MEDICAL PROGRESS

OCCUPATIONAL MEDICINE

(First of Two Parts)

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THE clinical discipline of occupational medicine, largely unstudied, untaught, and unpracticed in major medical centers as recently as a decade ago, underwent unprecedented rejuvenation in the 1980s. Spurred by national regulatory programs and requirements, widespread litigation concerning toxic injury, and an altered public perception of environmental risks, the demand for the services of occupational medicine has risen sharply, especially outside the workplace.[1] An outgrowth of this increase in demand has been an explosion of new investigations and new information as the field rejoins the mainstream of medicine, as well as new academic faculties, journals, and training programs.

The goal of this article is to describe and review some of the new knowledge about clinical occupational medicine. Given the breadth of the subject, we cannot discuss every important topic in occupational medicine; instead, we shall attempt to cover the areas most relevant to clinical practice, emphasizing those that tend to be ignored in the nonspecialized medical literature. In a few instances, we discuss major advances involving less common disorders, because of their conceptual importance to developments in the field as a whole.

SPECTRUM OF OCCUPATIONAL DISEASE IN THE UNITED STATES

Ideally, this review would begin with a summary of the latest data on the prevalence of each occupational disease, highlighting temporal and geographic trends. Such data would be invaluable to clinicians in recognizing and treating common problems, just as similar data have been useful in the management of communicable diseases. Unfortunately, despite the upsurge in practice and research, reliable surveillance for occupational diseases began only in the late 1980s. Case definitions have not yet been agreed on for most common conditions, and strategies and resources to develop reporting schemes remain severely limited.[2] Precise data are unavailable, and estimates of prevalence and incidence (for example, that 125,000 fatalities occur annually due to occupational disease as a result of 500,000 incident cases) are neither based on verifiable quantitative data nor specific enough to facilitate their use by practitioners.[2,3]

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Some fragmentary data have been developed in recent years that may offer general guidance. A crude ranking of the relative prevalence of occupational diseases in regions dominated by manufacturing, shipbuilding, and general construction may be inferred from a recent report from Connecticut (Fig. 1).[4] Viewed another way, the same data offer insight into the most common causes of occupational disease in this region dominated by manufacturing and construction: asbestos, organic solvents and oils, plastics, and repetitive trauma.

The types of hazardous exposures evaluated and the occupational diseases diagnosed at the University of Washington Occupational Medicine Clinic in Seattle were similar to those in Connecticut. Among the 1424 patients evaluated in the Seattle diagnostic clinic during a five-year period (1982 to 1987), 881 (62 percent) were found to have one or more work-related conditions. The most prevalent conditions were asbestosis (n = 312), asbestos-induced pleural disease without asbestosis (n = 127), noise-induced loss of hearing (n = 132), upper respiratory irritation, including bronchitis (n = 114), acute and chronic intoxication with solvents (n = 70), occupational asthma (n = 67), other respiratory conditions (n = 46), and carpal tunnel syndrome (n = 33). Using all available information, including an interviewer-administered occupational history, an industrial hygienist assigned up to four hazardous-work exposures to each patient; the most prevalent exposures were to asbestos (53 percent), noise (49 percent), solvents (42 percent), welding fumes (35 percent), fibrous glass (11 percent), vibration (9 percent), and lead (4 percent).

Dermatoses and injuries due to repetitive trauma are probably severely underrepresented in these case series because of limited referrals from specialists with long experience of these occupational disorders. The role of occupation in the genesis of multifactorial chronic diseases (such as heart disease and cancer) is also likely to be underestimated in such series. These limitations and the lack of rigorous diagnostic criteria notwithstanding, the most common occupational diseases almost certainly include the asbestos-related disorders, industrial bronchitis and asthma, intoxication with organic solvents, upper respiratory and ocular irritation, noise-induced loss of hearing, and musculoskeletal dysfunction due to repetitive trauma. Important but less frequent disorders are heavy-metal poisoning (especially lead poisoning), silicosis, toxic hepatitis, and dysfunctional psychological reactions to exposures and accidents in the workplace.

No comparable clinical series have been reported

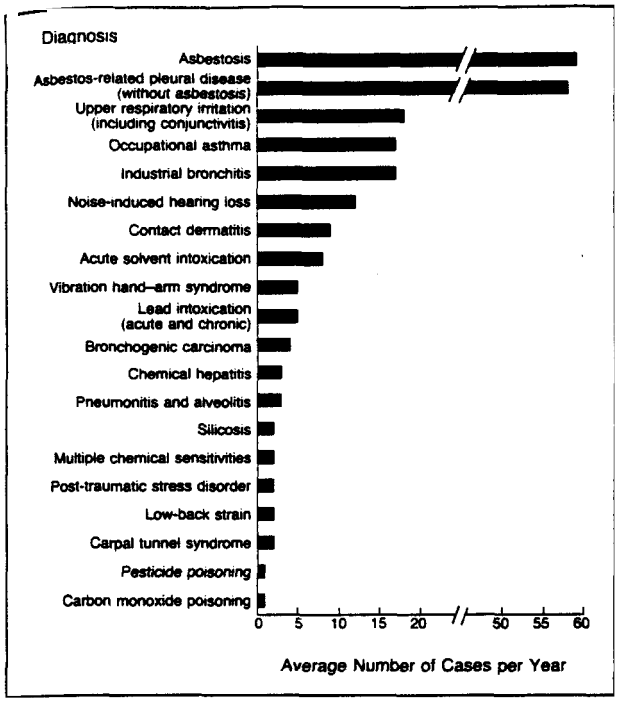

Figure 1. The 20 Most Common Occupational Diseases Diagnosed at the Yale Referral Clinics in New Haven and New London, Connecticut, between 1979 and 1987.

The calculations are based on the average number of new cases annually. Cases of contact dermatitis, low-back strain, and carpal tunnel syndrome are underrepresented because of referral bias. Cases of industrial bronchitis and bronchogenic carcinoma are underrepresented because of the counting methods. See text for a description of multiple chemical sensitivities.

Calculated on the basis of data from Cullen and Cherniack.[4]

from regions of the country dominated by mining activities. There is clear documentation, however, that despite the regulations imposed by the Mine Safety and Health Act of 1969, which limit dust levels in underground and surface mines, both pneumoconiosis of coal workers[5] and silicosis[6] remain endemic in the United States, and new cases still occur, although less frequently than in the past. The reasons include noncompliance with standards, long latency from first exposure to the onset of disease, and presumably, enhanced detection because of mandated examinations and an increased awareness of occupational diseases. What remains to be proved is whether mining standards, based largely on the experience of the United Kingdom and Europe, will be effective in preventing new cases among younger workers who are exposed only to the lower levels of coal and quartz dusts mandated by regulations enacted nearly 20 years ago. Early U.S. data[7] suggest that the coal standard may protect those who work with bituminous coal. but concern about those who work with the more pathogenic anthracite coal. mostly in the eastern United States, remains high.[8]

Data on the occurrence of occupational diseases in agricultural regions are scarcest of all. although the available data on work-related mortality rates in this sector show that agriculture and mining compete as the two most dangerous occupations.[9] Pesticides and herbicides can produce both acute and chronic disorders,[10] but how often these come to medical attention is unknown. Although rates of traumatic injury are known to be very high in this sector,[9] the medical consequences of repetitive trauma among agricultural and wood-products workers have been delineated only in lumbering, in which vibration-related disorders are ubiquitous.[11] The unique, diverse, and potentially serious effects of exposure to animal and vegetable products in the food-processing industry, especially on the respiratory tract, have recently been reviewed,[12] but quantitative data and regional variation remain unreported.

