Meetings

Air Pollution Medical Research

Epidemiological studies show convincing associations between air pollution exposure and decreased respiratory function or increased respiratory symptoms. Epidemiological research in this field is not a study of the incidence and prevalence of disease as much as it is of the frequency of symptoms or altered laboratory tests. More emphasis than ever before has been placed on where and how pollutants react within the respiratory system. Research on such reactions was discussed at the eighth in a series of air pollution medical research conferences held by the American Medical Association in Los Angeles, 2–4 March 1966. Substantial attention was paid to reaction patterns, such as adaptation, which can increase the body's defenses against pollutant exposure. The possibility that indoor air pollution was a serious factor in chronic respiratory disease was also discussed. The urgency of taking reasonable protective measures against air pollution was stressed, while the community of basic research scientists responded to what was recognized as being fundamentally a social problem, for the solution of which problem biological research, engineering innovation, and public and professional support would all be necessary.

Methods for comparative study of pathological changes of emphysema and bronchitis presented by Thurlbeck (McGill University School of Medicine, Montreal) looked toward comparisons of the prevalence of these conditions in areas with differing levels of atmospheric pollution. Nadel (University of California, San Francisco) spoke of Wright's experience with arsenic fixation of washed lungs, and in particular of the reproducibility of mechanical studies of the lung with borax added to simulate the effect of surfactant.

The nature of irritation from air pollution and the relation between exposures to known compounds and the development of irritative reactions were the subjects treated by Corn and Burton (University of Pittsburgh). No substance is present in the air in sufficient concentrations as a community air pollutant to produce the classical picture of tissue inflammation. Another criterion would be ability to produce functional reactions without necessarily altering morphology. Since small particles impinge in the lung on regions different than larger particles, it becomes important to sample particulate pollution in relation to particle size. In all likelihood the combination of irritant gases and particles is responsible for the measurable alteration in respiratory function associated with community air pollution. Present sampling procedures do not permit an adequate prediction of the irritating capacity of community air pollution.

The structural similarities between animal species with respect to the anatomy of the respiratory system were emphasized by Tyler, McLaughlin, and Canada (University of California, Davis), but it is the lung of the horse which is anatomically most comparable to the human lung. They reported briefly on the possibility of demonstrating emphysema in the horse based on occlusive lesions of the bronchial artery.

Sixteen emphysematous patients lived for periods of a week in rooms whose air supply could either be filtered to remove the ambient pollution of downtown Los Angeles or who could breathe the ambient atmosphere, according to the desire of the investigator, Oscar Balchum (University of Southern California Medical School, Los Angeles). The filtration system excluded nearly all the oxidant, about half of the oxides of nitrogen and four-fifths of the particulates. When the average ambient oxidant level was 0.11 ppm, compared with 0.02 ppm in the filtered chamber, there was a 64 percent increase in average airway resistance though not all of the subjects had an increase. In addition, the oxygen consumption upon exercise increased on similar exposures in 9 out of 12 subjects. At the high level of exposure, half of the subjects had increased work of breathing. However, a direct metabolic effect of the exposure may also account for some of the increased oxygen uptake.

Social and environmental factors in respiratory diseases developing in children are being studied by Colley and Holland (St. Thomas' Hospital Medical School, London). The basic population were families with newborn infants but all family members were studied for respiratory symptoms. Respiratory function tests were also obtained even in newborns, using a newly developed pneumotachograph, which records a measurement of air-volume flow while the infants were crying. Methodological evaluation of survey data has been carried out using postal techniques and reinterview. With respect to positive replies to questions concerning cough, social class gradients were more clearcut for fathers than mothers, and were also present among nonsmokers, ex-smokers, and current smokers. In the mothers, the effect of smoking was the only one detected. The fathers show effects of occupational exposures and all of the groups of subjects appeared to show differences by area of residence. The question of some interest is whether there are increased symptoms in children of parents who smoke. One important need is for air sampling equipment that can be used within dwellings.

The relationship between air pollution and economic status by area in Buffalo was studied by Winkelstein and co-workers (State University of New York, Buffalo) in connection with total and respiratory system mortality. When economic status had been controlled, a direct association between air pollution and total mortality among white men, aged 50 to 69, was found. The same association occurred for chronic respiratory disease in males. No association was found between air pollution and cancer of the trachea, bronchus, and lung.

