

Some recent developments in occupational epidemiology

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AXELSON O. Some recent developments in occupational epidemiology. *Scand J Work Environ Health* 1994;20 special issue:9—18. Occupational epidemiology has grown rapidly since the late 1970s. Case-referent studies have become popular, but more recent development relates to analyses of cohort data. Length of follow-up and employment status can now be adjusted for in such analyses. Attention should also be given to "time windows" of relevant exposure, not only in cancer studies. In cross-sectional studies of common diseases, the prevalence rate ratio should be used rather than the currently popular but unintelligible odds ratio as obtained by logistic regression. Exposure assessment should involve measures that would best reveal an existing risk and dose-response relationships. New achievements in molecular biology are currently influencing the development in occupational epidemiology. Not only DNA (or protein) adducts as markers of exposure or early effect, but also the possibilities to use data on metabolic polymorphism to identify genetically susceptible individuals attract interest. Activated oncogenes and inactivated tumor suppressor genes are useful for subspecifying various cancer types so as to obtain more sensitive studies.

KEY TERMS — cohort, confounding, cross-sectional, ethics, exposure, molecular biology, mutation, oncogene, review, time window.

In the past, occupational diseases were often thought of as specific entities and described in terms of detailed case reports. Such clinical observations are certainly still important in modern occupational medicine, but for a case report to convince a reader of a causal relationship, both disease and exposure have to be characteristic. In contrast, and especially for the less specific disorders, a quantitative approach can reveal an unequal distribution among occupational groups and thereby indicate the causal role of an occupational exposure. Epidemiologic studies have therefore become an important and integral part of occupational medicine.

Epidemiologic studies on occupational health issues rapidly increased throughout the late 1970s and 1980s. The integration of epidemiologic courses into occupational health training, along with methodological achievements in general and access to computers and statistical packages, certainly catalyzed this development. Cancer epidemiology attracted considerable research interest in this period, but other branches of occupational epidemiology developed as well. As a matter of fact the development went so fast in various directions that it is no longer possible to obtain a clear view as to which aspects represent the more thrilling and important achievements for the future. Under these circumstances, my choice is not to provide any comprehensive review, but rather to indicate some trends and select a few areas

in which some noteworthy developments and interesting achievements have been made or seem to be under way. Several other research areas would have been equally important to consider, however.

Framing the past against the present

As background to recent developments in occupational epidemiology, a brief summary of the past is warranted. The first quantitative epidemiologic views on occupational disorders appeared long ago, whereas in general the methods of epidemiologic research have been refined throughout the past half-century or less (1). For example, WA Guy in 1843 studied "pulmonary consumption" in letter press printers and found a higher risk among compositors than among pressmen (2). Interestingly, Guy applied a sort of case-referent (case-control) approach, but it took until 1951 before this study design was more thoroughly developed (3). Another example of early occupational epidemiology comes from the first observations in 1879 of an increased occurrence of lung cancer among Schneeberg miners (4). Some decades later an excess of bladder cancer among German aniline workers was reported (5). Many more decades were to pass, however, before further insights into these problems were obtained through refined epidemiologic studies.

Another, more modern example of occupational epidemiology is the proportionate mortality study of lung cancer among British workers exposed to inorganic arsenic (6). Still other examples exist of how epidemiology emerged in occupational health during the earlier part of this century, even if study designs were undeveloped.

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It is hardly possible to pinpoint when modern occupational epidemiology started, but it seems reasonable to suggest that it began in the 1950s and early 1960s, for example, with bladder cancer studies on rubber workers (7) and lung cancer investigations among gas workers (8) in the United Kingdom, and also among asbestos workers (9) and miners (10) in the United States, especially among uranium miners (11). Observations on cardiovascular disease appeared also relatively early in work-related epidemiology, regarding, for example, carbon disulfide workers (12, 13).

