Ethical Aspects of Epidemiological Research

IV.7

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7.1 Introduction

> Every UK citizen has the right to medical care, but those rights also involve responsibilities. Better treatments that save more lives come from research into previous patients' experience.
> Peto (2001)

> I think you need to give conscious consent to having any data, any personal data used, whether you are identified or not. That's certainly a right. That's your information, it's your medical history. Whether it's identified or not, you should control it.
> Patient 14, in Willison et al. (2003)

These two quotes are about values and expectations, about perceived responsibilities, about community benefits and individual rights in medical care and research, and reflect thereby compellingly the tensions, the paradoxes, the different views and ethical aspects concerning biomedical research (Coughlin 2000). Epidemiology is part of the arena of biomedical research and is particularly focussed on determinants of disease occurrences in populations. Ethics is the systematic analysis of values and norms (Weed and Coughlin 1999; Weed and McKeown 2001). Usually ethical reasoning and conduct are not issues that are at the top of a epidemiologist's menu chart (Beauchamp et al. 1991). In previous chapters of this handbook we have seen that most epidemiological methods are non-interventional, e.g. observational by design, meaning that conventional ethical aspects of experiments with human beings (e.g. protocol review, randomisation, placebos, informed consent, etc.) are not applicable as such. Many ethical committees have been struggling with the review of protocols of non-interventional studies because of the rationale and design of the study being directed at not influencing the 'natural' disease course of patients, but at determining statistical inferences between various exposures (e.g. environment, drug treatment, medical practice) and effects in the population in a non-experimental fashion. Observational epidemiology possesses the attractiveness, but also the practical paradox, of scientific investigation with a priori objective of not intervening in the normal course of the study object.

There have been several drivers within and outside the field of epidemiology that have changed the picture of ethical aspects significantly over the last decades. First of all, since the mid-eighties of the last century the development and availability of automated record linkage databases, capturing both exposure and outcome data on an individual level, have raised questions about confidentiality of patient's medical records, authorizing access to person-specific information, and misuse of such databases (Knox 1992). A second driver has been the debate about integrity and conflict of interests related to epidemiological research, in particular in cases of sponsored epidemiological studies and/or when the results of such studies

were contradictory and subject of controversy and discourse. Finally, the growing interest of epidemiologists to include molecular variables in their studies (e.g. laboratory data, biomarkers, genetic factors) has fuelled ethical questions and debate about the design, conduct and what to do with the study results of such epidemiological research.

As a consequence, the last decades have shown that concern about the ethical aspects of their research activities has become engaging epidemiologists as much as others who deal with public health, clinical decision making, prioritising and policy making in health care. Ethics guidelines have been prepared and accepted by several epidemiological organizations (Bankowski et al. 1991; IEA 1998) in response to a growing awareness among epidemiologists that ethical conduct is essential to epidemiology. Basic principles of integrity, honesty, truthfulness, fairness and equity, respect for people's autonomy, distributive justice, doing good and not harming have been made explicit. Essentially, the appreciation of these values have their origins in the follow-up of the Nuremberg trials, the UN Declaration on Human Rights, the Declaration of Helsinki, and many later declarations, guidelines and codes of conduct. Basically, these declarations and guidelines reflect a major shift in current society from less priority to collective interests and benefits towards the primacy and protection of the individual (World Medical Association 2000; Coughlin 2000).

Drivers of Awareness of Ethical Aspects in Epidemiology 7.2

Surge of Automated Databases 7.2.1

One of the visionary founders of medical registries has been William Farr who understood already in the nineteenth' century clearly the importance and potential of keeping person-specific records on diagnoses, medical treatments, environmental factors and disease course (Farr 1875). Later various approaches of building and linking datasets for evaluating medical treatments and other determinants of health have been developed. In the early sixties and seventies of the twentieth century, consistent and protocol based medical record keeping became also recognized as an essential tool for clinical practice, and worldwide famous centres of clinical and epidemiological excellence like the Mayo Clinics or the Oxford Radcliff Infirmary earned their appreciation mainly because they were champions in collecting and managing clinically relevant person-specific information in an era when paper charts, pencils and several primitive collecting and retrieving machineries where state of the art technologies (Gostin 1997). The introduction of advanced computer and information technologies changed that picture dramatically in the mid and late eighties of the twentieth century. Storing, assembling and linking clinical information became 'push button' actions and fascinating avenues for epidemiological

research capturing data of hundreds of thousands, even millions, of individuals became feasible (Quantin et al. 1998). However, the 'push button' nature and the big numbers involved of these developments gave rise to various ethical questions, in the beginning still vaguely phrased but later in very pronounced way on the table.

The overwhelmingness of the potentials of new information technologies and the speed of the developments have driven the need for a comprehensive balance sheet of all the social, political and ethical aspects involved. Moreover, the owners and stake holders of these automated databases are usually not health care providers or professionals but third party payers, e.g. health insurers, Health Maintenance Organisations, or governmental bodies. These organisations have mostly not their origins in the professional and ethical environment of Hippocratic medicine, and have invested in these data systems with other purposes (e.g. reimbursement of health care providers, cost-containment, risk management) than supporting medical practice (Gostin 1997).

