or the ham salad, or whatever it was, and the food sat around a while at room temperature and everybody got sick. It happens all the time. We've had this in Pittsburgh over the recent years at one of the very famous country clubs. One sad but humorous one was at a very good private school in Pittsburgh where the lettuce was contaminated and the girls got sick, and they were hysterical because they all got sick. It turned out that the lettuce was doing it—not the hysteria. And the second one was at one of the religious temples in Pittsburgh where they served a Passover Seder meal and people got dreadfully sick.

Now let's look at the problem. In a traditional common source epidemic, people call you and say: "We're sick, we got a problem, we're sick." You investigate it by finding out what the disease is, how you can define it, and how you can identify what the people ate. Compare the people who got sick with those who didn't get sick and then try to isolate the agent and estimate what the risk

is. That's traditionally what we do.

Now what happens in an environmental exposure? It's exactly backwards, and this is what gets us all into big trouble. What happens is that somebody thinks that they got exposed—nobody knows there's a disease. We go back and try to find out who got exposed. We don't know what they're being exposed to or how to measure it, but sometimes we have an idea. Then we try to measure whether there is a problem. We don't even know if there is a problem, we know that there is an exposure, but we don't know if there is a problem. So we have to see whether there really is a problem. Well, this is a very tough thing to do in epidemiology because we don't know what the problem is and we don't know what is the population at risk. This is a good example of what happened with the implant story. There is a lot of women who got exposed to breast implants, the breast implants leaked and silicone got into the tissue, and silicone might cause some type of reaction. Do we have an epidemic? Well, we didn't ask them. We didn't have an epidemic of disease and we didn't suddenly have a large group of women who had a disease increasing in the population with unusual frequency. We started out with the fact that we had an exposure and we had to find out who got exposed and what disease they have—and we still can't figure that out.

Now, what are some of the issues? First, we often can't define the population at risk. So we have a class action and everybody who was potentially exposed becomes the population—millions and millions of people. Everybody exposed—whether they're exposed or not they become the population. This is especially true if it takes fifteen years between when the disease develops and the time that people got exposed. We have to figure out who was exposed fifteen or twenty years ago. We also don't know what disease we're looking at. We are not clear what diseases are and are not important. So what we're doing is using epidemiology to study a nonepidemic, and it just doesn't work very well, and that's a problem. We don't have an epidemic and we don't know if there is an epidemic. We also don't know what the agent is that we're looking at. Is the agent of concern, or are other chemicals, or is it exposure to viral disease? We often get confused between the environment and the agent that causes the disease. We often say that because you were there—because you were in this little town—you were exposed to the agent. That's not causal, that just says you happen to be living there, and that doesn't say you got exposed to the agent. We often don't know whether the person was exposed to the agent, especially if there's no fingerprint of the agent. The only thing we

can tell you about the agent is that it's somewhere in the environment, and most agents have no good fingerprinting of exposure. We have all these interesting problems about people who are convinced that they live near a toxic waste dump, that the water is polluted. There is something in the water that is causing their disease, that air pollution is causing a lot of cancers, and this goes on and on. Some of it is real and some of it is not real. Our problem is how you separate what's real from what is not real in science.

The typical epidemiological study is of two types. One is what we call experimental studies in epidemiology, and I do most of my work in this area. The other is what we call observational studies, in which we're observing what's going on and trying to interpret it—we don't manipulate the system. It's very hard in environmental studies to experiment because it's hard to give people lead or mercury or asbestos and then see what happens, especially with long incubation periods. So we're stuck with two types of observational studies. In one, we start out with people who already have a disease and we go backwards and try to find out what caused the disease. We look at a comparison of some control group. Second, we start out with people who are exposed to some agent and we try to find out what the risk is of developing disease. They are called cohort studies, and case control studies. We start out with the exposure and look for the risk of disease and we start out with people who have the disease and go backwards and see if we can find out what caused it. Now just very simply, what you have to look at is whether the study is worthwhile. There are certain things you can ask. First you have to find out if there is an epidemic and if somebody can't prove to you that there is an increased frequency of disease in relationship to the exposure, whether it is an occupational group, a community, or a group of people exposed to some drug, then everything after that should be suspect, at least in my mind, and I'm somewhat conservative about this. Then you have to ask if there is an epidemic, who's been exposed and what's the population at risk? How have you documented that these people really are part of an epidemic? Then you have to ask how the disease got transmitted in the population, what's the mode of transmission, was it in the water, the air, or in the food, was it person-to-person and is it actually a chemical? You also want to know what the risk is. That's not only whether the risk is one in a million, but is the risk to 20% of the people that get the disease? Women who have, what we call the breast cancer gene—the BRCA genes—their risk of getting breast cancer is about 80% during their lifetime, which is extraordinarily high.