A close association in men over forty between cigarette smoking, chronic airway obstruction, morphologic evidence of emphysema, and mucous gland hyperplasia was noted by Petty,

Ryan, and Mitchell (University of Colorado Medical Center, Denver). Black pigmentation of the lung was more closely associated with the presence of emphysema or mucous gland hyperplasia than with cigarette smoking. When the subjects stopped smoking, if there was an improvement in the symptoms of cough, there were also improvements in other evidence of chronic airway obstruction.

A population of presumably normal persons was studied by McCarroll (Cornell University Medical College, New York). Morbidity and the population's health status was determined weekly with respect to each day's experience. This was examined in conjunction with atmospheric sampling data from the immediate vicinity. Cross-correlation and auto-correlation methods were used and sulphur dioxide was used as an index of total pollution exposure. A slight correlation of eye irritation with the pollution index was found, but it decreased with a one-day lag. However, the cross-correlation of cough with the pollution index was greater after a two-day than a one-day lag, and this in turn was greater than for contemporary day correlations. Time series analysis permitted the detection of periodicity in both pollution and symptoms at weekly intervals.

The application of basic information on lung function to field studies of air pollution effects was discussed by Henderson (University of Maryland, Baltimore). She emphasized the need for information on the levels of actual exposures to pollutants to relate to physiological and pathological data. The epidemiologist can often obtain information, not available from laboratory studies or routine statistics, for three questions: (i) Are there pollutants in the places where we live and work to which exposure can initiate obstructive airway disease? (ii) What is the natural history of such disease and what effect can pollutant exposure have upon it? (iii) In what fashion do groups in the community differ in their susceptibility to the condition and in the influence (if any) of pollutants on it?

The methods often used have not always been capable of answering these questions.

The effective driving pressure of the forced expiratory maneuver was shown by Macklem and Mead (Harvard School of Public Health, Boston) to be the elastic recoil pressure of the lung. The flow produced is primarily dependent on the cross-sectional area of large airways at high lung volumes; at low lung volumes the flow is dependent on frictional resistance of small airways. They compared the respiratory flow-volume curves after inhalation of histamine and of sulfur dioxide, and suggested on the basis of theory that general caliber narrowing was produced by the latter while unequal distribution was the result of histamine inhalation.

The possible mechanisms in subjects unusually reactive to air pollutions were presented by Nadel (University of California Medical School, San Francisco). By injecting histamine into the isolated bronchial circulation of dogs, airway resistance changes were produced. But since the reaction was blocked by vagal cooling, it was thought to be reflex. Small inhaled particles (less than 2.5 microns) produced peripheral airway constriction not blocked by vagal section or cooling; however, the reaction was blocked by isoproterenol.

Clearance from the human lung of colloidal FeO_2 tagged with radioactive colloidal gold was studied by Albert (New York University, New York). Small particles (3 microns) are retained longer than larger ones (5 microns). The use of radioactive technetium will permit much lower radiation doses.

Airway resistance changes after experimental exposure to SO_2 were studied by Lawther (St. Bartholomew's Hospital Medical School, London). One subject tolerated 30 ppm with hardly any reaction, while a second had marked increases in resistance when exposed to 10 ppm. Correlations of lung function after a brisk walk in the outdoors suggested a possible association with pollution and also with temperature. In longitudinal study of subjective reactions of bronchitic patients, previous work had shown the average condition of the group was worse when both SO_2 and suspended particulate levels were elevated. The Clean Air Act has greatly reduced particulate pollution in London, and there was doubt that in the presence of low particulates in the winter of 1964–65, there would be any important association with SO_2. One chronic bronchitic patient showed a significant negative correlation of peak flow with SO_2 during November, but not later in the winter. This suggested the development of tolerance or adaptation.

