

Commentary

What Is an Adverse Health Effect?

by Russell P. Sherwin*

Health is defined as homeostasis of the cellular ecology, and a state where there has not been an inordinate loss, reversible or irreversible, of the structural and/or functional reserves of the body. An adverse health effect is defined as the causation, promotion, facilitation and/or exacerbation of a structural and/or functional abnormality, with the implication that the abnormality produced has the potential of lowering the quality of life, contributing to a disabling illness, or leading to a premature death. Experimental animal studies indicate that poor air quality has the potential for serious adverse health effects through perturbations of the cellular ecology over long-term periods. Some of the most important concerns are inordinate depletions of lung reserves (in particular, emphysema), the facilitation of cancer metastasis to the lung, the facilitation of immunologic deficits with the concomitant expression of opportunistic organisms, and amplification of cardiovascular abnormalities (in particular, ischemic heart disease). It is argued that air quality standard setting should more strongly consider adverse health effects that are presently subclinical in nature in order to achieve early prevention instead of late correction.

A definition of adverse health effect is a beginning step towards assistance in the establishment of reasonable air quality standards. As a part of that definition, consideration must be given to the question, what is health. Defining health is not an academic exercise, since there is no sharp line between a normal state of health and subclinical diseases. For example, some degree of coronary artery disease and emphysema is essentially ubiquitous in the adult "well population," and there is in fact a progressive deterioration of health with time and not necessarily in accordance with age. Within the health-disease spectrum there are four basic categories of adverse effects on health. The end stage category, death, provides mortality data that are relatively insensitive for assistance in the setting of air quality standards. Moreover, mortality rate increases that are acute, as occurred in the London episodes of the 1950s, and long-term rises, as for example the 20-30 year delayed mortality increase of lung cancer secondary to cigarette smoking and asbestos exposure, are obviously prohibitive sources for future air quality data. The category of morbidity ranges from the earliest or mildest symptoms of ill health to exacerbations of terminal illnesses of

diverse kinds. Morbidity data can and does provide useful data for air quality evaluation, but, again, at a level that is often less sensitive than required, or if highly sensitive, e.g., eye irritation in a highly susceptible individual, may not be considered to be a significant health hazard. A third category is subclinical disease or morbidity (1), i.e., the patient either does not have symptoms or fails to recognize them, and the level of sensitivity of clinical tests is inadequate for diagnosis. This category is an especially important and largely neglected source of data for air quality evaluation. A majority, if not most of the adult well population has some form of chronic disease at a subclinical level, ranging from early lesions to nascent clinical disease. Improvements and new developments in clinical testing are urgently needed to open up the greater part of the category of morbidity to clinical recognition, especially with respect to the major chronic diseases and the needs of air quality control. The fourth category of adverse health effects has been all but overlooked insofar as air quality standards are concerned, namely, a state of health where there has been an inordinate depletion of cell, tissue, and organ reserves, or so-called hypopenia (1). Reserve loss involves both reversible and irreversible alterations of cell population and includes metabolic abnormalities and alterations of the

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intercellular milieu. In actuality, the earliest adverse health effect is an altered ecology at the cellular level. Extraordinarily serious alterations may be sustained at this level without coming to clinical attention until structural and functional loss reaches an end-stage, as will be discussed with respect to emphysema. Thus, definitions of health and of adverse health effect must start with a consideration of the human body as an ecologic entity comprised of multitudinous cell societies.

What Is Health?

Over 30 years ago, the World Health Organization (2) defined health as a "state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity." As Callahan stated (2), the definition puts "medicine and society in the untenable position of being required to obtain unobtainable goals." No other definition has since been made available, at least not for air quality control consideration. The immediate relevancy of defining health for standard setting purposes is that the well population may not be as well as presently believed, and this would mean a far larger subpopulation of susceptible individuals than is presently appreciated. As implied earlier, the question of susceptible subpopulations must ultimately focus largely on cellular inventories, i.e., the structural and functional reserves of the cell societies and their environments that constitute the human ecology at the cellular level. Health, then, is fundamentally homeostasis of the cellular ecology, and a state where there has not been an inordinate reversible or irreversible loss of reserves.

What Is the Present Level of Health?