Cancer risks have been extensively studied in many occupational groups, especially in relation to chemical exposures. The results, in this respect, are well reflected by the monograph series of the International Agency for Research on Cancer.

There has also been an increasing interest in several other diseases, for example, in cardiovascular disease, also with regard to its psychosocial determinants. Several recent studies concern the more or less specific neurological disorders and their relationships to occupational exposures. Ergonomic risk factors and musculoskeletal disorders, as well as reproductive hazards in relation to occupational exposures, are other fields attracting considerable interest. From the exposure point of view the health effects of electromagnetic fields currently seem to be among the most intriguing questions in occupational and environmental epidemiology (14–16).

The more rigorous principles introduced for epidemiologic study design in the 1970s and the spread of these principles in Europe through the teaching of several American epidemiologists certainly enhanced epidemiologic development in general, perhaps more rapidly in occupational health than in other disciplines. The importance of the annual courses led by Olli S Miettinen at the Finnish Institute of Occupational Health can hardly be overestimated as a stimulus to especially Scandinavian, Italian, and other European researchers in occupational health. Several textbooks on epidemiologic methods have also appeared since the early 1980s to guide the use of proper study designs and analyses. Some of these books have specifically considered the issues in occupational epidemiology (17–19).

Turning from the past to the present, and with a glance at the future, it remains to be seen whether any new, fundamental ideas and methods will appear in epidemiologic research or if the development will essentially relate to subject matters in different specialties. In occupational epidemiology, one of the most specific, but still general aspects to consider and develop is exposure assessment. Related questions would deal with the effects of combined exposures. The rapid developments in molecular biology are also currently a part of occupational epidemiology, not only for markers of exposure or early effects (20, 21), but also for identifying susceptible persons and specifying disease entities (22). These latter aspects

will be of increasing interest when epidemiologic studies have to be sharpened because of decreasing exposure levels and decreasing populations with a particular exposure, at least in the industrialized countries. The following sections have been limited to these matters, along with some analytical aspects.

Methodological issues and concerns

Some analytical aspects

The methods in occupational epidemiology essentially follow those applied in epidemiology at large. Personal computers and commercially available statistical packages for handling data and analyses have certainly contributed to the development in all fields of epidemiology, and the quality of studies is likely to have improved. However, the use of various statistical packages involve the risk that researchers lose insight into their data and, as a consequence, that some types of errors slip through. It remains important to display epidemiologic data in a manner that enables the reader to check the analyses presented, if not, for example, the regression analyses at least the corresponding crude calculations (23).

Although the case-referent study has become increasingly popular in occupational epidemiology over the past decade, more of the recent development seems to have occurred in the analyses of cohort data. The classical cohort approach in occupational epidemiology may therefore become even more sophisticated and informative in the future, at least when sufficiently large materials are at hand. In the past, the occupational cohort studies have usually taken only age at risk and calendar year into account, sometimes also cumulative exposure and possibly lag time. In these studies, the healthy worker effect has been a well known and disturbing phenomenon, especially affecting younger ages in the early phase of follow-up (24). Negative trends for the standardized mortality ratio (SMR) with duration of employment can appear as an artefact and create interpretive problems. For example, such a negative trend in a cohort study was confusing in a comparison with the opposite trend in case-referent results regarding arsenic exposure and cardiovascular disease (25). However, as recently shown, such confusing negative trends for the SMR have appeared in many cohort studies (26).

In a recent paper Pearce (27) has summarized and developed some new and relevant aspects of cohort analyses. With regard to the problem of the healthy worker effect, the remedy seems to be adjustment for length of follow-up and employment status if associated with the disease, independent of the exposure. Computer programs have become available to provide appropriate person-time data for such adjustments (28). When employment status is taken into account, an otherwise negative SMR trend with employment duration can disappear if due to the healthy

worker effect (26). When workers leave employment because of the exposure, the analyses become more complicated, however (26, 29).

