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Roles for Epidemiology: The Impact of Environmental Chemicals

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Aside from the well-recognized role of documenting the extent of any health impact from exposure to environmental chemicals, epidemiology has other potential roles. Arguing by analogy from the function of epidemiology in the infectious disease field, two practical public health functions are mentioned. The first is rumor abatement: simply characterizing the population exposed and documenting the frequency of salient complaints and providing this to the affected population, so as to separate fact from fiction. Another practical public health function is to review available data bases to document the number of individuals exposed to such chemicals and a review of gross trends by place and time to set public fears in proper perspective. There are important descriptive scientific functions as well, namely, to document any syndromes or symptom patterns which may be associated with chemical exposures and to document the natural history and progression of clinical and preclinical conditions associated with chemical exposures. The sensitivity, specificity and predictive value of tests for preclinical disease are discussed.

The most dramatic applications of epidemiology to environmental exposures in recent times have been controversial and widely publicized. One thinks of the role of epidemiology at the Love Canal, Three Mile Island and as it relates to Agent Orange. These studies have been aimed primarily at testing the hypothesis of adverse health outcomes as a result of those exposures. The application of epidemiology to exposures from hazardous waste sites is particularly problematic because the sample size is usually too small to demonstrate the expected excess risk of cancer, malformations or prematurity. Subjective problems may be more common but are commonly discounted as being too subject to bias by the complex socioeconomic factors which usually operate. It is difficult to characterize the full range of single chemicals and chemical combinations to which the population is exposed in most waste sites. The exposure dosage is usually unknown, and the expected illnesses, given low exposures by unverified routes, are poorly specified. Thus the classic task of epidemiology is made difficult under these circumstances. In this presentation, I will explore some other potential roles for epidemiology as it relates to environmental chemicals. I shall argue from analogy by exploring the familiar roles for epidemiology in infectious disease, using these roles as a paradigm for possible roles in environmental settings.

I propose to divide the activities of infectious disease epidemiology into five categories: (1) delineate the dynamics and determinants of the natural history of disease; (2) characterize the range of clinical presentations of various stages in the natural history of disease; (3) provide information regarding the magnitude of infectious disease problems with and without intervention so as to guide allocation of resources for cure or prevention; (4) rumor abatement; and (5) provide timely reliable quantitative information about alleged problems in a community.

It should be noted that only the first two items of the list deal with scientific uses of epidemiology—descriptive or hypothesis testing activities—worthy of broad biological generalization. The last three items are public health applications whose relevance is limited in time and geographically. Our success in the public health applications of epidemiology will have a great impact on our ability to pursue its scientific functions. For this reason I will begin with the last items on my list.

A community which has just discovered that it is

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living near a hazardous waste site is a little bit like a port town which has just discovered that a boatload of foreigners with the bubonic plague has just drawn into its harbor. The uncertainty and danger promptly fractures the community into at least three camps. One group desperately wants to minimize the problem for fear of the economic impact of adverse publicity. Another group is desperately anxious about health effects and made doubly frantic by the lack of unanimity among public officials and by the inevitable hesitation of public officials to take the problem seriously enough to devote the considerable resources necessary even to properly characterize the problem much less mitigate it. A remarkably large third group remains oblivious to the problem which has polarized the other two and which increasingly occupies the time of public officials. The conflict which results unmasks all kinds of personal and political vendettas, and the press, who sense a good story when they see it repeat all rumored anecdotes about ill health, the more florid the better.

To be really effective in this setting, the epidemiologist needs to be part anthropologist and ethnoscientist. The rumors which need to be addressed may seem totally incredible to the toxicologist or physician but make sense from the perspective of some important segment of the community. It does no good to ignore those concerns or to focus only on problems which are objectively measured or which seem scientifically plausible. If the rumors have to do with bleeding gums, urinary retention and childhood temper tantrums, it does no good to ignore these to deal with rates of low birth weight.

Another thing to remember is that the subjective magnitude of the risk feared by the community is several orders of magnitude greater than what a reasonable epidemiologist would expect. Without being able to articulate this, the community is concerned about risk differences of the order of 10-20%, which, if we talk about malformations or cancer, translates into risk ratios of 10-20. Fairly simple and quick epidemiological studies can pick up differences of this magnitude. Risk ratios of 2-3, which translate into an extra case or two, are not only equivocal to the scientists, but are of relatively little interest to the local community.

