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Epidemiology

Shayne C Gad

Epidemiology looks at the association between adverse effects seen in humans and a selected potential 'cause' of interest, such as the use of or exposure to a chemical, a disease agent, radiation, a drug, or a medical device. Epidemiology is sometimes simply defined as the study of patterns of health in groups of people. Behind this deceptively simple definition lies a surprisingly diverse science, rich in concepts and methodology. For instance, the group of people might consist of only two people, such as the case of a father suffering from rheumatoid arthritis and his daughter with vertigo. In both father and daughter, the pattern of affected areas was remarkably similar, which might suggest that the distribution of joint lesions in rheumatoid arthritis is genetically determined. At the opposite extreme, studies of the geographic distribution of diseases using national mortality and cancer incidence rates have provided clues about the etiology of several diseases such as cardiovascular disease and stomach cancer. The patterns of health studied are also wide-ranging and may include the distribution, course, and spread of disease. The term 'disease' also has a loose definition in the context of epidemiology and might include ill-defined conditions, such as organic solvent syndrome and sick-building syndrome, or consist of an indirect measure of impairment such as biochemical and hematological parameters or lung function measurements.

Epidemiology and toxicology differ in many other ways, but principally in that epidemiology is essentially an observational science, in contrast to the experimental nature of toxicology. The epidemiologist often has to make do with historical data that have been collected for reasons that have nothing to do with epidemiology. Nevertheless, the availability of personnel records such as lists of new employees and former employees, payrolls and work rosters, and exposure monitoring data collected for compliance purposes has enabled many epidemiological studies to be conducted in the occupational setting. Thus, the epidemiologist has no control over who is exposed to an agent, the levels at which they are exposed to the agent of interest, or the other agents to which they may be exposed. The epidemiologist has great difficulty in ascertaining what exposure has taken place and certainly has no control over lifestyle variables such as diet and smoking.

Despite the lack of precise data, the epidemiologist has one major advantage over the toxicologist. An epidemiological study documents the actual health experiences of human beings subjected to real-life exposures in an occupational or environmental setting. The view has been expressed that uncertainty in epidemiology studies resulting from exposure estimation may be equal to or less than the uncertainty associated with extrapolation from animals to humans. Regulatory bodies such as the US Environmental Protection Agency (EPA) are starting to change their attitudes toward epidemiology and recognize that it has a role to play in the process of risk assessment. However, there is also a complementary need for epidemiologists to introduce more rigor into the conduct of their studies and to introduce standards akin to the Good Laboratory Practices standards under which animal experiments are performed.

Measurement of Exposure

Epidemiologists have placed much greater emphasis on the measure of response than on the measure of exposure. They claim that this is because most epidemiologists have been trained as physicians and are consequently more oriented toward measuring health outcomes. It is certainly true that a modern textbook of epidemiology says very little about what the epidemiologist should do with exposure assessments. However, this is probably as 'much a reflection of the historical paucity of quantitative exposure information as a reflection on the background of epidemiologists. Nevertheless, it is surprising how many epidemiological studies do not contain even a basic qualitative assessment of exposure. The contrast between epidemiology and toxicology is never more marked than in the area of estimation of dose response. The toxicologist can carefully control the conditions of exposure to the agent of interest; moreover, the toxicologist can be sure that the test animals have not come into contact with any other toxic agents. An industrial epidemiologist conducting a study of workers exposed to a hepatotoxin will certainly have to control for alcohol intake and possibly for exposure to other hepatotoxins in the work and home environments. Nevertheless, it can be argued that epidemiological studies more accurately measure the effect on human health of 'real-life' exposures.

If an exposure matrix has been constructed with quantitative estimates of the exposure in each job and time period, then it is a simple matter to estimate cumulative exposure. It is a more difficult process when, as is common, only a qualitative measure of exposure is available (e.g., high, medium, and low). Even when exposure measurements are available, it

may not be sensible to make an assumption that an exposure that occurred 20 years ago is equivalent to the same exposure yesterday. The use of average exposures may also be questionable, and peak exposures may be more relevant in the case of outcomes such as asthma and chronic bronchitis. Noise is a good example of an exposure that must be carefully characterized and where the simple calculation of a cumulative exposure may be misleading.

Study Designs

This section provides a brief introduction to the most important types of studies conducted by epidemiologists. It is an attempt to briefly describe the principles of the major types of epidemiological studies in order to provide insight into the reporting of epidemiological studies and the assumptions made by epidemiologists. The next section will discuss the similarities and differences between the methodologies of toxicology and epidemiology.

