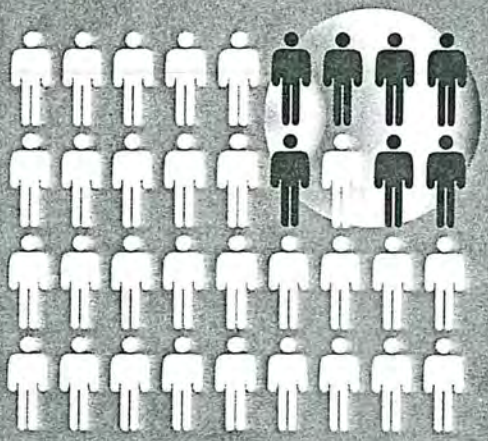

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Towards an integrated epidemiological approach to occupational risks

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Der Weg zu einem integrativen Zugang zu beruflichen Risken (Kurzfassung)

Viel von der jüngsten Kritik an der epidemiologischen Forschung ist auf die Tatsache zurückzuführen, daß sie nicht mit anderen Informationsquellen zusammengeführt wird. Zu oft war der Ansatz der, Risikofaktoren zu identifizieren, ohne auf unterstützende biologische Informationen zurückzugreifen. Im Gegensatz dazu sind manche epidemiologischen Studien so sehr mit der Beurteilung biologischer Mechanismen beschäftigt, daß sie weit davon entfernt sind, einen Beitrag zur Verbesserung des Gesundheitswesens oder der Berufsgesundheit zu leisten. Weiters verändern sich auch die Art der Berufskrankheiten und -verletzungen ständig. Viele der wichtigsten Einzelursachen wurden identifiziert. Krankheiten und Verletzungen jedoch, die auf multiple oder kombinierte Exposition, schwache Exposition oder Interaktionen zwischen Genen – Umwelt – sozio-kulturellen Faktoren zurückzuführen sind, werden von den aktuellen epidemiologischen Methoden nicht entsprechend erfaßt. Sechs Schritte wurden zur Verbesserung der epidemiologischen Forschung zu Berufskrankheiten und -verletzungen herausgearbeitet: 1) Entwicklung strengerer Kriterien für das, was die biologische Plausibilität einer Assoziation ausmacht; 2) Entwicklung neuer Ansätze zu komplexen nicht linearen Mechanismen; 3) Verwendung eines vielschichtigen Ansatzes – Genetik, Gesellschaft und Ökosystem; 4) Entwicklung von Kriterien für die Veröffentlichung negativer Studien; 5) Verwendung qualitativer Information; und 6) Anerkennung der spezifischen Verbindung zwischen epidemiologischer Forschung und den Bedürfnissen der Bevölkerung sowie der Prävention.

Vers une approche intégrée en épidémiologie des risques professionnels (Résumé)

La principale critique récemment faite à la recherche épidémiologique est que ses résultats ne sont pas intégrés à d'autres sources d'information. Trop souvent la démarche des chercheurs a consisté à identifier des facteurs de risque sans le support d'une information biologique. A l'inverse, certaines recherches épidémiologiques sont tellement impliquées dans l'évaluation des mécanismes biologiques qu'elles sont loin de pouvoir apporter une contribution significative à la santé publique et à la santé au travail. La nature des maladies professionnelles et des accidents du travail change également. Les principales causes en ont été identifiées pour la plupart. Les maladies et accidents résultant d'expositions multiples ou combinées, d'exposition à de faibles doses ou d'interactions gènes/environnement/facteurs socioculturels ne sont pas bien pris en compte par les méthodes épidémiologiques actuelles. Six étapes ont été identifiées pour faire progresser la recherche épidémiologique sur les maladies professionnelles et les accidents du travail: 1) mise au point de critères plus stricts pour établir la plausibilité biologique d'une association; 2) mise au point de nouvelles approches des mécanismes complexes non linéaires; 3) utilisation d'une approche multi-niveaux (du niveau de la génétique à ceux de la société ou de l'écosystème); 4) mise au point de critères pour la publication des études négatives; 5) utilisation de l'information qualitative; 6) identification des relations entre recherche épidémiologique spécifique et besoins de la population et action préventive.