The evidence in favor of the existence and nature of the surfactant in the lung of humans was presented by Pattle (Chemical Defense Experimental Establishment, Porton Down, England). Surfactant is thought to include lecithin in combination with a lipoprotein, based on material obtained after the collapsed lung was irrigated. However, the main action of gaseous pollutants was on the blood-gas barrier rather than on the surfactant itself. Particles deposited in the alveolar portion of the lung must be presumed to coat themselves with surfactant and hence remain dispersed. No doubt the surfactant tends to be moved up the tracheobronchial tree till it reaches the mucous layer but the reactions there are not known. Nor is it known whether inhaled particles can stimulate secretion of surfactant as they do of mucus. One could investigate the amount of intra-alveolar saturated lipid in exposed and unexposed animals. Lungs exposed to nitrogen dioxide are still capable of producing surfactant. Electron microscopy may also be helpful in detecting subtle changes in the surfactant layer, though the methods for imbedding lung specimens without destroying the surfactant are not well developed as yet.

Pulmonary function tests in normal subjects and patients with respiratory disease living in the vicinity of the hospital were done by Spicer (University of Maryland Medical School, Baltimore). He found acute and long-term patterns of variations in respiratory function in normal subjects and in patients with chronic obstructive lung disease. He suggested that temporal measurements would allow separation of disease groups and aid in the detection of the abnormal at an early age. Airway resistance was found to be highest at 4 a.m. and lowest at noon. Airway resistance was correlated negatively and lung volumes positively with contemporary temperature measurements. The latter suggests that perhaps ambient temperature may affect muscle tone.

Extensive studies of the factors influencing asthma attacks in children were reported by Tromp (Biometeorology Research Center, Leiden, Netherlands) who took exception to the current view that biological allergens are important factors in asthma and bronchitis. His studies suggested that it was the rapid onset of cold weather; neither fog nor, in most cities in the Netherlands, air pollution was found to be important. This is not the case, in

his experience, with bronchitics who are generally worse in winter and in foggy weather. He suggests that asthmatic subjects have an inadequate thermoregulatory mechanism and this has been evaluated by immersion tests. Also he cited the favorable experience of asthmatics with climato-therapy using chambers in which low atmospheric oxygen tension could be produced, simulating the altitude of mountain areas.

Three types of immune reactions and their relationship with pulmonary disease were described by Rose and Phills (Royal Victoria Hospital, Montreal). They cited bronchial asthma as an example of the first type, farmer's lung as an example of the second type, and the delayed tubercular reaction as an example of the third type. They postulated that metallic pollutants might produce the delayed or third type of immune reaction.

Alveolar macrophages were obtained by irrigation of the rabbit lung. Myrvik and Evans (Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina) used the uptake of mycobacterium by these cells as an index of their phagocytic activity. This system permits metabolic studies of the macrophages and also their role in the development of immunity. After 48 hours, the mycobacterium could no longer be cultivated. Experimental work indicates that oxidant gases, such as nitrogen dioxide, impair the phagocytic activity in vitro. This may also interfere with development of immunity. Along with the effects of these pollutants on the mucous and ciliary system, they increase the susceptibility to respiratory disease.

Ciliary and mucous transport reactions to air pollution were reviewed by Kilburn (Duke University Medical Center, Durham, North Carolina). Such mechanisms would not influence reactions at the alveolar level. The volume of mucous secretion has been estimated to be only about 10 ml per day when sampled at the trachea but possibly as much as 600 ml per day at the point of secretion, the difference being largely due to evaporation into the expired air. A wide variety of endogenous and exogenous factors have been shown to influence both mucous secretion and ciliary activity. As little as one part per million of ozone will destroy this defensive mechanism. The role of this and other irritants in carcinogenesis and bacterial pneumonia is just beginning to be studied. With long-term exposures to irritants, the secretory epithelium may be altered.

Adaptive mechanisms to inhaled air contaminants were reviewed by Morrow (University of Rochester, New York). These include increased production and clearance of mucus, increases in macrophage activity and the acquisition of tolerance against edemagenic agents. Relatively little work has been done with realistic low-level, long-term exposures, and indeed, there is some doubt as to whether longitudinal studies of pulmonary changes over several decades can be used without risk of bias.

