EPIDEMIOLOGY for the TRIAL LAWYER

By
Eugene C. Brooks, IV.

I. Introduction

Epidemiology is defined as the study of the relationships between various factors that determine the frequency and distribution of diseases in human and animal populations.[1] The purpose of epidemiology is to better understand disease causation and to prevent disease in groups of individuals.[2] Epidemiology assumes that disease is not distributed randomly and that identifiable subgroups are at an increased risk of contracting particular diseases.[3] Epidemiology is a science which utilizes statistics and probabilities in determining whether a particular exposure is significantly associated with a disease. Epidemiology is utilized by the Center for Disease Control in monitoring the health of the world's population. Epidemiology is also used by the FDA in approving drugs for and in withdrawing drugs from the market. Epidemiology has been used to identify the adverse health effects of asbestos, cigarettes, childhood lead poisoning and numerous other exposures.

Epidemiology can be useful to the trial lawyer on issues of disputed causation in both toxic and traumatic injuries. Causation, particularly in the field of occupational disease and pharmaceutical injury, can be proven to generally occur with epidemiology. Proving that an exposure can cause a disease or injury is the first step in proving specific causation to an individual. Causation of a disease to an individual may also need a medical opinion specific to the individual. Epidemiology provides a basis on which doctors may rely in forming their opinions of causation to a specific individual.

Epidemiology is one of the touchstones now used by the federal courts in determining whether there is an adequate scientific foundation for allowing an expert witness to testify on the cause of particular injuries.[4] In *Daubert*, the U.S. Supreme Court modified the prior *Frye* test on whether certain scientific evidence was admissible. The Courts now examine the scientific methodology supporting the expert opinion instead of looking exclusively at

whether a particular scientific theory is generally accepted by the scientific community.[5] The Federal Judicial Center has published a manual which addresses the admission of scientific evidence. The manual addresses epidemiology in more detail than this article.[6] Georgia has not adopted the *Daubert* test and has left the resolution of questions on scientific validity to cross examination.[7]

With all of its limitations, epidemiology can be a useful tool when its limitations are understood. The purpose of this article is to simplify the science and explain what epidemiology can and cannot do. Epidemiology is a word that is difficult to pronounce, but it should not be intimidating. An understanding of epidemiology is useful in screening cases.

Epidemiology uses statistical comparison between two groups, an exposed group and a control group. The exposed group is composed of people who have been exposed to the suspected injurious substance; the control group is not exposed. The rate of injury is then measured between the two groups. The rates in the two groups are then compared statistically to determine if the difference is greater than would occur by chance. The findings are referred to as statistically significant if it is unlikely that the difference occurred by chance.

There are biases and confounders which must be acknowledged in determining whether the conclusions of a particular study are reliable. There is no perfect epidemiological study. There are only those studies which are less flawed than others. The methodology of the studies must be examined to determine their value. Some studies are flawed to the extent that they are unreliable. Studies with good methodology and less serious flaws may still be reliable. Studies performed with good methodology should be viewed with other relevant studies. The entire body of literature should be evaluated for consistency of findings across different groups of persons with common exposures occurring in different geographic locations reported by different investigators.

Often there is not a large body of literature to review. Epidemiology is cumbersome and slow. Studies often take years to perform. The CDC and the FDA do not often wait for a large body of epidemiological literature to develop if a disease is developing in the population. A single well done study can establish a cause and effect relationship. However, when multiple studies are available, such as in studies of asbestos exposure and childhood lead poisoning, more confident opinions can be formed.

Epidemiology has been criticized as an insensitive indicator of disease since relatively large numbers of persons must develop disease before the disease or injury will be identified by a study.[8] By the time epidemiology identifies a cause and effect relationship, the injury is usually widespread and dramatic. The insensitivity also results from the focus of the study and whether the right definition or criteria of the disease is being utilized in the study. For instance, if the exposure under scrutiny is cigarettes and the disease definition for cancer under study is foot cancer, then the study will likely find that there is no cause and effect relationship between cigarette exposure and cancer.