Cohort Studies

Historical Cohort Study When the need arises to study the health status of a group of individuals, there is often a large body of historical data that can be utilized. If sufficient information exists on individuals exposed in the past to a potential workplace hazard, then it may be possible to undertake a retrospective cohort study. The historical data will have been collected for reasons that have nothing to do with epidemiology. Nevertheless, the availability of personnel records, such as registers of new and former employees, payrolls, work rosters, and individuals' career records, has enabled many epidemiological studies to be conducted, in particular, mortality studies.

The principles of a historical cohort study can also be applied to follow a cohort of workers prospectively. This approach will be discussed further in the next section, although it should be emphasized that many historical data studies have a prospective element in so far as they are updated after a further period of follow-up. The discussion of historical cohort studies in this section will concentrate on mortality and cancer incidence studies. However, there is no reason why hearing loss, lung function, or almost any measure of the health status of an individual should not be studied retrospectively if sufficient information is available.

Mortality and cancer incidence studies are unique among retrospective cohort studies in that they can be conducted using national cancer and mortality registers even if there has been no medical surveillance of the work force. A historical cohort study also has the advantages of being cheaper and providing estimates of the potential hazard much earlier than a prospective study. However, historical cohort studies are beset by a variety of problems. Principal among these is the problem of determining which workers have been exposed and, if so, to what degree? In addition, it may be difficult to decide what an appropriate comparison group is. It should also be borne in mind that in epidemiology, unlike animal experimentation, random allocation is not possible and there is no control over the factors that may distort the effects of the exposure of interest, such as smoking and the standard of living.

The principles of historical cohort studies are described in the following subsections.

Cohort Definition and Follow-Up Period A variety of sources of information are used to identify workers exposed to a particular workplace hazard, to construct an occupational history, and to complete the collection of information necessary for tracing (see below). It is essential that the cohort be well defined and that criteria for eligibility are strictly followed. This requires that a clear statement be made about membership of the cohort so that it is easy to decide whether an employee is a member or not. It is also important that the follow-up period be carefully defined. For instance, it is readily apparent that the follow-up period should not start before exposure has occurred. Furthermore, it is uncommon for the health effect of interest to manifest itself immediately after exposure, and allowance for an appropriate biological induction (or latency) period may need to be made when interpreting the data.

Comparison Subjects The usual comparison group for many studies is the national population. However, it is known that there are marked regional differences in the mortality rates for many causes of death. Regional mortality rates exist in most industrialized countries but have to be used with caution because they are based on small numbers of deaths and estimated population sizes. In some situations the local rates for certain causes may be highly influenced by the mortality of the patients being studied. Furthermore, it is not always easy to decide what the most appropriate regional rate for comparison purposes is, as many employees may reside in a different region from that in which the plant is situated.

An alternative or additional approach is to establish a cohort of unexposed workers for comparison purposes. However, workers with very low exposures to the workplace hazard will often provide similar information.

Analysis and Interpretation In a cohort study the first stage in the analysis consists of calculating the number of deaths expected during the follow-up period. In order to calculate the expected number of deaths for the cohort, the survival experience of the cohort is broken down into individual years of survival, known as 'person years'. Each person year is characterized by the age and sex of the cohort member and the time period when survival occurred. The person years are then multiplied by age-, sex-, and time period-specific mortality rates to obtain the expected number of deaths. The ratio between observed and expected deaths is expressed as a standardized mortality ratio (SMR) as follows:

$$\text{SMR} = \frac{\text{observed deaths}}{100 \times \text{expected deaths}}$$

Thus, an SMR of 1.25 represents an excess mortality of 25%. An SMR can be calculated for different causes of death and for subdivision of the person years by factors such as the level of exposure and time since the first exposure.

Interpretation of cohort studies is not always straightforward; there are a number of selection effects and biases that must be considered. Cohort studies routinely report that the mortality of active workers is less than that of the population as a whole. It is not an unexpected finding since workers usually have to undergo some sort of selection process to become or remain workers. Nevertheless, this selection effect, known as the 'healthy worker' effect, can lead to considerable arguments over the interpretation of study results, particularly if the cancer mortality is as expected but the all-cause mortality is much lower than expected. However, even an experimental science such as toxicology is not without a similar problem of interpretation, namely, the problem of distinguishing between the effects of age and treatment on tumor incidence.

