

Research Methods in Community Medicine

**Surveys,
Epidemiological Research,
Programme Evaluation,
Clinical Trials**

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Community Medicine, Jerusalem

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Beit Hakerem Community Clinic (Clalit Health Services)
and Department of Family Medicine,

The Hebrew University-Hadassah School of Medicine, Jerusalem

SIXTH EDITION



John Wiley & Sons, Ltd

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Preface

The purpose of this book is to provide a simple and systematic guide to the planning and performance of investigations concerned with health and disease and with health care, whether they are designed to widen the horizons of scientific knowledge or to provide a basis for improved care in a specific community. It is not a compendium of detailed techniques of investigation or of statistical methods, but an ABC to the design, conduct and analysis of these studies. It is written for students and practitioners of community medicine and public health (epidemiologists, family physicians, nurses, health educators, administrators, and others) interested in the planning of health surveys, cohort and case-control studies, clinical and programme trials, studies of the use of health services, and other epidemiological and evaluative research. It may also be helpful to readers who wish only to enhance their capacity for the judicious appraisal of medical literature.

The book's change of name from 'Survey Methods' to 'Research Methods' reflects the fact that it deals with observational studies of all kinds, and clinical and programme trials, and not only with what are commonly regarded as surveys. Whatever its name, the book remains a simple introductory text, assuming little prior knowledge.

The book has been extensively revised and updated. A new chapter on the use of the Web for health research has been added, and so has an appendix that lists free computer programs that may be useful in the planning, performance, or analysis of studies. As in previous editions, copious endnotes and references are provided, for the benefit of readers who wish to go into things a little more deeply. These notes and references have also been revised and updated.

As before, there are references to Internet sites. As long as these sites remain accessible, they can be helpful as sources of accessory material

Making Sense of Data, our self-instruction manual on the interpretation of epidemiological data (3rd edition, Oxford University Press, 2001) and the *WinPepi* statistical programs for epidemiologists (described in Appendix C) may be regarded as companions to this volume.

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1

First Steps

The purpose of most investigations in community medicine, and in the health field generally, is the collection of information that will provide a basis for action, whether immediately or in the long run. The investigator perceives a problem that requires solution, decides that a particular study will contribute to this end, and embarks upon the study. Sound planning – and maybe a smile or two from Lady Luck – will ensure that the findings will be useful, and possibly even of wide scientific interest. Only if the problem has neither theoretical nor practical significance and the findings serve no end but self-gratification may sound planning be unnecessary.

Before planning can start, a problem must be identified. It has been said that ‘if necessity is the mother of invention, the awareness of problems is the mother of research’.¹ The investigator’s interest in the problem may arise from a concern with practical matters or from intellectual curiosity, from an intuitive ‘hunch’ or from careful reasoning, from personal experience or from that of others. Inspiration often comes from reading, not only about the topic in which the investigator is interested, but also about related topics. An idea for a study on alcoholism may arise from the results of studies on smoking (conceptually related to alcoholism, in that it is also an addiction) or delinquency (both it and alcoholism being, at least in certain cultures, forms of socially deviant behaviour).

While the main purpose is to collect information that will contribute to the solution of a problem, investigations may also have an educational function and may be carried out for this purpose. A survey can stimulate public interest in a particular topic (the interviewer is asked: ‘Why are you asking me these questions?’), and can be a means of stimulating public action. A community self-survey, carried out by participant members of the community, may be set up as a means to community action; such a survey may collect useful information, although it is seldom very accurate or sophisticated.

This chapter deals with the purpose of the investigation, reviewing the literature, ethical aspects, and the formulation of the study topic.

First Steps

- Clarifying the purpose
- Reviewing the literature
- Ethical considerations
- Formulating the topic

Clarifying the Purpose

The first step then, before the study is planned, is to clarify its purpose: the ‘why’ of the study. (We are not speaking here of the researcher’s psychological motivations – a quest for prestige, promotion, the gratifications of problem-solving, etc. – which may or may not be at a conscious level.) Is it ‘pure’ or ‘basic’ research with no immediate practical applications in health care, or is it ‘applied’ research? Is the purpose to obtain information that will be a basis for a decision on the utilization of resources, or is it to identify persons who are at special risk of contracting a specific disease in order that preventive action may be taken; or to add to existing knowledge by throwing light on (say) a specific aspect of aetiology; or to stimulate the public’s interest in a topic of relevance to its health? If an evaluative study of health care is contemplated, is the motive a concern with the welfare of the people who are served by a specific practice, health centre or hospital, or is it to see whether a specific treatment or kind of health programme is good enough to be applied in other places also?

The reason for embarking on the study should be clear to the investigator. In most cases it will in fact be so from the outset, but sometimes the formulation of the problem to be solved may be less easy. In either instance, if an application is made for facilities or funds for the study it will be necessary to describe this purpose in some detail, so as to justify the performance of the study. The researcher will need to review previous work on the subject, describe the present state of knowledge, and explain the significance of the proposed investigation. This is the ‘case for action’.

Preconceived ideas introduce a possibility of biased findings, and an honest self-examination is always desirable to clarify the purposes. If the reason for studying a health service is that the investigator thinks it is atrocious and wants to collect data that will condemn it, extra-special care should be taken to ensure objectivity in the collection and interpretation of information. In such a case, the researcher would be well advised to ‘bend over backwards’ and consciously set out to seek information to the credit of the service. Regrettably, not all evaluative studies are honest.²

To emphasize the importance of the study purpose, and maybe to make it clearer, let us restate it in the words of three other writers:

The preliminary questions when planning a study are:

1. What is the question?
2. What will be done with the answer?³

Do not: say that you will try to formulate a good subject.

Do: tell what you want to accomplish with the subject.⁴

Discover the ‘latent objective’ of a project. The latent objective is the meaning of the research for the researcher, and gives away his or her secret hopes of what (s)he will achieve. To detect this latent objective, it is often fruitful to ‘begin at the end.’ How will the world be changed after the research is published?⁵

Reviewing the Literature

The published experiences and thoughts of others may not only indicate the presence and nature of the research problem, but may be of great help in all aspects of planning and in the interpretation of the study findings. At the outset of the study the investigator should be or should become acquainted with the important relevant literature, and should continue with directed reading throughout. References should be filed in an organized way, manually or in a computerized database.⁶ It is of limited use to wait until a report has to be written, and then read and cite (or only cite) a long list of publications to impress the reader with one's erudition – a procedure that may defeat its own ends, since it is often quite apparent that the papers and books listed in the extensive bibliography have had no impact on the investigation.

