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OCCUPATIONAL CARCINOGENESIS *

Editors and Conference Chairmen
UMBERTO SAFFIOTTI AND JOSEPH K. WAGONER

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* This series of papers is the result of a conference entitled Occupational Carcinogenesis, held by The New York Academy of Sciences on March 24, 25, 26, and 27, 1975 and cosponsored by Group Health Incorporated, the National Cancer Institute, the National Institute for Occupational Safety and Health, and the Society for Occupational and Environmental Health. Papers by Dr. Emmanuel Farber and Mr. John C. Kolojeski, although presented at the conference, unfortunately could not be prepared in time for inclusion in this volume.

Part III. Recent Approaches to the Control of Carcinogenic Exposures

Part IV. Prevention of Occupational Cancer—Toward an Integrated Program of Governmental Action

Part V. Carcinogenesis in the Metal Industry

Part VI. Radiation and Particulate Matter

Part VII. High-Risk Industrial Groups: Identification, Education, and Surveillance

Part VIII. Methodologies for Risk Assessment

Part IX. Discussions

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OCCUPATIONAL CARCINOGENESIS: THE TWO HUNDRED YEARS SINCE PERCIVALL POTT

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The worst sin towards our fellow creatures is not to hate them, but to be indifferent to them; that's the essence of inhumanity.

George Bernard Shaw

This year, we mark the 200th anniversary of the discovery of occupational carcinogenesis by Percivall Pott, who in 1775 reported scrotal cancer among London chimney sweeps. As children these chimney sweeps had been exposed to coal combustion by-products.[1] Today indeed is an occasion for sober reflection. For on this bicentennial, thousands of coke-oven workers in the steel industry of the United States alone are inhaling the very same class of substances that caused scrotal cancer in the chimney sweeps, and, as a result, are dying of lung cancer at a rate ten times that of other steel workers.[2]

In 1971, ninety years after miners in the Erz Mountains of Central Europe were observed to be dying of lung malignancy[3] and thirty years after radioactivity within these mines was generally accepted to be the cause of these lung cancers,[4, 5] thousands of American uranium miners were still working in radon daughter concentrations of such magnitude as to triple their prospects of dying from lung cancer. Indeed, in that same year MacMahon stated "the epidemic of lung cancer now in progress among American uranium miners could readily have been—and indeed was—predicted on the basis of past experience in other parts of the world."[6]

Today, 130 years after the observation of scrotal cancer in copper smelters exposed to inorganic arsenic,[7] fully 1,500,000 workers in the United States are inhaling the very same substance,[8] and many occupational groups exposed to inorganic arsenic are known to be dying of lung and lymphatic cancers at two to eight times the national average.[9-12]

In 1973, eighty years after the discovery that aromatic amines were causing bladder cancer in German dye workers,[13] and decades after amines such as benzidine and β-naphthylamine were banned or withdrawn in the United Kingdom, Switzerland, Japan, Italy, and the USSR, thousands of American workers were still literally sloshing in them.[14] As a result, these workers are now, and will continue to be, afflicted by bladder tumors at an epidemic rate. Indeed, as recently as 1973, 50% of former employees at one benzidine plant in the United States were reported to have developed bladder cancer.[15]

Seventy-five years after asbestos was known to cause fatal fibrosis of the lungs,[16] and nearly a quarter of a century after it was known to be a potent cause of lung cancer,[17] workers in dozens of asbestos factories and hundreds of asbestos-related trades in the United States were laboring in concentrations of asbestos dust of sufficient magnitude to obscure the light.[18] As a result, of one million current and former American asbestos workers who still survive, fully three hundred thousand can be projected to die of cancer.[19] Indeed one in five

of these men can be expected to develop cancer of the lung, one in ten cancer of the gastrointestinal tract, and another one in twenty of malignant mesothelioma, an always fatal tumor of the pleura or peritonium.[19]

Such are examples of the record in the field of occupational carcinogenesis during the two hundred years following the epic discovery of occupationally induced scrotal cancer among chimney sweeps by Percivall Pott.

