Bull. Environ. Contam. Toxicol. (1984) 33:682–695

Bulletin of Environmental Contamination and Toxicology

Lessons for Living in a Chemical World

Irving J. Selikoff

Environmental Sciences Laboratory, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029

When Dr. Ayres wrote to me asking me to come here he gave as an inducement the fact that this was the dioxin capital of the world. I was wondering about this because I am on the International Scientific Committee for Seveso in Italy and when I was there they told me that they were the dioxin capital of the world. The only explanation I have for that was that there must be a great deal that is not known to allow two excellent groups to make the same claim.

There has been a major change for the better, as you all know, at EPA. Mr. Ruckleshaus has already and will, I am sure, in the future make important progress there, but he is doing it against the frustration coming from the public. When I met with him recently he was looking for a first rate scientist to join EPA. He asked my advice because he said, "Do you think they are going to join an agency that would sell the Grand Canyon and buy Times Beach?"

He was jealous of the scientists, however, because we have none of his frustrations in our ivory towers. I quickly disillusioned him and pointed out to him the frustration of physicians who now have to deal with polybrominated biphenyls and polychlorinated biphenyls and pentachlorophenol and all that. Physicians who were trained and grew up in a totally different world now find themselves unable to answer the questions of their patients, unable to answer the questions that they themselves have.

I thought, however, that I would like to spend this hour in a different way. You are going to learn everything about dioxin that is known. (Some of the studies that I see nowadays, incidentally, remind me of Peter Medawar's admonition to all of us about studies. He said that a study that is not worth doing is not worth doing well.) I would like to spend my time with you, on the other hand, to give you some perspective, some background and some understanding, rather than the specifics of what is at one inch, two inches and six inches under the soil when I do not know what is a foot away; rather to tell you where we are and, even more important, how we got here.

It began about 100 years ago when infectious diseases began to decrease, a trend that sharply accelerated in the next 15-20 years. The importance of this decline in infectious diseases can hardly be overestimated. I might remind you that last year, 1982, was only the 100th anniversary of the discovery by Koch of the tubercle bacillus. Mind you, the decline was not due to better treatment with isoniazid, penicillin, etc. The declines began long before that and probably had much more to do with social factors like nutrition and housing. In any case, the decline in infectious diseases was remarkable. Sometimes we do not appreciate how devastating infectious diseases were. For example, in the mid-1800s in Ireland when they had a typhus epidemic, 20% of all physicians in Ireland died of the disease.

Around the end of the 1900s, changes began to occur. Intellectually, these changes were even more important because, with the discovery of the fact that serious diseases, like tuberculosis, pneumonia, septicemia, childhood fever, etc., were due to specific agents, it began to be understood that serious human disease could be due to exogenous sources, things outside of us. After 1900 this idea took hold and we refined much of our information. We explored metabolic diseases. Even here we are on recent ground. Was it in 1916 that Goldberger did his work on pelllagra? That is how recently most of the avitaminoses were found. It was only in 1923 that insulin and its connection with diabetes was discovered. So most of our concepts with regard to etiology of disease are relatively new.

Osler, in his History of Medicine (Osler 1919), told about the evolution of modern medicine from the early combination of religion and magic, to the 1400s, 1500s and 1600s, when we began to pay attention to the correlations between structure and function of the body. Excellent work was done on describing the pathology of the disease. Laennec described the hard liver of cirrhosis and Bright the small kidneys of Bright's disease and so forth. Around the 1920s, Osler stated, we entered a final stage in the history of medicine, that is, the study of causes of disorders.

By 1950 or so, another change occurred. It occurred because the statisticians began to notice that while the infectious diseases were decreasing, other diseases were increasing, namely, heart diseases, stroke and cancer. This was age-specific and we had no explanation for it. It has continued to this day. From 1950 to 1978 while there has been a steady decline for all diseases -- heart diseases, stroke, pneumonia, respiratory illness, TB, etc. -- this has not been true for cancer, where there has been a small but steady increase. For all the causes of death in our country, the only one that has been increasing has been cancer. At that point, around the 1950s and early 1960s, again the statisticians came to us with rather insecure data. When looking at the rates of various cancers in various countries, there were variations noted among them. For example, esophagus cancer was high in France, Uraguay and Costa Rica, but low in Mexico, Rumania and Israel. Stomach cancer was high