Papers should be read with a healthy scepticism; in Francis Bacon's words, 'Read not to contradict and confute, not to believe and take for granted ... but to weigh and consider'.⁷ Several guides to critical reading are available.⁸ Remember that studies that have negative or uninteresting findings are less likely to be published than those with striking findings.⁹

If the title and abstract suggest that the paper may be of interest, then you should appraise the methods used in the study (which requires the kind of familiarity with research methods and their pitfalls that this book attempts to impart), assess the accuracy of the findings, judge whether the inferences are valid, and decide whether the study has relevance to your own needs and interests. Do not expect any study to be completely convincing, and do not reject a study because it is not completely convincing; avoid 'I am an epidemiologist' bias (repudiation of any study containing any flaw in its design, analysis or interpretation) and other forms of what has been called 'reader bias'.¹⁰

Search engines such as Google Scholar, and the increasing tendency to provide free access on the Internet to the full text of publications, have made it very much easier to find relevant literature. Google Scholar not only finds publications, it also finds subsequent publications that have cited them, and related publications, and it provides links to local library catalogues.

But, at the same time, the explosive growth in published material in recent years means that a computer search may find so many references (and so many of them irrelevant) that sifting them can be a demanding chore, to the extent that one may be misguidedly tempted to rely only on review articles, or on the abstracts provided by most databases, instead of tracking papers down and reading them.

Conducting a computer search in such a way that you get what you want – and don't get what you don't want – is not always easy. It is particularly difficult to get *all* of what you want. Investigators who wish to perform a systematic review of all previous published researches on a particular topic, for example, may be well advised to enlist the help of a librarian. A biomedical librarian advises the use of regular Google as well as Google Scholar if hard-to-find government or conference papers are sought, and also advises use of PubMed and other databases if the aim is an exhaustive search.¹¹ Most users find Google Scholar easy to use and very helpful – the answer to a maiden's prayer – but its coverage (in its present incarnation) is incomplete,¹² and in terms of

accuracy, thoroughness, and up-to-dateness it falls short of PubMed, which provides access to over 16 million citations, mainly from MedLine, back to the 1950s. The way to use PubMed is explained on the website (<http://www.ncbi.nlm.nih.gov/entrez>), and it is easy to use if requirements are simple; but otherwise, it has been said, 'If you enjoy puzzles, MedLine is great fun'.¹³ A user-friendly simplified interface, SLIM, is now available.¹⁴

Ethical Considerations

Before embarking on a study the investigator should be convinced that it is ethically justifiable, and that it can be done in an ethical way. Ethical questions arise in both experimental and nonexperimental studies.

There is an obvious ethical problem whenever an experiment to test the benefits or hazards of a treatment is contemplated. However beneficial the trial may turn out to be for humanity at large, some subjects may be harmed either by the experimental treatment or by its being withheld. There is also an ethical problem in not performing a clinical trial, since this may lead to the introduction or continued use of an ineffective or hazardous treatment. 'Where the value of a treatment, new or old, is doubtful, there may be a higher moral obligation to test it critically than to continue to prescribe it year-in-year-out with the support merely of custom or wishful thinking.'¹⁵ But, it has been pointed out, 'this ethical imperative can only be maintained if, and to the extent that, it is possible to conduct controlled trials in an ethically justifiable way'.¹⁶ The heinous medical experiments conducted on helpless victims by Nazi physicians in the first part of the 20th century should never be forgotten.¹⁷

For an experimental study to be ethical, the subjects should be aware that they are to participate in an experiment, should know how their treatment will be decided and what the possible consequences are, should be told that they may withdraw from the trial at any time, and should freely give their informed consent. These requirements are not always easily accepted in clinical settings, and they are sometimes circumvented by medical investigators who feel that they have a right to decide their patient's treatment. Studies have shown that patients (especially poorly educated ones) who sign consent forms are often ignorant of the most basic facts. Special problems concerning consent may arise in cluster-randomized trials,¹⁸ where clusters of people (e.g. the patients in different family practices) are randomly allocated to treatment or control groups (see p. 351), or where a total community is exposed to an experimental procedure or programme, or when experiments (such as trials of new vaccines) are performed in developing countries.¹⁹

Ethical objections to clinical trials are reduced if there is genuine uncertainty about the value of the treatment tested or the relative value of the treatments compared (*equipoise*) – for some investigators, it is sufficient that there is genuine uncertainty in the health profession as a whole, whatever their own views – and if controls are given the best established treatment. 'The essential feature of a controlled trial is that it must be ethically possible to give each patient any of the treatments involved'.¹⁹

Decisions on the ethicality of trials may not be simple.²⁰ Bradford Hill has said that there is only one Golden Rule, namely 'that one can make no generalization ... the problem must be faced afresh with every proposed trial'.

The goals of the research should always be secondary to the wellbeing of the participants. The Helsinki declaration states:

Concern for the interests of the subject must always prevail over the interests of science and society ... every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.

But researchers sometimes argue that obtaining an answer to the research question is the primary ethical obligation, so that they then 'find themselves slipping across a line that prohibits treating human subjects as means to an end. When that line is crossed, there is very little left to protect patients from a callous disregard of their welfare for the sake of research goals'.²¹ This has raised debates about possible 'scientific imperialism', characterized by the performance of trials, sometimes with lowered ethical standards, in countries that are unlikely to benefit from the findings: 'Are poor people in developing countries being exploited in research for the benefit of patients in the developed world where subject recruitment to a randomized trial would be difficult?'²²

In 1997, a furore was aroused at the disclosure that, in developing countries, controls were receiving placebos in trials, sponsored by the USA, of regimens to prevent the transmission of human immunodeficiency virus (HIV) from mothers to their unborn children, although there was an effective treatment that had been recommended for all HIV-infected pregnant women in the USA and some other countries. A debate ensued, the main issue being whether the Helsinki declaration's requirement that controls should be given the best current treatment was outweighed by the claims that a comparison with placebo was the best way of finding out whether the relatively cheap experimental regimens would be helpful in countries that cannot afford optimal care, and that the investigators were simply observing what would happen to the infants of the controls, who would anyway not have received treatment if there had been no study.

How well the trial is planned and performed is also important:

Scientifically unsound studies are unethical. It may be accepted as a maxim that a poorly or improperly designed study involving human subjects – one that could not possibly yield scientific facts (that is, reproducible observations) relevant to the question under study – is by definition unethical. When a study is in itself scientifically invalid, all other ethical considerations become irrelevant. There is no point in obtaining 'informed consent' to perform a useless study.²³

It is generally accepted that a study that is too small to provide clear results is *ipso facto* unethical. But it has been argued that this is not necessarily so, since a larger sample size would impose the burden of participation on more subjects, without having a proportionate effect on the trial's capacity to yield clear results.²⁴

Other ethical considerations may arise after the trial has started. If it is found to be in a subject's interest to stop or modify the treatment, or to start treating a control subject, then there should be no hesitation in doing so. If there is reason to think that continuation of

the trial may be harmful, then it should be stopped forthwith. For example, the first randomized controlled trial of the protective effect against HIV infection of the performance of circumcision of young men, conducted in Orange Farm, a region close to Johannesburg in South Africa, was stopped as soon as an interim analysis revealed that the incidence of HIV infection was much higher in the controls than in the circumcised group.²⁵

In nonexperimental studies²⁶ ethical problems are usually less acute, unless the study involves hazardous test procedures or intrusions on privacy. But here, too, there is a need for informed consent²⁷ if participants are required to answer questions, undergo tests that carry a risk (however small), or permit access to confidential records. The investigators should give an honest explanation of the purpose of the survey when enlisting subjects, and respondents should be told what their participation entails, and assured that they are free to refuse to answer questions or continue their participation. Pains should be taken to keep information confidential. Any promises made to participants, e.g. about anonymity or the provision of test results, should of course be kept.