The surge of automated databases has been stirred by the progress in record linkage techniques. Record linkage is the process by which pairs of correctly matched records of person-specific information are brought together in such a fashion that they may be treated as a single record for one individual (Herings et al. 1992). Record linkage provides a powerful tool in epidemiology in order to stratify exposures according to patient outcomes, e.g. bringing data together on food intake and cancer events, or exposure to sleeping pills and hospitalisations for hip fracture. Record linkage has driven the expansion of automated databases and from an ethical point of view there has been at least two major concerns (Herings et al. 1992; Kelman et al. 2002). First of all the operational process of linkage of individual data from a number of sources using a unique person-specific ID (identification) requires patient identification. Researchers in epidemiology have developed for that reason probabilistic approaches of record linkage, using sets of in itself not unique identifiers. However, it is believed by some opponents that this approach of record linkage may also violate data confidentiality rules i.e. each pseudonymised method needs to be validated and then the use of person-specific data (e.g. name or other ID) is essential (Tondel and Axelson 1999). A second concern related to record linkage has always been the fear that (non)medical data (e.g. insurance status, life style, sexual behaviour, socio-economic position) are built-in epidemiological data frames enhancing the feasibility of making unintended and/or undesirable statistical inferences that could cause damage or distress to individuals (Kmietowicz 2001). As a consequence, in the advent of a surge in automated databases, many countries both in North America and Europe have taken comprehensive legal action to assure the protection of personal privacy (Vandenbroucke 1992; UK Parliament Acts 1998; US DHHS 2001; de Vet et al. 2003).

Today's balance sheet of the role of automated databases in epidemiological research looks very positive. Cancer epidemiology, cardiovascular epidemiology, pharmacoepidemiology are branches in epidemiology where such databases are key resources. They all have in common complex multivariate and time-dependent exposure-disease occurrences. Confidentiality of person-specific information is

one of the most imperative ethical aspects to consider. We will come back to this later on in this chapter.

Scientific Integrity and Conflict of Interest in Epidemiological Research 7.2.2

In the 'ideal' world, basic values of integrity, objectivity, respect and independence should be key to every field of science. Committed to the discovering of the truth, researchers design, conduct and report on study results (Levinski 2002). This notion gives the impression of science being a logical and unbiased human activity. Current society has long relied on scientists' professional commitment to truth and honesty. However, disclosure of for instance a case of fraud by a Dutch neurologist participating in the 'European stroke prevention study 2' (ESPS-2), a multicentre stroke study, scandalized both the medical research community and the public (Hoeksema et al. 2003). The neurologist had committed fraud, in the sense that he had used names and fingered data of existing patients without these patients actually being enrolled in the study. Recently, the University of Connecticut in the US announced clear misconduct by a vaccine expert who had falsified preliminary data in two grant applications (Malakoff 2003). The university removed the expert as head of the research centre and a series of lawsuits between the university and the vaccine researchers took place. We notice here two obvious cases of serious misconduct in biomedical science, e.g. doctoring of data. Other examples of questionable and unethical scientific behaviour include apparent study sponsor induced bias, as well known from research sponsored by the tobacco industry into the association between smoking and lung cancer (Barnes and Bero 1998), and at the very end of the spectrum, fraud and falsification of data. We will come back to industry sponsoring of epidemiological research into drug effects. But there are other more subtle constraints to scientific integrity.

In 2002 Levinski gave a very personal and historical account on how he started as a medical researcher, and reflecting visibly on major ethical questions, e.g. the protection and reimbursement of human research subjects, informed consent, disclosure of financial interests, prestige of the academic institution and personal career building. The account also shows that ethical weighing can vary strongly over time. What we believed as being ethically acceptable in the past, might not be today or vice versa:

> In 1963, before the advent of institutional review boards (IRBs), I was a young academic physician studying the regulation of sodium excretion by the kidneys. I paid medical students approximately $50 to serve as subjects for experiments involving only saline infusions and the collection of blood and spontaneously voided urine samples. I do not remember exactly what I told the students about the risks of the experiments but am quite certain that I characterized them as nominal. In one subject, severe phlebitis developed at the site of an intravenous

> infusion and required extensive therapy. The research project was funded by the National Institutes of Health. I had no possibility of financial gain from it. My primary motive was academic – the desire to advance knowledge about an important physiological mechanism with a bearing on clinical conditions such as edema. A potent secondary motive was to advance my career by publishing the results of the research and maintaining grant support – academic currency that buys prestige and promotion.
> (Levinski 2002).

For epidemiology, conflicts of interest related to research sponsoring are a very contemporary and controversial issue. Thompson has defined conflicts of interests as

> a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)
> (Thompson 1993).

Financial interests related to the tobacco industry have been subject of intense controversy since decades. This industry has been always active in engaging researchers (as well as public media) for promoting messages contrary to the available epidemiological evidence on health risks of both active and passive smoking. In the field of epidemiology of drug effects two archetypal cases have paved the pathway of debate and controversy on the ethics of research sponsoring, conflict of interest and scientific (mis)conduct:

Cardiovascular Risks of Calcium-Channel Blockers

In 1995 Psaty et al. reported in the JAMA about a population-based case-control study among hypertensive patients in order to assess the association between first myocardial infarction and the use of antihypertensive agents (i.e., beta-blockers, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, diuretics). The main result of the study was that the use of short-acting calcium-channel blockers, especially in high doses, was associated with an increased risk of myocardial infarction (Psaty et al. 1995). An intense controversy on the scientific validity of the study, the consequences for treatment of patients with hypertension, and the financial implications for the companies marketing calcium-channel blockers followed in both the medical literature and the lay press. A surge of commentaries, reviews and additional papers on the topic emerged in the literature. Stelfox et al. (1998) evaluated the obviously visible signatures of the debate in the medical literature and demonstrated a strong association between authors' opinions about the safety of calcium-channel blockers and their financial relationships with those industries having an apparent interest in the hypertension market. Supportive authors had more financial ties with manufacturers of calcium-channel antagonists, while critical authors were much less likely to be involved in industry sponsoring

and other financial connections with manufacturers. Although the paper of Stelfox et al. could be criticized for methodological reasons (lack of adjustment for dynamics of actions-reactions of time in the aftermath of the Psaty et al. paper) the overall message remains valid: there is and has been an association between ties with sponsors, choice of study questions and, possibly, study results.

Venous Thrombosis Risk of Oral Contraceptives

In the same year as the calcium-channel blocker controversy emerged 1995, several case-control studies reported on a two-fold increased risk of deep vein thrombosis and pulmonary embolism in females using the so-called third generation oral contraceptives relative to second-generation oral contraceptives (Skegg 2001). These findings engendered a surge of further (for the most part case-control) studies primarily driven by questions on possible confounding by indication (e.g. health user effect meaning preferential prescribing of third generation oral contraceptives to females with more risk factors of cardiovascular disease) and biases related to the method of exposure ascertainment to oral contraceptives.

Many of these studies were sponsored by the pharmaceutical industry and Vandenbroucke observed a contrast between the industry sponsored studies reporting a relative risk of 1.5 or less and the non-funded studies consistently showing an increased risk of about 2.0 (Vandenbroucke 1998) (see also Fig. 7.1).

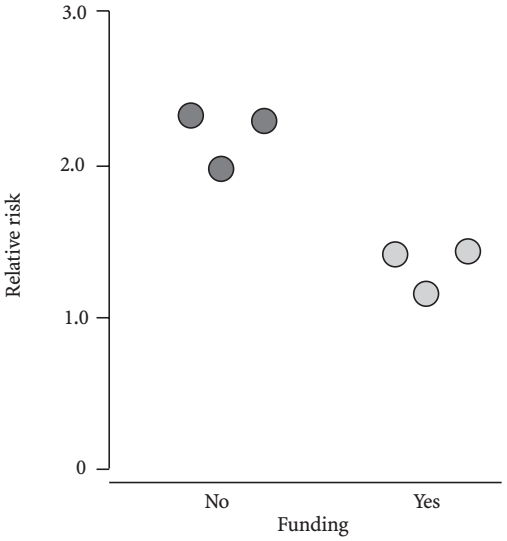

Figure 7.1. Risk of venous thrombosis with third-generation contraceptives stratified for industry sponsoring. From Vandenbroucke (1998)

Answering the question whether this contrast is real, implicating that industry sponsorship is followed by biased research, is much more difficult to answer and is still subject of an ongoing debate. To illustrate the bewildering impression fuelled

by the array of conflicting studies captured in Fig. 7.1, Vandenbroucke quotes a pharmacologist involved in early-phase studies for the industry:

> … this might very well mean that industry-sponsoring studies are the better ones
> (Vandenbroucke 1998).

Like in case of the calcium-channel blockers controversy, a surge of commentaries and additional papers on the topic emerged in the literature and the public press. Moreover, as the topic was also subject for several court cases, the legal press covered the issue as well. This controversy has been one of the most striking examples in the last decade of how to find the truth in studying drug exposure-outcome associations, to unravel possible biases and confounding factors, dealing with study sponsor's interests, and at the same time to protect scientific integrity. Researchers are exposed to myriad pressures (e.g. balancing individual and institutional needs, search for professional recognition, and sometimes, even rivalry). The science arena operates as a function of all the influences and pressures. Most progress to untangle the individual impact of all these factors has been made in demanding at least disclosure of all financial interests of the researcher by virtually all scientific journals and scientific communities (Levinski 2002). Epidemiologists need to continue to improve scientific and ethical conduct, to prevent unwanted conflicts of interest and to be aware of the great financial interests of the parties involved (Beauchamp et al. 1991; Coughlin 2000). Various avenues to achieve this goal are either proposed or already in place: (1) codes of ethical conduct are adopted by virtually all professional and scientific societies, (2) the same holds for guidelines for disclosure of possible conflict of interests by authors submitting papers to medical-scientific journals, (3) there is a surge both at the medical and other life science faculties, to include ethics classes in their standard curricula. In addition we think that researchers should submit a declaration of any potential conflicts of interest affecting the study to an institutional review board. These boards should evaluate each study in light of any declared conflicts and ensure that adequate means of mitigation are provided. When appropriate, the board may also require that a potentially conflicting interest be part of the information provided to the respondents. If a potentially serious conflict of interest cannot be adequately mitigated, the committee should not approve the project.