There is the impression that we are becoming progressively healthier, due mainly to better nutrition, sanitation, medical care, and personal hygiene. Germanely, vital statistics indicate that life expectancy at the time of birth extended to 73.6 years in 1980 (3). However, the number of years of life remaining at the age of 45 in 1980 is not remarkably different from the 1900 figure, i.e., 24.8 years versus 32.1 years, or a gain of 7.1 years (4). Moreover, life expectancy for those at age 75 has increased by only 3 years over the 80-year study period. In effect, there may be some gain for adults (3), but the longevity indicator is largely reflecting better neonatal and child care (4). There is another indicator that also cautions

against an optimistic view of the general health, namely the incidence of disability. Coldez and Blanchet (5) have called attention to a substantial increase in disability, 30% versus a 10% increase in the population. Very disconcertingly, the increase in disability included the younger and middle age groups, and the investigators concluded that environmental factors may in part be responsible for the increased incidence. A detailed treatment of the question "Do health indicators indicate health?" as cogently posed by Wilson (6), can be found in a Daedalus review (7).

What Is the Present Level of Health with Respect to the Lung?

The importance of the lung to health is of much greater magnitude than has been previously appreciated. For example, diverse metabolic activities have been identified in the lung and they warrant calling the lung an endocrine organ (8). To date, air quality studies have paid relatively little attention to pollutant-induced perturbations of the lung's diverse metabolic activities. From a clinical standpoint, the lung is gaining greater attention as a major health problem. The incidence of chronic obstructive pulmonary disease (COPD) is said to be quadrupling every 5 years, the trend beginning 15 years ago (9). There has also been a remarkable increase in the discovery of "new" lung diseases. Of special pertinence to air quality, many of the newly uncovered lung diseases are environmentally related, e.g., the ever growing list of hypersensitivity lung diseases (10), silicate pneumoconiosis (11, 12), and Legionnaire's disease (13). Moreover, the real impact on the community of some of the well-known dust hazards has yet to be established, in particular the ubiquitous occurrence of asbestos in the lungs of the well population (14). Space does not permit an expanded discussion of these serious encroachments on the structural and functional reserves of the lung, but a few additional comments on COPD are warranted.

A number of clinical studies (15, 16) have indicated that generally one of six (17%) of the working well population have COPD on the basis of both symptomatology and abnormal pulmonary function tests. For people in the well population over the age of 50, it appears that half have chronic lung disease. The autopsy, despite the use of relatively insensitive measurement methods, has provided strong evidence for substantial lung reserve depletion. Most pertinently, emphysematous disease in more than trace amounts has been found to be more often present than absent in the

lungs of adults (17-19). Further, Mitchell and his associates (20) concluded from their studies that "death certificates from two university medical center hospitals during a seven year period understated by about 20% the overall frequency with which chronic airway obstruction was the cause of death in subjects older than 40 years," and that "the reported death rates for 'emphysema' and 'chronic bronchitis' underestimated the presence of chronic airway obstruction at the time of death by about 50%." More sensitive methods of measuring emphysema, and a greater interest in the support of autopsy studies, will undoubtedly demonstrate a far greater loss of lung reserves in the well population than presently appreciated (21).

There is a special need for more sensitive pulmonary function tests as an aid in standard setting. We have speculated, from very limited clinicopathologic correlations, that pulmonary function tests first become indicative of chronic obstructive pulmonary disease (COPD) only when 50% or more of lung structure and/or function has been lost, with the loss being largely irreversible. Germanely, there is no disagreement that a patient who first complains of symptomatology referable to COPD may have incurred as much as 80% or more of irreversible lung damage. There is also a well-recognized progressive decrement in pulmonary function with aging (22) that very likely reflects a substantial rate of consumption of structural and functional reserves of the lung. Of further pertinence, experimental animal studies have shown that 75% of the lung can be extirpated without notably altering the animal's ordinary activities (23, 34).

The most obvious health implication of a loss of lung reserves is a poorer performance, as for example in competitive sports. More seriously, reserve loss tends to lower resistance to disease and leads to a greater vulnerability of the lung to disease in general. Of special pertinence is the report from the Framingham, Massachusetts heart study (24, 35) that poor lung function, in particular forced vital capacity (FVC) was "second only to age" as a predictor of potential heart problems and mortality in women, and is rivaled only by blood pressure among men. It is not clear whether the low FVC is a sign of generalized debility or reflects a direct effect of poor lung function on the heart.