Of particular importance is the question of what action should be taken if a survey reveals that participants would benefit from medical care or other intervention. In studies involving HIV antibody testing, subjects with positive results should obviously be notified, even if this affects the soundness of the study.²⁸

The notorious Tuskegee study in Alabama is a horrible illustration of an unethical survey.²⁹ It began in 1932, with the aim of throwing light on the effects of untreated syphilis. Some 400 untreated Black syphilitics (mostly poor and uneducated) were identified and then followed up; their course was compared with that of apparently syphilis-free age-matched controls. Treatment of syphilis was withheld. By 1938–1939 it was found that a number of the men had received sporadic treatment with arsenic or mercury, and a very few had had more intensive treatment. In the interests of science ‘fourteen young untreated syphilitics were added to the study to compensate for this’. Treatment was withheld even when penicillin was found to be effective and became easily available in the late 1940s and early 1950s. Participants received free benefits, such as free treatment (except for syphilis), free hot lunches, and free burial (after a free autopsy). By 1954 it was apparent that the life expectancy of the untreated men aged 25–50 was reduced by 17%. By 1963, 14 more men per 100 had died in the syphilitic group than in the control group. In 1972 there was a public outcry, and compensation payments were later made.

There are those who say that political decisions that may involve risk to human life, e.g. the raising of speed limits on interurban roads, without setting cut-off points for early termination in the case of adverse results, are unethical before–after experiments.³⁰

In many countries informed consent is mandatory for studies of human subjects unless there are valid contraindications, such as qualms about alarming fatally ill patients with doubts about the efficacy of treatment. Many institutions have ethical committees that review and sanction proposed studies. Some investigators feel that this control is too permissive, but there are some who think it is too restrictive (it ‘stops worthwhile research’).³¹ A fanciful account of the rise and fall of epidemiology between 1950 and 2000 (printed in 1981)³² attributed the fall to ethical committees and regulations designed to protect the confidentiality of records.

At a different ethical level, consideration should be given to the justification for any proposed study in the light of the availability of resources and the alternative ways in which these might be used. Does the possible benefit warrant the required expenditure of time, manpower and money? Is it ethical to perform the study at the expense of other activities, especially those that might directly promote the community's health?

An honest endeavour to clarify the purpose of the study may lead to second thoughts: is the study really worth doing? A great deal of useless research is conducted. This wastes time and resources, and exposes the scientific method to ridicule.³³

Formulating the Topic

When the purpose and moral justification of the study are clear, the investigator can formulate the topic he or she proposes to study, in general terms. In many cases this is easily done and almost tautological. For example, if the reason for setting up the study is that infant mortality is unduly high in a given population and there is insufficient information on its causes for the planning of an action programme, the topic of the study can be broadly stated as 'the causes of infant mortality in a defined population in a given time period'. If the reason for the investigation is that health education on smoking has been having little effect, and that it is considered that certain new methods may be more effective, the investigation will be a comparative study of defined educational techniques for the reduction of smoking.

In other instances the formulation of the topic may be less easy, since the researcher may have difficulty in deciding precisely what study is needed to solve the research problem, taking account of practical limitations. As an illustration, a problem arose in a tuberculosis programme; the extent of public participation in X-ray screening activities fell short of what was desired, and there were indications that the tuberculosis rate was higher among people who did not come for screening. It was decided to seek information that would help to improve the situation, but considerable thought was required before a study topic could be formulated. The alternative topics were the reasons for nonparticipation and those for participation. For a variety of reasons, it was decided that the latter approach would be more useful.³⁴

As another example, a researcher interested in a possible association between eating fish and coronary heart disease has several alternative approaches. One, for example, is to study the previous dietary habits of people with and without coronary heart disease; another is to follow up groups of people whose diets differ, and determine the occurrence of the disease during a defined period; and a third is to examine statistics on the disease rates and average fish consumption of different countries. The decision will be based both on the ease with which the required information can be obtained and on the probability of obtaining convincing evidence, one way or the other.

At this early stage, the formulation of the topic of study may be regarded as a provisional one. The feasibility of a valid study still has to be determined. When planning and the pretesting of methods get under way, it frequently happens that unpredicted

difficulties come to light, requiring a modification of the topic or even leading to a decision that there is no practicable way of solving the research problem.

Notes and References

1. Geitgey DA, Metz EA. *Nursing Research* 1969; 18: 339.
2. A dishonest evaluation of health care may be *eyewash* (an appraisal limited to aspects that look good), *whitewash* (covering up failure by avoiding objectivity, e.g. by soliciting testimonials), *submarine* (aimed at torpedoing a programme, regardless of its worth), a *postponement ploy* (noting the need to seek facts, in the hope that the crisis will be over by the time the facts are available), etc. Providers of care who evaluate services that they themselves provide should take pains to confute the criticism that this is like 'letting the fox guard the chicken house' (Spiegel AD, Hyman HH. *Basic health planning methods*. Aspen Systems; 1978).
3. Feinstein A. *Clinical epidemiology: the architecture of clinical research*. Philadelphia: W.B. Saunders; 1985. Cited by Vandenbroucke JP. Alvan Feinstein and the art of consulting: how to define a research question. *Journal of Clinical Epidemiology* 2002; 55: 1176.
4. Verschuren PJM. *De probleemstelling van een onderzoek*. Utrecht: Aula; 1986. Extract translated and cited by Vandenbroucke JP (2002; see note 3).
5. Vandenbroucke JP (2002; see note 3).
6. Numerous computer programs for *storing and managing references* are available. Google Scholar and other programs can automatically add citations to databases. For free reference managers, see Appendix C.

For investigators loath to use computers, a card index is a substitute (one reference per card), with full bibliographic details (names of all authors, first and last page numbers, etc.) to avoid another hunt when a bibliography is prepared for the report.

If printouts, photocopies, reprints or tear-out copies of articles or abstracts are collected, then they should be filed and indexed in an orderly way. The planning of a filing system is described in detail by Haynes RB, McKibbin KA, Fitzgerald D, Guyatt GH, Walker CJ, Sackett DL (*How to keep up with the medical literature*. *Annals of Internal Medicine* 1986; 105: 149, 309, 574, 636, 810, 978).