7.2.3 Molecular Epidemiology and Genetics

Molecular epidemiology is a rapidly emerging field and in Chaps. III.6 and III.7 of this handbook we have seen up-to-date accounts on scientific achievements and progress. A growing number of population based molecular epidemiology studies have been set up to explore the roles of molecular factors (e.g. immune response profiling, blood clotting factors, enzymes) and gene mutations and polymorphisms in disease occurrences (Maitland-van der Zee et al. 2000; Nuffield

Council on Bioethics 2003). Issues about participants' consent, confidentiality of information, and the feedback of findings, have been widely addressed. Growing knowledge about molecular pathway-disease associations have led to new opportunities for testing, increasingly important as a guide to prevention, clinical management, and pharmacotherapy. Tests are likely to vary in their predictive value, analytic and clinical validity, clinical utility, and social implications, e.g. access to care and affordability of testing, insurance or employment discrimination, stigmatisation, and long-term psychological harms from testing. Molecular epidemiology applying these tests is distinct from most other types of epidemiological research in that such biomarkers or genetic data obtained about an individual also may provide signatures of health about his or her relatives and person-specific future events. For example, concerning the latter, the implications of a positive test for the breast cancer genes BRCA1 or BRCA2 mutation differ considerably for a woman who has not yet had children compared with one who has daughters who might be susceptible as well (Burke et al. 1997).

A pivotal and informative case in identifying and understanding the ethical aspects of these developments is the area of pharmacogenetics (Bolt et al. 2002). The increasing knowledge on the genome has resulted on unprecedented advances in understanding why individuals respond differently to drug therapy (Venter et al. 2001; Roses 2000). Pharmacogenetics focuses on the question of the extent to which genetic variants are responsible for inter-individual variability in drug response among recipients of a specific drug therapy. Few drug therapies are effective for everyone. The ultimate goal of pharmacogenetics is to shape therapy with available medicines in an individualised fashion, e.g. 'tailor-made pharmacotherapy'. Pharmacogenetics integrates epidemiology, pharmacology and genetics and is focussed on an understanding of the genetic determinants of individual variability in drug therapy (Maitland-van der Zee et al. 2000). This research parallels the surge in discoveries of genes and protein expression patterns affecting the susceptibility to disease. There is evidence that certain disease susceptibility genes are also determining drug action, and thereby therapy response.

The Nuffield Council on Bioethics (2003) has identified a number of ethical issues specifically raised by pharmacogenetics: (1) consent, privacy and confidentiality (2) management of information about response to therapy likelihood (3) implications of differentiating individuals into groups based on response to therapy likelihood. The key question in pharmacogenetics is unravelling the genetic traits of efficacy and/or safety of medicines. When that information is available it can guide prescribers to select specific drugs or dosage schemes. Recently, it has been shown that on the one hand male carriers of the Apolipoprotein-E 44 variant are more prone to discontinue therapy with anticholesterol lowering agents (Maitland-van der Zee et al. 2003). Although the precise mechanism underlying this association is still not known, prescribers, pharmacists, and patients can improve therapy knowing this risk-factor of non persistence by enhancing compliance with the regimen, tailor-made counselling and the like. On the other hand, we know that Apolipoprotein-E is also associated with various cardiovascular and neurological risks (e.g. Alzheimer disease). The level of evidence of the mentioned

Apolipoprotein-E associations is still subject of ongoing research and all the three ethical issues mentioned by the Nuffield Council on Bioethics are visibly present in this case. This is particularly true in an area where we don't know today what kind of new genetic traits are discovered tomorrow and what kind of implications that has for already collected biological material (e.g. DNA samples). We see a surge in post-hoc genotyping in both clinical and epidemiological research. This is feasible as individual genetics do not change over time and when biological samples (blood, urine or buccal cells) are still available, a major ethical question is whether the informed consent (maybe completed decades ago!) still holds for the current new situation. And what about the ethical questions provoked by genotyping cases and controls in for instance a case-control study revealing that certain study subjects carry serious susceptibility genes (e.g. BRCA1 or BRCA2 mutations)? Genotyping of the cases may be well covered by informed consent in the protocol, but this may be not valid for the controls sampled from the study base anonymously. And what about the 'right not to know' of both the study subjects and their inherited relatives?

The application of pharmacogenetics information to drug development also fuels ethical questions. Preferential inclusion of tested full responders into clinical trials increases the efficiency of such programs. However, such an approach would hide important information about the actions of the drug in other patients. In case the group of responders would be (too) small to develop the compound to an economically feasible medicine, the industry might decide to discontinue the project. The latter picture has led to the illustrious quote 'Will all drugs become orphan drugs?' (Maitland-van der Zee et al. 2000)

7.3 Ethical Principles: Weighing Ethical 'Benefits' and 'Costs'

On the background of all the developments addressed so far, ethical principles are highly prevalent, but in many cases badly defined, virtually invisible or denied. Weighing of ethical 'benefits' and 'costs' is becoming an essential, additional perspective in designing and conducting sound epidemiological research (Nilstun and Westrin 1994). In the late eighties of the last century the Americans Beauchamp and Childress proposed four ethical principles in order to provide a more or less neutral, analytical framework to help doctors, researchers and all others who are engaged in medical decision and policy making, when reflecting on moral issues that arise at work: respect for autonomy, beneficence, non-maleficence, and justice (Beauchamp and Childress 1989). Despite rapid and thought-provoking changes in medical technology and the practice of medicine, we believe that these four principles, plus attention to their scope of application, may encompass most of the moral issues that arise in today's health care and public health arena (Gillon 1994, 2003).