in Japan, Chile and Hungary, but low in the United States, Australia, Denmark and Greece. It could have been that people in Greece were quite genetically different from those in Chile, and that might be one possible explanation. Incidentally, this geographical distribution continues. For example, cancer of the uterus is high in the United States and low in Japan, with a ratio of 30:1. Possibly Japanese women are quite different from those in the United States. Cancer of the ovary is high in Denmark but low in Japan with a ratio of 6:1. It could be that Danish women are quite different genetically from Japanese women, but as I say, it required an explanation.

The statisticians continued observing cancer incidence over time, and they found that these different groups of incidences were changing. For example, the incidence of stomach cancer went down over time from 1930 to 1975 (and we do not know why). Nor are we sure why it was not going down as much among non-white males or females as among the whites. One possible explanation was that there was a lot of genetic drift in one generation but that did not make sense; so an explanation was still needed.

The geographical pathologists then gave us additional data. They looked at migrant studies. What happens when Japanese move to the United States? There is a high stomach cancer rate in Japan and a low stomach cancer rate in the United States. When Japanese moved to the United States, their children born in our country have the same rates as all other Americans. The opposite is true for colon cancer, which is low in Japan, high in the United States. When they moved to the United States, the same high rates appeared in their group as all other Americans. Genetic drift was not a convincing explanation. Others had to be sought. In the United States, data continued to show increases in cancer rates, from 156 per 100,000 per year in 1955 for white males to 179 in 1977 with even more for non-white males. For white females it has gone down somewhat and stayed the same for non-white females. The latest data from the National Center for Health Statistics show that heart diseases and stroke have consistently gone down. From 1973-77 the drop was 8% for heart diseases, an amazing decline for a major cause of death. Stroke was 17% less, but during those years, cancer has gone up 7%.

We were faced with the question, why? Why is cancer increasing? We began looking at things exogenous to us, in our environment, that might explain the causes for these disease. The first hint came from the mountains between East Germany and Czechoslovakia. It went all the way back about 100 years ago when Harting and Hesse reported that in Schneidberg, on the German side of the mountains, they saw 150 miners who had died with what they called sarcoma of the lung. We now realize it was lung cancer. On the other side of the mountain was Joachmistal, where 50 years later exactly the same thing was found on autopsies of Czech miners. We did not know what did it until a young woman journalist gave us a probable answer. She said, "Aren't these the mines from which the Curies obtained the pitchblende that they used to discover radium?" Of course they were. She

said, "Isn't it the radiation within the mines that produces these cancers?" We knew then that we had one important explanation for exogenous cancer.

The next set of data that led us to our current understanding came from our worst public health error, our worst mistake, our failure in the 1930s and 1940s to predict what was going to happen as a result of the extraordinary increase in cigarette smoking that began at that time. I once asked Carl Hammond, my close colleague, what he would have said had I asked him in 1935 about this curious increase in cigarette smoking. He said, "Well, in 1935 I would have said 'Isn't this a wonderful thing! We are no longer are going to have cancer of the lip with clay pipes!'" Hammond, as you know, was the leader of the great American Cancer Society study that helped clarify the effects of cigarette smoking. That study was done of 1,000,000 people in one-third of the counties in the United States. All sorts of questions were asked. How long have you lived where you are? Where was your father born? How much fried food do you eat? How far down do you smoke your cigarette? How many hours do you sleep at night? All the guesses that we had at the time. What was found after the first five years was that people who smoked had much more lung cancer than people who did not smoke. In fact, there was a dose-response relationship. So here, then, was the most important cancer in men, lung cancer, with a causal link with an outside agent, cigarettes. This year we will have 115,000 deaths from lung cancer in our country (higher in men than in women, but women are catching up).