On the other hand, we have situations where we talk about the risk being increased twofold. The normal risk of a disease like breast cancer is three or four per thousand, and in women premenopausal, its about two per ten thousand. If I tell a woman her risk is increased threefold and it goes from two per 10,000 to six per 10,000, it may seem like a lot but if you turn it around the other way, 9,994 women aren't going to get it as opposed to 9,998. And if I tell somebody that, they're not going to care. So you have to know what the attack rate is and what kind of disease you are going to get. Is this going to be a disease which is relatively benign, self-limited and of no problem, or is this going to be a disease causing major disability? Next—what's the incubation period? Very often, in scientific investigations and reports, the presumption is that some guy got exposed to chemical x and three weeks later he got lung cancer. You need to have an incubation period. The incubation period for most cancers is fifteen to twenty years. I get people who tell me they were exposed to radon and six months later they got cancer. It can't be—it just doesn't work that way. You have to know what the incubation periods are of these diseases in relationship to the exposures.

Is there an epidemic? There are two areas that you can look at. One is geography and the other is temporal trends. In other words, is there evidence that there is a higher frequency of disease in relationship to a defined population by geography—it could be an occupational group, a little town, a census tract, or a group of people who have a certain social interaction. Do they have increased frequency of disease? Or the disease has increased dramatically and over time there is a temporal trend. One of the problems is that most of the chronic diseases that we deal with are very long in terms of their development—the incubation period. We really don't have good longitudinal or geographical data available to document an epidemic unless it is a big epidemic. So one of the problems is that you'll have an argument about whether there really is an increased frequency of a disease in a population, it's increasing over time.

A good example of a really red-hot epidemic was the so-called toxic shock syndrome, which was due to an infectious agent staphylococcal infection. It was due to the fact that a different type of tampon was introduced into the market and that tampon was associated with an increased risk of a substantial infection. We had an epidemic associated with the introduction of this changing tampon. As soon as they took the tampon off the market, and changed it, there was no more epidemic. This is an example of an epidemic, the association was clear-cut, and the

investigation showed what happened—they changed the product and no more epidemic. It happened to have a very short incubation period which makes life easy.

An example where you get into a real mess is a study we're doing in West Virginia, in the Charleston area. In the Charleston area you have the greatest concentration of chemical industries in the United States, and some of my colleagues have been very interested in the issue about whether there is an increase in leukemia, lymphoma, or Hodgkin's disease in the population in this area. From 1950 to 1954 and up until 1984 when the data was compared to the rest of West Virginia and to the United States there was an epidemic of, in this case, cancers, higher rates of disease.

We go into the county and we collect cases of people who died from either lymphoma or myeloma leukemia and from what we called comparison groups. People who died in this case from heart disease or colon cancer, all living in the same county, and we found a rather interesting phenomenon—that the risk in people who died under sixty-five is about three times higher for those who worked in the chemical industry in the county versus people who didn't work in the chemical industry in the county. I can't tell you in all honesty whether this epidemic in the county is related to exposure to the chemical industry, but what happens is an interesting story. When you show this data to all the chemical companies that are in the county the answer is very interesting—each chemical company says it's the other chemical company that is responsible for the problem. So you go round and round, and each one of them does one other interesting thing and that is they say we need to do more research. So the chemical companies say that it's somebody else's problem and you can't solve this problem until you do more research. Well, there is obviously more interesting research to do, but the reality of the situation is that the research may go on forever, and in the meantime the chemical industries might be related to specific cancers.

I did another study in West Virginia on air pollution from a plant that was in Ohio that was spewing air pollution into West Virginia. There was an increased risk of asthma and bronchitis and they invited us to come down there and talk. I did this study for the EPA and I found out that the community was suing Ashland Oil in a class action suit for a billion dollars. I can tell you that we got about \$5,000 from the EPA to do the study, and I walked into this room and I found out that they were suing for a billion dollars. I really couldn't tell them whether Ashland Oil was responsible for the increase in respiratory

disease because we did a little study there, and I couldn't tell them whether it was something else, but they were going to use this study to sue for one billion dollars.