Although the influence of occupational diseases on overall regional morbidity and mortality cannot be readily inferred from case series and data on specific exposures, population studies of respiratory disease suggest that workplace factors may be important. For example, the results of the Harvard Six Cities Study demonstrate significant increases in both chronic respiratory symptoms and functional abnormalities related to occupational exposure to dust, fumes, and gases, after adjustment for smoking habits and the level of ambient air pollution.[13] Such exposures were reported by half or more of the adults in every region of the United States studied. If occupational factors contribute even a small fraction of the rates of nonrespiratory illnesses, as our case series suggest, then occupational disorders are very prevalent.

Specific Occupational Disorders

Lung Diseases

The most frequently diagnosed work-related conditions in industrial regions and the best-established medical consequences of mining and farming involve the lower respiratory tract, because it is the most important portal of entry for toxic agents from the work environment. The health consequences of exposure to asbestos, the recognition of which paved the way for much of the resurgence of interest in occupational medicine, have been widely reported and reviewed[14] and will not be discussed further.

New data and insight have emerged in recent years regarding silicosis, the most prevalent chronic occupational disease in the world and stubbornly resistant to eradication in the United States. The disorder has been specifically targeted in the Centers for Disease Control's prevention objectives for 1990.[15] Although silicosis is classically associated with the mining of hard rock, anthracite coal, and metals, high rates of the disease have been reported in foundries, brickyards, glassmaking, ceramic manufacture, and industrial sandblasting.[6] Particularly aggressive outbreaks have been seen in the silica-flour and stone-processing industries; cases occur within a few years of the first exposure, and many advance rapidly to progressive massive fibrosis.[15,16]

Beyond the public health efforts mentioned, some

progress has been made in the past decade that can benefit physicians evaluating new cases and following up patients with established disease. Diagnostically, it appears that no strategy will soon replace the triad of careful assessment of past exposure, exclusion of masqueraders (for example, sarcoidosis and eosinophilic granuloma), and — more often as the disease becomes less common — pathological evaluation of tissue. Noninvasive procedures, including bronchoalveolar lavage,[17] computerized tomography of the chest,[18] and determinations of serum angiotensin-converting-enzyme activity,[19] have not demonstrated any strongly positive or negative predictive value. Long-term management has not become easier. Newer evidence supports the conclusion that silicosis can progress, even to massive fibrosis, despite the elimination or reduction of exposure.[20] Tuberculosis continues to complicate both simple silicosis (without massive fibrosis) and advanced disease[21]; short courses of antitubercular therapy have been proposed,[22] but their efficacy is not established. An elegant study has implicated anaerobic bacteria in the superinfection affecting patients with advanced silicosis[23]; these patients may present with the sudden cavitation of coalescent masses historically ascribed to either mycobacteria or ischemia. The proper management of patients with silicosis will also involve consideration of the excessive occurrence of lung carcinomas.[21,24,25] Although the epidemiologic relation between silica and cancer is still being explored (since other toxins in mines and foundries may be responsible),[26,27] the possibility that it may be a tumor must now be considered when a new lung nodule develops in an affected patient — not a trivial task in patients who already have underlying extensive and coalescing pulmonary nodules.

The future control and treatment of silicosis may be aided by cellular and molecular research. The central role of pulmonary macrophages, both in clearing silica and in elaborating chemoattractants for polymorphonuclear leukocytes and fibroblasts, seems established[17,28]; the precise sequence of events, probably involving interleukin-1,[29] is now being unraveled. Already, experiments with cell-specific and mediator-specific inhibitors are under way in animal models,[30,31] offering some hope that the prevention of secondary disease may become part of the ongoing effort to eradicate this preventable disease.

Beyond the pneumoconioses and their sequelae, the most important progress against occupational lung disease in recent years has been in the area of immunologically mediated disorders of the airways and parenchyma. Our knowledge of occupational asthma, probably the most prevalent of these disorders in developed countries,[32] has expanded considerably because patients and physicians are increasingly aware of environmental factors and because new forms of technology exist for studying its mechanisms. Although debate continues on a uniform definition of the disease, and although its incidence in most industries remains unknown," consensus has been reached on several issues.

A broad array of natural and synthesized chemicals are potential asthmogens; these include many small molecules. such as toluene diisocyanate and plicatic acid, and larger protein antigens. such as bacterial enzymes, animal proteins, and grains. The list of documented causal agents has expanded rapidly in the past five years (Table 1).[33-51] Many of the established causal agents appear in an extraordinarily diverse range of materials and processes, often as unlabeled minor constituents or contaminants. Finding specific culprits or excluding them from a patient's environment may therefore be very challenging. In many cases, this is less important than documenting temporal changes by examination, spirometry, or peak flowmetry that implicate some causal factor from which the patient can be removed.

Multiple mechanisms appear to be involved in inducing and sustaining occupationally induced asthma. In general, the larger molecules seem to act most frequently through classic IgE-mediated mechanisms, affecting atopic workers (especially smokers) more commonly.[32] Radioallergosorbent testing has been of some use in identifying those sensitized in this way.[42,52] The action of the smaller molecules typically does not involve the same host predisposition,[32,53] and studies have not reproducibly demonstrated antibodies to these agents or agent–protein complexes in affected patients, despite considerable searching.[54,55] Mechanisms involving the local release of bronchoactive mediators seem plausible,[54,56,57] although the characteristic differences between hosts in susceptibility and usual onset after repeated exposure remain unexplained by nonimmunologic mechanisms.

Although demonstrating a pattern of symptoms and signs consistent with occupational factors is usually possible, confirmatory tests for occupational asthma are not generally available. Work by Pepys and Hutchcroft[58] and Hendrick[59] suggested that an inhalation challenge with the suspected agent would be a sensitive and specific diagnostic tool, but subsequent experience has uncovered drawbacks for both the patient and the diagnostician; reactions in the laboratory sometimes dangerously exceed those in the workplace,[60,61] and for some agents, the test is very insensitive.[62]

Most important, several longitudinal clinical studies have refuted the long-held dogma that occupational asthma typically reverses after a patient is removed from exposure. Experience with western red cedar (plicatic acid), toluene diisocyanate, and other small-molecule agents plainly demonstrates that at least half of all patients will suffer persistent, even progressive asthma despite recognition and removal from exposure.[61,63-65] Evidence suggests that the duration of symptoms before removal is a strong prognostic indicator; a period longer than six months is generally predictive of the persistence of disease. Although the mechanism is highly speculative, the clinical impera-

Table 1. Materials Causally Linked to Asthma in the Workplace.