At this time in California, we find ourselves consumed by this problem. You have probably all read about our involvement with the malathion spraying for the Medfly in Santa Clara County, but this is only the most dramatic of a whole series of episodes relating to chemical substances in California. We feel that it is essential for us to become skilled at quick, simple and comprehensive descriptions of what has actually happened during these episodes. Here are some principles which it seems to me should guide such information gathering activities.

First, it is important to involve the several segments of the community in discussing the goals of the study, in deciding if the community wants to cooperate with it and obtaining consensus that that cooperation should be granted. We have established community advisory committees and identified technically competent ombuds persons to act as intermediaries with a community. We have even used community volunteers to hand out confidential mail-in census forms and simple questionnaires. It is not possible to rely completely on volunteers because there is inevitably a lag in interest. At the very least though, the most interested members of the community gain some insight into the difficulties of carrying out even the simplest epidemiological study, the good reasons why deadlines are often not met and the fact that not all of their neighbors share their views of the problem.

The second principle is to attempt to obtain a complete census of the affected population to establish a sampling frame and to create a roster for potential future study through death clearance or cancer registry clearance studies.

Third, we are experimenting with quick open-ended questions about odor and family health problems as well as a telephone number for future contacts or more detailed study. We wish to validate this approach with more structured follow-up questionnaires to assess the sensitivity and specificity of this open-ended approach. Our suspicion is that it will pick up the majority of problems which are salient enough to have entered the consciousness of the community.

A fourth principle is to maintain the confidentiality of individuals while giving the community a better picture of its own aggregate health status. Even a simple census of a household may convey information about marital or nonmarital relationships which are the business of nobody but the respondent. We have handled this problem by having respondents fill out simple census forms and questionnaires and sealing them into an envelope which is then returned to the Health Department either directly by mail or through volunteers or field staff.

The fifth principle is the importance of obtaining a control group using the same survey instrument. Both the community and even epidemiologists have little insight into the expected response rate among those not exposed. For example, in a dump site near Los Angeles nearly half of the population complained of eye irritation starting or getting worse since moving to this three-year-old neighborhood. Since eye irritation is not uncommon in smog-ridden Los Angeles, we did not know quite what to make of this finding. We were surprised to discover that only 10% of a similar control population had this complaint and only 2% of those who smelled odor in the neighborhood felt that these odors brought the eye irritation on. In those living near the dump site, half of the people who smelled odors complained that it brought on eye irritation.

Finally, it is important to obtain fast preliminary results and to keep communicating with all factions in the community. Direct communication is essential through letters sent directly to all residents or through community newsletters. Attempting to communicate with a neighborhood only by way of the local press often does not work, because the press needs to paint issues in terms of black and white and cannot devote the space that is sometimes necessary to explain issues of concern to the immediate neighborhood but not to the general readership. It is important to establish good communications with the press and to provide them with a glossary of technical terms, an explanation of basic concepts. Often their questions for clarification are invaluable clues to issues which we have failed to communicate to the lay public.

The objective of all this activity is to have contacted all potentially affected individuals and some appropriate comparison group, to identify any complaints which occur with excess frequency in the exposed group and which problems are not in excess. Finally, it should build the foundation for the possibility of future, more in-depth investigation, if that is necessary. One component of further investigation would be methodological, to follow a community over a period of time to document how newspaper coverage, political events and other factors influence the frequency of reported symptoms. In short, to help discriminate between the natural history of chemically induced problems and the natural history of psychosomatic problems created by the uncertainty, fear and stress of these situations.

Another major role for epidemiology mentioned in the list above was providing information regarding the magnitude of health problems with and without intervention to guide allocation of resources for cure or prevention. This boils down to providing a sense of proportion for the likely range of added risk. Epidemiologists have access to census data or even simple aerial photographs to assess the number of individuals exposed to any one particular hazardous waste site or even to those exposed throughout a geographical region, a county, a state. Death certificates, birth certificates and cancer registries provide population-based data which make it possible to estimate the expected number of significant health-related events in any population and whether there has been any obvious trend over time. Special surveys for liver and renal disease over time are also possible. The recent review of the literature relating to trends in cancer incidence and mortality by Doll and Peto (*1*) is a good example of such an exercise. These authors emphasize the importance of establishing exposed cohorts to carry out death clearance studies and the organized capability of carrying out intermittent case-control studies using population-base controls to look for environmental and occupational causes of the most common cancers (*1*).

Another major role for epidemiology has to do with characterizing the range of clinical syndrome associated with hazardous waste site exposures. Up to now, we have tended to focus on potential DNA damage from some of the chemicals known to be present at the site. In any short period of time, however, the incidence of cancer or congenital malformations would be too small to be studied in most neighborhoods near sites. In larger populations, one could look for excesses in specific kinds of cancer or kinds of malformations or could look for patterns in which several types of abnormality tended to move upwards in incidence together.

