TOXIC COMPOUNDS IN INDUSTRY

Epidemiology in Studies of Occupational Health

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Recently someone asked the head of the Bureau of Epidemiology of a large government regulatory agency what was epidemiology and an epidemiologist? He said, "Epidemiology is nothing more than common sense and statistics. We don't need any special training." That was an interesting response, and I'd like to explore with you the extent to which it is true.

More formally, epidemiology is a study of the distribution and the determinants of diseases in man. I want to underscore that last word "man," because this is what distinguishes epidemiology from other scientific efforts relating to cause and effect. Generally, it's not possible to experiment with man in the same way as with animals, so we must be satisfied to observe man within his environment. Essentially, we do not manipulate man; rather, man manipulates himself and the epidemiologist observes what happens.

Now I would not disagree that epidemiology is common sense, and I would hope most disciplines include an element of common sense. In 1854 there was a cholera epidemic in London and a physician named John Snow made some observations. To us they might seem like common sense observations, but at the time no others had made them. He observed the London epidemic was confined largely to people who purchased their water from one of the two water companies that served London. These two companies were in competition; one difference between them was one water company drew its water from the Thames below the city of London, where it was quite polluted, and the other company drew water upstream of London, where the water was cleaner and didn't contain London's sewage.

Snow observed that people who drank water from the company drawing from the polluted area of the river had a cholera death rate of 5 per 1,000 in the year 1854. By contrast, those people who drank water drawn upstream of London had a death rate of less than 1 per

1,000, a five-fold difference. Formally, epidemiologists call this the Method of Difference, and that seems like common sense. The difference had something to do with the water quality, and this made sense in the context of John Snow's observations.

Snow also found a section of the city where people could draw from one water company or the other. The water companies in some parts of London competed head on--they had pipes going down the same street, so that one might choose to buy from one company or the other. He studied those sections of London separately and noted the cholera death rate in these sections was just halfway between the death rate of sections of London that had clean water and that of sections that had dirty water. He compiled a table showing that in what we'll call the dirty water section, death rates were 5 per 1,000 in the mixed, half dirty - half clean section, 2.2 per 1,000; and in the unpolluted section, with people drawing water from the non-polluted section, about 1 per 1,000, a definite variation. Epidemiologists would call that, the Method of Concomitant Variation. It means that the more of what you believe to be the agent is present, the greater is the response. That's a level of epidemiological evidence, and it is also common sense.

Finally, Snow verified all these observations by looking at a single street where he noted two factories. One factory was making percussion caps, employed 200 workers, and in a single year had 18 deaths from cholera. The other was a brewery that employed 70 workers and had no deaths. He talked to some people about the brewery workers, and he said about one, "Mr. Higgens believes that these men don't drink water at all."

This is a form of replication. If one finds the same thing over and over again, there seems to be an element of truth that would not be present if one observed it once but did not observe it under any other condition.

So there are three methods, the Method of Difference, Method of Concomitant Variation, and the phenomenon of Replication. They all involve common sense. Another thing: John Snow didn't know what the agent was that caused cholera, but by using these methods, he figured out how to stop the epidemic: by changing the water supply, the incidence of cholera could be modified.

Now I would like to project this idea into the cancer problem. This does not seem as simple as the cholera problem, with disease following exposure and a short incubation period. Rather, we may have long exposure and a long incubation period with appearance of the disease much later, perhaps 20, 30, or even 40 years later. This poses serious logistical problems in conducting epidemiologic studies, and I would like to illustrate them.

Figure 1 shows that it takes a long time for cancer to appear. It also shows something else, that the pattern of appearance is fairly predictable. The figure demonstrates the incidence of leukemia following the explosion of the atomic bombs at Hiroshima and Nagasaki in 1945. Note there was some excess of leukemia in 1946, but not much above what might have been expected. There was a peak incidence of leukemia somewhere after 1950. Then the incidence began to decline, and after about 20 years or so, it fell back to normal.

This illustrates how a single exposure to radiation might affect the incidence of the disease. Not everybody got the disease right away, some people got it sooner than others, but there was a kind of modal period...a period when more people got it than in any other period.

The distribution of leukemia cases was close to a mathematical function called a "log normal distribution," which is shown in Figure 2, which represents exposure to a single dose of asbestos and the time to appearance of a tumor. Here, the mediam time is 24 years, but it is possible for some cases to show up within 6 years. It is also possible for some cases not to show up until 60 years. We fitted the log normal curve to a lot of data, and it seemed to be a pretty good predictor. If one knows the mathematical function that describes some phenomenon, it is very useful in research terms.