The next thing you must ask if there is an epidemic is: "What is the disease?" What is the definition of the disease? It's very unlikely that we would have any increase in all diseases. The only exposures I know that increase practically any or most diseases are large doses of radiation. You can't say the agent increases disease or cancer. Cancer is not one disease, so it's unlikely it's increasing all cancers. You have to be specific. The biggest problem you have is that people misinterpret whether it is essentially a new epidemic or an old epidemic. The problem is that the amount of disease, as I mentioned, is infinite. We have an epidemic of prostate cancer in the United States and some people have attributed that epidemic to exposure to chemicals. The epidemic of prostate cancer is due to the fact that we developed a test called the PSA test for measurement of early prostate cancer. Forty percent of men have what we call occult cancer. As you increase the number of men who have PSA testing, you create a beautiful epidemic of prostate cancer and it's growing huge. Some years ago we did a study and showed that the epidemic of prostate cancer in Pennsylvania followed Interstate 79. When you tested it, you find out that there was a group of urologists who were moving up the road and doing tests as they went. Somebody looked at that data and said it's due to some oil plant in Titusville that is causing prostate cancer. Of course, it's just nonsense.

Community awareness of disease may increase the likelihood of diagnosis. If you tell somebody you have an epidemic of disease and the disease might be brain tumors or heart disease, it will suddenly increase. Some years ago we had an epidemic of heart disease and bypass surgery in Westmoreland County which stirred up a great deal of controversy and concern until we found out that a couple of cardiologists had opened their practice in Westmoreland County and were successfully increasing the number of patients being referred to bypass surgery. Not to say that there is anything wrong with that—it's just that was the explanation for the epidemic.

Variations in high technology can account for all kinds of epidemics, so if you have women in one community having a lot of mammograms, and in another community they aren't, you'll find interesting differences. Sometimes the selection of one disease may lead to an increase in another, and by that I mean if you get people to quit smoking, the risk of heart disease drops dramatically and the risk of lung cancer hardly changes.

If you wipe out hypertension and treat it effectively, you reduce the risk of stroke dramatically and you reduce the risk of heart disease dramatically, but you have very little effect on renal disease and so it appears that renal disease is increasing. There is a lot of complex inter-relationships that one has to be worried about in terms of what appears to be new diseases or new epidemics.

You also have to determine what the population at risk is. How do we define who's at risk? What's the population that is likely to be affected if there is an epidemic? We can define it in terms of social phenomena—demography where the people live and their occupational exposures. We've now got better ways of defining populations at risk than traditional approaches. There are big differences between infectious diseases, where it's easy to ask people what they've been exposed to, where they've been, what food they've eaten, and what school they attend than it is when we're dealing with a chronic disease—especially in environmental exposure. For instance, ultraviolet light (sun exposure) is associated with epidemics of melanoma. So if you go to Queensland, Australia, the rates of melanoma are off the wall compared to the rates of melanoma for people living in Maine, or in the northern parts of the United States. In that case, the population at risk is people who happen to live in that area. You can redefine that a bit more by looking at people who have unusual recreational activities. For example, children who get bad sunburns early when they're youngsters seem to have a higher risk of melanoma, and that's primarily related to their lifestyles. So melanoma is an interesting disease because it appears to be of higher frequency in the upper social classes. Why the upper social classes? Because those are the people who can afford to sunbathe on the beach all the time and get sunburns.

Another example, as you probably know, is the famous studies that were done in Pittsburgh which showed that exposure of steelworkers to coke ovens and benzopyrene was associated with an increased risk of lung cancer. In this case the definition is by occupational epidemic, and within the occupation, by a specific exposure. So here we have two different levels of defining population. Another good example is lyme disease, which is due to a specific microorganism and to behavior. We have people who walk through woods or fields and live in certain areas where the deer tick is present with the organism. They have an increased risk of getting lyme disease. And again, lyme disease turns out to be, in most cases at least initially, an upper social class disease. In this case you could define it by geography and by behavior.