If the most important cancer in man was due to something exogenous, then we had to look for other causes of cancer. It was hard to look then and it is hard to look now at Times Beach. And it is hard to look in Missouri, and it is hard to look for needles in haystacks for things that are infrequent in any one year at any one time in any one population. Data from a large German chemical plant, an aromatic amine plant, showed that virtually everybody who worked with beta naphthyamine and benzidine died of bladder cancer. There were plants like that in Great Britain also. Yet in the population of the state in which the plant was located, the incidence was only 0.2%. Even in the population of the county in which it occurred it was only 0.1%. It would be almost impossible to detect such incidence. In the entire plant, the incidence was only 4.5%. In the department in which these substances were being used, it was 20-50%, but if you went to the specific process, of course, it was 100%. So, we have learned the importance of focusing on populations that could give us answers. If you use populations that are "diluted" you will only obtain inaccurate and misleading data.

We can use another illustration that is closer to home. Some years ago you will remember the swine flu epidemic for which the Centers for Disease Control (CDC) developed a vaccine. They tested it in 5,000 volunteers to see whether it was safe. No adverse effect was found. Yet when 42 million elderly people were vaccinated, over 200

became paralyzed with Guillain-Barre syndrome, illustrating the difficulty of depending on small numbers. This is a problem that we have, in general.

The next focus was learning to define exposed groups. Here we went back to Percivall Pott 200 years ago. Pott, as you will remember, described cancer of the scrotum in people in their thirties and, very wisely, took careful lifetime histories. He found that 20-30 years before they had worked, when they were small and were able to get down chimneys, as chimney sweeps. This was the beginning of our understanding of chemical carcinogenesis. A hundred years later, the same scrotum cancers were found in Great Britain in the mule-spinners, in textile plants. In 1915, cancer was found by painting rabbits' ears with tar and Kennaaway followed with his chemical studies, finding many such tars; this led to much of our current understanding of chemical carcinogenesis.

The second thread began with the observation of Rhen, a German surgeon, on three cases of bladder cancer. These were men who worked in a plant where there was exposure to aniline dyes (fuchsin). An etiological association was proposed. This was heresy in 1895 because we knew what caused bladder cancer. The great Cohnheim had already reported that it was due to epithelial cell rests in the bladder mucosa. However, others reported the same thing with a kind of epidemiological approach. In 1912, there were 12 deaths of bladder cancer found from 1902-1910 in Basel, a town with 56,000 males; and yet six of the 12 were in the relatively small number of dye workers in that city. The same thing was found in Frankfurt.

With this kind of information, many studies have been done since on groups at risk, focusing on specific rather than random populations. For example, we have now found that lung cancer will be increased in incidence among groups exposed to things as varied as nickel smelting, acrylnitrile, arsenic and asbestos as well as in press rooms, among roofers, talc workers, rubber workers, hematite mining and radiation. We learned how to detect agents that were causing cancer by defining the exposures in specific groups. The same cancers could be produced by a wide variety of agents.

So our first important step was taken: we learned tha we could find things that were causing cancer. This was a major advance in scientific history and had been made by about 1965. After World War II, many still conceived cancer as something that came as you got older, sort of programmed into our genes. By 1965, however, this was no longer held, not only among scientists but among the public as well. If, in 1970, 1975 or 1983 you hear of someone with a brain tumor or colon cancer, one of the thoughts that enters your mind is, "I wonder what caused it?"

We then had to meet another problem. It was too general to say, "Yes, we can find things that cause cancer." How much cancer? How much of the exposure? Under what circumstances? Here, again, we

have been looking at many of these groups to get more specific detail. I am going to talk about one that I have been able to work with, asbestos, but the problems one deals with are general.

The first case of death of asbestosis occurred in 1898. Dr. Montague Murray, a physician at the Channing Cross Hospital in London, saw a man who worked in an asbestos factory who was very short of breath, and a year later he suffocated and died. A post-mortem was done, and he had scarred lungs. Seven years later the British Parliament was planning to revise its workers compensation laws and they called Dr. Murray for testimony. They asked him, "Should we put asbestos on the list of things which could be compensable?" and he said "No." He said it did not make sense to burden that list because, he naively thought, now that we know asbestos causes disease, it is not going to occur any more. As a result of this expert testimony, asbestosis was omitted from the list of compensable diseases. We all ought to have humility in things of this type because when we make a mistake those mistakes are irretrievable.