Abstract

Much of the recent criticism of epidemiological research is the result of it not being integrated with other sources of information. Too often the approach has been to identify risk factors without drawing on supporting biological information. Conversely, some epidemiological research is so involved with the assessment of biological mechanisms that it is far removed from providing any meaningful contribution to public and occupational health. The nature of occupational disease and injuries is also changing. Many of the major single causes have been identified. Diseases and injuries that are the result of multiple or mixed exposures, weak exposures, or gene-environment-socio cultural interactions are not adequately addressed by current epidemiological methods. Six steps have been identified to enhance epidemiologic research on occupational diseases and injuries:

1. development of stricter criteria for what constitutes biological plausibility of an association;
2. development of new approaches to complex nonlinear mechanisms;
3. utilization of a multilevel approach from the genetic to social and ecosystem levels;
4. development of criteria for publication of negative studies;
5. utilization of qualitative information; and
6. identification of how specific epidemiologic research is related to population needs and preventive action.

1. Development of stricter criteria for what constitutes biological plausibility of an association

Biological plausibility is one of the criteria for assessing causal inferences. HILL [1965] included it as a criterion for distinguishing causal from noncausal epidemiologic associations. The definition of biological plausibility, however, has generally been variable and highly subjective. Most definitions follow along the lines of sound biological reasons to assume a causative relation. As SCHLESSELMAN [1987] observed, biological plausibility is probably the criterion that is used most often, either to dismiss an unexpected finding or to support an association from a study based on suspect methods. Although biological plausibility is an intellectually appealing and logically sound criterion, it is clearly limited by current understanding of, and adherence to, a particular theory. Thus, the criterion represents a conservatism that may occasionally impede acceptance of new facts revealing either deficiencies in current theory or incorrect inferences based on it. Despite this limitation, epidemiologists may not be receiving enough training in assessing the biological bases of associations. In fact, there is a lack of recognition of the importance of knowing or hypothesizing biological mechanisms. Moreover, there is not enough motivation or support to stimulate discussions or collaborations between epidemiologists and laboratory scientists on this issue.

The explosion in biological information brought about by molecular biology, genetics, and toxicology have produced numerous observations that can be used to corroborate an epidemiologic finding by a post-hoc search through the experimental or basic science literature, in some cases inappropriately so [MUSCAT, 1996]. Studies that link such biomarkers to the event that they mark may or may not add evidence to causality of a putative exposure-disease association. It is also important to link the biomarkers to the potential causal pathway in a way that allows for assessment of dose-response, appropriate temporality, and coherence with the known facts.

Although biological plausibility should be a gauge for assessing associations, it should not be an insurmountable barrier to publication, rather just to causal interpretation. Many of the breakthroughs in epidemiology may not have had strong biological plausibility upon publication of the first finding. Nonetheless, as a study is replicated, the criterion of biological plausibility needs to be strongly considered. Even in the first report of an association, investigators should raise the issue of biological plausibility, be more critical in assessing the scientific literature, and avoid jumping to post hoc justifications to corroborate findings. The challenge is to identify a coherent biological mechanism–based plausibility, not merely an inferred plausibility [McCLELLAN, 1995]. One problem in doing this is that mechanistic data should be appropriate for the exposure levels of interest. Some mechanistic research carried out with high levels of exposure may not be relevant for extrapolation to lower levels [McCLELLAN, 1995].