Experimental work on the development of tolerance to the inhaled air pollutants was discussed by Fairchild (Division of Occupational Health, Public Health Service, Cincinnati) with respect to two questions. First, can humans develop tolerance to respiratory tract irritants, and second, at what dose and with what consequences? Initially, it was clear that agents which produce tolerance also could produce edema. Possibly several mechanisms coexist. So far, it has not been shown that tolerance to air pollutants develops in man. In discussion, it was stated that a role of surfactant and mucous transport mechanisms in tolerance have not been identified but possibly macrophage changes are occurring in tolerant animals.

Respiratory conditions in two coal-mining villages, in which occupational conditions were known to be likely to produce respiratory disease, were reported by Enterline (McGill University School of Medicine, Montreal). In one of the two communities, coal miners, when compared with other workers, had significantly more respiratory symptoms and more frequent positive histories of pneumonia and pleurisy—but their wives did also. In the second community, there was little difference either between coal miners or their wives when compared with the group who did not have coal mining exposure. Both groups of miners showed x-ray evidence of pneumoconiosis and in the first community, the coal miners had significantly lower forced expiratory volume test results. The study raises the question as to whether domestic exposure factors may not be as important as occupational exposure factors.

The meteorological factors affecting air pollution phenomena in different parts of the world were reviewed by Neiburger (University of California, Los Angeles). Light winds and inversions occur in every location, while climate and source intensity together influence the severity of resulting pollution. Relatively continuous inversion conditions in summer are characteristic of subtropical west coast areas, such as Casablanca, Capetown, Santiago (Chile), and Los Angeles. The photochemical reaction is further dependent on solar radiation, which is also greater in lower latitudes. Low humidity is associated with anhydrous aerosols, of which most are smaller than 0.1 micron. The complex emission patterns of large urban areas pose difficulties in relating pollution levels to emission sources. Elimination of pollutants from the air is also dependent on meteorology, but we do not know whether the rate of injection of pollutants into the atmosphere on a worldwide basis exceeds their removal rate. Such a contingency should be prevented by fuel use and transport policies.

The present status of knowledge and research in atmospheric carcinogens was described by Sawicki (Division of Air Pollution, Public Health Service, Cincinnati). Four types of such substances have been studied, including polynuclear aromatic hydrocarbons, polynuclear aza heterocyclic compounds, polynuclear imino heterocyclic compounds, and polynuclear ring carbonyl compounds. The status of information on these four categories is not necessarily the same. In view of this complexity, he characterized attempts to correlate carcinogenicity of atmospheric pollution with concentrations of benzo(a)pyrene as naive. Even less was known about anticarcinogens and cocarcinogens in the atmosphere. Nevertheless, it was clear that combustion of coal was a major source of measurable atmospheric carcinogens.

In the discussion, the importance of using reasonable statistical design and treatment procedures was emphasized by Massey (University of California, Los Angeles) who described the task of statistics as the systematic collection of extensive volumes of data, descriptive methodology and inferential reasoning.

Despite the problems which hamper epidemiological and medical research, there was general agreement that control of air pollution should not be held

up merely because certain questions were unresolved.

Air pollution as a problem of human ecology, with particular reference to the metabolism and regulation of the ecosystem was the concern of Sargent (University of Illinois, Urbana). While the emission of pollutants is related to the metabolism, especially of urbanized regions, regulation may either be an adaptive function of the individual or a function of the social system seeking to reduce pollution or its effects. Since man's genetic or phenotypical adaptive capabilities are past-oriented, a strategy based on air quality standards is required, and included within it should be recognition of patterns of human variability.

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Antimicrobial Agents and Chemotherapy

If the 1940's and 1950's were considered the "age of the microbiologist" in antimicrobial agents, it is obvious that the 1960's mark the beginning of the "age of the chemist." This is the conclusion to be drawn from the sessions of the Sixth Interscience Conference on Antimicrobial Agents and Chemotherapy which was held 26–28 October 1966 in Philadelphia. Over 1200 clinicians, microbiologists, chemists, pharmacologists, and other specialists including representatives from 15 foreign countries attended the sessions.