The consideration of induction time has also become more sophisticated in the analyses of cohort data (ie, attention can focus on a particular "time window" with regard to the relevant exposures). Such an approach is related to the more traditional use of lag time, but with truncation of the exposure so as to exclude both early and late exposure in relation to the onset of disease. Time windows are more easily considered in case-referent studies (30) and were practically applied already long ago (31). The corresponding approach in cohorts is more demanding, but the principles are now both clear and applicable (17, 27). Considering time windows for asbestos exposure has revealed the strongest effect in the period 15 to 24 years prior to lung cancer (27). Somewhat similar principles were applied also in the analyses of lung cancer data for uranium miners already in the 1970s (32), as well as more recently (33). One of the reports (33) indicates a surprisingly strong effect of radon progeny exposure in the period 5 to 15 years prior to disease. These findings certainly suggest that cancer epidemiology should not only focus on very early exposures, but also on relatively late ones as well.

Considering the strength of the effect exerted by exposure in various time windows could produce further insight into mechanistic aspects, for example, the stage in which a carcinogen acts. However, the exposure in a particular time window tends to be confounded by the same type of exposure in adjacent time periods. Soon, there will probably be much interest in questions of this kind, but not too many studies will be large enough to permit proper analyses. Similar information is certainly of interest not only in cancer studies, but also in other fields of epidemiologic research, for example, in neuroepidemiology. Hence, agents acting relatively early in life seem to be important for the later development of diseases such as amyotrophic lateral sclerosis and Parkinson's disease (34).

A development without achievements in cross-sectional studies?

The importance of personal computers and statistical packages for epidemiologic research has already been mentioned, but these tools can also lead to some stereotypes in the analytic approach. The increasingly common but questionable use of logistic regression to obtain an adjusted odds ratio in cross-sectional studies is one example. Concern has also been expressed about this approach in occupational epidemiology (35, 36). The problem is the well-known fact that the odds ratio becomes a poor measure of effect in a closed study base, when the disorder is no longer rare. Especially when logistic regression is applied and is supposed to control confounding, the

resulting odds ratio can far exceed and not approximate the prevalence rate ratio, which would be the intelligible measure of effect in a cross-sectional study. Given that the duration of the disease is the same for the exposed and unexposed groups, it can still be argued that the odds ratio represents the incidence density ratio. (See reference 37.) The duration of the disease is usually not considered in cross-sectional studies, however, even if some estimation were possible for the enrolled cases. It is not unlikely that the prevalence of a disorder is high among exposed persons, not only due to an increased incidence rate, but also because of prolonged duration of the disease.

The problem of using the odds ratio in cross-sectional investigations is perhaps most clearly visible in studies of backache, neck and shoulder complaints, and other common disorders related to ergonomic work load. For example, in a meta-analysis of cross-sectional studies of ergonomic factors and median nerve entrapment, odds ratios of about 10 or more were presented (38). Disturbed nerve function was common and was as high as 28% in the reference group of one of the included studies. Therefore the calculated odds ratios are not particularly informative of risk, even if they indicate an association. Similarly, less proper odds ratios were reported in a study of osteoarthritis in the acromioclavicular joint among employees in the construction industry (39). The reference group was foremen with a disease frequency of 36.7% on the right side and 23.4% on the left.

The odds ratios could well have been presented merely as measures of association in the papers I have used for illustration, but they could also easily be mixed up with an estimate of the relative risk in terms of the prevalence rate ratio. However, the odds ratio is obviously also looked upon as an estimate of the relative risk in such studies, as sometimes explicitly stated (40). As long as the disorder is rare, there is no problem with this interpretation, but for common disorders the odds ratio cannot be considered a measure of effect; instead it is merely a more-or-less unintelligible measure of association. A routine use of logistic regression analyses to obtain adjusted odds ratios in cross-sectional studies of common disorders therefore hardly represents a sound development, at least not if the results are presented without clarification on this point. Instead, Cox's proportional hazards model (41), as modified by Breslow (42), should be applied (36).