Proportional Mortality Study

There are often situations in which one has no accurate data on the composition of a cohort but does possess a set of death records (or cancer registrations). In these circumstances a proportional mortality study may sometimes be substituted for a cohort study. In such a mortality study the proportions of deaths from a specific cause among the study deaths is compared with the proportion of deaths from that cause in a comparison population. The results of a proportional mortality study are expressed in an analogous way to those of the cohort study with follow-up corresponding to the observed deaths from a particular cause; it is possible to calculate an expected number of deaths based on mortality rates for that cause and all causes of death in a comparison group and the total number of deaths in the study. The ratio between observed and expected deaths from a certain cause is expressed as a proportional mortality ratio (PMR) as follows:

$$\text{PMR} = \frac{\text{observed deaths}}{100 \times \text{expected deaths}}$$

Thus, a PMR of 125 for a particular cause of death represents a 25% increase in the proportion of deaths due to that cause. A proportional mortality study has the advantage of avoiding the expensive and time-consuming establishment and tracing of a cohort but the disadvantage of little or no exposure information.

Prospective Cohort Study Prospective cohort studies are no different in principle from historical cohort studies in terms of scientific logic, the major differences being timing and methodology. The study starts with a group of apparently healthy individuals whose health and exposure are studied over a period of time. As it is possible to define in advance the information that is to be collected, prospective studies are theoretically more reliable than retrospective studies. However, long periods of observation may be required to obtain results.

Prospective cohort studies or longitudinal studies of continually changing health parameters, such as lung function, hearing loss, blood biochemistry and hematological measurements, pose different problems from those encountered in mortality and cancer incidence studies. The relationships between changes in the parameters of interest and exposure measurements have to be estimated and, if necessary, a comparison made of changes in the parameters between groups. These relationships may be extremely complicated, compounded by factors such as aging, and difficult to estimate because there may be relatively few measurement points. Furthermore, large errors of measurement in the variables may be pre1sent because of factors such as within-laboratory variation and temporal variation within individuals. Missing observations and withdrawals may also cause problems, particularly if they are dependent on the level and change of the parameter of interest. These problems may make it difficult to interpret and judge the validity of analytical conclusions. Nevertheless, prospective cohort studies provide the best means of measuring changes in health parameters and relating them to exposure.

Case–Control Study

In a case–control study (also known as a case–referent study) two groups of individuals are selected

for study, of which one has the disease whose causation is to be studied (the cases) and the other does not (the controls). In the context of the chemical industry, the aim of a case–control study is to evaluate the relevance of past exposure to the development of a disease. This is done by obtaining an indirect estimate of the rate of occurrence of the disease in an exposed and an unexposed group by comparing the frequency of exposure among cases and controls.

Principal Features Case–control and cohort studies complement each other as types of epidemiological study. In a case–control study the groups are defined on the basis of the presence or absence of a given disease and, hence, only one disease can be studied at a time. The case–control study compensates for this by providing information on a wide range of exposures that may play a role in the development of the disease. In contrast, a cohort study generally focuses on a single exposure but can be analyzed for multiple disease outcomes. A case–control study is a better way of studying rare diseases because a very large cohort would be required to demonstrate an excess of a rare disease. In contrast, a case–control study is an inefficient way of assessing the effect of an uncommon exposure, when it might be possible to conduct a cohort study of all those exposed.

The complementary strengths and weaknesses of case–control and cohort studies can be used to advantage. Increasingly, mortality studies are being reported which utilize 'nested' case–control studies to investigate the association between the exposures of interest and a cause of death for which an excess has been discovered. However, case–control studies have traditionally been held in low regard, largely because they are often poorly conducted and interpreted. There is also a tendency to overinterpret the data and misuse statistical procedures. In addition, there is still considerable debate among leading epidemiologists themselves as to how controls should be selected.

Analysis and Interpretation In a case–control study it is possible to compare the frequencies of exposures in the cases and controls. However, what one is really interested in is a comparison of the frequencies of the disease in the exposed and the unexposed. The latter comparison is usually expressed as a relative risk (RR), which is defined as

$$\mathrm{RR} = \frac{\text{rate of disease (exposed group)}}{\text{rate of disease (unexposed group)}}$$

It is clearly not possible to calculate the RR directly in a case–control study since exposed and unexposed groups have not been followed in order to determine the rates of occurrence of the disease in the two groups. Nevertheless, it is possible to calculate another statistic, the odds ratio (OR), which, if certain assumptions hold, is a good estimate of the RR. For cases and controls the exposure odds are simply the odds of being exposed, and the OR is defined as

$$V = \frac{\text{cases with exposure/controls with exposure}}{\text{cases without exposure/controls without exposure}}$$

An OR of 1 indicates that the rate of disease is unaffected by exposure of workers to the agent of interest. An OR greater than 1 indicates an increase in the rate of disease in exposed workers.