Perhaps the most interesting theme which was repeated throughout the meeting was the successes now being realized by chemists who are "manipulating" various antibiotic structures to produce chemotherapeutic agents with more desirable and useful properties than found in the parent compound. K. E. Price (Bristol Laboratories), examined the relationship of structures of more than 5000 semisynthetic penicillins (for example, penicillins which have been chemically modified) to their biological activities, and noted recent advances—increased oral absorption, acid stability, resistance to penicillinase (an enzyme inactivating penicillins), and higher blood levels. A number of clinical reports on hetacillin supplemented his remarks and emphasized the practical value of these laboratory-determined attributes. Hetacillin has all the properties of the widely used ampicillin and gives higher blood levels and perhaps fewer side effects than ampicillin.

E. Flynn (Eli Lilly and Co.) in discussing some of the successes and failures in manipulating the structure of cephalosporin C pointed out that cephaloglycin and related compounds are absorbed orally (cephalosporin C is not); have better chemical and physiological stability than the parent compound; and are useful against a variety of infections caused by Gram-negative microorganisms. However, these semisynthetic cephalosporins are inactivated by a variety of enzymes (as discussed by Mrs. C. H. O'Callaghan and associates, Glaxo Research Ltd.). The chemist still has to overcome these natural defenses found in certain infectious organisms. Synergism between ampicillin and a variety of other semisynthetic penicillins, including cloxacillin and oxacillin, was reported by J. A. Bach (Bristol Laboratories) in laboratory studies and by L. D. Sabath (Boston City Hospital) in clinical studies. The future objectives for the semisynthetic penicillins and cephalosporins should include elimination of the allergenicity since, according to a panel (L. E. Cluff, W. M. M. Kirby, and J. E. Johnson) cross-allergenicity occurs between all of the semisynthetic penicillins, and some cases of cross-allergenicity have been reported between penicillins and cephalosporins.

The best example of the success of the chemist in "improving" an antibiotic was shown by P. Sensi and S. Füresz (Lepetit, S.p.A., Milan, Italy). They have been successful in broadening the antibacterial spectrum of rifamycin and preparing derivatives which are orally absorbed. Rifaldazine (*N*-amino-*N'*-methylpiperazine of 3-formyl-rifamycin SV) has been absorbed orally; promising results have been obtained in clinical trials in patients suffering from pneumonias, urinary infections, tuberculosis, and osteomyelitis. In this work the chemist has expanded the spectrum of the antibiotic to include Gram-negative organisms; improved the chemical stability of the compound; and prepared a compound which is orally absorbed (whereas the parent was not).

Full exploitation of the chemical manipulation of the lincomycin molecule has not yet been achieved according to B. J. Magerlein (The Upjohn Co.), even though success in increasing the specific activity of the antibiotic and broadening its antibiotic spectrum has been noted. The lincomycin molecule can be modified in a number of areas and retain antibacterial activity. Introduction of halogens resulted in higher specific activity.

The value of chemical modification of the tetracyclines was evident in the studies on doxycycline (α-6-deoxy-5-oxytetracycline), which has been extensively investigated in the clinic and found to give rise to fewer side effects and higher blood levels than oxytetracycline. Preliminary studies with minocycline (7-methylamino-6-demethyl-6-deoxytetracycline) by G. S. Redin (Lederle Laboratories) show that it has a higher specific activity than any other reported tetracycline and a broader antibiotic spectrum than others of the tetracycline group in both in vivo and in vitro experiments.

Other topics of general interest included a symposium on nonpharmaceutical uses of antibiotics, which was organized by D. Pramer (Rutgers University) as a cooperative effort between the Society for Industrial Microbiology and the American Society for Microbiology. Among the papers included was a discussion of the practical usefulness of antimycin A as a teleocidal substance, and Claude Vezina (Ayerst Laboratories, Montreal) predicted its early use in removing unwanted fish from various ponds and lakes.

Most of the papers presented at this conference will appear in *Antimicrobial Agents and Chemotherapy–1966*, which will be published in June 1967 by the American Society for Microbiology. Plans for the 1967 Interscience Conference on Antimicrobial Agents and Chemotherapy are already underway. This conference will be held 25–27 October 1967 in the Edgewater Beach Hotel, Chicago. Further information on the meeting and abstract forms can be obtained from R. W. Sarber, American Society for Microbiology, 115 Huron View Boulevard, Ann Arbor, Michigan 48103.

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