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POLLUTANTS AND HIGH RISK GROUPS A CONFERENCE SUMMARY

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ABSTRACT

On June 5th and 6th, 1978 a National Conference on the Effects of Pollutants on High Risk Groups was held at the University of Massachusetts, Amherst, Massachusetts, U.S.A. sponsored by the U.S. Environmental Protection Agency.

The Conference focused on biological factors (developmental processes, genetic deficient conditions, nutritional status, and pre-existing disease conditions) which predispose individuals to toxicity and carcinogenicity. The implications of the knowledge of high risk groups in occupational health policies, practices and standard setting were discussed in panel discussions. This paper will provide a summary of the findings reported at the Conference.

On June 5th and 6th, 1978 the United States Environmental Protection Agency sponsored a conference on Pollutants and High Risk Groups which was conducted by the Division of Public Health of the University of Massachusetts, Amherst, Massachusetts. The intention of this paper is to present a summary of the conference findings with particular emphasis to its implications for occupational health policy and practices.

The conference rationale was based on the recognition that one of the most pressing issues in the area of occupational health concerns the identification and quantification of individuals at high risk to the development of toxic and/or carcinogenic responses following exposure to toxic substances. High risk groups are the first to experience morbidity and mortality as a result of exposure to a wide range of commonly encountered pollutants. Since a primary goal of occupational health policies is to protect all individuals from adverse health effects, it is necessary to more closely analyze the concept of increased risk. Thus, the conference participants presented evidence which identified specific biological factors which predispose individuals to adverse health effects. Those specific biological factors which were considered in detail included developmental processes, genetic factors, nutritional status, pre-existing disease conditions, and to some extent, personal habits and life style.

I will attempt to summarize representative papers which illustrate the type of hypersusceptibility unique to the general classifications of high risk conditions

noted previously. Also, since considerable emphasis at the conference was devoted to policy issues, the final third of this paper will attempt to illustrate the different perspectives of the various interest groups. Finally, I will present a personal conclusion concerning where I believe the general consensus of the conference lies on the issue of high risk groups.

DEVELOPMENTAL FACTORS

Embryos and fetuses are often exposed to a variety of potentially toxic and/or carcinogenic substances. Placental selectivity regulates the rates of chemical transfer from the mother to the embryo or fetus for a wide range of chemicals. The rate of entry is thought to be principally affected by the fat solubility of the nonionized chemicals while concentration gradients and the size of the molecules are of secondary importance. Thus, chemicals with a size of less than 600 molecular weight usually pass freely across the placenta while chemicals with a molecular weight greater than 1 000 usually do not pass the placenta. Numerous substances quite common to industrial settings which are known to pass the placenta have been shown to cause teratogenic effects. Some of these industrial teratogens are: benzene, cadmium, carbaryl, chromium, 2,3-dinitrophenol, formaldehyde, lead, malathion, mercury, paraquat, PCBs.

Toxicological studies of foreign compounds which transverse the placenta have clearly demonstrated that there are distinct biochemical differences between the developing fetus and adults with regard to the capacity of the liver to metabolize foreign substances. The prevailing view concerning compound metabolism in the human fetal liver is that the metabolizing enzymes are absent or have negligible activities.

According to Dr Jerry Rice of the National Cancer Institute, research with rodents has revealed that during the post-embryonic period of the prenatal development, the fetus is significantly more sensitive to certain carcinogens than adults. In certain cases the fetus may be upwards of 1 000 times more susceptible than adults. According to Dr Rice, the enhanced susceptibility of the fetus usually occurs with exposure to direct acting carcinogens. In contrast, the fetus may be less susceptible than adults to substances which require enzymatic transformation prior to the initiation of carcinogenesis.

In addition to immature detoxification enzymatic pathways which may predispose the unborn and neonate to carcinogenesis from certain agents within the environment, Dr Michael Bennett of Boston University presented information which illustrated that susceptibility to chemical carcinogens is frequently associated with a relative dysfunction of the immune system which seems to be age dependent. Numerous studies have now established that chemical carcinogens and promoting agents when given transplacentally to fetuses and during the neonatal period cause a greater incidence of tumors with reduced latency periods. According to Dr Bennett, during these early stages of development the immune system is relatively incompetent with various components maturing at different rates.