7. Bacon F. *1620 Novum organum*. English translation. Open Court Publishing; 1994.
8. *Guides to critical reading* include: (a) Greenhalgh T (*How to read a paper: the basics of evidence based medicine*, 2nd edn. London: BMJ Books; 2001). Ten excerpts from a previous version that appeared in successive issues of the *British Medical Journal* [vol 315] from 19 July 1997 are available on the Internet at <http://www.bmj.com/collections/read.dtl>. (b) Sackett DL, Straus SE, Glasziou P, Richardson WS, Rosenberg W, Haynes RB (*Evidence-based medicine: how to practice and teach EBM*, 3rd edn. New York: Churchill Livingstone; 2005. pp. 81–117). (c) A series of 'Users' Guides to the Medical Literature' occasionally published in the *Journal of the American Medical Association* between 3 November 1993 and 13 September 2000.

Also, see Crombie IK (*A pocket guide to critical appraisal*, 2nd edn. Blackwell Publishing; 2007) and Abramson JH, Abramson ZH (*Making sense of data: a self-instruction manual on the interpretation of epidemiologic data*, 3rd edn. New York: Oxford University Press; 2001).

9. *Publication bias* is an established fact in the health field: negative or inconclusive studies are often 'tucked away in desk drawers' or rejected; e.g. see: Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR (*Publication bias in clinical research*. *Lancet* 1991; 337: 867), Dickersin K, Min YI (*Publication bias: the problem that won't go away*. *Annals of the New York Academy of Sciences* 1993; 703: 135), Stern JM, Simes RJ (*Publication bias: evidence of delayed publication in a cohort study of clinical research projects*. *British Medical Journal* 1997; 315: 640).

'Health journals are ... interested in news – they will always want to report the earthquake that happened and not all the places without earthquakes', (Lawlor DA. Editorial: Quality in epidemiological research: should we be submitting papers before we have the results and submitting more hypothesis-generating research? *International Journal of Epidemiology* 2007; 36: 940).

Investigators who conduct meta-analyses that combine the findings of different studies often appraise the validity of their conclusions by computing a *fail-safe N*, i.e. the number of unpublished negative studies that would be needed to render the overall finding nonsignificant or trivial (for software, see Appendix C). A number of registers of clinical trials have been set up, in the hope that this will permit unpublished results to be sought and taken into account.

10. Forms of *reader bias* include *rivalry bias* (pooh-poohing a study published by a rival), *personal habit bias* (overrating or underrating a study to justify the reader's habits, e.g. a jogger favouring a study showing the health benefits of running), *prestigious journal bias* (overrating results because the journal has an illustrious name), and *pro-technology* and *anti-technology* bias (overrating or underrating a study owing to the reader's enchantment or disenchantment with medical technology). (Owen R. Reader bias. *Journal of the American Medical Association* 1982; 247: 2533.)
11. Giustini D. How Google is changing medicine. *British Medical Journal* 2005; 331: 1487.
Advanced search techniques for use with Google Scholar are described by Noruza A (Google Scholar: the new generation of citation indexes. *Libri* 2005; 55: 170).
12. Burright M. Database reviews and reports: Google Scholar – science & technology. 2006. Available at <http://www.istl.org/06-winter/databases2.html>.
13. Sackett *et al.* (2005; see note 8). For a simple guide to the use of Medline, see Greenhalgh T (How to read a paper: the Medline database. *British Medical Journal* 1997; 315: 180).
Finding a specific article, or a few articles on a specific topic, is easy. But an exhaustive search is another story. According to the Cochrane Handbook, an exhaustive PubMed hunt for randomized controlled trials (for a meta-analysis) requires 26 search terms over and above those specifying the topic of the trials (Higgins JPT, Green S (eds), *Cochrane handbook for systematic reviews of interventions* [updated September 2006], appendix 5b.3. Available at <http://www.cochrane.org/resources/handbook/hbook.htm>).
14. SLIM (Slider Interface for MedLine/PubMed Searches), is available at <http://pmi.nlm.nih.gov/slim>.
15. Green FHK, cited by Hill (1997; see note 20).
16. Roy DJ. Controlled clinical trials: an ethical imperative. *Journal of Chronic Diseases* 1986; 39: 159.
17. Seidelman WE (Mengele Medicus: medicine's Nazi heritage. *Milbank Quarterly* 1988; 66: 221) cites the horrors committed by Mengele and other Nazi physicians as warnings against 'ethical compromise where human life and dignity become secondary to personal, professional, scientific, and political goals'. Also, see Seidelman WE (Nuremberg lamentation: for the forgotten victims of medical science. *British Medical Journal* 1996; 313: 1463) and Annas GJ, Grodin MA (eds) (*The Nazi doctors and the Nuremberg Code: human rights in human experimentation*. New York: Oxford University Press; 1995).

Experiments on prisoners in the USA are described by Hornblum AM (They were cheap and available: prisoners as research subjects in twentieth century America. *British Medical Journal* 1997; 315: 1437).

18. In *cluster-randomized trials*, e.g. those in which communities or general practices are randomly assigned to treatment or control groups, it is generally impracticable to obtain informed consent for inclusion in the trial from every individual subject before assignment.

However, in cluster-randomized trials in which intervention is targeted at individuals (e.g. if vitamin or placebo capsules are administered), subjects may be given the option of leaving the trial (after assignment) and choosing an alternative, e.g. routine care. And in studies where outcomes are measured at an individual level, subjects may be required to give their assent to

measurements or access to their medical records; this may be regarded as less important if outcomes are studied only at a group level (e.g. changes in hypertension prevalence).

Opinions differ on the importance of informed consent in cluster-randomized trials, especially in control groups receiving conventional care. However, especially if intervention or non-intervention carries risks, informed consent should probably always be requested from the groups' 'gatekeepers' (who can provide access to their members) – or, preferably, 'guardians' (who can be expected to protect the groups' interests), such as head teachers, community leaders, or local health or political authorities. Because of possible conflicts of guardians' interests, particularly if the guardians are health authorities, approval should always be obtained from an ethics committee.

For fuller discussions of ethical considerations in cluster-randomized studies, see Donner A, Klar N (Pitfalls of and controversies in cluster randomization trials. *American Journal of Public Health* 2004; 94: 416), Hutton JL (Are distinctive ethical principles required for cluster randomised clinical trials? *Statistics in Medicine* 2001; 20: 473), and Edwards SJL, Braunholtz DA, Lilford RJ, Stevens AJ (Ethical issues in the design and conduct of cluster randomised controlled trials. *British Medical Journal* 1999; 318: 1407).