The situation in which we find ourselves today is all the more tragic for the fact that over the past few years we have begun to document the extension of cancerous agents from the workplace into the general community.

We now know that the wives, children, and relatives of many asbestos workers have died of mesothelioma and that others will do so as a result of the previously unregulated practice of asbestos carried into the home on work clothes or in other manners.[20, 21] We now know that people living in close proximity to asbestos factories have developed mesothelioma.[20–22] We now know that virtually 100% of all urban dwellers coming to autopsy show the presence of asbestos in lung tissue.[23]

We now also know that individuals living in areas where arsenical insecticide spraying was common are dying of lung cancer at an increased rate.[24, 25] We now know that children living near copper smelters have unusually elevated levels of arsenic in their urine and hair.[10]

We now also know that the aforementioned, and other, cancer-producing agents are present in much of our water as a result of uncontrolled waste disposal or other practices of industry.[14, 26]

Perhaps the most striking example of the problem we face in the future arose one year ago, when it was learned that vinyl chloride, a petrochemical gas used for the past 35 years as an ingredient in the manufacture of many plastics, is also a potent cancer-producing agent of the liver and possibly of other organs as well.[27] It is estimated that as many as several hundred thousand workers in the United States may be exposed to this agent in the workplace alone. It is not known how many tens of thousands of people are exposed to vinyl chloride as a result of everyday living in near proximity to a facility where vinyl chloride or polyvinyl chloride are made. It is not known how many hundreds of thousands of people have been exposed to vinyl chloride as a result of using aerosol sprays that employed the chemical as a propellant and solvent. Equally unknown, of course, are the biological consequences of what these exposures will be.

Today, as we enter into the second two hundred years since Percivall Pott, the problems of occupational carcinogenesis are greater, more visible yet more subtle, and more pervasive than they were in the past. Indeed, the past director of the National Institutes of Health, Dr. Robert S. Stone, recently stated that "most known environmental carcinogens are a result of our increased agricultural and industrial technology."[28] Of even more worrisome dimensions are estimates that hundreds of new chemicals are being introduced into industry each year, most without any prior testing to evaluate the potential for carcinogenesis. Furthermore, it has been estimated by the World Health Organization that 75–85% of all cancers are related to our environment.[29]

It seems only fitting at this point in time to suggest that society must take a new and dedicated commitment toward the war on cancer. Most assuredly the responsibility of health scientists and management and labor must extend beyond the scientific and economic issues to the moral and social issues. The scientific community must, in my opinion, not only investigate but inform, not only advise

but dissent when appropriate, and, most importantly, provide firm, prudent leadership in the formulation of public health policies. We must not allow the lay public, government, or management-labor to unwittingly remain complacent about the very long period of time necessary from the institution of controls to the eradication of occupationally related cancers, *all of which can and should be prevented.* Finally, as former United States Secretary of Labor Willard Wirtz so eloquently stated: "There is nothing more critically imperative today than this society's assertion of the absolute priority of the individual over institutional interests and of human over economic values." [30]

If we do not undertake such a commitment on an urgent basis, it seems clear that society may soon be faced with a public health hazard of monumental and perhaps irreversible proportions. Indeed, if we do not undertake such a commitment now, and if our progress in occupational carcinogenesis continues to be as painful and slow in the future as it has been in the past, we must ask ourselves what line of introductory remarks will be in order at a similar conference one hundred years from now, on the 300th anniversary of the discovery of occupationally induced scrotal cancer in chimney sweeps by Percivall Pott.

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A SIMPLE METHOD FOR DETECTING ENVIRONMENTAL CARCINOGENS AS MUTAGENS *

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In the past several decades there has been an extraordinary proliferation of man-made chemicals in the environment and the working place, with literally thousands of new chemicals added every year. It is a subject of increasing concern that, with few exceptions, these chemicals have not been tested to assess their potential danger to humans as mutagenic, carcinogenic, or teratogenic agents. To test such large numbers of chemicals by use of conventional animal systems would be virtually impossible because of economic, space, and time limitations.