VEGETABLE	ANIMAL	PLASTIC OR CHEMICAL	METAL	PHARMACEUTICAL
Grain dust	Danders	Acid anhydrides	Stainless steel	Penicillins
Flour	Insects	Epoxy resins	Galvanized steel	Cephalosporins
Fig plants	Silkworm larva	Diisocyanates	Aluminum fluoride	Piperazine
Wood dust	Shellfish	Persulfates	Vanadium	Psyllium
Seaweed	Pig or chicken excreta	Para-phenylenediamine	Cobalt	Methyldopa
Green coffee beans	Fish feed	Phthalic anhydride	Tungsten carbide (cobalt)	Spiramycin
Fungal spores	Animal enzymes	Dimethyl ethanolamine	Platinum salts	Tetracycline
Tragacanth		Azobisformamide	Nickel	Amprolium
Castor bean		Azodicarbonamide	Chromium	Cimetidine
Tea		Formaldehyde		Isoniazid
Tobacco		Ethylenediamine		Phenylglycine
Flax		Acrylates		
Hemp		Henna		
Cotton				
Hops				
Bacterial enzymes				
Colophony				

tive to remove patients from exposure if suspicion exists now seems unequivocally justified.

Perhaps even more surprising — and of great concern given the ubiquity of these agents — is recent evidence that persistent asthma may also result from exposure to workplace animal-protein asthmogens. Despite the conventional wisdom that bronchial hyperreactivity will disappear within months after the end of exposure to agents eliciting classic IgE-mediated bronchoconstriction, our own clinical experience and a long-term follow-up of patients with crab-induced asthma[66] suggest disease patterns similar to those observed with the smaller chemical agents.

Extrinsic allergic alveolitis, or "farmer's lung," which is characterized by recurring episodes of fever, chills, and pulmonary infiltrates, has also been the focus of renewed interest. Bronchoalveolar lavage, together with new techniques for identifying lymphocyte subpopulations, has helped elucidate the fundamental role of T lymphocytes in the disorder.[67] Although diagnostic efforts focused historically on finding IgG antibodies against offending agents, the standard approach is now the demonstration of intense alveolar lymphocytosis in lavage fluid. The cells, which are almost entirely of the T-cell class, are mostly suppressor cells, as shown by monoclonal-antibody labeling.[67,68] In the appropriate clinical context, this combination is almost pathognomonic for the disorder, readily distinguishing it from sarcoidosis (in which helper cells predominate) and idiopathic pulmonary fibrosis (in which polymorphonuclear cells are most frequent). Humoral immunity probably contributes to the pathogenesis as well, since IgM and IgG antibodies against the offending agents are frequently found in lavage fluid.[69,70]

These diagnostic advances have allowed the recognition of new classes of agents in the workplace that can induce allergic alveolitis. To the broad range of molds and spores have now been added synthetic chemicals, most notoriously the diisocvanates in most polyurethane paints. foams. and coatings.".'' Components of other plastics. especially epoxies. have also been incriminated,[73] making it likely that many reactive synthetic chemicals cause the disorder. **Curiously,** the now well-characterized disease associated with plastics appears to have a more insidious natural history than the traditional farmer's lung or "humidifier fever." Some patients have presented without the typical acute syndrome (fever or leukocytosis, for example) and have responded more slowly to removal from exposure alone. Weeks or months of treatment with systemic steroids may be required as the inflammatory response and restrictive lung dysfunction clear.[70,71]

Information on the respiratory effects of cotton dust has also grown. The historical description of byssinosis emphasized the peculiar temporal pattern of chest tightness, cough, and wheeze, which occurred dramatically on Mondays, after a weekend of no exposure, and diminished during the succeeding days. Recently, syndromes other than classic byssinosis have been recognized and classified. These include "mill fever" — a self-limited, influenza-like reaction to initial exposure to dust — and a rarer pattern involving the progressive bronchoconstriction typical of occupational asthma.[74] Although the relation between exposure and acute effects has been widely accepted, conflicting data have unfortunately been published about late risks, including chronic bronchitis and obstructive impairment. Updated longitudinal studies of cotton workers have shown dust-related excesses of severe obstruction,[75,76] thus confirming earlier work,[77] whereas autopsies have failed to show pathologic effects beyond those attributable to smoking." The recent demonstration of proteolytic enzymes in cotton[79] provides a plausible mechanism for long-term effects, but the debate continues. Vigorous debate also surrounds the search for the causal agent or agents in the cotton bract that are responsible for the acute byssinotic effects. Considerable evidence. both experimental and epidemiologic, has incriminated endotoxin from contaminating bacteria as the agent of disease.[80-83] On the other hand, Douglas and colleagues have demonstrated clear-cut bronchoconstrictor responses on inhalation challenge with dust rendered

free of endotoxin; they continue to propose a heat-stable, water-soluble component of the bract as the

Finally, remarkable insight into environmental disease has emerged from the study of chronic beryllium disease, a serious, if uncommon, occupational lung disorder that has puzzled clinicians and scientists for decades. The disorder was first recognized in the 1940s in the metal-processing, nuclear, and fluorescent-light industries, and by 1950 voluntary controls were imposed in the United States with dramatic effect.[85] The number of cases of this sarcoidosis-like disease dropped precipitously — even as the use of beryllium in industry expanded widely — despite inadequate knowledge of its mechanism and contradictory epidemiologic data showing that attack rates in some industries with relatively low levels of beryllium in the air were higher than in other industries with higher levels.[86] This victory of industrial hygiene illustrates the value of control, even in the face of biologic uncertainties.

Unfortunately, despite controls in industry, new outbreaks of berylliosis have recently been reported in aircraft, metal-smelting, and nuclear plants.[87,88] Bronchoalveolar-lavage studies in cases from these clusters and in previously diagnosed cases have revealed intense T helper–cell lymphocytosis, as in sarcoidosis. The two diseases, however, can be differentiated with lymphocyte cultures of the lavage material and peripheral blood; recent studies have documented specific in vitro reactivity to beryllium salts 'in patients with chronic beryllium disease, but not sarcoidosis.[89,90] The sensitivity of the proliferative response of lung lymphocytes to beryllium appears to be high (unlike earlier experience with peripheral lymphocytes), rendering the test highly useful for diagnosis and clinical studies.[87,90] The ability to diagnose the disease specifically has in turn helped to define a dose–response relation for beryllium in different settings.[87] Ultimately, immunologic and perhaps new molecular tools may allow the early recognition of those at risk for this idiosyncratic disease. In this way, appropriate controls to protect an estimated 800,000 U.S. workers could include more precise limits on exposure and could be reinforced by a medical strategy to prevent the full expression of the disease should workers become sensitized or otherwise susceptible.