2. Development of new approaches to complex nonlinear mechanisms

Many of the concerns of contemporary workers pertain to apparent disorders that occur in subgroups of a more widely exposed population. These disorders include more well defined conditions, such as some allergies and asthma, and less defined ones such as multiple chemical sensitivity, chronic fatigue, and sick building syndromes. In some instances, there has been little progress in actually defining the "disorder" beyond a broad general description (e.g. worker-perceived multiple chemical sensitivity). In other instances while the definition is clearer, the relation to exposure may not be directly dose dependent. There is little good occupational epidemiology on many sensitizing conditions (asthma and allergies being notable exceptions). In part, this is due to the lack of standardized case definitions and to the possible existence of complex pathways that connect multiple causes to multiple effects. Epidemiologists looking for single etiologies are now confronted with simultaneous impacts of host factors, agent, and environment. Now more than anytime in the past, it is possible to identify inherited and acquired host factors that have not been considered in epidemiologic investigations. In the past, causal inferences were made assuming linear relationships. Now, complex nonlinear mechanisms appear to be needed to account for sensitization, susceptibility and the interaction of multiple exposures and host factors [LEVI, 1997]. To assess these conditions, linear or sigmoid dose-response relationships may have to give way in some cases to u-shaped or other types of relationships. The presence or absence of threshold may also need re-examination to study these conditions.

For centuries, investigators have wondered why only some people become sick when all are exposed to a toxicant or infectious agent. To what extent does the distribution of disease reflect chance, and to what extent does it reflect individual predisposition or susceptibility [BRAIN, 1988]. The answer lies in understanding the extent of human variability and partitioning its components within and between populations. Sensitivity must be defined with respect to some reference population: both individuals and subpopulations can be sensitive [BAILER and LOUIS, 1988].

Identifying and analyzing a subgroup at higher risk of disease are strengths of epidemiology but can also be a source of problems in analysis and interpretation. Problems can arise through failure to specify the subgroups of interest a priori, and through examining large numbers of subgroups after the fact i.e. through multiple comparison testing [STALLONES, 1987]. Subgroup analysis can be useful in assessing weak associations by avoiding dilution effects and focussing on those people most at risk. If the subgroup is picked a posteriori it is possible that its definition (i.e. the cut points for inclusion or exclusion) are selected because of the distribution of the data and in a way that artificially shows a relation between exposure and outcome.

3. Utilization of a multilevel approach from the genetic to social and ecosystem level

There is a trend in epidemiology to interpret populations as a collection of individuals without regard to social structure or ecosystem pressures. This trend can lead to failure to account for these necessary and important factors in disease risk. Analyses must shift from purely biological to include bio-social analyses [ANDERSON, 1994]. ZIELHUIS [1985] has characterized four levels of the total environment on which workers simultaneously operate: a) the micro-level of the domestic environment, i.e. the individual worker at home with his/her personal nutritional habits, cooking facilities, crowding at home, use of drugs and cosmetics, consumption of tobacco and alcohol, leisure-time activities, etc.; b) the meso-level for groups at work, in schools, in vocational training, etc.; c) the macro-level for groups in their community, county, region, country, with its ambient pollution, traffic or aircraft noise, drinking water, recreational facilities, etc.; d) the mega-level for the population at large, e.g. their climatic zone, geographic longitude, latitude, altitude. The challenge for epidemiologists is how to use information from these various levels in a meaningful and practical way to enhance research. The first step is to acknowledge that these levels exist and then to attempt to better characterize the important non-work factors for a given study. The second step is to learn how to use this information in epidemiologic research.

In addition to the various environmental levels the need also exists to consider multiple levels within individuals. These include factors at the genetic, organ, and physiologic level of the individual. Rapidly increasing information on genotypes and metabolic phenotypes have lead to many studies of genetic susceptibility. These will likely increase as high throughput technologies and functional genomics research yield new and multiple markers that can be assessed on individuals. The ability to assess multiple markers simultaneously may allow for assessing gene-gene and gene-environment interactions to degrees never before possible. However, the impact of statistical power and multiple comparison issues must be considered. New definitions of interactions and new ways of conceptualizing genes, phenotypes and physiologic relationships will have to be developed.