The rapidly accumulating evidence that, with few exceptions, carcinogens are mutagens, has confirmed the desirability of using simple, rapid, and economical test systems capable of detecting carcinogens as mutagens as a prescreening technique to pinpoint potentially dangerous chemicals requiring more extensive testing in conventional animal systems. A great deal of evidence that carcinogens are mutagens has been obtained using a very sensitive and simple bacterial test for detecting chemical mutagens.[1-8] The development of this test system, recent improvements in the test, and evidence indicating that the test is reliable and efficient for the detection of carcinogens as mutagens will be summarized in this brief review.

THE BASIC TEST SYSTEM

The test method has recently been summarized in detail.[9] Compounds are tested on petri plates with specially constructed mutants of *Salmonella typhimurium* as tester strains. After hundreds of mutants were screened, several tester strains were selected for sensitivity and specificity in being reverted from a histidine requirement back to prototrophy by a variety of mutagens. Most mutagens can be detected by spotting a small amount (usually $<1{,}000$ μg) of the chemical on a lawn of the bacterial tester strain in a petri dish. A positive result is seen by growth of revertant bacteria around the spot (FIGURE 1). In this way a wide range of concentrations are tested simultaneously as the chemical diffuses into the petri plate. For quantitative results, different concentrations are tested individually by incorporating the mutagen into the thin agar overlay along with the bacteria, and dose-response curves are easily obtained (FIGURE 2). For most mutagens linear dose-response curves are obtained. At higher doses revertant colonies decrease due to toxicity of the chemicals.

By adding a microsomal activation system of rat (or human) liver to the petri plates a wide variety of carcinogens can be activated to mutagens and

* Supported by ERDA Contract AT(04—3)34 P.A. 156.
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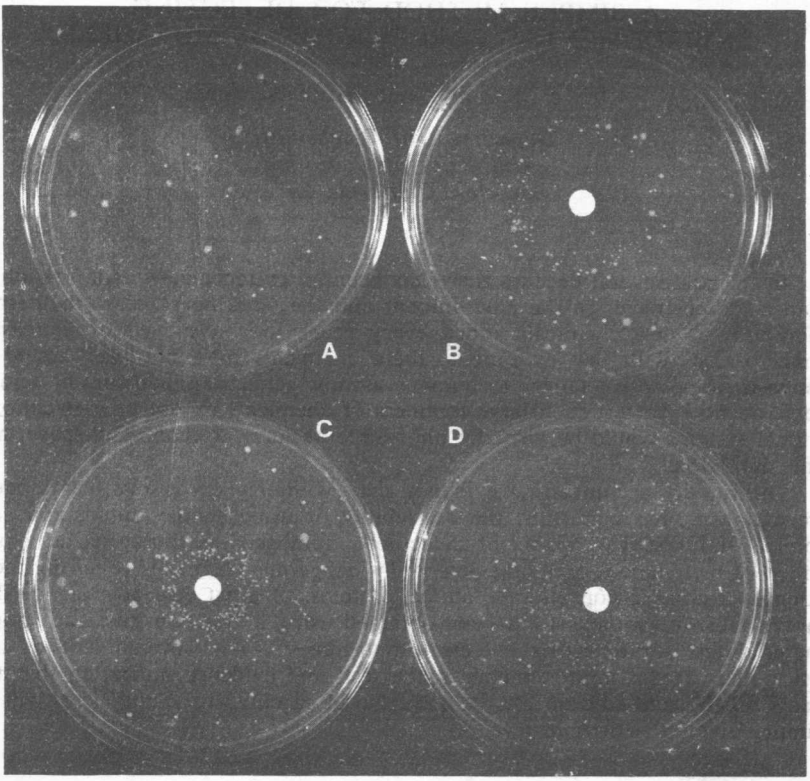