Complaints regarding hazardous waste disposal sites in our experience tend to be about headache, nausea, eye irritation, sinusitis, skin problems, infections and allergies. There is a temptation to think of these as psychosomatic or as hypochondriacal. However, I think it behooves us to take even the subjective symptoms seriously and to look at them not only separately, but to subject our data to techniques like cluster analysis and principle components analysis to see if patterns of simultaneous symptoms differ for exposed groups and unexposed groups. There we are using techniques from biological taxonomy (*2*) and which had been used in the epidemiology of colitis (*3*) and other poorly understood syndromes to see if the complaints we are receiving constitute any recognizable syndromes.

The final role for epidemiology which I would like to discuss has to do with delineating the dynamics and determinants of the natural history of disease. The paradigmatic model for infectious disease might be presented as in Figure 1. The model reminds us of a difference between the clinical and epidemiological perspective on disease. Instead of focusing on the classical full-blown clinical symptomatic presentation of the disease, we are aware of the series of stages through which a population can pass, including presymptomatic infected states, presymptomatic infectious, symptomatic, disease free with immunity or without, carrier stages and permanent disability and death. The characteristic

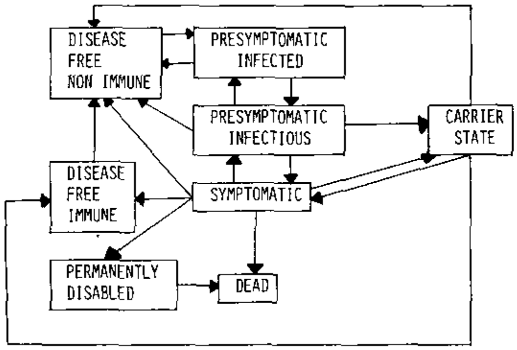

FIGURE 1. *Dynamics of the natural history of an infectious disease.*

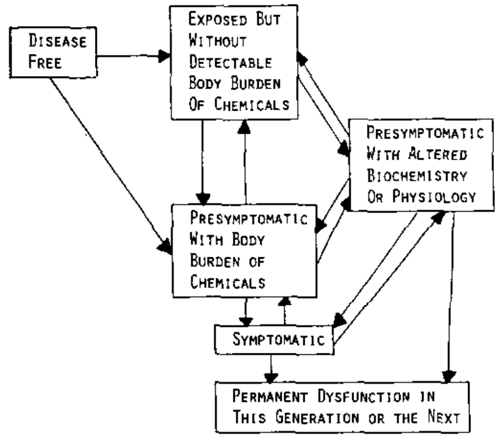

FIGURE 2. Dynamics of the natural history of chemically induced illness.

objects of the epidemiological study of this dynamic system are: the incidence in each state; the distribution of durations in each state; the magnitude of the influence of determinants of incidence and duration.

Thus, quite aside from determining the cause of gonorrhea, the epidemiologist may be interested in establishing the probability that a presymptomatic patient with gonorrhea enters into the carrier state, or he may be interested in the duration of the presymptomatic infectious period and what implications this has for strategies of gonorrhea control. Similarly, he may be interested in the impact of treatment, nutrition, social habits and environmental factors in the incidence and duration of the various stages. What anaolgies can we make to do the study of the dynamics of health problems related to environmental chemicals?

Figure 2 shows an example. The model shows us that there are presymptomatic phases of health problems related to chemicals. Some of these may be associated with measurable body burdens of chemicals; others may be characterized by altered biochemistry or physiology; still others may be undetectable by present means. There are a number of questions about duration of states which should be attracting our attention. For example, how long do symptoms persist, given continued or discontinued low dose exposure to environmental chemicals? How long do biochemical or physiological abnormalities last given continued or discontinued low dose exposure? Just as a vast majority of presymptomatic infections revert to a normal state because of body defenses, so too, even in the face of continued exposure, it is logically possible that presymptomatic states reverse themselves. Another question of interest is how long after exposure do symptomatic or physiological changes commence? That is, what is the incubation period? Focusing on these questions implies structuring cross-sectional studies so that answers of persons with varying residential duration can be compared. It also implies the necessity of follow-up studies.

There are a number of questions which relate to incidence as well. What is the incidence of altered biochemistry and physiology in the face of continued low-level exposure? Given an altered biochemistry or physiology, what is the incidence of symptoms or a permanent dysfunction?