A statistically significant relationship demonstrates an association between the exposure and the injury. The association may be strong or weak. Some doctors may believe that a cause and effect relationship between the exposure and the injury has been proven with a particular study while others may disagree with the strength of the findings. Differing interpretations of a study or group of studies are debated in federal *Daubert* hearings and during expert cross examination.

II. Epidemiological terms and methods

A. Comparison Groups

There are several different types of epidemiological studies. A cohort or longitudinal study is an investigation that studies groups over a period of years. The investigators gather data from two populations over time. This is an expensive method of study. A less expensive and more commonly used study is a cross-sectional study. A cross-sectional study gathers data from two groups at a set point in time and studies the differences at that one point in time.

In measuring two population groups, epidemiology requires that the same methods of testing and reporting be used between comparison groups. The methodology is better if the two groups are examined by the same investigators. It is not good practice to place much emphasis on the comparisons of groups from different studies. It is also not good practice to use a historical control group, one measured in the past, for comparison with a present study. This is because the two groups may have been measured by different criteria or the findings may have been reported differently by different investigators. The use of data in one study as a basis for comparisons with a group in a different study can easily lead to incorrect inferences. Good practice requires that the control and exposed groups be subjected to the same testing and reporting methods. Otherwise, the comparison would be between apples and oranges.

For instance, a 1985 governmental study reporting that a group of persons had a particular rate of disease should not be used as a control group for an epidemiological study in 1998. A comparison of those measurements to a group measured in a different study done by different investigators for purposes of identifying a statistical relationship would be bad methodology. Different investigators use different methods of measure and different criteria. The data used for determining a statistical comparison should all be from the same study. The data should be self contained in the study. Otherwise, the measures are uncontrolled and the quality of the comparisons is unreliable.

Additionally, it is best if the investigators of a study are blinded to the exposure. This means that the investigators are unaware of who has been exposed when they perform any tests on the group members. All tests are administered to everyone in the same way.

B. Bias

In interpreting epidemiological data, different biases must be considered. The presence of "bias" does not destroy the value of a study. However, the interpreter must consider biases when interpreting the data presented in a study.

There are four general types of potential bias. They are (1) sample distortion, (2) information bias, (3) confounding bias and (4) cause-effect reversal bias. Not all of these bias are present in each study. The degree to which any are present in a study is important for your analysis of the strength of the study. Epidemiologist refer to a study finding a strong association as "robust".

Sample distortion basis primarily involves sample distortion and survival bias. Sample distortion occurs when the people being studied are not representative of their group. For instance, if the study is attempting to determine whether a solvent exposure in a factory of 1,000 workers causes headaches and only 100 people with headaches appear for testing, then the sample would not be representative of the group of 1,000. The severity of the sample distortion would create a finding of 100% headache rate from exposure rather than the more accurate lower rate.

Survivor bias is the result of persons leaving employment or otherwise avoiding injurious exposure after they are ill. For instance, a cross-sectional study has a survivor bias which underestimates the occurrence rate of any caused injury. This is because only those persons who can withstand the exposure or are better adapted to the exposure will still be present at the time the cross-sectional study is conducted. The most susceptible persons to injury will have already died, left the occupation or learned to avoid the exposure. A longitudinal study would have caught these susceptible persons within its study and so would not have a survivor bias.

Survivor bias does not equate with unreliability. It is simply a fact which must be used in tempering any conclusions drawn from the data. All cross-sectional studies have this bias which underestimates the cause and effect relationship. Therefore, if a statistically significant relationship is identified in a cross-sectional study, it is likely that the relationship is actually higher than reported in the study. Also, a finding of no statistical significance in a cross sectional study should not be interpreted as proving that no cause and effect exists. The only conclusion from a single negative cross sectional study which can

truthfully be made is that no relationship was identified in the particular study.

Information bias is the result of gathering wrong information. The two types of information bias are non-systemic (imprecision) bias and systemic bias. Non-systemic bias is the result of gathering imprecise information. In many instances, this bias is unavoidable. For instance, it would be very difficult for an asbestos worker to exactly quantify how much asbestos he was exposed to. Also, tests such as E.M.G.'s and E.K.G.'s all involve some imprecision since the exact results of such tests on a person are rarely exactly duplicated. In many studies, the imprecision of the exposure or the degree of disease may be inconsequential. In any event, this bias can only underestimate the association between exposure and disease. Imprecision only weakens the association since either the exposure or the injury are not fully measured. Exposure and injury specifics that are not measured do not enter into the statistical analysis of the gathered data.