FIGURE 1. The spot test. Each petri plate contains, in a thin overlay of agar, a trace of histidine and biotin,[3] the bacterial tester strain (in this case TA98 was used), and plates C and D contain in addition a liver microsomal activation system from arochlor-induced rats.[12] Mutagens were applied to small paper discs, which were then placed in the center of each petri plate: A=spontaneous revertants; B=furylfuramide (AF–2) (1 μg); C=aflatoxin B_1 (1 μg); D=2-aminofluorene (10 μg). Mutagen-induced revertants appear as a ring of colonies around each disc. (By permission of the publisher of *Mutation Research*.[9])

detected easily. Thus, an important aspect of mammalian metabolism can be duplicated in an *in vitro* test. A large group of carcinogens—aflatoxin B_1, benzo(a)pyrene, 2-acetylaminofluorene, and others, have been detected as frame-shift mutagens after liver activation.[4] Each activated molecule contains a ring system capable of stacking interaction with DNA and an electrophilic group that can react with DNA.[5–8] Other groups of carcinogens have been detected as mutagens causing base pair substitutions: β-propiolactone, propanesultone, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, and so on.[1, 2, 4] Some carcinogens such as nitroquinoline-*N*-oxide cause both types of mutations.[3]

Detection of Mutagenic Metabolites in Urine

The method has been extended for the detection of mutagenic metabolites in urine.[10, 11] A wide variety of metabolites of drugs and other ingested compounds appear in the urine, many conjugated as β-glucuronides. The addition of commercial β-glucuronidase to the petri plates along with the urine, liver homogenate, and bacteria allows detection of metabolites that are excreted in

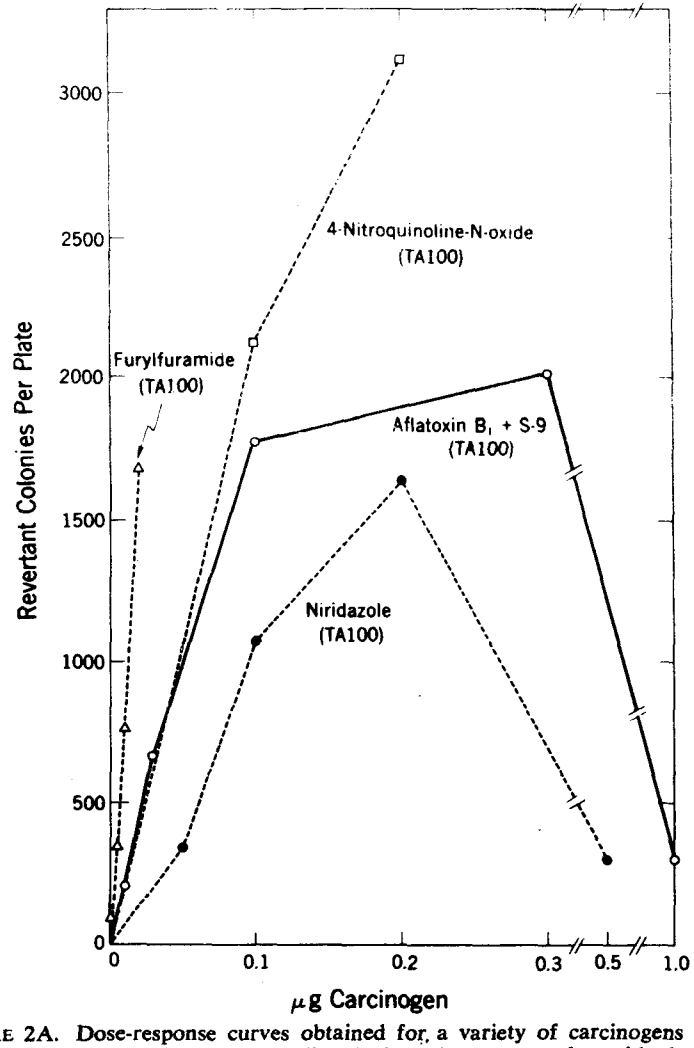

FIGURE 2A. Dose-response curves obtained for a variety of carcinogens and mutagens. Mutagens were incorporated directly into the agar overlay with the bacteria (TA100 or TA1538) and, where indicated, S9–Mix.[9, 12] (By permission of the publisher of *Mutation Research*.[9])

urine as β-glucuronide conjugates. By this method mutagenic activity is readily demonstrated with urine of rats administered as little as 200 μg (1.6 mg/kg) of the carcinogen, 2-acetylaminofluorene. This method can be used for the screening of human urines in order to detect mutagenic metabolites of drugs and of dietary components. It may also be useful for testing urinary metabolites of drugs and food additives in experimental animals.