Similar increased sensitivity to chemical carcinogens also becomes evident in old age and is associated with an atrophic thymus and a moderately suppressed cell-mediated immunity. According to Bennett, the influence of either an immature or aged immune system on the expression of chemically-induced cancer may, in fact, be mediated by hormonal influences in light of recent studies which have demonstrated endocrine regulation of various aspects of immune function. It was thus suggested that this could explain the frequency of tumors induced in offspring by carcinogens given during pregnancy and the occurrence of tumors in the aged.

GENETIC FACTORS

With respect to genetic predisposition to the toxic and or carcinogenic action of various substances in the environment, research was presented on recent epidemiologic studies which suggest the existence of an inherited susceptibility to aromatic amine induced bladder cancer. Based on considerable animal research which had demonstrated a relationship of susceptibility to aryl amine induced bladder cancer in animals lacking or low in their ability to detoxify aryl amines via N-acetylation, Dr Gerald Lower of the University of Wisconsin presented evidence which suggested that humans from the general population in Denmark and the State of Wisconsin in the United States who are »slow acetylators« were at somewhat increased risk (that is, by 10%) to experiencing bladder cancer. Since populations of "spontaneous bladder patients" would be expected to contain variable portions of disease related to arylamine exposure and would be less likely to display a detectable correlation than an industrial population with arylamine exposure would, the 10% increase of bladder cancer among the slow acetylators in Denmark and the State of Wisconsin suggests that the incidence of bladder cancer among those with a slow acetylator phenotype and working in industries where arylamines are present should be markedly increased over normal predicted values. Collaborative studies with DuPont's Medical Division are now underway to evaluate this hypothesis.

In recent years there has been considerable interest generated toward identifying biological factors which may predispose individuals to experience bronchogenic carcinoma. Kellermann and co-workers[1] have theorized that individuals with a high genetic capacity to metabolize procarcinogens such as benzo(a)pyrene to ultimate carcinogens presumably via the activity of aryl hydrocarbon hydroxylase (AHH) would be at increased risk to develop cigarette smoking related bronchogenic carcinoma. This hypothesis was based, in part, on observations of patients with bronchogenic carcinoma which revealed that groups with intermediate and high AHH inducibility had 16 and 36 times greater risk of lung cancer than the low inducibility group when reasonably matched for smoking behaviors.

However, this theory came under further scrutiny by Dr Richard Kouri of Microbiological Associates of Bethesda, Maryland who reported that mouse pulmonary tissue, in marked contrast to mouse and rat hepatic tissue failed to

activate particular fractions of 2A1 cigarette smoke condensate to forms mutagenic to strain TA98. Furthermore, these fractions failed to initiate lung cancers in C3H/f Cum or BC $3F_1$/Cum mice while markedly promoting benzo-(a)pyrene induced lung cancer. They suggested several potential explanations which are worthy of future study: 1) those chemicals which can be activated by pulmonary tissue are at concentrations too low to be detected; 2) cigarette smoke contains chemicals which are biologically active; however, the mouse lung is not capable of activating these chemicals; 3) the role of tobacco constituents in lung tissue is to function as a "promotor" rather than an initiator of carcinogenesis. From the work of Dr Kouri and his co-workers it is apparent that much remains to be determined with respect to the biochemical basis of polycyclic aromatic hydrocarbon (PAH) induced lung cancer before any definite conclusions can be made considering genetic susceptibilities.