Systemic bias can cause both underestimation and overestimation. The most common form of systemic bias is recall bias. Recall bias is the result of people who have ill health and who are more likely to recall exposure to hazards than healthy people. Also, ill people are more likely to recall various health problems they had at particular time. A healthy person is less likely to remember possible harmful exposures or actual adverse health problems he had in the past.

Information bias can best be controlled with objective measures of exposure and illness. In childhood lead exposure studies, the blood lead level is often used to quantify exposure; standardized neuropsychological batteries are used to measure the injury. In the recent fenfluramin and dexfenfluramine (Redux) studies, the measure of exposure is the dose drug and the injury is measured by echocardiograms.

Confounder bias can interfere with a study's findings. One of the primary efforts in a study is to have two comparison groups that resemble each other in every way except the exposure. If the groups differ in respect to additional exposures that can cause the injury, then confounding bias may be present. However, to create confounder bias, the confounding event must fulfill two criteria. First, it must be capable of causing the injury by itself. Second, the event must occur more frequently in the exposed group versus the unexposed group. Even if the potential confounder can cause the same injury as the primary injury being studied, it is of no consequence if the potentially confounding event occurs equally in both groups. The equality of the potential confounder's occurrence cancels out any confounder bias.

For instance, consider a study conducted to determine the effects of an air pollutant which is a suspected carcinogen. Assume the control group lives away from the area of contamination while the exposed group lives in the area of contamination. Assume that a statistically higher rate of lung cancer is identified in the exposed group. Now, let's determine what possible effects any confounder bias could have on this result.

If the exposed group contains a large number of cigarette smokers and the control group does not, then the results suffer from the confounding bias caused by another cause of lung cancer, cigarette exposure. However, if both groups contained the same number of cigarette smokers then there would be no confounding bias because both groups have experienced the same influence from cigarette exposure. In another scenario, if the exposed group watched more baseball games than the controls, the watching of baseball would not be a confounding bias. This is because watching baseball is not a cause of lung cancer, therefore the difference of this exposure between the groups is inconsequential.

However, if a study found a statistically significant relationship between a beer drinking group and lung cancer when compared to nondrinkers, then a confounder may be present. For instance, the beer drinkers may smoke more than the nondrinkers. Cigarette exposure would have confounded the study because (1) it causes lung cancer and (2) because more people in the imbibing group were exposed to

the cigarette smoke. The cigarette exposure would have satisfied both of the criteria for creation of confounder bias.

C. Statistical Analysis

Statistics are used in the study of epidemiology in determining whether an observation occurred by chance. Statistics are used to estimate the effect. A conclusion that an observed injury was caused by a particular exposure can be made if the effect is statistically significant and other factors are satisfied. The statistical analysis is rigorous and follows several steps. First, an estimator ratio must be determined. There are several types of estimator ratios which include the following: the odds ratio, the relative risk and the precedence ratio. If the value of the estimator is less than the value of 1, then the likelihood of injury is considered the same in the exposed and unexposed groups. An estimator ratio of greater than 1 demonstrates a greater likelihood of injury in the exposed group than in the unexposed group. An estimator ratio of 2 demonstrates that exposed persons are twice as likely to experience injury.

These estimator ratio's are not synonymous. They each apply to different situations but their purpose is the same. Their purpose is to quantify the likelihood that an exposed person will contract the disease when compared to an unexposed person. For example, if five people in a group of 100,000 people develops brain cancer when exposed to Solvent X, and only one person in another group of 100,000 unexposed people develops brain cancer, then the ratio is 5:1. In this study, an exposed person is five times more likely to develop brain cancer than the unexposed person.[9] If the ratio was 1:1, then the exposed group would not have a greater likelihood of contracting the disease as the result of exposure.