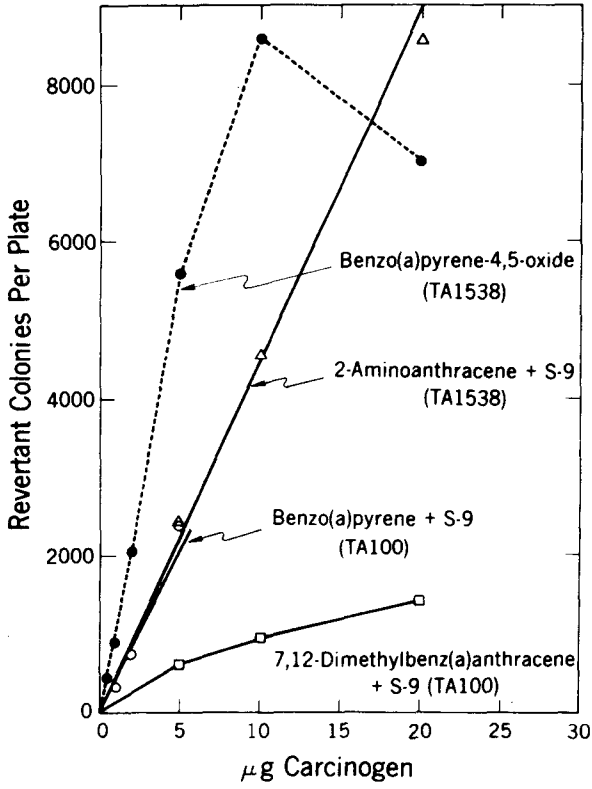

FIGURE 2B. See legend for FIGURE 2A. (By permission of the publisher of *Mutation Research.*[9])

Detection of Mutagenic Activity in Complex Mixtures

The economy of the bacterial/mammalian-microsomal assay suggests its usefulness as a tool for rapidly obtaining information about the mutagenic and potential carcinogenic activity of uncharacterized compounds in complex mixtures, and it can be used as an assay in purifying mutagenic components from complex mixtures. A detailed study has been made of the mutagenic activity of cigarette-smoke condensate and 12 standard smoke condensate fractions.[12]

The condensate from less than 0.01 cigarette could easily be detected. Recently, considerable mutagenic activity has been found in many commercial oxidative-type hair dyes,[13] and several of the individual mutagenic components in the hair dyes have been identified. We have also shown that there is considerable mutagenic activity in soot from city air (with D. Streitwieser, unpublished).

The Bacterial Tester Strains

Standard Tester Strains

There are several standard bacterial tester strains. One strain (TA1535) can be used to detect mutagens causing base-pair substitutions and two (TA1537 and TA1538) to detect various kinds of frame-shift mutagens.

The molecular basis of the frame-shift mutations in these strains has been investigated. Frame-shift mutations occur by shifted pairing in repetitive sequences of DNA, and frame-shift mutagens can be very specific for the particular sequences they mutate. TA1538 has a repetitive —C—G—C—G—C—G—C—G— sequence near the site of the histidine mutation,[14] and is reverted particularly well by many carcinogens, such as 2-nitrosofluorene. The other frameshift tester strain, TA1537, appears to have a run of C's at the site of the mutation,[3] and is reverted by activated 7,12-dimethylbenzanthracene and particularly well by 9-aminoacridine. In addition to the histidine mutation, each tester strain contains two additional mutations that greatly increase its sensitivity to mutagens: one causes loss of the excision repair system and the other loss of the lipopolysaccharide barrier that coats the surface of the bacteria.[3]

The Development of New Bacterial Tester Strains

We have recently developed two new tester strains (TA100 and TA98) by transferring a resistance transfer factor (R factor) to our standard tester strains TA1535 and TA1538, respectively. These new strains are extremely effective in detecting classes of carcinogens that we previously had not detected with our original strains, and they are much more sensitive to a number of carcinogens we had previously detected only weakly. These carcinogens include aflatoxin B_1, sterigmatocystin, furylfuramide (the nitrofuran food additive AF-2) and other nitrofuran carcinogens, acetylenic carbamates, methyl methanesulfonate, nitroquinoline-*N*-oxide, benzo(a)pyrene, 7,12-DMBA, benzyl chloride, and acetoxysafrole.