Our next mark was in 1935 when Kenneth Lynch, Professor of Pathology at the Medical University of South Carolina, reported a very unusual case -- a case of lung cancer in a man who also had asbestosis. "And," he said, "you know, there might be an association between the two." Well, he was castigated: "How do you know it is not a random association, even if they are two rare diseases?" In 1935, incidentally, lung cancer was a rare disease. Very few people smoked cigarettes in 1900 and 1910.

In the 1940s another unusual random case was seen of an individual whose pleura, mesothelial lining of the chest, became malignant, a condition we call mesothelioma. It is invariably fatal, generally within a year. In the 1950s the same thing was seen in other people who worked with asbestos, where the mesothelial lining of the abdomen, the peritoneum, became malignant.

In order to clarify this, we began to use the new epidemiological methods that have been so beautifully developed during the cigarette smoking studies by Hammond, by Doll in England and by others -- simply to define the group. In the New York City area on January 1, 1963, there were 1,249 asbestos workers. They called themselves pipe coverers. We invited them for examination and 1,117 came. Of the 725 men with less than 20 years from onset of exposure, most had normal x-rays. After that point most x-rays became abnormal, the so called "20 year rule." It still holds very, very well. Indeed, when we made a list of all the men in this union on January 1, 1943 and then traced all of them to 1963, this is what was found: instead of the 32 deaths of cancer that were expected, 95 had occurred; instead of six deaths of cancer of the lung, there were 42. Dr. Lynch had been correct.

This was a small group, only 632 men. However, it did raise a very important question, which is with us now everywhere. We no longer

could talk about asbestos workers, no longer could talk about men working in factories or in mines. For every man in the factory, there were 500 who then used the product. So users wree a group at risk.

The whole question before us in every industry now is really the "cradle to the grave" concept: what happens to these materials after they leave the plant? By the way, by 1982 the results in this group of 632 men discussed above show that instead of 64 expected deaths of cancer, there are 238; instead of the expected 16 cases of cancer of the lung, there have been 105. One out of every five of these men, 20%, dies of lung cancer -- simply a disaster.

A much larger group was then studied, because one cannot draw too many conclusions from only 632 people. On January 1, 1967, we made a list of every single man in this small, little union. There were 17,800 men on that day. We have followed them since, and they are still under observation. In the first 10 years, by 1977, instead of 1,659 deaths there were 2,271. Instead of 320 deaths of cancer, there were 995. Instead of 106 deaths of cancer of the lung, there were 486, and 175 deaths of mesothelioma. The expected number for mesothelioma is around one out of 10,000. It almost never occurs in the absence of asbestos exposure. And curiously, a two to three times increase in cancer of the esophagus, stomach, rectum, colon, pharynx, kidney and larynx was found in this group.

I have been talking about statistics and every time I do, I feel embarrassed, because really what I am talking about is people. I thought that all of us might be reminded about the old adage in medicine, "Vital statistics are human beings with the tears wiped off."

For asbestosis you see virtually no deaths in the first 20 years, and then it begins to go up. For lung cancer, the difference between expected and observed rates -- again, very little difference until 20 years have passed, then it begins to rise. The same thing is true for mesothelioma, nothing in the first 20 years and then it begins to increase. People are exposed, as, let us say, apprentices when they are 17, 18 or 19 years old; they do not die until they are 60, 55, 45. Two-thirds are dead before the age of 65.

The ideal of critical importance is latency. We do not understand the molecular biology of latency at this time -- yet clinically, this is the important thing. The same is true with cigarette smoking. Kids beging smoking when they are 16, 9, 15, 20. They do not die at 22. They die at 58, 60, 65. We know very little of hat happens during that long incubation period. All we know really is that the disease we are seeing now is a result of past exposure, and that exposure now will result in future disease. For cigarette smoking, the importance of latency is extraordinarily clear. What we are suffering from now is our ignorance of the '40s and '50s and even the '60s.

That is why we are concerned with the chemicals of which you have been speaking. The human disease associated with vinyl chloride was not clarified until 1974. In 1950, we produced 250 million pounds in this country; in 1977 it was six billion pounds. For synthetic organic chemicals in general, in 1940 we produced one billion pounds; in 1976 we produced 300 billion pounds. Over all of these statistics lies the mantle of latency, of which we know very little in any one specific set of circumstances. The question of latency, the question of time lies over all of us, even with dioxin.