Figure 3 adds another dimension, and that is the fact the time it takes for a tumor to appear is dependent upon the intensity of the dose. For a very mild dose, the tumor might not appear for a very long time. For a very severe dose, the tumor might appear rather quickly. The figure shows a series of log normal curves. These incorporate two additional ideas. The first idea is that the amount of disease is directly related to the dose. We say this is

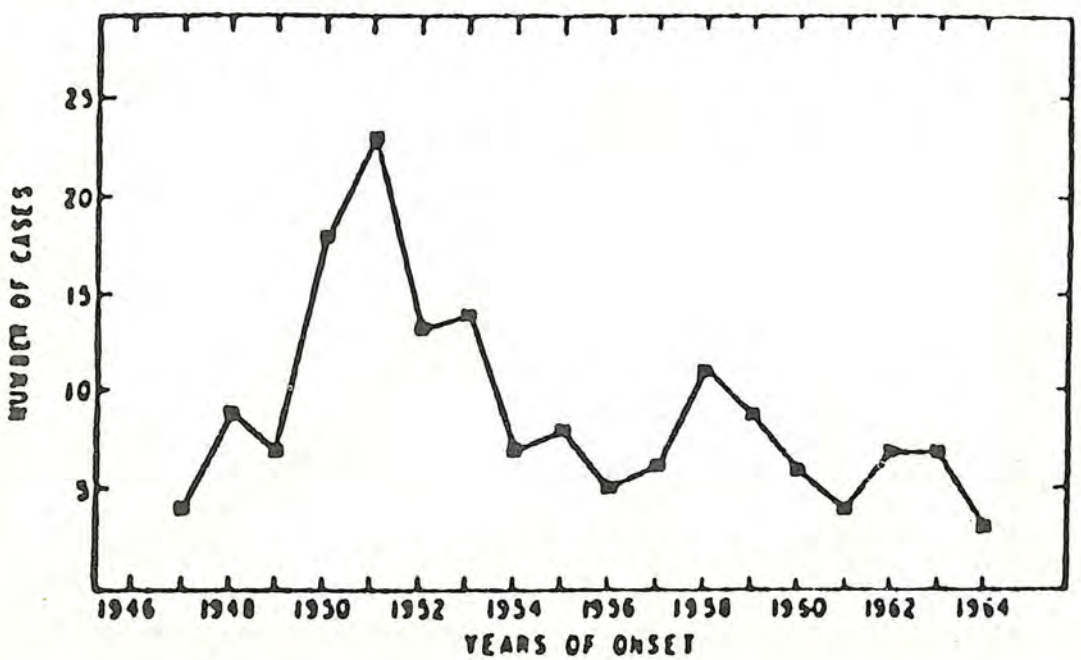

Figure 1. Incidence of leukemia at Hiroshima and Nagasaki

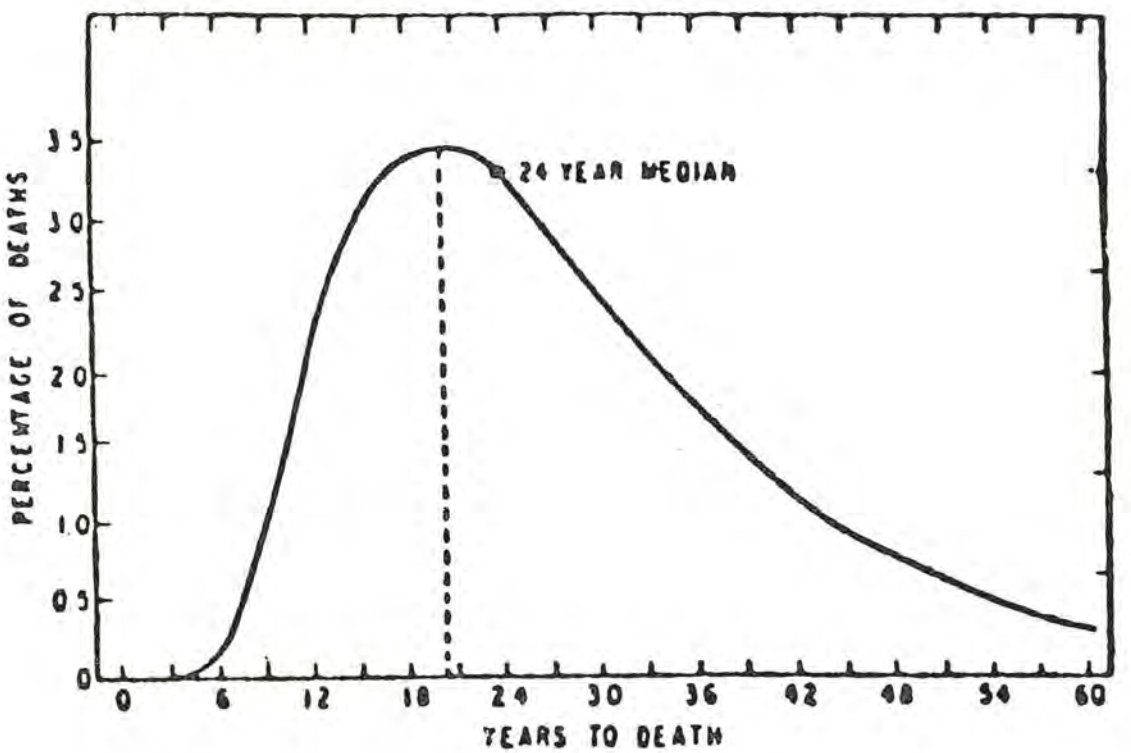

Figure 2. Respiratory cancer resulting from a single exposure to asbestos.

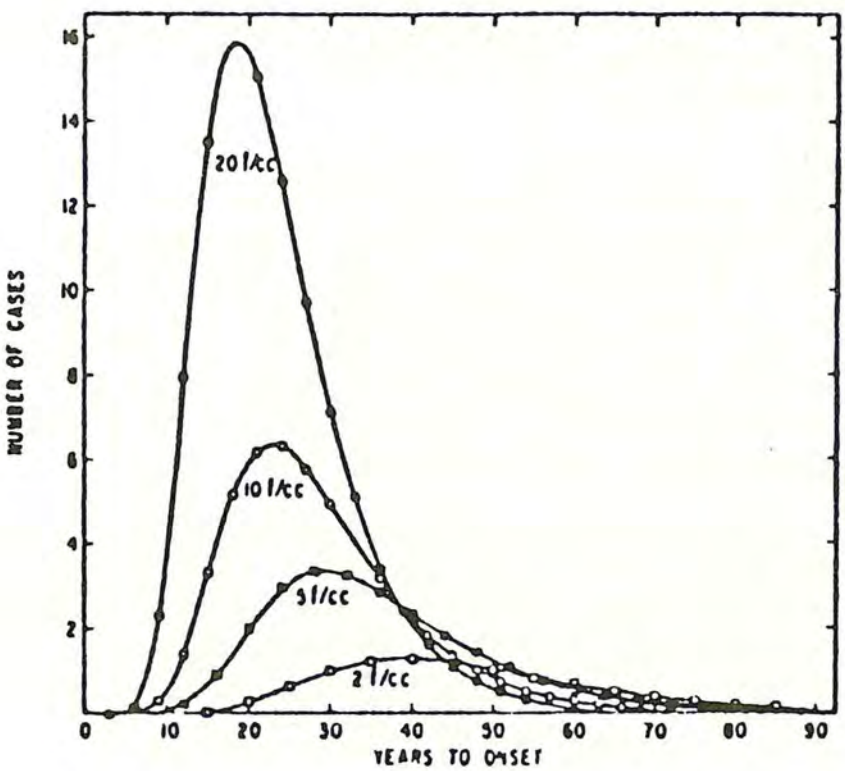

Figure 3. Respiratory cancer resulting from single asbestos exposure at 4 level.

a simple direct linear relationship. Secondly, the time to tumor is a function of dose. This was discovered about 1967, and it appears the function is one over the cube root of dose -- the inverse cube root of dose. In the asbestos example, then, for exposure to 1.5 fibers per cc, large numbers of tumor would show up after about 80 years, and some could appear as late as 120 or 140 years after the exposure.

The foregoing example is very theoretical, but the practical meaning is that not many people are going to be concerned about tumors that show up 80 years after the exposure, because they will not be around. But it adds another dimension to the business of setting threshold limit values, a warning that we might have to consider a dose level where the tumors would show up in 150 years. It is important to realize in studying the epidemiology of cancer that we may have long latent periods, determined to some extent by how intense the exposure is that we are investigating.