The 1991 CIOMS International Guidelines for Ethical Review of Epidemiological Studies state: 'When it is not possible to request informed consent from every individual to be studied, the agreement of a representative of a community or group may be sought, but the representative should be chosen according to the nature, traditions and political philosophy of the community or group. Approval given by a community representative should be consistent with general ethical principles. When investigators work with communities, they will consider communal rights and protection as they would individual rights and protection. For communities in which collective decision-making is customary, communal leaders can express the collective will. However, the refusal of individuals to participate in a study has to be respected: a leader may express agreement on behalf of a community, but an individual's refusal of personal participation is binding.' (cited by Donner and Klar 2004, *op. cit.*)

19. Regarding *research in developing countries*, international guidelines state: 'Rural communities in developing countries may not be conversant with the concepts and techniques of experimental medicine ... Where individual members of a community do not have the necessary awareness of the implications of participation in an experiment to give adequately informed consent directly to the investigators, it is desirable that the decision whether or not to participate should be elicited through the intermediary of a trusted community leader. The intermediary should make it clear that participation is entirely voluntary, and that any participant is free to abstain or withdraw at any time from the experiment'. (Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects published by the World Health Organization and the Council for International Organizations of Medical Sciences. Cited by Hutton JL (Ethics on medical research in developing countries: the role of international codes of conduct. *Statistical Methods in Medical Research* 2000; 9: 185)).

It may also be practicable to obtain the subjects' informed consent as a second stage, after consent has been received from a community leader, as demonstrated in a vaccine trial in Senegal (Preziosi M-P, Yam A, Ndiaye M, Simaga A, Simondon F, Wassilak SGF. Practical experiences in obtaining informed consent for a vaccine trial in rural Africa. *New England Journal of Medicine* 1997; 336: 370).

Ethical considerations in field trials in developing countries are reviewed by Smith PG, Morrow RH, (eds) (Methods for field trials of interventions against tropical diseases: a 'toolbox'. Oxford: Oxford University Press; 1991. pp. 71–94).

20. The *ethical aspects of clinical trials* were emphasized by Sir Austin Bradford Hill 1977 (A short textbook of medical statistics. London: Hodder and Stoughton. p. 223), who on his election to the Royal Society was recognized as 'the leader in the development in medicine of the precise experimental methods now used nationally and internationally'.

The basic principle is neatly summarized in the following exchange: ‘Mr Ederer: “If you could give only one bit of advice to a clinician planning a clinical trial, what would you tell him?” Dr Davis: “A one-word answer might be ‘don’t’. If you are determined to do it, my advice would be from the beginning put yourself in the patient’s position and develop the protocol so you would be happy to be one of the subjects. If you cannot do that, you’d better not start.”’ (Davis MD. *American Journal of Ophthalmology* 1975; 79: 779).

See the *Helsinki declaration*, available at <http://www.wma.net/e/policy/b3.htm>.

21. Angell M. Editorial: The ethics of clinical research in the Third World. *New England Journal of Medicine* 1997; 337: 847.
22. Wilmshurst P. Editorial: Scientific imperialism. *British Medical Journal* 1997; 314: 840. Other extracts: ‘Should research be conducted in a country where the people are unlikely to benefit from the findings because most of the population is too poor to buy effective treatment? ... Drug companies have performed research on children and adults in countries such as Thailand and the Philippines that do not conform to the Declaration of Helsinki and could not be conducted in the developed world. Reasons quoted for conducting research in Africa rather than developed countries are lower costs, lower risk of litigation, less stringent ethical review, the availability of populations prepared to give unquestioning consent, anticipated underreporting of side effects because of lower consumer awareness ... In some experiments in developing countries it is difficult for patients to refuse to participate ... participation in a trial may be the only chance of receiving any treatment’.
23. Rutstein DD. In: Freund FA (ed), *Experimentation with human subjects*. London: George Allen & Unwin; 1972.
24. Bacchetti P, Wolf LE, Segal MR, McCulloch CE. Ethics and sample size. *American Journal of Epidemiology* 2005; 161: 105.
25. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. *PloS Medicine* 2005; 2: 1112.
26. For *ethical aspects of epidemiological research*, see: Coughlin SS (Ethical issues in epidemiologic research and public health practice. *Emerging Themes in Epidemiology* 2006; 3: 16) and Susser M, Stein Z, Kline J (Ethics in epidemiology. *Annals of the American Academy of Political and Social Science* 1978; 437: 128 [reprinted in Susser M. *Epidemiology, health and society: selected papers*. New York: Oxford University Press; 1987. pp. 13–22]).
27. A specimen ‘informed consent’ form for use in an interview survey is provided by Stolley PD, Schlesselman JJ (Planning and conducting a study. In: Schlesselman JJ (ed), *Case-control studies: design, conduct, analysis*. New York: Oxford University Press; 1982. pp. 69–104).
28. The ‘To tell or not to tell’ dilemma in studies involving HIV testing, and possible solutions, are discussed by Avins A, Lo B (To tell or not to tell: the ethical dilemmas of HIV test notification in epidemiologic research. *American Journal of Public Health* 1989; 79: 1544), Kegeles S, Coates TJ, Lo B, Catania J (Mandatory reporting of HIV testing would deter men from being tested. *Journal of the American Medical Association* 1989; 261: 1989), and Avins A, Woods W, Lo B, Hulley S (A novel use of the link-file system for longitudinal studies of HIV infection: practical solution to an ethical dilemma. *AIDS* 1993; 7: 109).
29. Thomas SB, Quinn SC. The Tuskegee syphilis study, 1932 to 1972: implications for HIV education and AIDS risk education programs in the Black community. *American Journal of Public Health* 1991; 81: 1498.
30. Richter E, Barach P, Herman T, Ben-David G, Weinberger Z. Extending the boundaries of the Declaration of Helsinki: a case study of an unethical experiment in a non-medical setting. *Journal of Medical Ethics* 2001; 27: 126.
31. Waters WE. Ethics and epidemiological research. *International Journal of Epidemiology* 1985; 14: 48.

32. Rothman KJ. The rise and fall of epidemiology, 1950–2000 A.D. *New England Journal of Medicine* 1981; 304: 600.
33. 'Time, talent, and money are sometimes squandered on the measurement of the trivial, the irrelevant, and the obvious ... A friend of mine who has a gift for felicitous expression has distinguished between "ideas" research on the one hand and "occupational therapy for the university staff" on the other, and once referred to a research project as "squeezing the last drop of blood out of a foregone conclusion"' (Lord Platt. *Medical science: master or servant*. *British Medical Journal* 1967; 2: 439).

See an amusing compilation by Hartston W (*The drunken goldfish: a celebration of irrelevant research*. Unwin Hyman; 1988) of actual research results (Do rats prefer tennis balls to other rats? Can pigeons tell Bach from Hindemith? Does holy water affect the growth of radishes?) that serves 'to drop a gentle hint that there might be too much research going on, and much of that is taken far too seriously'.

Useless research is satirized in the *Journal of Irreproducible Results* (for details and a sample of contents, visit www.jir.com on the Internet).
34. Rosenstock IM, Hochbaum GM. Some principles of research design in public health. *American Journal of Public Health* 1961; 51: 266.

2

Types of Investigation

Before discussing the detailed planning of a study, we will consider the types of investigation and their nomenclature. The primary distinction is between surveys (or observational studies) and experiments (trials). The various types of epidemiological and evaluative studies will be reviewed in this chapter.