Cigarette smoking is not an important risk factor for breast cancer, but there is an issue of susceptibility. Individuals who metabolize the carcinogens in cigarette smoke in a certain way have an increased risk of breast cancer. So in this case the epidemic is defined by specific molecular and genetic characteristics. That chemical causes cancer in only people who have a certain genetic characteristic, so if you exclude those people from that particular chemical exposure, you protect them from disease. They are the only people who are at risk in the population—those who have specific genetic characteristics.

If there is no epidemic, there are four possibilities. First, there really is no epidemic and no association. Second, there's no epidemic because the people weren't exposed. The third possibility is you have no epidemic because the risk is limited to a small subgroup which is missed in your analysis. In other words, if you look at breast cancer and cigarette smoking you find no relationship when you include all cigarette smokers and all women. It's only that little subgroup, which you can only find by looking for it, that has that relationship. So it may well be that there's no risk because you missed the subgroup that's at very high risk. Exposure may also be limited to a specific time in lifespan—you get no epidemic because the exposure occurred at the wrong time in life. Finally what happens is there is no epidemic and there's no disease because they haven't studied the people long enough. If you come back ten years later, the epidemic which you didn't see is now an epidemic.

The next question is what's the mode of transmission? We really have to understand how these diseases are transmitted to understand who's at risk. A very good example is lifetime average blood lead exposure and its relationship to I.Q. There's solid evidence that exposure to lead is associated with a decrease in I.Q. Even a small change in I.Q. points is not good. In the population level it has a major effect on the number of children who are disabled, so it is a very important issue. Now the question is where does the lead come from? You ask the automobile industry and they will tell you it's because the kids are eating the ceilings and they're eating the walls and they're getting it from the paint. If you ask the paint companies, they'll tell you it's because the kids are exposed to lead in gasoline. Now one of the implications is that we took the lead out of gasoline. We made the presumption that the lead was in gasoline. In general, the blood levels in the average child declined as lead in gasoline came down. Now studies show that blood lead levels in general are extremely low in the community, except in certain communities where people live in houses which are very old and still

have a lot of lead paint. But, in essence, the majority of the lead in the environment came from lead in gasoline. Once that was taken out, the epidemic was reduced but still existed in certain populations. This is an example of where the source mode of transmission is what we call a common source—the majority of the exposure is from lead in gasoline.

Now, I'll give you another example of where this occurs. I did a study in 1985. In this case, we asked men whether their wives were cigarette smokers. These were men who never smoked at all in their lives. We asked them whether their wives smoked and we found that if the wife smoked and the man had never smoked, their risk of getting a heart attack was twice as high as for a husband married to a woman who never smoked. This is so-called environmental tobacco smoke and it's another hot issue.

Does environmental tobacco smoke really increase the risk of having a heart attack? It has led to changes in our laws and it has led to a lot of law suits. A study took a group of individuals and they exercised them on a treadmill. The individuals had minimal coronary heart disease and at one part of this experiment they were exposed to air. In the next experiment they were exposed to carbon monoxide levels which would be consistent with the levels that you would find in a moderate smoker or in people who were in an office building or a room with moderate ventilation and half the people were smoking. And again these studies were done when a lot of people were smoking. What happens here is that when they are exposed to air, they were able to exercise longer.

You can show, in what we call a case control study, the risk. We can show experimentally the risk. Here we can begin to document how the disease is transmitted. In this case it's transmitted by exposure within the household environment to environmental tobacco smoke. Now you can say the effect is small. The real problem is susceptibility. In other words, if I have congestive heart failure and I get exposed to low levels of carbon monoxide and I happen to walk two blocks or something, I could get into trouble. And there is a paper recently published from Los Angeles showing that if I'm perfectly healthy and thirty-five years of age, environmental tobacco smoke is not going to affect my health. So you set up regulations and issues to protect a very small segment of the population, and it might be 10% of the population is at risk to be benefitted by these regulations.

Now what actually is the causal factor or agent? We have some idea of how it's transmitted, and we have some idea how to define the disease, we have some idea about what the risk is.

What we really want to know is the cause of the disease. As previously mentioned, we have two different study designs—a classical case control study and a prospective study. One of the real problems is dealing with low order risk. What is risk? Normally if I looked at toxic shock syndrome or Reye's Syndrome, or smoking and lung cancer—the risk is ten times as high and relatively easy to find the agent. Most of the exposures that we talk about are relatively low risks. Generally, these are very low order risks. People get very excited. For example, we have a big population and the increased risk can be in the neighborhood of 1.01—that is it's a risk of 1 in 100 increase in risk of something which normally has a risk of 2 in 1,000, which means you increased the risk of 2 in 1,000 to 2.001 in a thousand. This requires complex statistical analysis to understand what is going on. I can only stress that no matter how complex the statistical analysis is, the biological plausibility is often very difficult to determine.