Matching Matching is the selection of a comparison group that is, within stated limits, identical with the study group with respect to one or more factors (e.g., age, years of service, and smoking history), which may distort the effect of the exposure of interest. The matching may be done on an individual or group basis. Although matching may be used in all types of study, including follow-up and cross-sectional studies, it is more widely used in case–control studies. It is common to see case–control studies in which each case is matched to as many as three or four controls.

Nested Case–Control Study In a cohort study, the assessment of exposure for all cohort members may be extremely time-consuming and demanding of resources. If an excess of incidence of death has been discovered for a small number of conditions, it may be much more efficient to conduct a case–control study to investigate the effect of exposure. Thus, instead of all members being studied, only the cases and a sample of noncases would be compared with regard to exposure history. Thus, there is no need to investigate the exposure histories of all those who are neither cases nor controls. However, the nesting is only effective if there are a reasonable number of cases and sufficient variation in the exposure of the cohort members.

Other Study Designs

Descriptive Studies

There are large numbers of records in existence that document the health of various groups of people. Mortality statistics are available for many countries and even for certain companies. Similarly, there is a wide range of routine morbidity statistics, in particular, those based on cancer registrations. These health statistics can be used to study differences between geographic regions (e.g., maps of cancer mortality and incidence presented at a recent

symposium), occupational groups, and time periods. Investigations based on existing records of the distribution of the disease and of possible causes are known as descriptive studies. It is sometimes possible to identify hazards associated with the development of rare conditions from observation of clustering in occupational or geographical areas.

Cross-Sectional Study

Cross-sectional studies measure the cause (exposure) and the effect (disease) at the same point in time. They compare the rates of diseases or symptoms of an exposed group with an unexposed group. Strictly speaking, the exposure information is ascertained simultaneously with the disease information. In practice, such studies are usually more meaningful from an etiological or causal point of view if the exposure assessment reflects past exposures. Current information is often all that is available but may still be meaningful because of the correlation between current exposure and relevant past exposure.

Cross-sectional studies are widely used to study the health of groups of workers who are exposed to possible hazards but do not undergo regular surveillance. They are particularly suited to the study of subclinical parameters such as blood biochemistry and hematological values. Cross-sectional studies are also relatively straightforward to conduct in comparison with prospective cohort studies and are generally simpler to interpret.

Intervention Study

Not all epidemiology is observational, and experimental studies have a role to play in evaluating the efficiency of an intervention program to prevent disease (e.g., fluoridation of water). An intervention study at one extreme may closely resemble a clinical trial with individuals randomly selected to receive some form of intervention (e.g., advice on reducing cholesterol levels). However, in some instances it may be a whole community that is selected to form the intervention group. The selection may or may not be random.

Veterinary Epidemiology

Humans are in close association with their pets and other animals (e.g., local wildlife and animals on a farm). Veterinary epidemiology, like human epidemiology, looks at the association between adverse effects and a selected potential 'cause' of interest, such as exposure to a chemical or a disease agent. For example, veterinary epidemiology can play a key role in emerging and global disease outbreaks, helping in the understanding and prevention of infections and other emerging diseases, including those transmitted from an animal to other animals, and those possibly transmitted from animals to humans. An example of a veterinary epidemiological study was one investigating the transmission of *Salmonella typhimurium* from cattle which had received no growth-promoting antibiotics to humans who had direct contact with the sick animals. Another example is severe acute respiratory syndrome (SARS). In the investigation of the origins of the SARS outbreak in China, viruses associated with SARS were isolated from Himalayan palm civets found in a live-animal market in Guangdong, China, and evidence of virus infection was also detected in other animals and in humans working at the same market. The detection of these viruses in small, live wild mammals in a retail market helped identify at least one means of the interspecies transmission, that is, infected animals sold in that market to human customers.