Renal Disorders

Because of the considerable amount of intrinsic renal disease whose origin is unexplained and because of the role of the kidney in detoxification and filtration, new methods for evaluating industrial nephrotoxicity continue to be explored.[91] Two nephrotoxins — lead and organic solvents — have been the targets of extensive investigation. Although lead poisoning sufficient to cause direct renal injury occurs only rarely in the United States,[92] moderate exposure remains commonplace among foundry workers, battery makers, glass and ceramics workers. and those who weld, burn, or sand painted metal or wood. This fact, combined with the concern over past accumulations, has focused attention on the interaction of small accumulations of lead with hypertension and gout, two conditions frequently but not invariably associated with renal disease. Batuman and others have provided provocative data suggesting that among patients with hypertension[93] or gout[94] much of the variability in glomerular function can be explained by body lead levels, estimated by measuring urinary lead excretion for 72 hours after a challenge injection of calcium EDTA. Batuman et al. infer from their findings that lead indirectly causes serious renal injury at doses far below its recognized nephrotoxic level; this inference may be premature in the light of each study's cross-sectional design and the lack of animal models to explain the role of lead. Nonetheless, the prevalence of hypertension and gout in the population and the ubiquity of lead (although it is generally well controlled in the modem workplace) make the hypothesis extremely important.

Organic solvents, such as trichloroethylene, carbon tetrachloride, and toluene, have long been recognized as causes of renal tubular injury, but recent data and the reinterpretation of previous findings implicate this wide class of agents as potentially important causes of acute and chronic glomerular disease.[95-97] Numerous case reports have linked exposure to solvents and gasoline with anti-glomerular basement membrane antibody glomerulonephritis alone or in conjunction with pulmonary hemorrhage (Goodpasture's syndrome).[98-106]

A review of nine case–control studies exploring the relation between exposure to solvents and various types of glomerulonephritis found that all but one supported the association; in the five positive studies in which risk could be systematically calculated, a 2.8- to 8.9-fold higher risk was found among persons exposed to solvent.[97] On the other hand, the cross-sectional evaluation of various exposed groups has failed to demonstrate more than minor differences in function as compared with control groups, and observed abnormalities have not been consistently referable to glomerular functioning, as was hypothesized.[107-109] Although anti-glomerular basement membrane antibody glomerulonephritis has been experimentally induced by mercuric chloride,[110,111] no solvent-induced model has been demonstrated. Experimental exposures to solvent have, however, been reported to cause glomerular lesions, although usually with tubulointerstitial injury.[112-116]

Hematologic Disorders

Although toxic levels of workplace chemicals have long been known to affect circulating blood elements — producing, for example, hemolysis due to lead or arsine or methemoglobinemia due to nitrites[117] — at-

tention has turned in recent years to possible long-term, irreversible changes in bone marrow, especially myeloproliferative disorders. Much attention remains focused on benzene, because it is ubiquitous (gasoline is up to 3 percent benzene) and because it serves as a useful disease model.[118] For many years it has been known that workers exposed to benzene — especially those involved in the production of petrochemical and rubber goods and other work using mixed organic solvents — are at risk for bone marrow suppression, acute leukemia, and chronic myelogenous leukemia.[119,120] Although regulation has reduced exposure considerably, concern remains about the effects of the low-level contamination of other solvents, petroleum products, and chemicals with benzene. Recent laboratory advances include the first reproducible animal model of chronic myelogenous leukemia (but not yet of acute leukemia).[121,122] In addition, the effects of benzene metabolites on target bone marrow cells at the cellular and molecular levels have been partially elucidated. They include covalent bonding to DNA, forming DNA adducts with the inhibition of RNA synthesis,[123] and a slowly reversible decline in the number of stem cells, measured as colony-forming units in the spleen or in culture.[124] The relation between these demonstrated effects and the evolution of irreversible alterations in the marrow remains unexplained, as does the apparent variability in host responses to benzene, long noted in humans[125] and recently observed in a population of homogenic rats.[122]

More immediately relevant from the perspective of public health are new data on quantitative risk. Although controversy still exists, Rinsky and colleagues recently demonstrated a strong linear dose–response relation between benzene and leukemia, with a substantial excess leukemia risk among people exposed to less than 10 ppm, the standard set by the Occupational Safety and Health Administration until recently.[126] In the light of the longstanding difficulty of producing cancer in animals, even with very high doses of benzene, these findings suggest that humans are considerably more sensitive than laboratory animals and current testing systems to the effects of benzene.

Mounting evidence that another group of widely used solvents, the ether derivatives of ethylene glycol, may also be myelotoxic provides a disturbing Parallel. Ironically, these derivatives are now used as substitutes in many printing, painting, coating, and cleaning operations that once depended on benzene. In addition to the demonstration of depressed cell counts in toxicity studies in animals,[127,128] several well-studied cases of aplastic anemia in humans[129-131] and a cross-sectional survey of painters showing a 15 percent prevalence of hypoproliferative anemia or neutropenia[132] lend credence to this suspicion. The long-term consequences of the use of ether derivatives are unknown. as are strategies for medical Intervention, other than reducing exposure wherever effects are observed.

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MEDICAL PROGRESS

OCCUPATIONAL MEDICINE

(Second of Two Parts)

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Neurologic Disorders

The tendency of certain workplace toxins, including organic solvents such as n-hexane, metals such as lead and arsenic, and certain organophosphate compounds, to cause profound and occasionally irreversible damage to the axons of peripheral nerves has been known for several decades.[133] The irreversible central nervous system effects of related compounds have also been well characterized in defined settings: the organic psychosis caused by the solvent carbon disulfide, the diffuse encephalopathy observed in glue sniffersexposed to toluene, and the devastating consequences of lead intoxication in children, for example.[134-136] In the past several years a new and far more serious question has been raised: does repeated exposure to legally acceptable and widely occurring levels of these kinds of compounds result in chronic neurologic dysfunction, especially of the central nervous system?

The impetus to examine this possibility has come from two directions. In the late 1970s two Scandinavian case–control studies found a disproportionate number of workers who had been exposed to organic solvents among groups of men who had retired prematurely because of neuropsychiatric problems.[137,138] During‘ the same period, the nature of dementia among elderly people in developed countries was characterized with increasing evidence that mental deterioration was not an obligatory physiologic consequence of aging, but a pathologic disturbance. Given the realities of the ubiquitous use of solvents in the workplace and an increasingly aged population, the clinical and public health implications of an effect are considerable.