In human terms, here is an example of a man with mesothelioma who was a Naval aviator. I was asked to see him at Bethesda. When a biopsy was done, the fibers of asbestos were, of course, seen. When we took his history, we found that he was in the Navy from 1939 to 1966 as a test pilot. He entered the Navy when he graduated from Rutgers in 1939 and then, he told us, in 1937 in order to make some money to go to school he worked for six weeks in an asbestos factory. There he was 40 years later with his mesothelioma. He has since died.

Another example of latency is provided by a factory in Patterson, New Jersey, the Union Asbestos and Rubber Company Plant. From 1941 to 1945, 933 men worked in this plant. It closed in 1954. During wartime many people worked for short periods of time while waiting to go in the service, for example, or waiting to get a better job. When we traced these 933 people to the present, this is what we found: the more they worked, the more cancer they had; however, even one months work in the plant was more than enough to double the cancer risk. In other words, even brief exposure, if excessive, may be hazardous.

We recently have updated our studies of vinyl chloride workers. We have been following a cohort of vinyl chloride workers and from 1974 to 1982. The industry had cleaned up, by the way, in 1974. They did a magnificent job bringing down vinyl chloride exposure to less than one part per million. They really did a first rate job, but it made no difference. We still found that among the deaths from 1974 to 1982, one out of eight was due to angiosarcoma of the liver -- again, the problem of latency.

I would like to get back to mesothelioma now to see why this disease is invariably fatal. It has been a very rare disease in the past. At Mount Sinai, we saw three cases in 30 years from 1930 to 1960. We are a pretty big hospital, with 1200 beds, and do about 18,000 operations a year. We saw only one every 10 years. You can imagine our consternation then, when in 1960, Chris Wagner reported from South Africa that he saw 47 cases of mesothelioma in five years. Dr. Stewart at the National Cancer Institute did not believe it. He flew to Johannesburg to see the slides. They were mesotheliomas. Dr. Wagner was very clever. He had visited the relatives of these people, and found that in 45 of the 47 there had been opportunity, 30-35 years before, for asbestos contact. Most did not work with asbestos, but rather, as children, they had played on the tailings

heaps outside of the asbestos mines. One lived on a road along which donkey carts were taking bags of asbestos to the mill. This demonstrated for the first time the fact that you do not need much of a carcinogen to cause mesothelioma. You need enough to start it, apparently; then it is on its own.

With this knowledge, Molly Newhouse, a very good epidemiologist at the London School of Hygiene, then looked at the 76 cases of mesothelioma in the files of the London Hospital. Most of them were around 1960, but one dated back to 1917. She also visited the relatives and found that 31 out of the 76 had worked with asbestos. Well, that came as no surprise. What was a surprise was that nine had not worked with asbestos but simply lived in the household of an asbestos worker. These were women who had washed their husbands' clothes when they came home from work. Eleven had simply resided within a half mile of one of the asbestos plants in London. This again demonstrated that you did not need much of a carcinogen to initiate the process. We have since been looking at the wives and children of asbestos workers who had worked in the UNARCO plant. One-third have abnormal x-rays. They feel fine, they are not short of breath, but so far 1% of all deaths more than 20 years after onset of the workers' exposure have been due to mesothelioma; and lung cancer rates have been about double expected rates.

As an example, we treated a very nice young woman whose father had died of lung cancer; her mother had died of mesothelioma. Following this, she had been x-rayed and had a normal film. Three years later, she developed a mesothelioma and she came to us because she did not want to die. She was 35 years old, she had three children. Her husband was bitter and hoped that we could help her. We could not. She developed tracheal compression and died. While she was with us, she told us her dad would come home from the shipyard and her mother would take his overalls and shake them out while the kids were playing on the floor nearby. There she was, 20 years later, with mesothelioma. So we learned the next thing: the importance of low level exposure.

We recently did a study in Michigan where there had been polybrominated biphenyl exposures. We took serum from children who were breast fed and children who were not breast fed. Forgetting about PPBs for the moment, we looked at DDE, a derivative of DDT, and PCBs. Mary Wolff in our laboratory showed that children who are breast fed have considerably more of the DDE and PCBs than children who are not breast fed. So there can even be low level exposure to these chemicals as a result of breast feeding.