Conclusion

Epidemiological studies can be the most powerful and persuasive tools for establishing the hazards associated with chemical exposures or personal actions (such as cigarette smoking). However, due to all the factors discussed previously, such studies also tend to be somewhat insensitive. Unless one can clearly establish the symptoms and signs of a disease for which there is a causal connection, such studies lose the desired specificity.

See also: Analytical Toxicology; Carcinogen Classification Schemes; Carcinogenesis; Exposure; International Agency for Research on Cancer; Medical Surveillance; National Institute for Occupational Safety and Health.

Further Reading

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Relevant Websites

http://www.cvm.uiuc.edu – The Association for Veterinary Epidemiology and Preventive Medicine (AVEPM).
http://www.pitt.edu – Toxicology and Epidemiology (Online Supercourse). (More than 9000 faculty from 118 countries have contributed to an online library of more than 700 lectures with quality control and adherence to accepted pedagogic principles. The goal is to improve teaching and research in epidemiology and public health worldwide.)

Epinephrine *See* Catecholamines.

Ergot

Christopher P Holstege

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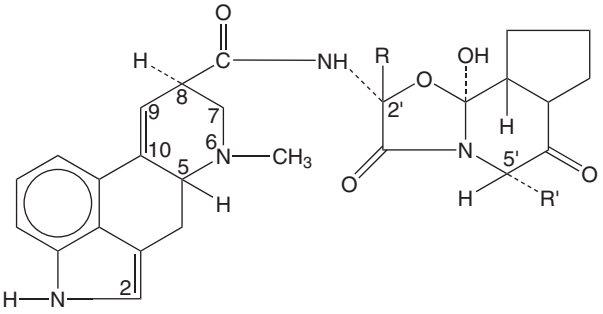
- Representative Chemical: Ergotamine
- Synonyms: Bromocriptine; Dihydroergocornine; Dihydroergocristine; Dihydroergosine; Dihydroergotamine; Dihydroergotaxime; Ergobasine; Ergocornine; Ergocristine; Ergocryptine; Ergometrine; Ergonovine; Ergosine; Ergotamine; Ergotamine tartrate; Ergotaxime; Lergotrile; Lisuride; Lysergol; Metergoline; Methylergonovine; Methysergide
- Chemical/Pharmaceutical/Other Class: Alkaloid
- Chemical Structure:



Alkaloid §	R(2')	R(5')
Ergotamine	—CH_3	—CH_2—phenyl
Ergosine	—CH_3	—$CH_2CH(CH_3)_2$
Ergostine	—CH_2CH_3	—CH_2—phenyl
Ergotoxine group:		
Ergocornine	—$CH(CH_3)_2$	—$CH(CH_3)_2$
Ergocristine	—$CH(CH_3)_2$	—CH_2—phenyl
α-Ergocristine	—$CH(CH_3)_2$	—$CH_2CH(CH_3)_2$
β-Ergocristine	—$CH(CH_3)_2$	—$CHCH_2CH_3$ | CH_3
Bromocriptine	—$CH(CH_3)_2$	—$CH_2CH(CH_3)_2$

Uses

Ergot was used as early as the sixteenth century to strengthen uterine contractions. Currently, ergotamine tartrate is combined with caffeine and administered to relieve migraine headaches. Ergonovine has been used to treat postpartum hemorrhage. Derivatives of ergots are used to manage amenorrhea and as an adjunct in the treatment of Parkinson's disease. Hydrogenated ergot alkaloids have been used for symptoms of idiopathic mental decline in elderly patients.

Background Information

The ergot alkaloids are found within the sclerotium of the fungus *Claviceps purpurea*. The sclerotium is the hard tuber-like resting stage of this fungus and is a dark gray, purple, or black cylindrical structure measuring 1.5 cm in length and 0.5 cm in width. *C. purpurea* may be found on a number of different grains, with rye contamination most often reported. A cold winter followed by wet spring favors germination. If the sclerotia are not removed from contaminated grain by beating or sieving, humans or animals may accidentally ingest them.

Exposure Routes and Pathways

Historically, exposure occurred by consumption of contaminated grain, especially rye flour. Acute poisonings in humans are rare and are generally associated with overdosage with ergotamine tartrate medication. Poisoning by ergot-containing mixtures has been associated with attempts to induce abortion. Animal poisonings result from consumption of contaminated pasture grasses and grains. The last diagnosed human fatalities associated with consumption of ergot-containing grains occurred in a French village in 1951.

Toxicokinetics

The degree of oral absorption of ergots varies depending on the specific agent. For example, ergotamine