Autonomy 7.3.1

Autonomy is a widely discussed principle in bioethics and the word has several meanings. By and large, however, two focusses can be discerned: on the one hand autonomy can be perceived as a right to self-determination, and on the other as an ideal of deliberated self rule. The first is about sovereignty, the second about authenticity. With respect to research ethics, autonomy is most visible in the practice of informed consent. Autonomy may be infringed if individuals are denied the right to choose whether or not to be enrolled in clinical or epidemiological research. Respecting people's autonomy requires consulting patients or other study subjects and obtaining their agreement before inclusion in a study. Medical confidentiality is an instrument to protect privacy, which in itself is based on the respect for a patient's autonomy.

Privacy refers to freedom of the person to choose for himself or herself the time and circumstances under which and, most importantly, the extent to which, his or her attitudes, beliefs, behaviour, and opinions are to be shared with or withheld from others. Confidentiality refers to managing private information; when a subject shares private information with (confides in) an investigator, the investigator is expected to refrain from sharing this information with others without the subject's authorisation or some other justification. Without confidentiality patients will be also far less open about all their personal concerns, symptoms and other pieces of highly private information. Such information is very often critical to assign diagnoses and treatment scenarios to individual patients. This will have implications for clinical practice, but also for research. Study subjects should have more than enough reasons to trust researchers. Respecting autonomy also means not abusing this trust.

Beneficence and Non-maleficence 7.3.2

The principle of beneficence means that health-care professionals and investigators have a responsibility to do good for those whom they treat. The traditional Hippocratic moral obligation of medicine is to provide net medical benefit to patients with minimal harm. Therefore, beneficence and non-maleficence are viewed as basic components of a balance sheet aiming at producing net benefit over harm. For epidemiology this means that a research project should add to the existing knowledge base on exposure-disease occurrences in order to treat populations of patients effectively and to prevent health hazards or even mortality in the community. In epidemiology the interests, and thereby the benefits, for the individual patient are less obvious, since often no treatment is offered. However, part of the benefit that communities, groups and individuals may reasonably expect from participating in studies is that they will be told of findings that pertain to their health. Where findings could be applied in public health measures to improve community health, they should be communicated to the health authorities. In informing individuals of the findings and their pertinence to health, their level of literacy and comprehension must be considered. Research protocols should include provision

for communicating such information to communities and individuals (Bankowski et al. 1991).

The principle of non-maleficence applied to epidemiology reflects the moral obligation not to do harm to study subjects. In many cases of research it is still uncertain what the benefits are of a specific intervention (as this is part of the study question). The principle of non-maleficence teaches that at least participating in the study should do no harm and should involve only minimal risks. Likewise, epidemiological investigators studying activities that pose risks to the well-being of subjects are ethically obligated to propose to subjects with whom they interact any feasible steps that can be taken to minimise their exposure to risk. Furthermore, harm may occur, for instance, when scarce health personnel are diverted from their routine duties to serve the needs of a study, or when, unknown to a community, its health-care priorities are changed. It is wrong to regard members of communities as only impersonal material for study, even if they are not harmed. Ethical review must always assess the risk of subjects or groups suffering stigmatization, prejudice, loss of prestige or self-esteem, or economic loss as a result of taking part in a study.

7.3.3 Justice

This principle underpins the moral obligation of a fair distribution of burdens and benefits between people. One way of looking at justice is treating those with equal need equally. Justice can also be described as the requirement to act on the basis of fair settlement between competing claims or demands. Equity is at the heart of justice, and since centuries people have argued about the morally relevant criteria for regarding and treating people as equals and those for regarding and treating them as unequals. This principle has become prominent in an era of cost-containment and rationing of health care resources. Allocation of resources may conflict between several common moral concerns (e.g. individual access to and affordability of resources, fair distribution of scarcity, autonomy of professionals to make the best decisions for their patients). All concerns may be morally justified but not all can be fully met simultaneously. Epidemiology is the science of landscaping and explaining differences (in health, socio-economic status, resources, risk factors) within populations and is thereby a critical 'monitor' of (in)equity (Weed and McKeown 2001).

7.3.4 Balancing the Four Principles

Although, all the four principles together are seen as a comprehensive frame for moral reflection in medicine and epidemiology, we can observe a shift in emphasis and a greater prominence of autonomy as the leading manual for ethical conduct. This shift of putting the individual first is welcomed with mixed feelings and has made balancing individual rights with those of the whole society to become a key issue in contemporary Western society:

> Autonomy is, then, de facto given a place of honour because the trust of individualism, whether from the egalitarian left or the market oriented right, is to give people maximum liberty in devising their own lives and values.
> (Callahan 2003).

Nilstun and Westrin have proposed a model to cross the four ethical principles with the perspectives of each of the parties involved, and then to assess and weigh the ethical 'benefits' and 'costs' for each individual party in the event the study is or is not conducted (Nilstun and Westrin 1994). Earlier in this chapter we have addressed the scientific and political debate about the risk of deep vein thrombosis and pulmonary embolism in females using the so-called third generation oral contraceptives relative to second-generation agents. In 1999 Herings et al. published a follow-up study on this topic using anonymous exposure data related to females using one of these oral contraceptives and anonymous, but person-specific, outcomes data on hospitalizations for either deep vein thrombosis or pulmonary embolism (Herings et al. 1999). The study confirmed the differential risk between the two categories of oral contraceptives and showed that the highest risk was in young females, newly starting with this contraceptive method. We use the study accessible through this paper to illustrate the model of Nilstun and Westrin.