Unfortunately, almost a decade of prodigious effort has not yielded clear answers about the pattern and extent of solvent-induced neurologic dysfunction. Relying heavily on the clinical interpretation of batteries of neuropsychological tests, Scandinavian investigators have defined a “psychoorganic syndrome” characterized by fatigue, memory loss, difficulty in concentration, and emotional lability after 5 to 10 years of the regular use of solvents such as styrene and toluene in groups of painters. metal degreasers, plastics workers, and chemical workers.[139] Although compensable in Sweden, Finland, and Denmark, reproducible abnormalities have not been found consistently on routine tests such as neurologic examination, electrophysiologic studies, or radiography.[140,141] Longitudinal studies of workers removed from exposure have shown that the disorder is generally stable, with some regression of symptoms in milder cases and only rare progression, making the syndrome clearly distinct from the broader group of disorders involving dementia, especially Alzheimer’s disease.[142,143]

Studies and clinical observations in the United Kingdom and North America have been far less consistent. Although new tools, such as computerized batteries of neuropsychological tests, have been developed to facilitate epidemiologic study,[144] only the tendency toward poorer test results in workers with longer and heavier exposure has been proved. Clinically meaningful sequelae have not been seen with the frequency that the Scandinavian experience would predict.[145,146] Studies among patients with Alzheimer’s disease have failed to identify exposure to organic solvents as an associated risk.[147] Moreover, neither human neuropathological observations nor data from experiments in animals have provided confirmatory evidence.[148]

Putting all the discrepant facts together, it seems most prudent to presume that repeated and heavy exposure to solvents can lead to chronic neuropsychological dysfunction, which may become irreversible in patients who are not removed from exposure soon after the onset of symptoms. In patients who are removed from exposure, the prognosis appears favorable. On the other hand, it seems unlikely on the basis of available data that much of the Alzheimer’s disease epidemic can be attributed to organic solvents. The contributory role of solvents and other occupational or environmental contaminants, such as aluminum,[149,150] should not be excluded from further investigation, however, until the pathogenesis of this devastating disorder is fully understood.

Gastrointestinal Disorders

Although early investigations of the effects of carbon tetrachloride on hepatic structure and function became a classic model for the study of occupational disease, there has been surprisingly little recent interest in the role of occupational factors in the pathogenesis of liver or gastrointestinal diseases.[151] A few recent reports suggest that toxic hepatitis or, more accurately, hepatic injury (since inflammatory cells

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may not be part of the histologic appearance) may occur more frequently than is assumed. perhaps masquerading as alcohol-, drug-, or virus-related illness. Three well-documented outbreaks in developed countries have been reported since 1982, related to the epoxy hardener methylenedianiline (the cause of Epping jaundice), the solvent dimethylformamide, and a chemical mixture.[152-154] In each outbreak, a number of cases occurred under normal operating conditions in textile coating, chemical production, and plastic manufacturing. The differing clinical patterns of disease in the outbreaks are also disconcerting: methylenedianiline caused rapidly resolving cholestasis, whereas dimethylformamide and the chemical mixture were associated with hepatocellular injury and widely varying recovery periods. Although a tendency toward clinical improvement was described in each cluster, longitudinal follow-up was insufficient to exclude late sequelae, especially chronic hepatitis or cirrhosis, whose relation to toxic exposures remains unelucidated. Reviewers have stressed the fortuitous circumstances that led to the recognition of these outbreaks, emphasizing the need for diagnostic vigor when seronegative hepatic abnormalities develop in workers exposed to chemicals.[155]

Endocrine and Reproductive Effects

Despite a growing public perception that toxic exposures may be responsible for infertility, spontaneous abortion, and birth defects, accumulated knowledge about adverse effects in humans remains extremely limited; adequate information exists for only a handful of agents. Male infertility, in theory the easiest outcome to study because the entire physiologic pathway converges into a single, readily quantifiable body fluid, has in practice been difficult to evaluate because many workers find testing unacceptable, and specimens require immediate analysis.[156] Fortunately, animal sperm have been a reasonable substitute. Adverse effects in women, both before and after conception, are harder to study. Infertility cannot be diagnosed by any simple clinical test, birth defects are generally too rare and heterogeneous for causal analysis, and spontaneous abortions are very common but are usually undetected,[157] rendering studies in large populations highly susceptible to recall bias. -Moreover, the differences between the physiology of women and that of nonprimate mammals make extrapolation from experimental models highly speculative.

These limitations notwithstanding, some credible associations have emerged in the past several years. Starting with the highly publicized discovery of epidemic oligospermia and azoospermia among chemical workers producing the pesticide dibromochloropropane,[158] studies have demonstrated depressed sperm counts related to exposure to lead and the solvent carbon disulfide.[159-161] For a variety of other solvents (ethylene glycol ethers, for example), pesticides (such as ethylene dibromide), metals (such as mercury and arsenic), and alkylating agents (ethylene oxide. for example), data from studies in animals predict the likelihood of human spermatotoxic effects.[127,162-164] Interestingly, data suggest that the disruption ot the relevant endocrine function — hypothalamic. pituitary, or testicular — may be the primary or associated affected pathwav in some instances.[159,165] This was evidently the mechanism in a recently reported case of infertility in an embalmer exposed to a chemically complex massage cream with estrogenic activity.[166]

As noted, the data base on female workers is more precarious. Excesses in the reported rates of spontaneous abortion or perinatal death have been described in many occupational settings: among medical and dental workers exposed to anesthetic gases,[167] ethylene oxide,[162] or viral agents[168]; lead workers[169]; rubber workers exposed to organic solvents[170]; workers producing semiconductors[171]; and women doing heavy labor.[172] Biologically plausible hypotheses exist for each outcome, and they are corroborated by the results of experiments in animals that, although of questionable predictive value, are sufficient to suggest that job modification or transfer is a reasonable prescription for pregnant workers until more data are available. For those exposed to excessive amounts of lead, the metal's documented transplacental deposition, combined with its known adverse developmental impact in infants, probably justifies an aggressive stance. Removing from exposure women who are contemplating future pregnancy may also be reasonable, because of lead's long skeletal storage and potential mobilization by pregnancy or lactation.[173] Removal also seems reasonable for those exposed to ionizing radiation or organic mercury, the only documented nonpharmaceutical occupational teratogens in human and for those exposed in the workplace to pharmaceuticals of proven teratogenicity, such as estrogenic or cytotoxic agents. A recent unexpected finding may also have clinical ramifications. In a prospective study of over 4000 consecutive pregnancies, maternal exposure to organic solvents was a strong predictor of preeclampsia and other hypertensive disorders,[174] outcomes that put both the mother and fetus at risk.

Given the importance of reproductive health in an era in which the majority of women work outside the home, the most exciting new contribution to the field has been the development and field testing by Wilcox and colleagues of a new and simple method of ascertaining pregnancy and fetal loss early and virtually completely in women followed up prospectively.[157] Using daily urine collections and a highly specific immunoradiometric assay for the beta chain of human chorionic gonadotropin that is sensitive enough to detect pregnancy soon after implantation, the method should make true rates of pregnancy and early fetal loss readily measurable in women exposed to agents of concern. Since losses are frequent — 31 percent of all pregnancies in an early trial of the method[157] — it

should be possible to expand the human data base quickly in the coming decade through the study of relatively small groups.