One more aspect should be added that bridges the odds ratio and calculations of the etiologic fraction or attributable fraction (ie, the fraction of cases attributable to the exposure). This fraction seems to play a role in some countries for determining the likelihood that a particular case of a disease has been caused by an exposure at issue. However, both excess cases and etiologic cases can be distinguished, the former being a subset of the latter (43). Tradi-

tionally the etiologic fraction relates to excess cases, but other cases would have a relation to the exposure as well, for example, by appearing earlier in life in the presence of the exposure. The term excess fraction has therefore been proposed as a more specific concept (43). Consequently, the etiologic fraction would then be a more general notion, comprising both the excess fraction and the proportion of cases whose appearance has been influenced by the exposure.

In reference to the earlier discussion about the use of odds ratios in the context of common disorders in closed populations, it is obvious that the excess fraction in cohorts and cross-sectional studies becomes highly biased if calculated by means of an odds ratio. Given no important difference in the duration of a common type of disorder and the odds ratio being taken as an incidence density ratio, the incidence density fraction can be calculated (43). This fraction has been suggested to serve as an upper limit for the excess fraction, but such information seems to be of less value. Thus it seems justified to suggest that it should at least be more clearly stated whether the odds ratio is taken as an estimate of effect or merely as a measure of association when calculated in cross-sectional studies of disorders that are not rare.

New insights into exposure assessment

Exposure assessment has been a key issue in occupational epidemiology from the very beginning, but interest has increased during recent years. This interest covers a range of issues from conceptual aspects on exposure and dose to the risk of biased study results due to inadequate assessment or classification of exposure. Exposure classification is not only concerned with the particular exposure(s) in a study, but also with the problem of properly handling various potentially confounding background variables. Conferences held specifically on the assessment of exposure in recent years certainly reflect the efforts made in this respect to improve the quality of occupational epidemiology (44, 45).

Measures of exposure are usually either exposure intensity, exposure duration, or cumulative exposure. Cumulative exposure in terms of intensity-time products or merely duration are usually considered in studies of chronic disease. Peak exposures in terms of intensity might be thought of as particularly relevant for acute diseases. With regard to genotoxic and carcinogenic agents, it is often assumed that cumulative exposure is a proper determinant of risk. There are also specific arguments suggesting that the dose to the tissue and the resulting damage to the susceptible tissue is related to cumulative exposure (46). For such a view to be tenable, linear kinetics is required for the metabolism of an agent, however. This assumption is presumably correct for many, but not

all potentially carcinogenic agents in the work environment.

Other experiences can also be noted regarding the question of proper measures of exposure in epidemiologic studies. Interestingly, a literature survey on cancer studies has shown that an exposure variable based on some measure of intensity of exposure yielded monotonically increasing exposure-response gradients and larger relative risks more often than those based on duration of exposure (47). When pharmacokinetic relationships between cumulative exposure and tissue dose for insoluble respirable dust particles and toxic metabolites of a nonpolar organic solvent were considered, no linear relationship was found between cumulative exposure and tissue dose for typical exposure intensities (48). It was suggested that this observation could help explain why a disproportionately high risk of pulmonary effects is commonly seen for workers with relatively short but intense dust exposures. Such seemingly paradoxical dose-response relationships, including the aspect of exposure-driven duration of employment, have also been discussed by others (49).

Using epidemiologic data analyses, some scientists have attempted to determine the measures of exposure indicating the greatest increases in risk and the clearest dose-response relationships. The results seem somewhat equivocal, however, and may lead to conceptually difficult measures, such as relative peak exposure and relative nonpeak exposure being considered better predictors of silicosis risk than cumulative exposure (50). A problem is obviously that explorative experiences of this kind refer to the analysis of particular data sets. There might not be too many opportunities to investigate the utility of such particular measures of exposure in other epidemiologic materials. Nevertheless the search for measures of exposure that would maximize the risk estimate would be helpful for understanding the mechanistic aspects of disease development. Especially in studies not showing effect, it is certainly of value to use several measures of exposure to obtain greater confidence that the lack of an effect is not simply due to improper measures of exposure or misclassification (47).