Our next piece of bad news came from a very good young physician in Davenport, at the Royal Navy dockyard there. He was the medical officer and, in 1968, he reported five cases of mesothelioma. Not one was in an asbestos worker -- rather, a boilermaker, a fitter, a laborer, a shipbuilder and a welder. Immediately, we knew the import. By 1973, there were 55 cases; only two in asbestos workers,

and the rest in other trades -- electricians, boilermakers, welders, etc. One look at the inside of a ship and you know why. Everyone inhales the next one's dust. For this country, this was a disaster because when we took over shipbuilding and ship repair for the free world in the early 1940s, we employed four and a half million Americans in our yards, with virtually no precautions. In November of 1943 we reached 1,750,000. About 10% in some yards were women. Remember Rosie the Riveter? At the present time, the calculations are that shipyard cancers as a result of these uncontrolled exposures, primarily during wartime, now reach somewhat over 2,000 excess cancer deaths each year. Over 800 mesotheliomas are occurring each year as a result of our past inadequacies in shipyards.

Because of this, we looked at all sorts of trades. Nobody told the brake repair people to vacuum out the dust, which contains about 50% asbestos, instead of blowing it out. Nobody told the drywall construction workers that spackle and taping compound had about 15% asbestos, nobody told the steamfitters or plumbers. There are three and a half million Americans in our construction industry. In the 1950s, when they began to fireproof steel, they actually sprayed asbestos into the air. This spraying occurred in such diverse places as the World Trade Center in New York and in Missouri schools. This is important because of the environmental persistence of these materials, a problem you are very much aware of with regard to dioxin.

We now come to the next piece of information that we badly needed, because none of us live in an environment in which there is only one exposure. We do not live in pristine worlds in which there is only one chemical or one dust. We will go back to the example of cigarette smoking and lung cancer. The question became how smoking interacts with asbestos.

In the group of 370 men who were still alive on January 1, 1963, we took smoking histories. There were 87 men who never smoked cigarettes and we did not expect many deaths among them. There were 283 who did smoke and there should have been three deaths of lung cancer by 1967. In any event, not one of the 87 died of lung cancer. When they died, their lungs were examined and were found to be full of asbestos. They did not die of lung cancer. On the other hand, instead of three deaths among the cigarette smokers, there were 24. So the problem came up of multiple factor interaction.

When we did the study of the 17,800 men in the asbestos union, we again took smoking histories. For those who did not smoke and did not work with asbestos, the rate was 11 per 100,000 per year. For those who worked with asbestos but did not smoke, it was five times as much, 58. Five times a very low figure is still very little. On the other hand, for those who smoked but did not work with asbestos it was 122, and in those who smoked and worked with asbestos it was 601 per 100,000, an this extraordinary increase. These rates, by the way, are different for every tissue. It was true for lung cancer,

for the esophagus and for the larynx. It was not true for mesothelioma and it was not true for the remainder of the gastrointestinal tract. Each tissue did or did not react to this combination. For toxic chemical waste sites, multiple factor interaction is obviously of tremendous importance. We do not know the chemicals in most of these sites and yet the potential for multiple factor interaction is great. Incidentally, we now have alive somewhere around 20 million workers who were exposed to asbestos by 1980. We expect somewhere around 9,000 excess cancer deaths a year as a result of our inadequacies of the past.

Getting back to Montague Murray in 1906 in Britain, with the workers compensation: I do not think I have to tell you what is going on now with litigation. Our courts are clogged. A few weeks ago the Rand Corporation published a study of 25,000 suits, of which 3,800 were settled, mostly out of court. There was $400 million in awards. The plaintiffs got $235 million, their attorneys got $165 million. At the same time, the defense legal costs were $565 million. One billion dollars was spent. Three-quarters went to lawyers.