KRIEBEL [1994] has shown some direction in this regard by proposing a method for merging dosimetric models with epidemiologic models estimating disease risk. This approach could be a prototype for linking other detailed biologic data with disease, PBPK, and risk models. More research is needed to integrate biologically based dose response models with epidemiologic models, and then ultimately linking these models with population and ecosystem models.

4. Development of criteria for publication of negative studies

A negative epidemiologic study is "a well designed and executed study where the hypothesized association with an adverse effect was found to be very weak or non existent" [BUFFLER, 1989]. A negative finding in epidemiology research can range from being highly informative to being of little or no meaning. The critical criteria of negative studies is whether there is adequate statistical power, objective exposure assessment and well-defined outcomes. However, it is also important in many of the studies of complex contemporary diseases to understand the extent to which there are imprecisely delineated cluster of symptoms or ill-defined exposures. [BRACKEN, 1997]. Additionally, infrequent exposures may lead to negative findings.

When power is good and methods clearly defined and objective, a negative study can contribute to societal well being by providing reassurance that a risk is low. Negative studies can also provide useful mechanistic information, such as whether particular metabolic polymorphisms are effect modifiers or confounders.

Negative studies are often used to reassure a doubting public, but when scrutinized closely, the studies are deficient to a point of being uninformative. Criteria exist for distinguishing between informative and uninformative negative studies. In assessing negative evidence, the random (chance) and nonrandom (bias, confounding) sources of variation need to be considered, as well as dilution effects, dose-response patterns, biologic plausibility, and methods of data pooling (meta-analysis) [BUFFLER, 1989].

There appears to be a publication bias against epidemiologic studies that are considered negative solely because they do not demonstrate adverse health effects or because they are descriptive in nature [BUFFLER, 1989]. There have been proposals to register studies so that even if they are negative and not published, there is at least a record of them.

5. Utilization of qualitative information

Epidemiologists have been criticised for collecting data on individuals as if they were essentially interchangeable units within the study population without regard to the population's social structure [NEEDLEMAN, 1997]. As NEEDLEMAN notes "what gets lost in this approach is the social context of exposure, disease, and health – the local history, cultural, values, social networks, norms of health behaviour, economic and power relationships and other relevant features of the social system." Information on the social context cannot be captured through individual data. "Epidemiologists are not used to including system level variables in research designs, and analyses. To do so would require a change in how the research is conceptualised so as to include factors that transcend the individual." More use of analytic approaches, such as path analysis and structural equations modelling, might enhance epidemiologic research. Also, rephrasing research questions from "does A cause B?" to "what are the factors involved in the occurrence of B" might yield more useful information. Finally, in intervention research, which utilises epidemiologic principles, the use of qualitative information is of paramount importance in assuring that the intervention is effectively applied and that what is being evaluated is the intervention and not some latent work environment or social system factors. NEEDLEMAN and NEEDLEMAN [1996] have reviewed qualitative research methods for intervention research. These methods draw on the approaches of disciplines in which the study of social phenomena in naturalistic settings is common—particularly sociology, cultural anthropology, and human service program evaluation.

6. Identification of how specific epidemiologic research is related to population needs and preventive action

Epidemiology is one of the engines of prevention. Recognition of hazards, populations at risk, and causal pathways for disease and injury are what motivates prevention efforts. Historically, epidemiologists, especially occupational epidemiologists, have not been moved to disseminate the findings outside the scientific literature or use them in developing preventive efforts. Epidemiologists and their funding or parent agencies were supportive of an emphasis on etiologic research with scientific publication as the end product. The "right-to-know" movement pushed the limit of informing to include workers and their families so that they could take preventive action, or at least so that occupation risk information would be available for them or their physicians. More recently, modern epidemiology has been characterized by biophysiologic reductionism and heavy inclusion of genetic factors leading to an approach that diverts limited resources, blames the victim, produces a lifestyle approach to social policy, decontextualizes risk behaviours, and seldom assesses the relative contribution of nonmodifiable genetic factors, and modifiable social and behavioural factors [PEARCE, 1996].