Assessing the risk of recognized illness among persons with physiological or biochemical changes is a problem whose structure is familiar to the epidemiologist, used as he or she is to assessing screening tests in cardiovascular disease or in cancer. A number of classes of preclinical tests are being proposed to assess environmental exposures (*4*). There are tests to document traces of the offending chemicals in body fluids or tissues. I refer here to test for heavy metals, mutagenic substances in urine or serum, chemicals in breast milk, chemicals in fat biopsies. There are also a variety of tests to assess somatic tissue damage, damage to the liver, kidney and nervous system. There are tests also for hypersensitivity. Usually these tests have some obvious functional implication and do not imply an inevitable progression for some fixed proportion of the population to a more serious clinical stage. As such these tests do not present uncertainty as to their prognostic value. A variety of tests have been suggested to assess genetic damage, for example, alkylation of amino acids or proteins is thought to be correlated with the alkylation and damage of DNA itself. Various morphological tests for chromosomal damage, sister chromatid exchange, have been proposed. Simi-

Table 1. Hypothetical test for cancer.[a]

	Clinical cancer	No clinical cancer	Rate
RIA positive	96	1998	5%
RIA positive	4	97902	0.004%
RIA positive	100	99900	

[a]Prevalence = incidence × duration
= 100 ÷ 100,000 × 10 yr = 1%.

larly, altered sperm morphology and motility as well as the appearance of micronuclei in leukocytes are also thought to correlate with genetic damage and the subsequent risk of cancer or congenital malformations. Finally, there are tests for the early diagnosis of cancer itself. I am thinking here of the various radioimmunoassays (RIA) which would detect macromolecules associated with neoplastic change, tests such as the carcinoembryonic antigen, alpha fetoprotein and newer, more specific tests. Some of these RIA tests detect a high porportion of cancer patients, while only a small percentage of the general population tests positive. To some this suggests that a positive RIA test is tantamount to having preclinical cancer. An epidemiological perspective on such claims is worth presenting here.

Assume that the incidence of clinical cancer in a year is about 1/1000. Now suppose that a new RIA test was discovered which detects 96% of clinical cases, while only 2% of persons free of clinical disease in the general population tested positive. If we screened 100,000 individuals in the general population, we would come up with results such as those demonstrated in Table 1. We can see from Table 1 that in any one year 2094 individuals will test positive, but only 96 of them, or 5%, will have developed cancer. What of the remaining 95%? It may well be that they all represent preclinical cancer and that 96 of them each year will finally develop clinical cancer, so that at the end of 20 years each and every one of them will have finally succumbed. In a steady-state situation, to maintain the 2% of RIA positives in the population, 96 new individuals would have to have been exposed and entered into the preclinical stage. We are invoking here an average duration of about 20 years for the preclinical stage of cancer. Does this square with what we know about the natural history of cancer? One does hear talk about 20-year incubation periods for cancer but these usually include some precancerous phases which would probably not be shedding the antigens of interest. If the average preclinical stage which was RIA-positive lasted only 10 years, the expected prevalence of RIA positively in the population would be expressed by the formula:

$$P = \text{incidence} \times \text{duration}$$

$$= \frac{100}{100{,}000} \times 10 \text{ years} = 1\%$$

If this were true, then the 2% prevalence of RIA positives would be off by a factor of two. This might mean that our assumptions about duration or incidence were wrong, or that half the RIA positives, a thousand individuals, would not have preclinical cancer at all. Similar reasoning could be applied to the tests for DNA damage which are far less sensitive and specific and purport to test things which are logically more removed from the actual conditions of interest.

These considerations do suggest the need for further studies. For example, in animal carcinogenesis and teratogenesis experiments to demonstrate the occurrence and persistance of these immunological and biochemical changes in exposed and control animals and to relate these to the actual outcomes of interest. In human epidemiology we should consider identifying existing serum banks taken on individuals a number of years ago. We could study and follow those individuals who had tested positive or negative in previous tests and indicate the incidence of cancer with age and as time elapsed. One might also consider prospective studies of Navy or Army recruits or of large numbers of individuals in two different kinds of industries looking for the stability of the RIA and DNA damage tests with follow-up and prognosis.

In short, there are more roles in epidemiology in this field than the mere documentation of the presence or absence of excess morbidity or mortality among those persons exposed to environmental chemicals. There are the important public health functions of rumor abatement setting a general sense of perspective. There are scientific goals of characterizing the range and clusters of symptoms which are related to the exposures, and for studying the dynamics and determinates of the natural history of conditions related to chemical exposure. These descriptive scientific activities provide information useful both to prognosis and policy.

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