Another development regarding exposure assessment seems to be an increasing involvement of hygienists in obtaining more precise information about work conditions and measurements for the study population. A large-scale cancer study from Canada can serve as an example (51). Not surprisingly, exposure assessments by an expert team appeared to be more efficient in this study than the use of a job-exposure matrix (52). Similarly, interviews resulted in several increased odds ratios in a study of mental retardation and parental occupation, whereas the use of a job-exposure matrix did not (53). Structured questionnaire information is rather valid, as recently confirmed; nevertheless the underreporting of exposures can be more of a problem than overreporting (54).

Still, used properly, the job-exposure matrix has been a valuable supplement in many studies and should be superior to using only occupational titles as the measure of exposure (55).

Efforts to engage hygienists in occupational epidemiology are certainly well motivated, especially for evaluating documented exposures from the past. It is easily realized that both the measurement strategies and the methods of sampling and analyzing have varied over the years, but the consequences for the classification of exposure in a study are not equally apparent. The sampling strategies may be most relevant to consider when earlier hygienic measurements are utilized for epidemiologic purposes (56). Many, if not most, samples may have been taken for control measures and tend to be biased dependent on whether they were taken before or after changes in an industrial process for hygienic reasons.

Within- and between-worker variance of occupational exposure has also been subject to recent consideration (57). There can obviously be considerable differences in exposure between workers from the same factory and with the same job titles. Hence only 25% of the worker groups had individual mean exposures within a twofold range for 95% of the subjects. Furthermore, as many as 30% of the worker groups had a greater than 10-fold range for 95% of the subjects. There were also great day-to-day variations, especially for outdoor workers and intermittent processes. Indoor work in a continuous process led to more homogeneous exposure situations. Within- and between-group variance in exposure can perhaps be studied as an indicator of how appropriate different groupings are; they require repeated individual measurements, however (58).

The various circumstances referred to seem to suggest that considerable uncertainties are likely to affect any exposure assessments, mainly by causing nondifferential misclassification. As a result, the risk estimates tend to be biased towards the null and make it difficult to discover adverse health effects, or the risks indicated may well be underestimations. These circumstances, acting in a conservative direction, can perhaps be thought of as somewhat beneficial from the scientific point of view. When the consequences for the assessment of confounding are considered, the situation gets more problematic, however. Should the exposure under study exert a relatively strong effect, somewhat poor control of confounding would not be too influential for the overall result of the study (59). To demonstrate a rather weak effect of an exposure, however, the need for eliminating confounding is well known, especially from a strong determinant that is also closely associated with the exposure. In this situation nondifferential misclassification of the confounder is deleterious to the control of its effect (60). The problems already presented for properly assessing an exposure of interest obviously also affect the information on a confounding factor and its classification.

In view of the complex patterns of both occupational and other exposures, considerable potential for mutually confounding effects certainly exists (61). Therefore, but also for various other reasons, it has become increasingly common to consider many exposures, especially in case-referent studies. This tendency can be illustrated by a somewhat extreme example, a lymphoma study including some 150 occupations and about as many industrial categories (62). With so many possible exposures, there is usually some concern about false positive findings due to the many comparisons; there is no general agreement about the importance of what is called mass significance, however. Instead, or in addition, there should perhaps be more concern that the poor control of mutual confounding due to nondifferential misclassification produces the increased risks appearing in a series of exposure evaluations.