Surveys and Experiments

Since a survey is most easily defined negatively, as a nonexperimental investigation, we will start by defining an experiment.

An *experiment* is an investigation in which the researcher, wishing to study the effects of exposure to, or deprivation of, a defined factor, decides which subjects (persons, animals, towns, etc.) will be exposed to, or deprived of, the factor. Experiments are studies of deliberate intervention by the investigators. If the investigator compares subjects exposed to the factor with subjects not exposed to it, this is a *controlled experiment*; the more care that is taken to ensure that the two groups are as similar as possible in other respects, the better controlled is the experiment. In a controlled experiment on the effect of vitamin supplements, for example, it is the investigator who decides who will and who will not receive such supplements; in a survey, by contrast, people who happen to be taking vitamin supplements are compared with people who are not.

A study is a true experiment only if decisions about exposure to the factor under consideration (e.g. to whom will vitamin supplements be offered) are made by the experimenter. A researcher who wants to conduct an experiment does not always have full control over the situation, and may be unable to make such decisions. It may be possible, however, to construct a study that resembles an experiment, although in this respect it falls short of being a true one. For example, it may be feasible to make observations before and after some intervention not under the investigator's control (medical treatment, exposure to a health education programme, etc.) and to make parallel observations in an unexposed group. The study may then be called a *quasi-experiment*¹ (although some experts prefer to regard such studies as nonexperimental). This term is also sometimes used if the allocation to experimental and control groups (even if under the experimenter's control) is not random (see *randomization*, p. 328).

Although quasi-experiments are sometimes given the unflattering appellation of ‘pseudo-experiments’, they are often well worth doing when a true experiment is not feasible (see pp. 347 and 349); but their findings must be interpreted with caution – it may be difficult to be sure that the outcome is, in fact, attributable to the intervention.

The term *natural experiment* is often applied to circumstances where, as a result of ‘naturally’ occurring changes or differences, it is easy to observe the effects of a specific factor. A famine may permit a study of the effects of starvation. A recent example is the demonstration of a raised schizophrenia rate in the offspring of mothers who were exposed to a famine at the time of conception or early pregnancy.² Snow’s classic comparison of cholera rates in homes with different water sources, some more contaminated than others, in London in the middle of the 19th century,³ may also be termed a ‘natural experiment’ or ‘experiment of opportunity’. ‘Natural experiments’ are surveys or, at most, quasi-experiments (if they examine the effects of man-made changes not planned as experiments, as in the demonstration that the incidence of myocardial infarction in a community in Montana was lower during the operation of a smoking ban in public places than before or after the enforcement of the ban).⁴

Manipulations of animals or human beings are not synonymous with experiments. An investigator who studies bacteriuria in pregnancy by needling the bladders of pregnant women through their abdominal walls in order to collect urine for examination is conducting a survey, not an experiment. An experiment is always a study of change.

A *survey* (or *observational study*)⁵ is an investigation in which information is systematically collected, but the experimental method is not used; that is, there is no active intervention by the investigators. In this book, ‘survey’ is used in a broad sense to mean a nonexperimental study of any kind and does not have the narrow connotations sometimes associated with the term, such as a public opinion survey, a questionnaire survey, a descriptive study of population characteristics, a field survey, or a household survey. Surveys are not necessarily brief operations; they may involve long-term surveillance (see p. 25) or repeated interviews or examinations.

Descriptive and Analytic Studies

Studies may be *descriptive* or *analytic*.

A *descriptive* study sets out to describe a situation, e.g. the distribution of a disease in a population in relation to age, sex, region, etc. An *analytic* (or *explanatory*) study tries to find explanations or examine causal processes (Why does the disease occur in these people? Why do certain people fail to make use of health services? Can the decreased incidence of the disease be attributed to the introduction of preventive measures? Does treatment reduce the risk of complications?). This is done by formulating and testing hypotheses, which may have various sources,⁶ including the findings of previous descriptive studies.

An analytic study may be used to explain a local situation in a specific population in which the investigator is interested, or to obtain results of a more general applicability, e.g. new knowledge about the aetiology of a disease.

All descriptive studies are surveys, but surveys can also be analytic; experiments are obviously analytic. The distinction between a descriptive and an analytic survey is not always clear, and many surveys combine both purposes.

Cross-sectional and Longitudinal Studies

Studies, whether descriptive, analytic or both, can be usefully categorized as cross-sectional or longitudinal, depending on the time period covered by the observations. A *cross-sectional* study (an ‘instantaneous’, ‘simultaneous’, or ‘prevalence’ study) provides information about the situation that exists at a single time, whereas a *longitudinal* (‘time-span’) study provides data about events or changes during a period of time.

A survey in which children are measured in order to determine the distribution of their weights and heights, or to compare heights at different ages, is cross-sectional; the children are examined once, at about the same time (not necessarily on the same day). A survey in which the same children are examined repeatedly in order to appraise their growth is longitudinal. If the influence on child growth of parents’ smoking habits is investigated in any of these surveys, the study is an analytic one. Most experiments are longitudinal studies that follow up different groups to measure events or changes; some only compare the status of the groups after the experimental exposure (‘postmeasure only’ trials), without measuring their initial status.

Any longitudinal survey in which a group (or ‘cohort’) of individuals (however selected) is followed up for some time may be called a cohort (‘follow-up’, ‘panel’) study; but the term ‘cohort study’ is generally used more restrictively, to refer to an analytic longitudinal study (see p. 20). ‘Cohort study’ should not be confused with ‘cohort analysis.’⁷ A study of the occurrence of new cases of a disease is an *incidence* study, and a follow-up study of persons born in a defined period is a *birth-cohort* study.

Note that the distinction between cross-sectional and longitudinal studies depends only on whether the information collected refers to a particular time. The *timing* of the study – *when* it is conducted, i.e. at the same time as the events studied (a *concurrent* study) or afterwards (a *historical* study) – is not relevant. Nor does it matter whether the study uses previously recorded data, or data collected after the start of the study; these two kinds of data are best termed *retrolective* and *prolective* respectively (from the Latin root of the word ‘collect’)⁸ rather than ‘retrospective’ and ‘prospective’, to avoid confusion with other meanings of the latter terms. Note also that the term ‘cross-sectional’ is sometimes used in other senses, e.g. for studies of total populations or representative samples (‘cross-sections’) of them.

In some studies, data that refer to the present time are treated as if they referred to the past. Reported disease in the subject’s relatives, for example, may be taken as evidence of prior exposure to genetic or other familial factors; or in a study of the association between lead poisoning and behavioural problems in school, the lead content of milk teeth may be used as an indicator of lead poisoning in early childhood.⁹ It has been suggested that such studies should be called *pseudolongitudinal*.