The analysis starts with identifying the relevant parties (females using OC, society at large, industry, prescribers). In Table 7.1 possible outcomes of an analysis of the most relevant 'benefits' and 'costs' are listed concerning the two dimensions of ethical principles and parties involved in the event that the study will be conducted. If the study is done, there are possible 'benefits' for society at large, for prescribers, for (other) women using oral contraceptives. For the industry the conduct of the study results in an ambiguous picture. Manufactures of the second generation oral contraceptives considered the study as 'good news', for manufactures of the third generation the results of the study were less favourable. For industry as a whole one may argue that every piece of science that contributes to the benefit-risk balance is advantageous, although this is not perceived like this in real life. Although this is reasonably understandable, it marks also the complexity and paradoxal nature of such multi-interest cases. Because the study confirmed earlier findings that most of the risk is concentrated in the very young users, the paper provided important guidance to decision makers and young females in choosing the most suitable oral contraceptive.

With respect to the potential 'costs', respect for autonomy (violating privacy, absence of individual informed consent) of the females and (possibly) the prescribers involved in the study is critical. Data used in the study were anonymous but person-specific, meaning that the investigator could not link the research data to any individual women. The linkage procedure of the Dutch Pharmaco-Morbidity (PHARMO) record linkage database has been internationally acknowledged (PHARMO data have been used in more than 100 studies) and brings community pharmacy and hospital data within established hospital catchments regions, together on the basis of patients' birth date, gender, and general practitioner (GP) code (yielding a sensitivity and specificity of linking person-specific

data from two separate databases of over 98% each, which means that 98% are correctly linked) (Herings et al. 1992). PHARMO has been linked also to primary care data, population surveys, laboratory data, cancer and accident registries, and other outcomes data using the same linkage model. Individual informed consent from all females involved in this study was not obtained and there are certain autonomy advocates who argue that this should be accomplished. Practical and methodological (those who refuse are mostly most relevant to the research) constraints would make individual informed consent virtually unfeasible. Instead, general informed consent in order to use the data for research purposes is obtained at the time a person enters the PHARMO area. The same holds for the participating physicians. PHARMO assures to them that all analyses are doctor-anonymous in order to prevent personalized auditing or other ways of influencing prescribing practice. Looking at the principle of 'beneficence', participating females have contributed (although not in conscious fashion) to the research and have taken their share in the solidarity of bringing together relevant data for solving an important public health problem.

Table 7.1. Most important possible 'benefits' and 'costs' when the study is done

	Autonomy	Beneficence non-maleficence	Justice
Study subjects	Costs	Benefit	Mixed
Physicians	Costs	Benefit	
Industry		Mixed	
Society at large		Benefit	Benefit

Whatever the outcomes of such an exercise are they provide a systematic frame for reflection and identification 'where things can go wrong'. The latter is a pivotal role of ethics in epidemiology (Coughlin 2000). Each preliminary idea of a study protocol should be accompanied with such an 'ethical scan'. Not only for the purpose of moral justification of the research but also for reasons of improving the quality of the research. Experiences in coping with requirements to assure data privacy have been dominated mainly by technical (e.g. probabilistic linking, de-identification, introduction of random error on an individual level, but not on a population level, etc.) or procedural (e.g. standard operating procedures, good practice standards, security, etc.) dimensions (Roos and Nicol 1999). From a pragmatic view these dimensions may fully satisfy. However, ethical weighing of 'benefits' and 'costs' also includes critical reflection of the aims, deliverables and consequences for the stakeholders (e.g. patients, physicians, etc.) involved. The latter goes beyond finding 'smart tricks' to deal with privacy regulations or clinical trial directives.

As stated before, the ability to link person-specific clinical, exposure and disease course data is a critical objective of epidemiology. Of all ethical issues and considerations, respecting autonomy by protecting privacy and confidentiality are the most crucial ones. Virtually all current legal systems in the Western world

acknowledge the basic right of the patient to be assured that all his medical and personal data are confidential. Only in case of few well-defined exceptions disclosure of person-specific information is allowed, e.g. prevention of serious risk to public health, order by a court of law in a crime case, and under certain safeguards, scientific research. The tension between assuring personal privacy and access to medical data for epidemiological research has drawn ample attention from various stakeholders (individual patients, the public, politicians, health professionals, and the research community). In Table 7.1 possible violations of personal privacy related to either study subjects or physicians are classified as 'costs'.

The scientific community of epidemiologists struggles with these two concepts and tries to convince politicians and policy-makers of the importance of collective benefit to society from research with medical data and that we cannot rule out significant adverse effects to public health when epidemiological research has been made virtually impossible. Others take the pragmatic route using methodology that includes contemporary computer and statistical technology in order to build, within the framework of existing privacy legislation, aggregated, de-identified but person-specific, information. Court cases in several parts of Europe have concluded that the use of fully anonymous, de-identified patient data for the purpose of scientific epidemiological or clinical research is permissible under current law. In cases where it is not feasible to use primary data (collected directly from clinical practice for a specific, well-defined, purpose) in an anonymous fashion, informed consent should always be obtained. Epidemiological researchers may rely on access to non-anonymous medical records but access to patient records for a research purpose requires individual patient informed consent.