Returning to the Method of Difference, I began to get involved in industrial epidemiology 20 years ago, and some of the first data I received had to do with death rates in chromate workers and oil refinery workers as shown in Table 1.

Table 1. Lung cancer mortality experience for U.S. chromate workers* compared with oil refinery workers+

	Annual rate per 100,000	
	Age $\leq$ 50	Age $>$ 50
Chromate Workers (1930-47)	197	480
Oil Refinery Workers (1923-38)	5	22

*Based largely on group life insurance records in six plants - 11,019 man-years.
+From Machle and Gregorius, 1948

Here, we are dealing with deaths from lung cancer. One can see the magnitude of the difference is simply overwhelming. The chromate workers under 50 years old have a death rate of around 200 per 100,000, and the oil refinery workers had a death rate of 5, a forty-fold excess. It is almost as bad if one considers ages 50 years and over. This is a 1948 study, one of the early observations on industrial cancers.

The Method of Concomitant Variation is very important in occupational disease epidemiology. This involves working with industrial hygiene people to try to find out what were the different exposure levels. I think that is one thing very much lacking in many studies today and certainly in the old studies. There were no estimates of what the exposures were that caused the observed response.

Table 2 is from a study we did on asbestos workers. These people go back to the 1920s in terms of their exposure, to fairly high levels. The purpose here is to show there is a dose-response relationship, and the Method of Concomitant Variation suggests there is a cause and effect relationship.

Table 2. Relative risk for respiratory cancer among retired asbestos workers

Years since first exposure	Mean dust level	
	10 mppcf*	10 mppcf+*
Under 20	1.2	3.1
20 - 29	1.8	3.6
30 or more	2.8	4.7

* Millions of particles per cubic foot

Table 3. Observed and expected respiratory cancer deaths and standardized mortality ratios by intensity and duration of exposure

Intensity of exposure (μg/1 urine)	Duration of exposure					
	Under 25 years			25 years and over		
	Obs	Exp	SMR	Obs	Exp	SMR
50 - 199	2	2.1	95.2	10	3.6	277.8*
200 - 349	4	1.5	266.7	8	2.2	363.6*
350 and over	3	0.5	600.0*	5	0.6	833.3*

*P<.05

To demonstrate this with another subject. Table 3. (above) shows some data on smelter workers who were exposed to arsenic. Notice in the lower right hand corner the very high relative risk for people that had urinary arsenic levels of 350 or over, and who were exposed for a very long time. Here is very clear evidence of a dose-response relationship, whether we measure dose as the average intensity of exposure or as duration of exposure. In

fact, there are almost perfect linear relationships, and either variable is a good predictor of the amount of disease that will be observed. Note the numbers are moving in a systematic way across this chart, from the upper left hand corner to the lower right corner.

A very important part of the epidemiologic method is to show there is a dose-response relationship. That has been one of the prime pieces of evidence on cigarette smoking, that the more you smoke, the higher is the risk of lung cancer. This is a very important leg upon which to base evidence of cause and effect relationships in any kind of population and particularly an industrial population.

Considering again the Method of Consistency, Table 4 shows results of all the epidemiologic studies that were done on asbestos in North America which could be compared. They all show an excess in relative risk. Unfortunately, all were done a little differently, and I had to do some correction of the data. In the last column, however, after making the corrections, we find all show the same thing--that the excess risks are high and not dissimilar.

Table 4. Relative risks and corrected relative risks for respiratory cancer for 6 studies, 20 years at entry since first exposure

Reference	Relative risk	Death certificate + corrected	Death rate corrected
Selikoff	9.2	7.6	6.2
Enterline	3.0	3.0	2.9
Cooper	7.8	7.8	6.7
Wagoner	2.8	2.8	3.6
Selikoff	8.2	6.8	5.5
Selikoff	5.8	4.7	4.7

Finally, a word about what cannot be done. One thing we cannot do with epidemiologic studies is prove an agent or substance does not cause disease. All we can do is find out whether there is an excess of the disease given the conditions under which workers are exposed. I am currently engaged in a study of the health of fibrous glass workers. Average concentrations of respirable fibers in fibrous glass production facilities are very low, below even the lowest of the government's proposals for exposures to fibers.

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OCCUPATIONAL SAFETY AND HEALTH SYMPOSIA 1977

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Cincinnati, Ohio 45226

June 1978

For sale by the Superintendent of Documents, U.S. Government
Printing Office, Washington, D.C. 20402

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Contract #210-77-0088

DHEW (NIOSH) Publication No. 78-169