Morbidity and Cardiovascular Disease

Diseases of the cardiovascular system are the single greatest cause of death, and exacerbation

of these diseases, e.g., carbon monoxide-induced myocardial ischemia is an important consideration for air quality standards. Of special interest, Graboy (25) stated that an estimated 40 million Americans will be involved in some form of sustained aerobic activity by 1980. At least half will be over the age of 35 and therefore candidates for exercise stress testing. Of the 20 million asymptomatic individuals in this group, approximately 10% can be expected to have electrocardiographic changes suggestive of myocardial ischemia, thus warranting consideration for coronary angiography. Of the 10% with ECG abnormalities (2 million persons), 25% or 500,000 will, as a conservative estimate, have multivessel coronary disease. Thus there will be half a million candidates for bypass surgery in view of the "extrapolated assumption that the asymptomatic person with multivessel diseases carries an annual mortality similar to that of the symptomatic coronary patient." This illustration of heart disease at a subclinical level is in accord with routine autopsy experience. Like destructive lung disease, destructive coronary artery disease with some degree of luminal alteration is the rule and not the exception at autopsies of adults. It is also not uncommon to find atheromatous plaque formation in the young adult, or even in the child. Germanely, a 1953 report on coronary disease in soldiers killed in action in Korea stated that 77.3% of 200 soldiers, age 18 to 48 (mean age 22) had some evidence of coronary arteriosclerosis (26). In 5.3% of the hearts, luminal narrowing of the artery was over 90%, and complete occlusion of one or more vessels occurred in 3%. While a more recent study of 105 U.S. soldiers killed in Vietnam (18 to 37, mean 22.1 years) showed less coronary disease (? methodology difference or improvement in health), there was nevertheless evidence of some coronary artery atherosclerosis in 45% and severe disease in 5% (27). The fact that one can live to "a full lifespan" despite a totally occluded left coronary artery, or in rare instances with marked occlusion of both right and left coronary arteries, largely reflects great reserve capabilities.

Diminished body reserves and increased subclinical disease due to poor air quality will be eventually reflected in mortality statistics. Needless to say, the immediate standard setting need is to avoid adverse health effects that will lead to end-stage disease, especially considering that large segments of the well population will have sustained substantial covert and irreversible damage to their health by the time mortality statistics would indicate the seriousness of the

poor air quality. Mortality data can, however, serve a number of important purposes, not the least of which is providing epidemiologists with a more precise identification of primary and contributory causes of death. There is a need not only for improvements in the uniformity of death certificate recording, considering their flagrant inaccuracy at the present time (20, 28), but also for a greater use of the autopsy for verification of the clinical diagnosis. In a recent review, Wheeler (29) stated that a reliance on clinical diagnosis alone results in an overall inaccuracy rate of 40% to 50% for death records, and the error is of major significance for at least 10% of the records. Furthermore, there is relatively little appreciation for the fact that the autopsy itself is commonly the source of major error in the interpretation of the cause of death and contributing factors. An example of great pertinence to air quality evaluation is the relatively crude and nonuniform diagnosis of emphysema at autopsy (21). More specifically, Thurlbeck (30) has pointed out that "... expert pathologists have found uninflated lungs valueless in recognizing emphysema at necropsy. Even when inflated lungs were used experts in the pathology of emphysema showed startling discrepancies in their estimates of emphysema ..."

What Is an Adverse Health Effect?

Noxious air pollutants, and noxious agents in general, adversely affect the cellular ecology (cells, tissues, and environs) to produce abnormalities ranging from minor perturbations that are compensable or reversible to totally destructive lesions and functional abnormalities that lead to death. It should be emphasized that reversible as well as irreversible abnormalities of relatively minor magnitude can nevertheless have a serious impact on health by exacerbating other disease processes or by creating a state of increased susceptibility to disease in general. To meet the real needs of air quality control, special efforts must be made to increase the sensitivity of discriminants used for assistance in standard setting, not only with respect to the present emphasis on pulmonary function testing and the recording of acute respiratory disease, but also in terms of unmasking the greater part of disease and abnormal function that presently exists at a sub-clinical level in the well population. Thus, a definition of an adverse health effect must encompass the entire spectrum of disease. We propose the following definition: an adverse health effect is the causation, promotion, facilitation, and/or ex-