The effect on research quality will be determined by the proportion of individuals who refuse consent, or in the case of large automated databases, who are simply not contactable. Researchers, cautioned by privacy advocates, very often overestimate participation rates in consent procedures. There is growing evidence available that patients are willing to allow personal information to be used for research purposes. Several studies have shown that refusal to comply with consent procedures are most often not higher than in about one out of ten. A recent study form Canada suggests however, that study subjects want to be actively consulted before the start of an epidemiological study where personal information is collected, whenever this is practically feasible (Willison et al. 2003). Secondary use of data (use of existing data for purposes other than those for which they were originally obtained) remains controversial as some interpreters of the law feel that secondary data use is prohibited because of the requirement for data to be used only for purposes compatible with those for which it was originally collected. In practice we see that this requirement is solved by obtaining general informed consent, although many researchers have sought exemption from the consent requirements in order to minimise selection bias, logistical obstacles, time consumption and costs. Record linkage provides a powerful tool for the study of the natural history of diseases, the aetiology of rare diseases, or the study of drug-effect associations with a (long) induction period between exposure and outcome (Herings et al. 1992). The process of linkage of individual data from a number of sources, such

as primary care records, secondary care records, prescribing and mortality data, requires patient identification and in many countries is not permitted because this is believed to breach data protection laws. In order to comply with confidentiality rules, researchers very often rely on medical staff providing them with a list of patients' names and addresses to be used as a sampling frame. Although no medical details are given, the provision of names and addresses is clearly not anonymous and this is likely to be in breach of European and US legislation (UK Parliament Acts 1998; US DHHS 2001). Experiences so far in record linkage represent a patchwork of various approaches to link individual sets of drug exposure and clinical data. In absence of a (national) unique identifier, researchers have to rely on other approaches for bringing separate datasets together to a patient-specific linked set.

7.4 Ethical Issues Specific to Epidemiology

7.4.1 Unethical Quality of Research

This brings us to another ethical angle of epidemiological research, namely poorly conducted research. That kind of research will for sure not benefit patients or society, but may cause harm when it leads to unsubstantiated and wrong decision making in clinical practice or policy making in public health. Taubes (1995) has addressed this issue in his thoughtful paper on the limits of epidemiology where he accuses the field for producing repeatedly exposure-outcome associations that do not hold very long because subsequent studies either contradict the findings or are unable to reproduce the main study results. Although scientific controversies are essential to progress and evolution in science, conflicting data and secondary turmoil in epidemiology do most often more harm than good (Vandenbroucke 1998; Skegg 2001). This means the 'Good Epidemiology Practices' with the purpose to prevent or adjust a priori poorly designed studies, are as important for quality assurance as for ethical reasons (IEA 1998).

7.4.2 Global Bioethics and Inequity

A remaining, but not less important ethical challenge for future epidemiological research is the gigantic inequity in global health. Large differences in disease burden, variable access to efficacious and safe medical technology, gaps in pharmaceuticals and health services are an enormous concern (World Medical Association 2000). Fighting against inequity in global health as a feature of modern medical and epidemiological ethics goes beyond the application of the Hippocratic oath. It is about prioritising, about creating affordability and access, and epidemiology is and will be the pivotal science of fuelling policy making and strategic action with quantitative evidence for managing this global problem (Reich 2000; World Health Organization 2003). The triangle global inequity, epidemiology and ethics contrasts extremely with the ethics of individual 'autonomy' of for

instance a patient objecting against participating in a database study in the US or Europe. So far, ethicists have been struggling with 'prioritising' ethical issues. Questions whether a disease burden of an orphan disease with a prevalence of less than 1 : 10,000 in the EU is, or should be, as equally important as the burden of a tropical disease affecting millions and millions of people are still difficult to address. The future will teach us how far we can go with the 'equal' approach. We will face important challenges for epidemiologists and ethicists involved in these 'contrasting' areas. Some criteria, however, have been developed already. Both the declaration of Helsinki in its fifth amendment (2000) and the CIOMS guidelines for biomedical research state that research undertaken in populations with limited resources should be responsive to the health needs of the population. Moreover sponsors and investigators must ensure that products or knowledge generated by the research will be made reasonably available for the benefit of the population.

Epidemiological Determinism and Preventive Medicine 7.4.3

In the late nineties of the last century, James Le Fanu, a UK based general practitioner, wrote a reflecting and alluring book titled the 'Rise and fall of modern medicine' (Le Fanu 1999). In his book, the author is very critical about numerous features of contemporary medicine and health care, in particular about the role of epidemiology in medical education, knowledge building and clinical practice. Many of his arguments are close to the ethical questions arising from the determinism of epidemiology resulting in stratifying populations in categories of disease susceptibility, consequently leading to screening, 'healthy' behaviour and preventive medicine. The promise of genomics and other molecular strategies for improving the practice of medicine must be pursued taking into account the fundamental ethical principles of autonomy, beneficence, non-maleficence and justice. Because genetics are linked to family ties the 'right of not to know' for instance goes beyond the individual judgement and decision making of the persons involved in the study themselves.