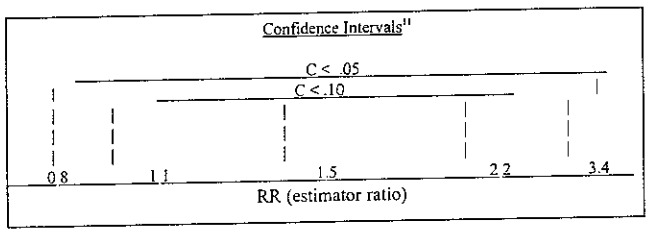
Once a ratio of greater likelihood is found, the investigators must determine if the outcome is the result of random error. The epidemiologist begins with a null hypothesis which assumes that there is no greater likelihood of disease. He assumes a ratio of 1:1. The burden of proof is placed on the study to disprove the null hypothesis.

The epidemiologist also considers other associations in his statistical analysis. They are the "true association" and the "positive association". The "true association" between an exposure and disease is a hypothetical value. It is the actual association between the exposure and the disease as would be determined by a perfect, although nonexistent, study. Although we may never be able to determine the true association, a range within which the true association most probably falls can be determined. A "positive association" is simply a ratio of greater than 1:1. If a positive association is found of 1½:1 or 2:1, the true association may be more or less than this ratio. The null hypothesis assumes there is no greater likelihood of disease caused by the exposure.

Epidemiology uses the concept of statistical significance to determine if the null hypothesis can be disproved. Statistical significance is used to determine whether the observed differences between the exposed and unexposed groups occurred by chance alone. The result of this statistical analysis is known as the "p-value" (probability). A p-value represents the probability that the positive association is the result of chance or is, in fact, true. A p-value of 0.05 means that five out of 100 times the result would have occurred by chance above. A p-value of 0.01 means that 1 out of 100 times the result would have occurred by chance alone. A p-value of 0.50 means that the difference would have occurred by chance 50 out of 100 times, or one out of two times. A p-value of 0.50 would be obtained by flipping a coin. Epidemiology accepts a p-value of 0.05 or less as a positive association that would not have occurred as a result of chance alone. Any p-value of greater than 0.05 does not disprove the null hypothesis.

The p-value does not provide an analysis of the stability of the exposure-disease association. The "confidence interval" can provide this information based on the p-value utilized in the study. When the p-value of a study is less than 0.05, then the confidence level is meaningful. If the "p-value" is greater than 0.05, the confidence interval is not as useful because the estimator ratios may have occurred by chance.

A confidence interval reports on the range of values within which the true association falls. The investigator can be 95% confident that the true association falls between certain values. These are the outside boundaries into which the true association probably falls. If the confidence interval places the likelihood of the true association being over 1.0 for 95% of the time, then a statistically significant finding has been found. If the confidence interval extends below the level of 1, then the positive association reported is not statistically significant. For instance, if the 95% confidence interval ranges between values of 0.8 and 3.4, then there is no statistical significance. The larger the sample size, then the narrower the confidence interval boundaries are expected to be. The narrower the confidence interval, the more precise the study is considered to be. The confidence interval reports the range of values within which the results of a study would fall if the study was repeated numerous times. The confidence intervals can be found for various levels of confidence, such as for 95% of the time, using a value of .05, or 90% of the time using a value of .10.



In the above graph, two confidence intervals are shown for an estimator ratio of 1.5. The particular estimator ratio used above is relative risk (RR). The top confidence interval is shown for a confidence value of .05 which equates with a confidence level of 95%. The lower confidence interval is shown for a confidence value of .10 which equates with a confidence level of 90%. The top confidence interval shows a study that is not statistically significant for a confidence level of 95% because the confidence interval ranges below 1. This top interval shows that 95% of the time during repetitive studies the true association would range between 0.8 and 3.4. Since the range allows for the true association to fall below the estimator ratio of 1.0, the finding is not statistically significant.

However, under a less stringent analysis with a confidence level of 90%, the study is statistically significant. The lower confidence interval in the graph shows that 90% of the time during repetitive studies the true association would range between 1.1 and 2.2. Since the range of the interval is at all times above the estimator ratio value of 1.0, the finding is statistically significant for the lower levels of 90% confidence.

Once a statistically significant association is reported, the analysis must determine whether various biases and confounders may have skewed the results. These bias are subject to interpretation by epidemiologist and public health officials. Whether the biases or confounders are significant depends upon interpretation.