acerbation of a structural and/or functional abnormality, with the implication that the abnormality produced has the potential of lowering the quality of life, causing a disabling illness, or leading to a premature death. A special attribute of the definition is the focus on the earliest stage of disease. This can mean detection before covert disease becomes extensive and widely distributed in the well population, as for example may very well be taking place with respect to emphysema for reasons presently unestablished. In the latter respect, there is obviously a need to determine the rate of depletion of lung reserves in the well population, and to employ animal models in a search for alterations at the level of the cellular ecology (discussed further below). The definition also encourages a search for relatively minor adverse effects on cells and tissues that may serve to facilitate or otherwise amplify other disease processes. A cogent example is the facilitation of cancer metastasis to the lung (as opposed to a role in the causation or promotion of cancer) by an ambient level of an air pollutant, as discussed by Richters elsewhere in this symposium presentation. One other relatively overlooked area of health concern that falls under the covert part of the adverse health effect definition is the low-grade, chronic disease process caused by subtle hypersensitivity type reactions, of which there is a rapidly growing and still relatively unappreciated list of responsible agents (10), and also by relatively unappreciated infectious diseases that are caused by diverse organisms indigenous to the lungs and other organs (discussed below).

The Endogenous Infectivity Experimental Animal Model

Presently, the infectivity animal model, based on exposing animals to aerosols of highly concentrated bacterial populations (31), is receiving special attention for its high level of sensitivity in demonstrating an adverse effect of air pollution. The end point of the testing is a greater incidence of mortality in the pollutant exposed group compared to the number of deaths in the control group of animals. Recently, an animal model system has been developed that addresses the opposite end of the infection spectrum, namely the facilitation of expression of infectious organisms that are indigenous to the lung. In an earlier study, a phenomenon of delayed outgrowth of *Pseudomonas aeruginosa* was observed in tissue cultures of the lungs of guinea pigs that had been exposed to NO_2 (32). More recently, viral RNA

has been found to be increased in the spleens of mice exposed to ambient levels of NO₂ (33). Of related interest, spleen weights of NO₂-exposed mice initially increase then fall below normal (34). There may also be a relationship between the expression of retrovirus in lung cells and the occurrence of an increase in macrophage interactions with lung cells (35, 36). The potential importance of the endogenous infectivity model is that it can provide data on the mechanisms involved in the facilitation of virus expression by poor air quality. Germanely, the opportunistic expression of infectious organisms of diverse kinds in human lungs is a growing health hazard due to immune deficiency conditions that are not well understood, e.g., the recently identified syndrome of acquired immune deficiency related to blood contact, hepatitis, drugs and other factors (37). Among the opportunistic organisms commonly involved in human lung disease are cytomegalovirus, herpes simplex, pneumocystis carinii, and candida.

Pollutant-Induced Alteration of the Cellular Ecology of the Mouse Lung

A number of studies have been carried out in this laboratory to determine the influence of ambient levels of NO₂ and ozone, singly and in combination, on the Type 2 cell of the guinea pig and mouse alveolus. In two of the most recent investigations, adult Swiss-Webster mice were exposed to either 0.34 ppm NO₂ or to 0.3 ppm ozone, the exposures being intermittent (7 hr/day, 5 days/week) for 6 weeks, after which the very strongly lactate dehydrogenase positive Type 2 cells were quantitated by computer-assisted image analysis. The measurements included number of Type 2 cells, their area, the area and perimeters of the alveolar walls, and other parameters. An increase in Type 2 cells that was statistically significant for the NO₂ and ozone exposed animals was found (38, 39). Further, unpublished data indicate that the influence of NO₂ on the response of the Type 2 cell, including alteration in size as well as number, had not reversed at the longest postexposure period so far evaluated, i.e., 10 weeks after a 6-week NO₂ exposure period (40). An apparent protein leakage has also been found (41). The significance of the Type 2 cell hyperplasia is that damage and loss of Type 1 cells is followed by an increase in the Type 2 cell, the progenitor cell for the Type 1 cell. Since the loss of substantial numbers of alveoli is common to essentially all

human adult lungs, and since Type 2 cell hyperplasia is an early and common denominator type event for human lung disease in general, the ultimate requirement for answering the question of reversibility of Type 2 cell hyperplasia in both the human and animal model lung is an inventory of alveoli. In fact, we consider an inventory of alveoli in the lungs of the well population (primarily from coroner cases) to be the single greatest need for assistance in the setting of reasonable air quality standards. A monitoring of reserves is in line with the cardinal principle of conservation of the ecology in general. The protection of human health must be extended to include the ecology at the cellular level.

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