Musculoskeletal Disorders

Even after the consequences of accidental injuries are excluded, acute and chronic disorders of the trunk and extremities remain extraordinarily frequent causes of morbidity and consequent lost work time and productivity. Although an occupational basis for many common problems, such as low back pain and degenerative arthritis, remains far from clear,[175] recent epidemiologic studies have implicated occupational factors in the carpal tunnel syndrome,[176-182] a common example of the so-called cumulative-trauma disorders. Using quantified biomechanical measures and videotaped documentation of work practice, ssudies have shown that force, repetition, and vibration are the most relevant occupational risks for this common condition.[176,182-184] Experimental models that use such extrinsic stressors have begun to cast doubt on the pathophysiologic axiom involving the compression of the median nerve at the wrist. New data suggest the possible primary involvement of glabrous skin receptors and other distal small nerves due to edema of the nerve sheaths inducible by pressure or vibration.[185-187] The complexity of such a mechanism, involving large and small nerves, may explain why standard clinical and electrodiagnostic tests often fail to explain symptoms[188] or predict the clinical course or response to surgery.[189,190]

At the practical level, the data are sufficiently clear to add a careful review of work activities to the diagnostic evaluation of every patient, irrespective of other personal risk factors or conditions. This is best accomplished by having the patient demonstrate work activities. For those such as assembly-line workers, materials handlers, grinders, mechanics, and even clerical workers who are exposed to forceful, repetitive, or awkward wrist motions or vibrating tools, a trial of removal from exposure may be appropriate, whether or not the results of standard diagnostic tests are definitive. Surgery should probably be reserved for cases involving evident weakness or atrophy and those that fail to respond to conservative management. Where multiple cases have occurred, interventions to modify the way work is done are certainly warranted.

Vibrating hand-held tools may also cause severe hand dysfunction. The vibration white finger syndrome involves a vascular spasm induced by cold that may be difficult to differentiate from Ravnaud's phenomenon. Recent plethvsmographic studies have documented temperature-sensitive changes in digital-blood flow. even in asvmptomatic grinders. sawvers. jackhammerers, and others with heavv exposure.[191,192] The use of pharmacologic blocking agents has suggested both central and local sympathetic dysfunction.[193] These physiologic effects notwithstanding, the most notable advances in the past decade have come from further clinical observations of affected populations. Documenting that these workers often have a diffuse constellation of shoulder, arm, and hand problems, including pain and numbness, investigators, largely from Scandinavia, have coined the concept of the hand–arm vibration syndrome.[191] Patients may present with features suggestive of cervical, ulnar, or median-nerve entrapments, with or without overt digital vasospasm.[191] Although the results of traditional electrophysiologic tests have been inconsistent,'* an overlap with abnormalities more typical of isolated nerve entrapment may be seen, complicating differential diagnosis." This finding is compatible with data from experiments that demonstrate comparable neuropathic consequences from pressure and vibration.[187,195]

Although a definitive strategy for the evaluation and treatment of such patients awaits further investigation, certain clear implications have emerged. For those with evident vasospasm, permanent removal from exposure to vibration is probably unavoidable, in view of the mounting evidence that vascular changes are reversible only slowly if at all and that reversibility is related to the duration of exposure once symptoms are present.[196] Calcium-channel blockers benefit some patients, as in Raynaud's phenomenon due to other causes. In the absence of vascular symptoms, conservative approaches, including temporary removal from the job, splinting, and antiinflammatory regimens, may suffice, although objective therapeutic end points may be lacking. Surgical interventions, such as release from entrapment, should be reserved for rare cases with clear-cut neural abnormalities in which medical therapy has failed.

Cancer

The success of epidemiologists in the 1960s and 1970s in establishing the excess cancer risk for workers exposed to several widespread workplace agents, most notably asbestos, benzene, and benzidine dyes, raised the possibility that cancer overall might largely be attributable to exposure in the workplace. Ecologic data showed some congruity between regions with high rates of cancer and high levels of industrial activity, and an unpublished government document purporting to show that 20 to 38 percent of all cancers were attributable to workplace exposures received circulation and attention. The past decade has witnessed a considerable sobering and refinement of the prevailing views. Although over 300 compounds have been shown to have carcinogenic potential on the basis of their effects in laboratory animals, no new class of compounds has been added to the list of previously established human carcinogens (Table 2). Newer estimates of the total influence of workplace exposure on the U.S. cancer rate have ranged from 4 to 10 percent.[209,210]

Despite this reduced estimate, important contributions relevant to clinical practice are emerging. First,

Table 2. Established Causes of Cancer from Workplace Exposure.

AGENT	INDUSTRIES AND TRADES WITH PROVED EXCESS CANCERS	PRIMARY AFFECTED SITE	REFERENCE
Para-aminodiphenyl	Chemical manufacturing	Urinary bladder	Melick et al.[197]
Asbestos	Construction, asbestos mining and milling, production of fricaon products and cement	Pleura, peritoneum, bronchus	Mossman and Gee[14]
Arsenic	Copper mining and smelting	Skin, bronchus, liver	Pinto et al.[198]
Alkylating agents (mechlorethamine hydrochloride and bis[chloromethyl] ether)	Chemical manufacturing	Bronchus	Figueroa et al.[199]
Benzene	Chemical and rubber manufacturing, petroleum refining	Bone marrow	Rinsky et al.[126]
Benzidine, beta-naphthylamine, and derived dyes	Dye and textile production	Urinary bladder	case et al.[200]
Chromium and chromatcs	Tanning, pigment making	Nasal sinus, bronchus	Hayes[201]
Ionizing radiation			
Gamma rays	Nuclear, health care	Skin, thyroid, bronchus, bone marrow	National Research Council[202]
Radon	Uranium and hematite mining	Bronchus	National Research Council[203]
Radium	Watch painting	Bone	Polednak et al.[204]
Nickel	Nickel refining	Nasal sinus, bronchus	Grandjean et al.[205]
Polynuclear aromatic hydrocarbons (from coke, coal tar, shale, mineral oils, and creosote)	Steel making, roofing, chimney cleaning	Skin, scrotum, bronchus	Hammond et al.[206]
Vinyl chloride monomer	Chemical manufacturing	Liver	Waxweiler et al.[207]
Wood dust	Cabinetmaking, carpentry	Nasal sinus	Acheson et al.[208]

there has been progress in elucidating the effects of relatively low doses of exposure to the established carcinogens in order to modulate predictions that are based on experience with very high doses in humans or on extrapolation from studies in animals. Since millions of workers are still exposed to small amounts of agents such as nickel and chromium (in welding and toolmaking, for example), polynuclear aromatic hydrocarbons (in mineral oils and vehicle exhaust), benzene (in gasoline and solvent mixtures), and ionizing radiation, such data are crucial in protecting or reassuring patients. Although polemicists have generally argued that low doses should be classified as either unquestionably safe or generically unacceptable, the accumulating data suggest that experience is mixed. The work of Rinsky et al.[126] suggests that the leukemogenic effects of low levels of benzene are sufficient to dictate a strong effort to eliminate exposure to this agent wherever feasible. Published studies of nuclear-defense workers suggest that achievable low levels of alpha and gamma radiation may be associated with small but measurable increases in the risks of lung cancer and leukemia,[211,212] although more dire interpretations have been offered.[213] On the other hand, data have not demonstrated measurable cancer risks in industries — such as grinding or plating — that use nickel.[205] Chromium in the steel alloys most often encountered in the workplace has not been proved carcinogenic, although chromic acid used in plating operations and pigments and tanning solutions that contain chromate are a problem.[201,214] The possibility that oil mists cause excess lung and gastrointestinal cancer at levels commonly encountered in the workplace has been suggested but not proved; excess skin and scrotal cancer does occur in exposed groups.[215] Diesel exhaust appears to be carcinogenic, and small increases in lung cancer have been noted among bus and truck drivers and mechanics.[216,217]