The effect of the resistance transfer factor on mutagenesis has important implications for the mechanism of mutation. We believe the class of mutagens detected by the new tester strains may be causing nicks in the DNA, and mutagenesis is a consequence of an error-prone repair which is enhanced by the R factor.[15] G. Walker, in this laboratory, has isolated several mutant R factors that have lost the ability to enhance mutagenesis, and has shown that the effect of the R factor on mutagenesis does not occur in *lex* mutants of *E. coli*, thus implicating the involvement of the error-prone repair pathway. New endonuclease (D. Lackey, N. Spingarn, S. Linn, G. Walker, and B. N. Ames, unpublished) and DNA polymerase [16] activities have been observed in bacteria containing R factors, and these new enzyme activities could be involved in the effects on mutagenesis.

Three additional tester strains are under development that will be useful for the detection of special classes of mutagens: 1) a new frame-shift tester strain to replace TA1537; 2) a new tester strain with normal excision repair designed to detect certain DNA cross-linking agents such as mitomycin C [15] (with E. Choi); and 3) new tester strains lacking nitroreductase enzymes. Many nitrocarcinogens, such as nitrofurazone and furylfuramide, are activated directly to mutagens by bacterial nitroreductases. Mammalian nitroreductases can also activate this class of carcinogens. Bacterial nitroreductase mutants have been isolated by others,[17, 18] and in collaboration with M. Vore we are isolating nitroreductase mutants in our tester strains. These new strains will be useful for comparisons between bacterial and mammalian nitroreductase activities.

Validation of the Test System

We propose that the *Salmonella*/microsome test be used for the screening of food additives, drugs, and chemicals to which humans are exposed, and for the routine screening of all new chemicals under development that are potential sources of human exposure. The system is very inexpensive, sensitive (ng or μg can be detected), and rapid (results are seen in two days).

Many carcinogens and noncarcinogens have been tested with the original four bacterial strains. We are currently compiling results obtained using the test in this and in many other laboratories throughout the world (McCann, et al., in preparation). So far, about 85% of the carcinogens tested (117/139) have been detected as mutagens. These include a wide variety of carcinogens such as direct alkylating agents, nitrosamines, polycyclic hydrocarbons, fungal toxins, aromatic amines, nitrofuran carcinogens, a variety of antineoplastic agents, and antibiotic carcinogens such as adriamycin, daunomycin, and mitomycin C. Also, most of the known human chemical carcinogens that have been tested are positive. These include β-naphthylamine, benzidine, cigarette-smoke condensates, BCME, aflatoxin B_1, vinyl chloride, 4-aminobiphenyl, and a variety of coal-tar components. Carcinogens not yet detected include acetamide, dimethyl hydrazine, safrole, urethan; metal carcinogens, such as lead acetate and titanocene dichloride; and promoter carcinogens such as phorbol. Most of these chemicals have not yet been tested in our new tester strains (TA100 and 98), and we feel that the increased efficiency of these new strains in detecting carcinogens will lend even more support to the correlation of carcinogenicity and mutagenicity.

The test is highly selective for the detection of carcinogens. To date, 59 noncarcinogens (chemicals negative in tests for carcinogenicity) have been tested, most of which are close relatives of carcinogens. Extremely few (5/59) are mutagenic in the test and for several of these carcinogenicity tests have been extremely limited, and there is some doubt as to the classification of these chemicals as noncarcinogens. Many hundreds of common chemicals of unknown carcinogenicity have also been tested, and in general, very few chemicals are positive. We feel that chemicals to which humans are exposed that are clearly positive in the test should be considered potential human health hazards, and should be thoroughly tested in animal systems, and, where extensive human exposure has occurred, appropriate epidemiologic studies should be done.