Molecular biology in the realm of occupational epidemiology

Achievements in molecular biology over the past decade seem to have resulted in some new approaches in occupational epidemiology. So far, interest has been particularly devoted to the identification of chemical adducts to deoxyribonucleic acid (DNA) in various worker groups. Chemical binding to surrogate molecules for DNA have also been considered, such as hemoglobin or albumin. The adducts to DNA or surrogate molecules can be thought of as markers of exposure or as markers of early adverse health effects. Another aspect of molecular epidemiology involves the combination of various clinical and histopathological disease characteristics with information on biochemical or genetic features, such as specific enzyme patterns, activated oncogenes or inactivated suppressor genes.

A high frequency of specific mutations in the p53 gene in liver tumors has been observed in regions with widespread exposure to aflatoxin B₁ and hepatitis B virus (63, 64). Similarly, specific mutations in the p53 gene in squamous skin cancers have been associated with exposure to ultraviolet light (65). Such more-or-less specific relationships might be found for occupational exposures as well, which would then result in sensitive studies and more firmly associate adverse health effects with occupational factors. Since various exposed-worker groups are likely to be smaller in the future, any possibility to design more specific and sensitive studies should be utilized. Thus the application of epidemiologic tools to evaluate molecular biology data will probably be interesting in occupational epidemiology in the future.

The following three aspects are important when the possibilities to combine molecular biology with epidemiologic analyses are being considered: (i) adducts, (ii) genetically determined metabolic polymorphism and susceptibility, and (iii) changes in the ac-

tivity of oncogenes and suppressor genes. The term molecular epidemiology (66—68) could be used to encompass all three. Other aspects of the utility and development of molecular epidemiology for occupational health purposes can be found in some recent reviews (20—22, 69).

Character of data and study designs

From an epidemiologic point of view, the different types of data from molecular biology can lead to various approaches. A common feature, however, is the cross-sectional nature of the information obtainable with molecular biology methods. Studies of adducts tend to reflect recent exposure because of the turnover of cells and proteins in the blood. Thus adduct studies have some similarity to investigations using chromosome aberrations, sister chromatid exchanges, and micronuclei. Genetically determined metabolic polymorphism is stable, and mutations in tumors are persistent and cumulative and therefore are likely to reflect some etiologically important events. These circumstances provide for potentially valuable epidemiologic research through the application of well-established study designs and analytical methods.

For adducts, cross-sectional study designs are the natural first choice (ie, comparing exposed and unexposed groups and taking some level of adducts as the outcome). A further follow-up is then possible through a prospective cohort approach, namely, by taking the occurrence of adducts as an indicator of exposure. The outcome of interest would then be, for example, some type(s) of cancer or perhaps also some other disorder(s). Case-referent evaluations within the cohort could also have a retrospective role in elucidating some specific exposure relations. Such a cohort follow-up would, however, require a large study population, and therefore economic and practical aspects become a problem.

The activity of oncogenes or suppressor genes in tumors has been suggested for study by means of what has been called case-case studies (70), but traditional case-referent designs are more preferable (22). Similarly, the case-referent approach is also well applicable in studies with data on metabolic polymorphism. In both study situations the cases are divided into subentities as defined by some genetic characteristic, and each such subentity of cases is compared with referents regarding exposure. The rationale for this division is that one particular subentity may relate more specifically to the exposure than the rest. The principle is simply the same as when subentities of clinical disease, such as histopathologic subtypes of lung cancer, lymphoma, and the like, are considered in relation to a particular exposure. As always, chance findings might well appear, and repeated studies would be needed to confirm any associations, especially since there would be few if any *a priori* hypotheses in the early phase of this research.

So far, there are relatively few examples of epidemiologic analyses of data obtained from molecular biology, and only exceptionally do they involve occupational aspects. A main problem in studies of this kind is obviously the costs of obtaining information on parameters with a molecular biology character. A practical obstacle is also the need for creating research teams covering the various technologies in both molecular biology and epidemiology, including the problems of proper exposure assessments.