Second, estimates of the risk to humans for some of the more widely used suspected carcinogens (suspected largely because of their effects in animals) have been developed. The most important suspects are listed in Table 3, along with common sources of occupational exposure. Although there is no definitive evidence against any of the suspected carcinogens, the studies cited provide clues to effects in humans and in some cases delineate target sites for future investigations. Serious debate continues over each agent, with potentially important legal and regulatory ramifications, but sufficient data already exist to allow some broad generalizations to guide clinical and public health practice. On the one hand, none of these common substances can be exonerated of the potential to cause cancer in humans, and this has led in virtually every case to strong recommendations for changes or actual regulatory changes lowering the acceptable limits of exposure in the United States. On the other hand, a review of the upper confidence limits of the risk estimates (the worst-case prediction) shows that none of these agents, with the possible exception of ethylene oxide, will cause the markedly altered cancer risks typical of the confirmed carcinogens listed in Table 2. Relative-risk estimates have generally ranged between 1 (normal background risk) and 2 (doubled risk). Since most studies were conducted in populations exposed to relatively high, often uncontrolled levels of the agents, clinicians can safely take

Table 3. Widely Used Suspected Human Carcinogens.

AGENT	INDUSTRIES AND TRADES	SUSPECTED HUMAN SITES	REFERENCE
Beryllium	Beryllium processing, aircraft manufacturing, electronics, secondary smelting	Bronchus	Mancuso,[218] Wagoner et al.[219]
Cadmium	Smelting, battery making, welding	Bronchus	Thun et al.,[220] Elinder et al.[221]
Ethylene oxide	Hospitals, production of hospital supplies	Bone marrow	Hogstedt et al.[222]
Formaldehyde	Plastic, textile, and chemical production; health care	Nasal sinus, bronchus	Nelson et al.[223]
Synthetic mineral fibers (e.g., fibrous glass)	Manufacturing. insulation	Bronchus	Goldsmith[224]
polychlorinated biphenyls	Electrical-equipment production and maintenance	Liver	Brown,[225] Bertazzi et al.[226]
Organochlorine pesticides (e.g., chlordane, dieldrin)	Pesticide manufacture and application, agriculture	Bone marrow	MacMahon et al.,[227] Epstein and Ozonoff[228]
Silica	Casting. mining, refracting	Bronchus	Finkelstein et al.,[24] Zambon et al.,[25] Hepleston,[26] Goldsmith et al.[27]

an alert but reassuring attitude toward exposed patients. Agent-specific clinical interventions — other than the advice to limit further exposure to the extent feasible (by using personal protective equipment offered by the employer, for example) — are generally unwarranted, although such patients may be enrolled in company surveillance programs as part of ongoing investigations or employee-monitoring policies.

The studies reviewed above focused on the effects of specific chemicals or agents on the basis of previous experiments in animals or observations in humans. Efforts have also been made to evaluate the patterns of disease in industries, trades, and occupational groups with complex and mixed exposures to chemical and physical agents. These investigations have demonstrated the elevated risk of certain cancers in identified populations without revealing the causal factor or factors. Important examples identified by several studies include colorectal cancer in those who make the wood, plastic, or metal models and patterns from which machines are designed,[229,230] leukemia and lymphoma in farmers,[231] and glioblastoma multiforme in electrical workers.[232,233] Innumerable cancer clusters or epidemiologic associations between cancers and occupational groups have been reported; many remain unconfirmed. Although specific prescriptions for disease control or the evaluation of individual workers are severely handicapped by the absence of an explanation for these associations, concern among workers and employers often runs high and must be addressed by physicians. Efforts to reduce exposure to all work-Place toxins (by good ventilation. for example), together with education and screening. if the cancer site is amenable. have in our experience lessened anxiety; the effect on the risk or outcome of cancer remains obscure.

Finally. substantial progress has been made in late cancer control among workers shown to be at high risk by virtue of past exposure. Late cancer control has become increasingly important as more workers are notified of the health implications of confirmed cancer studies. The existence of large cohorts of chemical and textile workers exposed to benzidine with a known exceedingly high lifetime risk for bladder cancer has prompted the development of automated urine-cytology techniques to provide ongoing surveillance, with promising early results.[234] Similarly, the risk of colorectal cancer in model makers and patternmakers has prompted a novel study of the efficacy of serial sigmoidoscopic screening in the automobile industry, which employs many of these workers.[235] High-risk workers also figure prominently in new chemoprevention trials; the large number of men who were heavily exposed to asbestos provides an ideal population to study prospectively the effect of dietary and supplemental retinoids on lung cancer.[236]

NEW PROBLEMS IN OCCUPATIONAL MEDICINE

Technological changes, current social perspectives, and historical events have put several new hazards and diseases into the spotlight in occupational medicine. Since these issues are likely to influence all but the most specialized clinical practices, we conclude this review with a brief summary of the field's current causes célèbres.

Dioxin

No toxin more clearly epitomizes the public's dread of the chemical environment than 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, usually referred to simply as dioxin. Its emergence as a potential occupational risk factor in Vietnam veterans who sprayed Agent Orange and other defoliants coincided with the rising awareness that environmental contaminants could insidiously cause illness. On the basis of experiments in animals thar show mutagenicity, neurotoxicity, and marked metabolic disruption at very low doses, virtually every conceivable adverse health outcome has been suspect-

ed among exposed veterans, chemical workers making herbicides and wood preservatives, and the victims of environmental accidents in which materials containing dioxin have leaked or spilled, such as that at Seveso, Italy, in 1976.