A study was conducted on the pilots/personnel who flew the planes in Vietnam. They were the most occupationally exposed group in Vietnam to Agent Orange dioxin. There was a study in 1990 to follow up on all of the Air Force veterans who were occupationally exposed to dioxin in Vietnam. They compared the deaths of the flyers with a so-called comparison group and tried to estimate whether there's any excess mortality. There is no excess mortality. The numbers are very small, but in essence the study to date has found absolutely nothing—no evidence at all of any excess disease.

A very complex exposure study looked at women who served in Vietnam—and you could do the same thing for men—versus non-Vietnam veterans through 1987. As you might expect, the women who served in Vietnam have substantially lower mortality than the women who didn't serve in Vietnam. The rationale is that the women who went to Vietnam were very healthy, a majority of them were nurses. When they came back, they just lived longer because they were healthy people. It's called the "healthy worker effect." There was no evidence of any increased risk of cancer. So we have this study and almost all the studies that we have done in relationship to Vietnam exposure and Vietnam experience have been negative. Now why is that the case? You can say that means that dioxin doesn't cause cancer but that's pure nonsense. Dioxin does cause cancer, without any question. So why do you get these different kinds of results? The problem is that you get a negative result like that because the individual has to be exposed—because they went to Vietnam doesn't mean they were exposed to dioxin. Agent Orange had a

very small amount of dioxin. You have to have evidence that somebody got exposed to the agent of disease. Exposure to the environment is not the same. Because I live in Pittsburgh does not mean that I'm exposed to some chemical that might increase the risk of cancer in a certain group of people who live in Pittsburgh. If a specific agent results in a tenfold increase in the risk of disease, but the specific exposure is only in half of the exposed, then it would appear that the risk is only fivefold. If you think everybody is exposed, only a quarter is exposed, then the risk will only be 2.5 because the other seventy-five percent who you think were exposed weren't exposed. If the exposure is less than a quarter in the population then you find nothing even though there really is a tenfold increase in risk. You find absolutely nothing, not because the agent hasn't caused the disease but because you decided that everybody is exposed. So I would not deny that there are women who were exposed to silicone with breast implants who probably have a definable disease.

For example, as crazy as it may seem, the most interesting thing about Three Mile Island is that few people got exposed. The only diseases that came out of Three Mile Island were the psychiatric diseases. Because the people thought they got exposed to a lot of radiation, they became terrified and it affected their lifestyles. A study showed almost no exposure with any relationship of disease, and yet, we have a class action lawsuit to collect money for people who were exposed to Three Mile Island to a disease which never occurred in relationship to an exposure that never occurred. So we now have an interesting situation, we have no exposure, no disease, and a population of people who unfortunately developed psychiatric problems associated with this so-called exposure which didn't occur. We were very fortunate that we had very good control mechanisms. It doesn't mean radiation doesn't cause disease because it does—people just didn't get irradiated.

Dioxin may increase the risk of non-Hodgkin lymphoma, but exposure to Agent Orange dioxin in Vietnam is too low to identify the epidemic. So you have to improve the exposure classification and figure out who really got exposed. We convinced the powers to develop testing for dioxin in tissues and blood in Vietnam veterans. Dioxin lasts for a long period of time—the half-life is very long—and you can measure it in fat as well. They looked at veterans who were exposed, and there was a little dioxin in tissues and there was also a higher level in the flyers, but the vast majority of veterans had similar levels to the people in the population that were hardly exposed. They did some interesting studies. They asked people if they thought they were

exposed to dioxin, and looked at their blood levels. There was no correlation at all. There was no relationship. They asked the military to tell us where people were in terms of exposure to dioxin and then compared that with the blood levels. They found no relationship, and worse yet they found that when they went back the second time to the military and gave them essentially the same people, they didn't know it was the same people, and asked them to reclassify all these people. They reclassified them all the wrong way. There was no relationship between the first classification and the second classification. Congress is spending millions of dollars to try and do the same thing over again because it's perplexed by the fact that there is a negative study and no positive study. We're doing the same thing over and over again. But the reality is that we can't define exposure, and if you can't define exposure, how are you going to define a relationship to disease?