Especially a cohort approach considering adducts as an indicator of a particular exposure tends to be costly because of the required screening of a relatively large study population. Cost-effective methods therefore need to be developed to permit a (repeated screening and) determination of various types of adducts. An automated method for analyzing 8-hydroxydeoxyguanosine (8-OHdG) in urine (71) can be mentioned as an example of a step forward in this respect. The levels of 8-OHdG in the urine probably reflect both exposures that cause free radical formation, notably OH radicals attacking the guanosine base, and the DNA repair capacity of the subject. Nevertheless, the analyses seem to distinguish between worker groups with different exposures, for example, in the rubber, azo-dye, and asbestos industries (72). In general, the adduct studies certainly represent a rather recent and important advance in risk assessment, and there is considerable activity in this field, which is more or less closely related to occupational epidemiology. Since there are both shorter overviews (20, 21) and extensive conference proceedings available (73), I will not deal with this aspect of molecular epidemiology any further in my review.

As already mentioned, the case-referent design is a proper approach with which to deal with health effects in relation to the polymorphism of enzyme patterns and metabolic capacity. Some general examples can be found in studies relating to the metabolism of debrisoquine, antipyrine, and some other compounds (74). For example, a risk ratio as high as 4.3, with a 95% confidence interval of 2.0—9.4, was obtained for lung cancer among persons showing a decreased half-time for antipyrine. Risk ratios of about the same magnitudes were also found for pancreatic and gastric cancers. Similarly, the risk of lung cancer among smokers has been associated with good ability to metabolize debrisoquine by oxidation (75, 76).

In occupational epidemiology the relations of interest are more complex and involve both enzyme patterns and exposures in the work environment. The assessment of exposure is traditional and can involve interviews, questionnaires, job-exposure matrices, or some other more objective method if available. For the referents, representing the exposure pattern of the study base, only the exposure frequencies, and no data on their molecular biology characteristics, are required. As in epidemiology at large, the case-ref-

erent approach becomes cost efficient also in this context. Various such studies on the interaction between occupational exposures and genetically determined characteristics are likely to increase rapidly in the near future.

Some examples of studies in this field can be mentioned. The slow acetylator phenotype has been associated with an increased risk of bladder cancer, especially among chemical workers (66, 77). Studies of this kind have not always represented proper epidemiology regarding numbers and analytic methods, however, for example, the one in which all 13 persons (100%) with bladder cancer were slow acetylators among those who had been exposed to aromatic amines (78). Among bladder cancer cases without such exposure, only 53% (17 persons) were slow acetylators, a percentage more similar to the 45% of slow acetylators in the reference group (10 persons). Hence, even if the numbers were small and the design less rigorous in this example, it seems to confirm rather well the earlier observations that the acetylation phenotype tends to determine the risk of bladder cancer from exposure to aromatic amines.

A more straightforward epidemiologic approach has been demonstrated with regard to debrisoquine oxidation, smoking, and occupational exposures, for example, to asbestos (76). Hence, extensive metabolizers showed a fourfold risk of lung cancer compared with poor metabolizers with the greater risk associated with the squamous and small-cell types. Overall a history of exposure to occupational carcinogens increased the risk ratio to 2.8 after adjustment for smoking and age, but extensive metabolizers who were smokers and also exposed to asbestos had an 18-fold increase in lung cancer risk.

Not only cancers, but also other disorders have been associated with particular metabolic patterns. For example, motoneuron disease tends to occur more frequently among people with poor sulfoxidation or sulfatidation, again with such fairly high risk ratios as 5.2 and 9.7, respectively, the confidence intervals excluding unity (74). Although not specifically considered, such metabolic characteristics can be part of the explanation of an almost 17-fold risk of motoneuron disease associated with male gender, hereditary factors, and solvent exposure (79). Parkinson's disease has also been found to be related to genetic characteristics. It occurs more frequently among people with poor debrisoquine metabolism (80). Odds ratios of about 2.5 have been reported in this respect, and the possibility to evaluate the effects of various exposures have been discussed but not supported by any data.