Epidemiological Studies

Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems.¹⁰

Epidemiological studies have three main uses. First, they serve a diagnostic purpose. Just as a diagnosis of the patient's state of health is a prerequisite for good clinical care, so a *community diagnosis* (see Chapter 34) or *group diagnosis*, leading to a *needs assessment*,¹¹ provides a basis for the care of a specific community (or other defined group). Epidemiological studies – descriptive and analytic – provide the required information about health status and the determinants of health in a specific community or group. Second, epidemiological studies (mainly analytic surveys) can throw light on aetiology, prognostic factors, the natural history of disease, and growth and development. Such knowledge is of general interest and has a wide applicability, in addition to the help it provides in specific local situations. Third, epidemiological studies (surveys and experiments) can contribute to the evaluation of health care both in specific local situations (how well an accident prevention programme is working) and in general (whether this vaccine prevents disease). Surveys of population health, it has been said, 'can be both the *alpha* and *omega* of health care by being the vehicle for both the discovery of need and the evaluation of the outcome of care and treatment'.¹²

The role of epidemiological studies in community-oriented primary care, which integrates the care of individuals with the care of the community as a whole, will be described in Chapter 34.

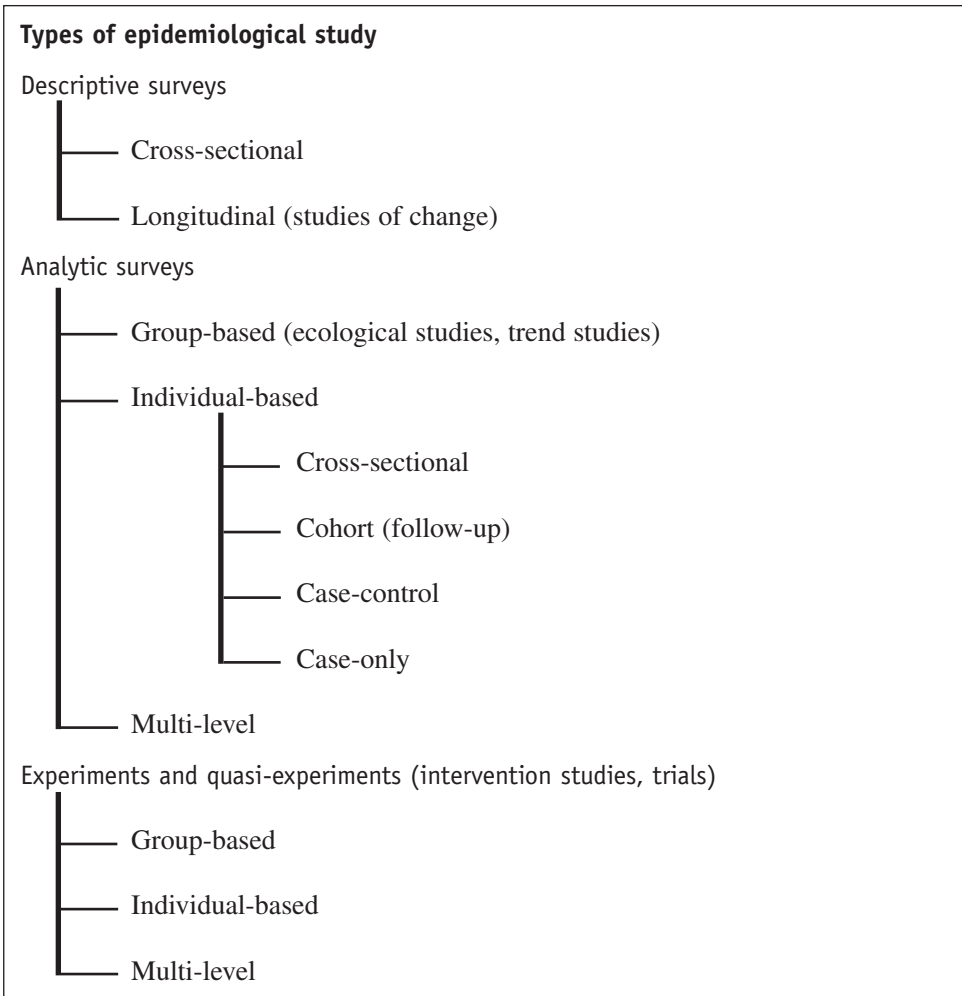
A schematic classification of epidemiological studies is shown on the next page.

Descriptive epidemiological surveys may be cross-sectional (how many blind people there are in the population) or longitudinal. Longitudinal surveys investigate change, e.g. studies of child growth and development, or a changing suicide rate, or the 'natural history' of disease (what the course of events after infection with HIV is), or the occurrence of new cases of disease or deaths in the population. They include clinical studies that describe the features or progress of a series of patients. Descriptive epidemiological surveys do not aim to find explanations, but their findings are often presented by age, sex, region, and other demographic variables. If the associations with the latter variables are explored in detail, then the survey can be regarded as both descriptive and analytic.

Analytic epidemiological surveys and *experiments and quasi-experiments* may be group-based, individual-based, or multilevel.

Group-based analytic surveys

A *group-based analytic survey*¹³ is a comparison of groups or populations. It is a study of a group of groups, not a group of individuals. Such studies are sometimes termed *ecological* or *correlation* studies. As an example, a group of countries could be compared with respect to their death rates from cirrhosis of the liver, on the one hand, and the average consumption of alcohol and various nutrients on the other hand.¹⁴ Or



general practices could be compared, as in a recent study in England that showed that statins (lipid-lowering drugs) were prescribed more in practices serving deprived communities, irrespective of the prevalence of coronary heart disease and diabetes and the proportion of ethnic minorities and elderly patients.¹⁵

We could also conduct a *trend or time-series* study¹⁶ by comparing the findings of descriptive studies performed in the same group at different times, e.g. by analysing the changing mortality rate from a disease in relation to changes in average fat intake and per capita tobacco consumption.¹⁷ Such studies often produce results of considerable interest, like the doubling of the rate of fractures of the proximal femur in Oxford over a 27-year period.¹⁸ Comparisons of trends in different populations may be instructive: a study of liver cirrhosis mortality in 25 European countries between 1970 and 1989 showed different trends in different regions, but the rates declined in all regions a few years after a decrease in per capita alcohol consumption; there was also evidence

of a birth-cohort effect,⁵ portending a future decrease in mortality in western and southern Europe, and an increase in eastern and northern Europe.¹⁹

Group-based studies are sometimes denigrated, on two main grounds. First, because they sometimes yield misleading results as a result of the inaccuracy, inappropriateness or unavailability of data, often obtained from national statistical offices or other official sources. But even then, they may serve to draw attention to differences or trends meriting further investigation. The strong positive correlation between infant mortality and the number of doctors per 10,000 population demonstrated in 1978 in a comparison of 18 developed countries in Europe and North America did not necessarily mean that infants should be kept away from doctors, but it raised important questions, even if the correlation was a reflection of other (then unknown, and now partly known) factors for which data were not available.²⁰ Doll and Peto have pointed out that although the striking correlations between colon cancer and meat consumption and between breast cancer and fat consumption, observed in international comparisons, may not mean that eating meat or fat is a major aetiological factor, they certainly show that the large international differences in the rates of these neoplasms are not chiefly genetic in origin, and suggest that these cancers are largely avoidable.²¹

Second, it may be misleading to apply the findings of a group-based study at an individual level; this has been termed the *ecologic fallacy*, a type of *cross-level bias*. Death rates from road accidents may be higher in richer countries, but within countries they may be higher in poorer people. If we find that populations with a high consumption of beer tend to have a high death rate from cancer of the rectum,²² this does not necessarily mean that *individuals* who drink more beer are prone to develop this tumour; this should be tested in an individual-based survey, or maybe in a rather pleasant experiment.