Precautionary Principle and Scientific Evidence 7.4.4

Closely related to the former issue of epidemiological determinism is the question how strong the evidence of the relationship between a hypothesised cause (i.e. environmental factor, medical intervention, drug treatment) and the effect should be before implementation and public health action is justified (Rogers 2003). This is at the heart of the science of epidemiology, as we have seen in previous chapters, and there are many cases of 'established' exposure-outcome associations which had to be revoked afterwards because new studies and data became available, e.g. reserpine and breast cancer or fenoterol and asthma death (Fraser 1996; Spitzer et al. 1992). According to the precautionary principle, a principle widely embraced nowadays by politicians and consumer advocates, particularly in the area of assessing environmental risks, it is uncertainty that justifies and requires pro-active

measures and regulations, and a reversal of the burden of proof. A manufacturer intending the marketing of a new product or a government planning to build a new power plant have the obligation to provide solid evidence on efficacy and safety of the innovation before authorisation is granted. The pharmaceutical market knows this system already since the early sixties of the last century, but also other areas of medical technology anticipate more pro-active assessment of the benefits and risks. The application of the precautionary principle is controversial because, according to its opponents, it drives behaviour of counterproductive risk-avoidance and defensive strategies in balancing risks and benefits of innovation. Assessment and prediction of health effects of any intervention depend on a synthesis of all available epidemiological and mechanistic evidence to produce a valid estimate of the likely effect. Epidemiology is an important scientific resource to fuel the precautionary principle. From that perspective the adverse effects of this principle in terms of, for instance, exclusion of susceptible patients from certain medical technologies because proof of safety is still lacking (e.g. pregnant women, children), or neglecting and discontinuing research and development in specific risky areas, call for ethical reasoning.

7.4.5 Medical Ethics and Epidemiology

Singer and colleagues (2001) have identified a number of important drivers in medical ethics:

- New ethical challenges posed by advances in biotechnology
- Maturation of clinical ethics by strengthening the research base and developing graduate programmes and fellowships
- Emphasising the intersection between clinical ethics and health policy, including a focus on ethics of health care institutions and health systems
- Increasing public education and involvement
- Developing the conceptual foundations of bioethics
- Changes in the doctor-patient relationship.

Epidemiology is very close to clinical medicine, as epidemiologists provide scientific underpinnings of (1) the diagnosis, (2) aetiology of the disease, and (3) the prognosis (and determinants of disease) in populations, both healthy and diseased. We anticipate that all major developments in medical genetics will have consequences for epidemiology ethics as well, directly or indirectly. But because epidemiology is frequently directed at the healthy part of the population, meaning those who are not (yet) ill, the field carries specific ethical responsibilities with respect to predictive competences, e.g. identifying risk factors and preventive medicine. Moreover, as stated before, there are not many scenarios in epidemiological research where study subjects individually can benefit directly from the study and/or the research results. Partly this is a consequence of the historical nature of for instance retrospective case-control or many cohort studies, the anonymity of the data, and the large numbers involved, making person-specific implementation of the study results to study subjects hardly feasible. These features contrast with

clinical research with more options for direct patient benefit. Direct patient benefit (or harm) is also an important driver of the discussion on the ethics of placebo-controlled clinical trials in case there is an efficacious therapy available and not treating might harm the patient for sure, e.g. by severe worsening of the disease or mortality in oncology research, or suicide risk in evaluating antidepressive therapies (Storosum et al. 2001; Michels and Rothman 2003). In general it is accepted that placebo controlled trials are only morally acceptable in the absence of proven effective therapy.

7.5 Conclusions

Among many other factors, innovation in automated databases, the surge in molecular and genetic knowledge, and controversies about scientific integrity, conflict of interest and related issues, have increased apprehension of the importance of ethical aspects in epidemiology. In the beginning, concern about loss of privacy has been a key driver of ethical questioning in epidemiology and various techniques have been developed to cope with the confidentiality issue. The creation of unbiased person-specific histories (including both data on various exposure and outcomes) is a crucial requirement in epidemiology. Ethical weighing of 'benefits' and 'costs' can play an additional and relevant role as a vehicle for thoughtful reasoning (Beauchamp et al. 1991). Indeed, there have been expressed concerns about the various ways of misusing such data. In particular in the era of genetics and the increased interests of health insurers to reduce their business risks, there is a great need for prudence, protection and careful weighing (Bolt et al. 2002; Nuffield Council on Bioethics 2003). Discovery of genes determining the response to drugs is an emerging area of genomic research as well and will produce new and intriguing ethical questions.

When considering the four ethical principles of beneficence, non-maleficence, autonomy and justice on a scale of individual versus society as a whole, it is apparent that most of the 'benefits' of epidemiological research can be attributed to the collective level (community, society), and that most of the 'costs' fall down on the individual level. That makes epidemiology vulnerable for controversies where the individual-collective dimension is sensitive. The two examples of calcium-channel blockers and the users of oral contraceptives exemplified that participating study subjects themselves are virtually not benefiting from the study results. Current or future users of both drug categories however are in a much better position after the research has been done than before.

It is not a rare occurrence that epidemiological researchers perceive ethics as cumbersome, conservative and anti-scientific. Although these feelings may be justifiable in some cases, the ultimate balance sheet of more ethical weighing and reasoning will be positive. Ethical reasoning helps also to be concise in defining the research question, the design and conduct of the study. Ethics and the linked formal and legal frameworks (e.g. scientific conduct guidelines, privacy protocols,

ethical review board, etc.) undoubtedly have delivered in terms of quality push, critical reflection and scientific enlightenment, and will continue to do so in the future. The research community, clinical medicine and patients, all are major stakeholders in searching for and achieving mutual benefit from integrating ethics into epidemiological science (Gillon 2003).

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