We are beginning to learn the causes of cancer, then, and extraordinary progress has been made. Yet, among scientists there has been disappointment. We had belived that we wore white hats back in 1900, when we found that diptheria was due to a bacterium, then we knew what to do. When we found the tubercle bacilli in milk, sewers were installed and clean water supplies were provided. Information was utilized. Now, we find the situation is different. Now, when a cause of cancer is found, all sorts of questions are raised. You might think, "Well, in 1900 there was no trade association on behalf of the tubercle bacillus, there was no company manufacturing the cholera vibrio." And yet, there has been disappointment. You have to the industry people to criticize. I have often heard the quotation "If you must walk in the woods, you have got to feed the mosquitos." I am not sure that is right. I think industry should question us all the time.

There are major problems that have nothing to do with industry. For example, not only industry but scientists in general, especially our regulatory agencies, are very reluctant to apply laboratory observations. We do not how to apply them. For example, how is Renata Kimbrough's work going to be applied in terms of what she found with dioxin? Would we take what she has done and use it to the hilt in terms of carcinogenicity, in terms of birth defects and so forth? For at least a half dozen agents the carcinogenicity of the substance later found to be cancerous in humans was first seen in animals -- DES, mustard gas, vinyl chloride, aflatoxins, bischlorolmethyl ether, estrogens, 4-aminobiphenyl. When you look at animal data there will always be arguments for uncertainty; and, if there is uncertainty, we fail to act. There may be human experience, but no animal data. Let's not act. There may be animal data but inadequate human data. Let's not act. There may be human and animal data but they are different tumors. Experimentally, with vinyl chloride,

we found zymbal cell tumors of the ear. We did not act until, in humans, we found angiosarcoma of the liver. There are residual problems that are not resolved.

The whole question of species differences has been a bitter lesson for us. Remember the terrible phocomelia that was found in children whose mothers had taken thalidomid in Great Britain and in Germany? When we looked at the animal data, we found that humans are 700 times more sensitive than the hamster in which it was tested. We have 230 chemicals that are now known to produce cancer in animals to which humans are exposed, yet these have never been studied in humans. This is a vast array of scientific information that is not used. One basic problem that we have, and I think we are going to live with it for the rest of our lives, is that private industry has responsibility for public health.

Ernst Mayr wrote an extraordinarily valuable book, published last year, The Growth of Biological Thought, in which he discussed scientists and their objectivity. He said that objective scientific research often leads to conclusions but they are value-laden at the same time. Judge Baselon believes that we just have to let it hang out. Speak about your value choices, say what you are doing. What are your asumptions? The American courts have to insure that these value choices are not abdicated to experts who are insulated from political and social accountability. A proposal has been made that the EPA build its new offices in Times Beach and that they should build homes for the administrators there -- playgrounds, sports fields, expense account restaurants and all the usual Washington amenities. They thought that all EPA lobbyists should be there to be close to the decision-making process. I do not think this proposal was serious but it gives you something of the sense of the exasperation that exists.

I think that Judge Bazelon was wrong when he said he felt that the scientific revolution has led to specialization and expertise beyond understanding of judges and juries. I do not think that is the whole answer. Rather, I believe that the agencies dealing with the consequences of science and technology are simply not giving us the data we need. They have not sought the data, basically, necessary for evaluation. The judges seem to think the scientists know and are hiding the data; however, we do not know. In very large part, we do not have information. We have some, from which we extrapolate the best we can. The Chicago Tribune, I thought, said this very well when they talked about Dr. Falk's report: they summarized his feeling that medical sleuths are now in a world of unknowns, and I agree with them. For example, if a father goes to a doctor and says "My child has kidney trouble. Should she drink the water?" The doctor does not know how to answer that, he simply does not know. Or a physician asks, "My patient operates a bulldozer at one of the toxic waste sites. Which test should I do when I examine him?" The CDC did standard SMAs and CBCs and urinalysis; that is inadequate. These tests were never designed for subtle biological effects such as

those we now see. They were designed for people entering the hospital with heart attacks, with cirrhosis, with overwhelming diabetes, with kidney failure. SMAs were designed for hospital patients. They were not designed for measuring P_{450} and P_{448}. They were not designed for measuring urinary nucleosides, for measuring urinary porphyrins, for measuring chromosome aberrations, for measuring immunological defects. These are the things that we now can do and which we are basically not doing. There are still others that should be done. The Chicago Tribune referred to Dr. Falk as saying that he could not tell precisely what dioxin would or would not do. He could only say what was happening in animals.