Much of occupational epidemiology has resulted in extensive information on causes of disease and injury but little on choosing or evaluating what are effective preventive interventions. WEGMAN [1992] has observed that the academic occupational health disciplines have become increasingly divorced from application of prevention in the workplace. Epidemiologic methods can be applied to assessing interventions but intervention research is more difficult and costly than etiologic research and has not been widely conducted. A review of the literature on intervention research revealed a lack of disciplinary rigor [GOLDENHAR and SCHULTE, 1994]. In the U.S. a group of 500 representatives of industry, labour, academia, and government under the auspices of NIOSH identified Intervention Effectiveness Research as one of the high priority areas.

Occupational epidemiologists are uniquely suited to conduct such research. If epidemiology is to be effective in preventing disease, it must bridge the gap between individual and biological level characteristics, social behaviour, political structure and economic power [COLDITZ, 1997]. Currently, there is a lack of a population perspective in epidemiology. A population perspective involves interest in the population factors as causes of disease and the ability to see epidemiologic research as part of other public health activities [PEARCE, 1996]. This lack of a population perspective may be due to the personal and professional situations in which epidemiologists find themselves. In many countries the main source of funding are government or voluntary agencies that have little interest in or sympathy for studies of socio-economic factors and health [PEARCE, 1996]. As WEGMAN notes, the price to be paid is not only financial: the price is also the acceptance of preventable damage to health and loss of life.

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Combining the results of epidemiological studies with those of other studies for the national inspection needs

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Kombinierte Nutzung epidemiologischer und nicht epidemiologischer Studienergebnisse für staatliche Aufsichtszwecke (Kurzfassung)

Die Beurteilung der Risiken für verschiedene Berufe, Branchen und Arbeitsplätze ist meist einer der ersten Schritte in der Planung von Arbeitsplatzinspektion und Kontrolltätigkeiten auf nationaler oder regionaler Ebene. Verschiedene Formen landesweiter Statistiken zu Arbeitsverletzungen aufgrund von Unfällen oder Krankheiten werden kombiniert.Die Quellen der statistischen Informationen sind in den verschiedenen Ländern sehr unterschiedlich und machen einen Vergleich daher sehr schwierig. Für Planungszwecke innerhalb eines Landes ist allerdings die Vergleichbarkeit zwischen Industriezweigen, geographischen Regionen und Arten von Verletzungen wichtiger. Für einen Vergleich zwischen verschiedenen Perioden oder Branchen werden Inzidenzzahlen benötigt, wohingegen für das Design von Präventivmaßnahmen eher tiefergehende Fallstudien nützliche Information bieten können. Informationen von Versicherungen sind wahrscheinlich bei Verletzungen durch Unfälle vollständiger, während sowohl für akute als auch für chronische Berufskrankheiten die Daten besser aus Quellen der Gesundheitsvorsorge kommen sollten.

In mehreren Ländern geht man nun dazu über, Daten zu Berufsverletzungen von Versicherungen mit allgemeinen Daten aus den Sozialversicherungssystemen zusammenzuführen. Dadurch werden die Kombination von Statistiken zu Berufsverletzungen schwieriger und die Daten selbst weniger zuverlässig. Auch die aktuellen Änderungen der Arbeitsbedingungen könnten zu geringerer Zuverlässigkeit führen. Daraus wird sich ein gesteigertes Bedürfnis an Datenkombinationen aus unterschiedlichen Quellen ergeben. Es wird auch wichtiger werden, die Ergebnisse zu evaluieren und zu interpretieren, statt nur eindimensionale Tabellen zu produzieren.
Zur Vermeidung von Verletzungen durch chemische oder physikalische Faktoren kann nicht oft genug betont werden, daß die relevanten Daten zur aktuellen Exposition von ungleich höherer Bedeutung sind als Statistiken zu Auswirkungen Jahre oder Jahrzehnte später. Doch die Gesetzgebung eines Landes wird es nicht immer möglich machen, solche Daten von einzelnen Arbeitsplätzen zu erfassen und zu verarbeiten.