The other problem we've got is an interesting one. That is the fact that what you see and believe in is not necessarily true. Just because somebody worked at a certain company and has cancer does not necessarily mean that working there caused cancer because, in essence, you have to have some idea of what the rates are. There are two problems with this. One of them has been called "confounding." By confounding we mean that the association between a factor and a disease is more common in the people who are also exposed to some type of an agent of interest. The best example is that people who smoke also happen to drink a lot. Another example is the fact that people don't like to live near pollution. They don't like to live near an area where there's a waste treatment plant, a sewage treatment plant, a toxic waste dump or a chemical plant. The people who are healthy and upwardly mobile move out so that the social class gradient is huge. The people who are sick and have health problems can't move out because they can't get the money to move out. So what happens is that you are impressed by the phenomenon that there's a high prevalence of sick people living around the toxic waste dump and you presume the toxic dump made them sick. In reality the problem is that poor people live near a toxic waste dump and are living there because they can't afford to move out. Anyone who can afford to move out and is healthy and has a job isn't there any more. It's a very classical problem. When I was at Johns Hopkins, we spent ten years trying to improve the environment and the health status of the people who lived around Johns Hopkins Hospital, and they did all kinds of beautiful studies, and it was wonderful. The problem was that after working there ten years there was never an im-

provement. I just came back some time ago and somebody presented another study doing exactly the same thing, and the study we did in the 1960's was similar to a study that somebody did in the 1930's. Programs started in 1930, 1960 and 1990 all came up with the same results—there is no change. Why is there no change? Well it is very simple. All the people who are successful move out and don't live around Johns Hopkins Hospital any more. They moved out and they live in the suburbs. And who moves in? People who can't afford to live anywhere else. So it looks like it never can succeed. The only way you'll succeed is like they did in Washington around George Washington University. There they knocked all the houses down and there aren't any more people there, so now they're very successful.

One study surveyed people and asked them: "Do you think you were exposed?" These were farmers, and they asked them two questions: "Do you think you were exposed to DDT or a pesticide or herbicide?" Thirty-three percent said they were exposed to DDT. Then they said we're going to probe and going to ask detailed questions to see if they were exposed. The study asked more detailed questions. Sixty-seven percent of the people said they were exposed. So when first asked, only 33%, but now when you change the questions to ask them more detailed questions—67%. These are the same people—now 67% are exposed. Now you can imagine what would happen if I took my cases and I probed very carefully about exposure and in my controls I just asked for volunteer answers in a letter. I find out there's a phenomenal exposure to the chemicals between the exposed and not exposed in the cases in controls. This is an example of bias. The experience in Vietnam was the same. The experience in Vietnam was that when they asked people who got cancer: "Were you exposed to Agent Orange?" They'd reply: "Yes. It was raining down on me every day." So it looks like there is a relationship which doesn't exist.

A study we did years ago in an area of Pittsburgh, called the Lawrenceville area, demonstrated a great bias problem. The issue that occurred was that Lawrenceville had phenomenally high rates of lung cancer. There were a lot of industries in Lawrenceville and a lot have closed down. So we decided we were going to look at this and see what was going on. We compared the mortality rate in Lawrenceville with people who lived in the South Hills of Pittsburgh, and there is obviously a big economic difference. We found that the women who lived in Lawrenceville had a substantially higher mortality rate than women who lived in South Hills, and even after we adjusted to age it was a one-and-a-half fold difference. This is a huge differ-

ence. We said: "What's going on here?" People have attributed this to environmental exposures. We also compared lung cancer in Lawrenceville with the rates in the South Hills and there was a big difference and it persists over time. Why did this occur? Well, it turns out that there is a phenomenal gradient of cigarette smoking by social class. Ninety-nine percent of the phenomenon can be explained by the fact that as you go down the social class gradient smoking rates increase. It's interesting in Allegheny County that as you go all the way from judges and college professors, and all the way down to people who were unemployed, it was a perfect gradient, and a phenomenal gradient. Smoking is associated with a tenfold increased risk of lung cancer. This is an example of confounding of social class, smoking, geographics and lung cancer.