The next step is determining whether the statistically significant association reported establishes a cause and effect relationship. Factors which may be considered are the following:

1. Strength of the association- The more likely causal association is represented by higher estimator ratio values.
2. Temporal relationship - The exposure must occur before the disease.
3. Consistency with other research - This could include review of single case reports and meta-analysis (a combination of several different studies).
4. Biological plausibility - Consistency of the associated injury with biological knowledge.
5. Exclusion of alternative explanations to the extent reasonably possible.
6. Dose-response relationship. This criteria assumes that the higher the dose, the more likely the disease. However, this is not a necessary criteria for a causal relationship since a single threshold exposure or dose may cause the disease such as an infectious disease.[12]

III. Trial Considerations

In state court, epidemiology that supports expert testimony can be explained to the jury as the basis of his opinion. Direct reference to the studies may incite hearsay objections. Unless the actual author is testifying, some judges may disallow testimony describing the study.

However, an expert should be able to refer to studies that explain his opinion. The studies themselves cannot be put into evidence except for impeachment purposes.[13] In federal court, the studies themselves can be read into evidence.[14] If an opposing party reads an unfavorable study into evidence, you may need to explain key concepts of epidemiology to a jury. You may need to read a positive study into evidence in rebuttal. It is doubtful that reading an entire study to a jury would be beneficial and, hopefully, the Court will allow the reading of highlighted portions.

Proof of causation of a disease in a specific individual may be enhanced with an epidemiologist as a witness.[15] The burden of proof in a civil case requires proof with a preponderance of the evidence which means more probable than not. If the estimator ratio is 2:1, then the exposure is twice as likely as not to cause the disease. A statistically significant estimator ratio of greater than 1 should allow Plaintiff to carry the burden of proof that the disease was more likely than not caused by the noxious exposure. New Jersey has allowed estimator ratios of less than 2.0 but more than 1.0 to form the basis of an inference on causation.[16]

A trial is ill suited for fully explaining the intricacies of epidemiology to a jury. However, jurors understand probabilities. They organize their lives and finances around probabilities. The probability of harm can be considered the level of risk. When we get in our cars each morning, we know that a few people are going to die driving every day. However, the probability that you will die in a car on any given day is remote. Driving is not considered risky behavior unless it is performed recklessly.

A jury can understand that people who smoke are many times more likely to get cancer than those who do not smoke. They can understand that children with excessive blood lead levels are twice as likely to have decreased IQ and that this finding has been repeated in different countries over many different studies.

However, it would be best to keep the evidence even simpler. The argument can simply be made that the scientific evidence shows that smoking causes lung cancer and that childhood lead poisoning causes brain damage. The causative association is the bottom line. The jury will be most interested in the bottom line. A positive study should be persuasive because the data undergoes such a rigorous statistical analysis.

Epidemiology will be most useful with the experts. A positive study will strengthen a doctor's confidence in a causative diagnosis. A doctor may change his mind on causation once he reads a study. Your focus on the use of the studies should be with your client's doctors.

The studies are available on Medline and a search can be easily phrased to identify the relevant articles.[17] Review articles which describe and summarize a number of epidemiological studies may be extremely helpful. The bibliography of a review study will list all the individual epidemiological studies reviewed which can then be easily obtained.

Epidemiology is likely to become more important. Studies are continually being performed on all sorts of topics from repetitive wrist trauma to toxic exposures. It will be worth your time to learn if there are studies supportive of causation in your cases.

Endnotes:

1. Stedman's Medical Dictionary, (25th ed)
2. Federal Judicial Center, Reference Manual on Scientific Evidence, 125 (1994) [West Publishing Company] [hereinafter referred to as Federal Manual]
3. Id
4. *Daubert v. Merrill Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 113 S.Ct. 2286, 2796 125 LEd 2d 469 (1993); In Re: Paoli RR Yard PCB Litig. (Paoli I), 916 F.2d 839, 853-60 (3d Cir., 1990). In re: Paoli R.R. Yard PCB Litig. (Paoli II), 35 F.3d 717, 778-84 (3d Cir., 1994)