More than a decade of intensive research, including the epidemiologic study of those identifiable as the most heavily exposed — workers with the disfiguring acneiform lesions known as chloracne — has left a surprisingly different picture. Although the final word is surely not in, some conclusions seem secure. Other than a possible excess of soft-tissue sarcoma or lymphoma,[237-239] neither cancer nor any other cause of death seems to be occurring in excess.[240-242] Morbid effects, including mild chronic liver and peripheral-nerve dysfunction, as well as altered lipid and porphyrin profiles, appear to be slight and limited largely to those who were most intensely exposed (especially those with chloracne).[243,244] These findings are far from definitive, but confirmation by additional observations would suggest that humans are less susceptible to this dreaded toxin than the results of studies in animals would have predicted. An analytic technique to measure the amount of dioxin in tissue (in parts per trillion) has been developed and validated[245] and should greatly facilitate the further study of this contaminant in humans.

Video-Display Terminals

Since their widespread introduction into offices in the past decade, video-display terminals have had a profound effect on every aspect of work. In the resulting upheaval, many questions have been raised about their safety, with effects ranging from the predictable — eye strain, musculoskeletal symptoms, and emotional stress — to the unpredictable: skin disorders (maculopapular facial rashes) and adverse reproduction outcomes (birth defects and spontaneous abortions, for example). Dozens of reports, studies, and conferences have addressed these issues around the world.

The current consensus suggests that work with video-display terminals is associated with an increase in subjective ocular problems, including pain, burning, and irritation, and transient visual disturbances, including blurring, diplopia, and altered light accommodation. On the other hand, no chronic disorders (myopia or cataracts, for example) have been confirmed.[246,247] Similarly, the operators of video-display terminals are as prone to musculoskeletal symptoms as other clerical workers, probably because of poorly designed workstations and furniture.[248,249] Mood disturbances are probably due to problems in job design rather than to exposure to the video-display terminal itself.[250,251] The cause of the rashes occasionally observed in operators is uncertain; therapy may nonetheless include trials of job modification or removal from exposure, since no alternative explanation has emerged.[252] Finally, despite some widely publicized clusters. insufficient data exist to incriminate video-display terminals as teratogens.[253,254] The possibility of an increased risk of spontaneous abortion has been raised,[253] but reducing exposure in pregnant women is probably not vet warranted on the basis of the information available.

Sick-Building Syndrome

An unforeseen consequence of the fuel conservation measures that followed the oil shortage of the 1970s was the concentration of common pollutants in "tight" buildings served by closed systems of ventilation. In the late 1970s and 1980s, outbreaks of illness characterized by intractable upper respiratory symptoms, ill-defined central nervous system dysfunction, and low morale and productivity have occurred in countless offices. Although the evaluation of individual patients is typically unrevealing, the epidemiologic pattern of illness unmistakably incriminates the workplace.[255] Unfortunately, early attempts to investigate the outbreaks generally failed, raising the diagnostic possibility of mass psychogenic illness.

With the increased frequency of reports, however, the evidence became overwhelming that environmental factors, including smoke, formaldehyde, oxides of nitrogen, microorganisms, and climate, were culpable, sometimes singly but more often in concert.[256] Results of the investigations of hundreds of outbreaks demonstrate a correlation between symptoms and airborne levels of carbon dioxide, which is not the cause of illness but a marker of inadequate ventilation. The best evidence indicates that the solution is usually straightforward, involving the elimination or reduction of indoor sources of pollutants, the regular cleaning and filtering of ventilation systems, and an increase in the proportion of fresh rather than recirculated air.[257] Although palliative job changes or medication may be indicated in some patients, especially those who are highly atopic or sensitive, the focus of treatment should be on the building, not the victim.

Multiple Chemical Sensitivities

The most puzzling clinical entity emerging in the 1980s is the syndrome of ostensible allergy or sensitivity to almost all organic and synthetic chemicals.[258] Patients, typically previously healthy people, usually present during a sick-building outbreak or in the aftermath of an accidental overexposure to an established toxin (a solvent, irritant gas, or pesticide, for example) and report recurrent, intensified symptoms to progressively smaller amounts of the toxin, often mere traces of the original offender. Workups fail to reveal physiologic abnormalities to explain these sequelae, but generalization begins to occur, with a broader array of symptoms, almost invariably including symptoms of the central nervous system, in response to an expanding repertoire of chemical stimuli. Many patients

are unable to work because of their responses to even well-controlled workplace substances. In extreme cases, patients become environmental exiles from modem life.

Although the data are sparse, a sufficient number of such cases have occurred to spur the development of a subculture of practitioners called clinical ecologists or environmental physicians. Armed with unproved theories and diagnostic tests that demonstrate that the immunosuppressive effects of an excessive "total-body burden" of organic chemicals cause "environmental illness" or "20th-century disease,"[259,260] these practitioners encourage patients to avoid contamination and may offer various treatments, including nutritional supplementation, anticandidal medication, and regimens for increasing the turnover of fat-borne chemicals with long biologic half-lives.

Although data have been presented to refute the claimed immunogenic basis of the illness[261] and to provide alternative diagnoses in some cases,[262] the disorder does appear to be prevalent and often devastating, particularly with respect to occupational functioning, since the work environment cannot readily be controlled by the patient. Unfortunately, although there is real controversy, most practitioners remain unaware of the problem or skeptical, and little constructive investigation has been reported. Descriptive studies have attempted to characterize small subgroups of patients in psychological terms, considering the disorder as a variant of post-traumatic stress disorder[263] or "psychological sensitization to the workplace."[264] Coliaborative efforts to define the problem — like those recently undertaken for the possibly related chronic fatigue syndrome[265] — could serve to legitimize and stimulate future research. Meanwhile, the placebo value of radical therapies notwithstanding, most therapeutic effort has been supportive, encouraging patients to improve their functioning through tolerance and understanding of the symptoms.

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CASE RECORDS
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Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 10-1990

PRESENTATION OF CASE

A 15-year-old girl was admitted to the hospital because of pain in the right wrist and multiple radiolucent bony defects.

The patient was in apparent good health except for scoliosis. for which she was seen in periodic orthopedic follow-up examinations. Three days before admission, on a routine visit to her orthopedist, she mentioned pain in the right wrist of approximately one year's duration. with worsening on vigorous use of the right upper extremity. Physical examination revealed no swelling or tenderness of the wrist. X-ray films of the right wrist (Fig. 1) showed a well-circumscribed osteolytic lesion, 5 mm, with thickening of the overlying cortex, 7 cm proximal to the distal end of the ulna; a poorly circumscribed osteolytic area, 1.5 cm, was seen in the distal radial metaphysis; no cortical reaction or expansion was detected. Several days later x-ray films of the left wrist revealed a lesion with similar features, 2.5 cm, in a comparable location in the distal left radius. The girl was referred to this hospital.

The patient gave a history of incision and drainage of a left axillary lymph node at the age of two years and of a febrile seizure at about the same age; phenytoin sodium was administered for 1½ years, without recurrence of a seizure. She reported a very mild, intermittent cough in spring and fall that usually responded to antihistamine medications. Ten months before entry she consulted her physician because of acute pain in a rib. without known trauma. An s-ray film of the chest was reported to show a healing rib fracture. There was a history of malignant tumors in many paternal relatives, including the patient's