Given such general observations, it seems well worth investigating whether various occupational exposures further increase the risk among susceptible persons. Equally interesting is obviously the possibility that the work environment could play a relatively greater role when individuals without any in-born susceptibility nevertheless develop the disease.

The ethical consequences of this new kind of research should be noted, namely, if the knowledge about genetically determined susceptibility to occupational exposures is used to select workers for risky jobs. Instead, the proper goal should be to create a safe work environment even for those individuals who are susceptible in one respect or another.

As mentioned, the case-referent design is well applicable also to data on activated oncogenes or inactivated suppressor genes in tumors. A study illustrating this principle has been conducted on acute myeloid leukemia involving 62 cases and 630 referents (81). The 10 leukemia patients who were positive for *ras* mutation had worked more often in what was a priori defined as high-risk occupations. Odds ratios were calculated not only versus the referents but also between the *ras*-positive and *ras*-negative subjects. Interestingly, in the *ras*-positive versus the *ras*-negative comparison, rather high cross-sectional odds ratios were emphasized, as reported in the abstract of the paper. As discussed elsewhere in this paper, such odds ratios hardly represent any intelligible epidemiologic measure of risk, however, although they indicate association. The more proper odds ratios obtained by using the referents representing the study base were also rather high, however, ranging between 1.9 and 7.2 for the various exposure categorizations made. In contrast, the odds ratios for the *ras*-negative cases ranged from 0.6 to 0.9. Obviously these differences in odds ratios mean a gain in useful epidemiologic information.

Finally, a study (82) on mutations in 19 lung cancer cases among underground miners, although not classifiable as epidemiologic, showed nine p53 suppressor gene mutations in seven patients, none of the mutations being G:C to T:A transversions, as commonly associated with tobacco smoking. Additional such work on lung cancers among miners with exposure to radon and decay products seems warranted, and the results should then be evaluated more specifically by proper epidemiologic methodology.

Concluding remarks

In some perspective, it is clear that the development in occupational epidemiology has been steadily accelerating through the years, both with regard to methodology and the number of studies conducted. The field has certainly belonged to the frontiers in epidemiologic research at large and has attracted interest also from researchers who have not been primarily engaged in occupational health. The reason for this interest could well be both the importance of the field and the clarity of the questions asked and also the tradition for applying distinct study designs.

How the future will develop is always an open question, but some of the issues discussed in this review are likely to attract many investigators for some time ahead. The most specific but still general as-

pect to develop will probably concern exposure assessments in the work environment. Even if issues in molecular biology might attract epidemiologists, it is also likely that the traditional type of epidemiologic research in occupational health will continue, for example, with further studies of cancer and mortality at large. The demands on future studies will probably increase in various respects, both regarding size and design, exposure aspects included. The problems encountered in this development may turn out to be considerable, however.

The rather nonspecific neurotoxic effects of solvents and other agents have been of interest in the past. More well-defined entities, like multiple sclerosis, Parkinson's disease, motoneuron disease and so forth, are also likely to attract some interest in the future, since occupational exposures could sometimes be an etiologic component. Work-load epidemiology is also an example of how a rapidly developing new area has recently come into the focus of occupational epidemiology. Psychosocial risk factors in the workplace and their health implications is another field that attracts interest, and there seems to be a connection with ergonomic problems as well. Accidents should perhaps deserve more attention, and this field of research would benefit from better methodology than hitherto.

Finally, there is certainly a growing need for epidemiologic follow-up on the preventive efforts that (should) have been made as a result of the work-related risks that have been discovered over the years. It is likely though that many more cases still have to be harvested from the many hazardous exposures that took place in the past. Furthermore, even when the risks are believed to have faded away, it will not be easy either to obtain proper funding or enough enthusiasm to conduct the potentially negative (or rather nonpositive) studies that should be expected to follow from successful prevention. Nevertheless such studies would be a receipt of the success or failure of occupational epidemiology in reaching its ultimate goals.

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