There has recently been a study that some of you are going to hear about. It was a study done by Dow Chemical. (Among the chemical companies, there are very few that have better expertise and better scientists than Dow.) The study is going to be quoted to as showing that they did not find anything among their workers exposed to TCDD. I think it is worth looking at that study in detail. What did they do? They took the routine company screening program, which was a questionnaire and blood chemistry done routinely for the annual health examinations of their workers. Then they took the group medical insurance claims and examined those from 1976 to 1978. That means if you got sick and left the company before, you are not in the study. The controls were other men at Dow with all kinds of other exposures -- exactly what we would not do in a scientifically sound study. Routine chemistries were done; they simply took the results of the studies that were in the files. The group insurance claims only included those eligible in 1978. So if you died of whatever in 1977, 1976, 1975, you were not included: only hospital care was included. Physician office visit diagnoses were excluded. The diagnoses were made "by a registered nurse" and there was no validation of the diagnoses. They were either right or wrong, and nobody knows. There was only one observation per individual allowed, and nothing is said about which one was selected. Only a minority participated in the medical screening program. Among the trichlorophenol workers only 27 of 61 and among the 2,4,5-T wokers only 87 of 204 participated. If a study like this were brought before the NIH, the study section would turn it down. Some tests did show differences between the exposed and controls, but they were not regarded as clinically significant. So the Dow study on health outcomes was limited to active or recently retired workers. Those who left the company for reasons other than retirement could not be studied. "Inferences from the present study concerning the health status of former employees must be drawn carefully, owing to possible retirement of former employees on the basis of health." (I would certainly say that.)

Now let's go back to Dr. Rhen. We are still importing benzene and beta-naphthyline into the United States. With regard to Dr. Pott, last year they were still using coal tar pitch all over the United States on roofs. We are still advertising for people to become chimney sweeps. The EPA in the October 1983 issue of Environmental

Science and Technology of the American Chemical Society stated: "EPA officials announced that the amout of hazardous waste being generated in the United States is almost four times higher than previously estimated." The previous estimate was 40 million tons. It is now considered to be 150 million tons. An additional 300 million tons is being managed by the industry producing it, mostly by two methods: underground injection and surface impoundment. Ruckleshaus then concludes: "The scope of the hazardous waste problem is staggering." Let me show you how staggering. He projects 22,000 sites. He has a priority list of 546 with some type of action, somebody visiting them, in 349. Federal funds have been provided for 146, and removal has been completed in five. So I think his conclusion is correct. He has an immense problem. How immense? Let's take one, the Woburn, Massachusetts site, 225 acres. There are 22 million cubic yards. The EPA estimates it will cost $200-300 per cubic yard, which is around $4,400,000,000 for that one site. The Superfund all together has $1,600,000,000.

We have been talking science, and might now turn to the real world. The real world is this: what we have been talking about is basically not a scientific problem. Nick Ashford has called this a transscientific issue. This is largely because there is absent epidemiological evidence. We have to extrapolate from high dose to low dose, we have to extrapolate from animals to humans; there is this extraordinary problem of latency and there is disagreement on scientific interpretation. We do not know the significance of benign tumors nor of mutagenicity in in vitro studies. We do not know the importance of initiation and promotion and enzyme induction.

What do you do when you do not know? These are no longer scientific problems. They are social problems, they are political problems, and they are problems in which the scientist can only make a contribution, which, however necessary, is not sufficient.

I would like to close now with a test for you. On October 29, 1983, I received a call from Bruce Karrh of DuPont. They had just finished a study on titanium dioxide. They found that at certain levels it produced cancer in animals. There was squamous cell carcinoma of the lung in about 10% of the animals. Fifteen percent had adenomas. The significance of this is that titanium dioxide replaced lead in paint around 1946. It is now everywhere. It sheds, so that it leaves a clean layer underneath all the time, and you always have nice, clean walls. The dust in all rooms now has titanium dioxide. It is found in almost all papers. It is a wonderful metal that keeps light from penetrating. We all have titanium dioxide in our lungs now. It will, at rather high levels in airborne studies, produce cancer of the lung in the rat. What should we do with titanium dioxide?

REFERENCES

Osler, William. A concise history of medicine. Abbott, New York, 1919.