The term 'ecologic fallacy' has unfortunately tended to throw ecologic studies into disrepute. But the findings of group-based studies can be important in their own right, and there is no reason to expect that their findings will necessarily be valid at an individual level²² (or, conversely, that findings at an individual level will necessarily be valid at a group level, which has been called the '*atomistic fallacy*').²³ A comparison of villages in Mexico showed a strong association between dengue infection (the presence of antibodies) and exposure to *Aedes aegyptii* mosquitoes; this was a useful finding, although no such association existed at an individual level.²⁴ Similarly, the observation that after floods in Bangladesh there was an increase in the proportions of children who manifested aggressive behaviour and enuresis is of interest, although the behaviour of individual children did not vary according to the danger of drowning they personally experienced.²⁵

Group-based studies are sometimes the only appropriate study design, e.g. in comparisons of groups exposed to different environmental influences²⁶ or differing with respect to processes of intra-group transmission or interaction, and sometimes they facilitate the study of relationships with environmental exposures that are difficult to measure at an individual level. Group-based studies have assumed greater importance with the resurgence of interest in the influence of societal and other group processes on health, and in the determinants of the health status of human populations.²⁷

Individual-based analytic surveys

Individual-based analytic surveys are, of course (like all epidemiological studies), studies of groups, but they utilize information about each individual in the group. In their simplest form, such surveys are performed to test a hypothesis that a specific causal factor is a determinant of a specific disease (or other outcome), by measuring each individual's exposure to the postulated causal factor and the presence of the disease in each individual.

Most individual-based analytic surveys can be categorized as cross-sectional, cohort or case-control studies, or as combinations of these types.

An analytic *cross-sectional study* examines the associations that exist in a group or population (or a sample of a group or population) at a given time. The study may be based on retrolective i.e., (previously recorded) or prolective data.

A *cohort study* is an analytic *follow-up* or *prospective* study in which people who are (respectively) exposed and not exposed to the postulated causal factor(s), or who have different degrees of exposure, are compared with respect to the subsequent development of the disease (or other outcome under study); the people who are followed up are referred to as the cohort. If the disease is one that cannot be contracted twice, then people who have it at the outset (before the follow up) are generally excluded from the comparison.

Note two sources of possible terminological confusion: the term 'cohort study' is sometimes used for a descriptive (nonanalytic) follow-up study, and the term 'prospective' is often used to indicate the collection of data after the start of a study (prolective data; see p. 15), rather than a cohort-study design.

A cohort study resembles an experiment, except that exposure or nonexposure is not controlled by the investigator. Specific subjects may be chosen for follow-up because of their exposure or nonexposure to the causal factor, or a cohort may be selected in some other way (say, because of residence in a specific neighbourhood), characterized with respect to exposure status, and followed up. As an example, baseline information about drinking habits and other characteristics was obtained for a population sample of Finnish beer-drinkers; after a 7-year follow up, a comparison of men who initially had different drinking habits showed that mortality was three times as high among men who had beer binges (six or more bottles per session) than among those who usually drank less than three bottles each time (allowing for differences in age, smoking, total alcohol consumption, and other factors that might affect mortality).²⁸

Previously collected (retrolective) and historical data are often used in cohort studies. An extreme example is a comparison of the mortality of obese and nonobese persons, the data being their weight when they originally took out life insurance policies (before the study) and their survival from then until the time of the study. This may be called a *historical prospective study* (among other terms).²⁹ As another example, a cohort study that started in 1976, in which 121,700 nurses were followed up by postal questionnaire every 2 years, was able to demonstrate that their weight at birth had a strong inverse relationship with the occurrence of coronary heart disease between 1976 and 1992, using birth weights reported in the 1992 questionnaire; the

authors describe their design as 'retrospective self report of birth weight in an ongoing longitudinal cohort of nurses'.³⁰

In a typical *case-control study* to examine the relationship between a suspected causal factor and a disease (or other outcome), prior exposure to the causal factor is compared in people with the disease and in controls who are representative of the population 'base' from which the cases came.³¹ Ideally, the controls are people who would have become cases in the study if they had developed the disease. This condition is most easily met in a case-control study performed within a defined population. It can also be easily satisfied if the case-control study is performed in the framework of a cohort study, so that the experience of new cases identified in the study cohort can be compared with that of controls from the same cohort. This is a *nested case-control study*, where the controls are selected from cohort members who were free of the disease at the time the corresponding case developed it. If a case-control study is performed in a defined cohort, a *case-base* or *case-cohort* design can be used, by selecting controls who represent the total cohort, regardless of their future disease status.

There are two main types of case-control study: *classic*, *cumulative* or *cumulative-incidence* case-control studies, in which the controls are selected after the risk of becoming a case has passed (e.g. at the end of an epidemic); and *density* or *incidence-density* case-control studies, in which cases and controls are sampled throughout the period of the study (the cases at the time they develop the illness, and the controls from people free of the illness at the time the cases develop it).

The selection of cases and controls for a case-control study will be considered in more detail in Chapter 9.

As a simple example of a case-control study, women students who acquired their first urinary tract infection were compared with sexually active women without a history of urinary tract infection, drawn from a random sample of all students at the same university. Questions about condom use in the previous fortnight indicated that use of an unlubricated condom strongly increased the risk of urinary tract infection (compared with no birth control method); the increased risk was much smaller if the condom was lubricated or spermicide-coated.³²

Two examples of nested case-control studies are:

1. Men killed in road accidents during a 15-year cohort study of steelworkers were compared with control workers drawn from the same cohort. One of the findings was that exposure to high levels of noise at work was associated with an approximately doubled risk of being killed in a road accident.³³
2. Participants in the cohort study of 121,700 nurses were asked in 1982 to submit toenail clippings (and 68,213 did so) in order to permit use of the concentrations of iron, arsenic, zinc and other trace elements in the clippings as measures of the intake of these elements. The toenail trace element levels of new cases of breast cancer identified between 1982 and 1986 were then compared with those of 459 individually matched controls. A simple cohort design would have required assays of clippings from 68,213 nurses, instead of about 900.³⁴