Now, lets look at problems of how many people get the disease and what the implications are. What is the attack rate or incidence of the disease? One of the most common diseases that we see is angina, a type of heart disease. The incidence, even in older people, is about six to eight per thousand per year. So if we talk about a twofold increase in risk, we're talking about a risk going from six per thousand to twelve per thousand per year. It's still not a high risk.

However, we have another interesting problem—cumulative risk. The lifetime risk of developing cancer is about 35%, and that means if you live to your full lifetime, which is about eighty, you have about a 35% risk of getting a cancer. This essentially says that a lot of people get cancer. We're always looking to find out why. So when a group of people get cancer we have this problem about people calling us and saying that there are twelve cancer patients on their street. Cancer is common. One in three people ultimately get cancer, so if they live a long time and there are a lot of elderly people in the community, there's a lot of cancer. Fifteen percent of men have the risk of ultimately developing prostate cancer. Twelve percent of women ultimately are going to develop breast cancer if they live long enough. What that means is that we have a lot of people with disease or who are going to get disease. And we have a pool of people in which we can find with disease.

I just did a study that looked at the risk of breast cancer in women who take hormones. The evidence in the literature says thirty studies show very little risk, but our study showed that there's a substantial bias related to women who do and don't take hormone therapy, and if you adjust for that bias, the risk associated with hormone exposure could really be three times as high. We may be picking out the wrong people.

This next example deals with incubation periods. You have to know the incubation periods of the disease. For example, with cancer in asbestos workers, the mediate incubation period is something like thirty-six years. So somebody can't tell you they were exposed to asbestos last week and got cancer this week and say that's a causal association. Thyroid cancer following radiation is ten years. Leukemia in Nagasaki—seven years. Leukemia in people who got exposed to ankylosis spondylitis and were radiated—six and seven years. Bladder cancer and occupational cancer—sixteen or seventeen years. You must know the incubation period, otherwise you make very silly mistakes.

Another problem we get into is the problem of women being exposed to various things and having babies who have developmental abnormalities and malformations. The organs develop during the first six weeks or so of pregnancy. In fact, the organs are developing when many women don't know they're pregnant. You cannot get a teratogenic effect from anything unless the woman is exposed during those first critical six or eight or ten weeks of pregnancy—there is no possibility. You can get a growth change—the size of the infant can be different—but you can't get a teratogenic effect. A woman comes along and says she was exposed to a chemical in the last trimester of pregnancy—it's impossible to link that exposure to an organ defect. Women are presuming that two years after they were in the Gulf War that they are having babies with malformations from being in the Gulf. It's impossible and biologically it makes no sense. Exposure has to be in a defined period of time.

Let me stress that besides the risk not being identified because no exposure occurred, you may also miss the risk because you've missed the incubation period—the risk is too short. For example, aspirin may reduce the risk of colon cancer, but it turns out you have to wait ten or twelve years to see what is going to happen. So you have to ask when the exposure was and how long you have followed these people to figure out whether there really is or isn't a risk—unless you can find some early markers of disease, in which case you might shorten the incubation period.

The last item I want to stress is susceptibility. Not everybody has the same susceptibility given exposure to the same agent. Let me give you an example of susceptibility in time. The example looks at radiation in relationship to breast cancer in women who are exposed to radiation at one point in time—Hiroshima and Nagasaki. It turns out that the women who were at risk given the same radiation dose were younger at the time of the radiation. Sixty-year-old women were exposed to three or four

mammograms and then sued because they got breast cancer due to too much radiation. There is no biological evidence for that. The risk-relationship is primarily in women who are in their twenties. On the other hand, you don't want to do mammography on women who are thirty-five and forty years of age because they may be susceptible to radiation and risk of breast cancer. So a thirty-five-year-old woman who had four mammograms and then got breast cancer may have some justification. A women sixty years of age—there's no justification—this is susceptibility.

There is a tremendous number of similar phenomena that we don't know about where the interaction of your susceptibility and the environmental agent results in disease while in 95% of the population, nothing happens. And the critical question we face for the future is: "What are we going to do about this?"

I think the one message to go out is that epidemiology is very good if there's an epidemic. If there's no epidemic and they can't prove to you that there's an epidemic and they can't define the disease, then epidemiology isn't going to solve your problem. We must say there's an epidemic, define what the epidemic is, and then ask who's at risk, how the disease got transmitted, what's the agent, and what you can do about it. But the first rule is if there's no epidemic—epidemiology is not going to work.