Research at the University of Massachusetts by Dr Gary S. Moore and myself has focused on developing an appropriate animal model which could simulate the response of human G-6-PD deficient individuals to a variety of oxidant stressor agents. The fact that there are approximately 100 million individuals with this enzymatic deficiency throughout the world underlines the importance of developing a model which can accurately predict the differential sensitivity of G-6-PD deficients to various oxidant chemicals and their interaction. Studies were presented on two more strains, one with lowe and other with high levels of G-6-PD activity within red blood cells to evaluate their possible differential susceptibility for a variety of oxidant stressors. The results, although preliminary, indicated that the low G-6-PD strain of mice are markedly more susceptible to oxidant stress from sodium chlorite. Further research is necessary to validate the efficacy of this mouse model as a predictor of the human situation.

NUTRITIONAL STATUS

Considerable efforts have been directed toward elucidating the influence of nutritional status on pollutant toxicity. According to Dr Daniel B. Menzel of Duke University, knowledge of nutrition provides a critical component in developing an effective preventive medicine program. He stated that the potential influence of environmental stress on the requirements for certain nutrients has only recently been emphasized and that the capacity of humans to properly adapt to various degrees of environmental stress may be dependent on biochemical pathways which need certain nutrients in greater quantity than required in a pollution free environment. Among the research presented by Dr Menzel were the observations that vitamin E interacted with ozone or NO_2 catalyzed peroxidation of arachidonic acid to reduce the biological potency of the peroxides which were formed. The peroxides have biological activity which mimick the naturally occurring endoperoxides of the prostaglandin series. The presence of elevated levels of vitamin E concomitant with ozone catalyzed peroxidation of arachidonic acid diminishes the capacity of the peroxide formed to aggregate human platelets. Based on these and other studies, Menzel

concluded that vitamin E may play an important role in protecting humans from oxidant induced damages. In fact, Menzel suggested that the current RDA of 15 I.U. for vitamin E should be re-evaluated in light of its newly found protective effects from commonly encountered oxidant stressor agents.

However, according to Dr M.R. Spivey Fox of the Food and Drug Administration of the U.S.A., nutritional intervention to reduce heavy metal toxicity must be cognizant of the possibility of creating nutrient imbalances. She cited the example of supplementations of certain dietary factors such as zinc and vitamin C which may reduce cadmium toxicity. Yet, despite their protective effects against cadmium, adverse effects of excess zinc may be significantly increased by ascorbic acid supplements. Thus, although supplements of zinc and vitamin C have each protected against cadmium toxicity, their joint use at elevated levels may be undesirable. Thus, Dr Fox concluded that "an adequate and balanced nutrient intake is very important in countering adverse effects of metals; however, increasing recognition of subtleties in interaction of nutrients and evidence of the essentiality of even more elements should moderate the use of high level nutrient supplementation".

In addition to dietary factors influencing the toxicity of oxidant gases and heavy metals, Dr Paul Nettesheim of the National Institute for Environmental Health Sciences (NIEHS) has reported that low levels of dietary vitamin A not only lead to epithelial abnormalities of the respiratory tract such as squamous metaplasia but also predispose the organism to hydrocarbon induced carcinogenesis. In light of the well-established role that vitamin A and its analogs play in the differentiation of epithelial tissue, the National Cancer Institute is now conducting clinical trials using vitamin A analogs as a chemopreventive mechanism in those who are considered at increased risk to epithelial cancer.

PRE-EXISTING DISEASE CONDITIONS

Perhaps the best known of the high risk groups are those with pre-existing diseases such as asthmatics, bronchitics and those with heart disease. In a study reported by Dr Frances Silverman of the Gage Research Institute of Toronto seventeen well-documented male and female asthmatics were exposed for 2 hours in an environmental chamber to 0.25 ppm of ozone on one occasion and to air on another occasion. Statistical analyses of forced expiratory volume ($FEV_{1.0}$) and maximum expiratory flow rate (MEFR) at 50% of vital capacity reflected no significant changes between the ozone and air exposure. However, in other experiments she reported that one third of the asthmatics exhibited greater responses to 0.25 ppm of ozone than the largest change found in non-asthmatics exposed to 0.37 ppm of ozone. She concluded that exposure to ozone at commonly encountered concentrations in summer months can cause adverse effects in some asthmatics. Further research is necessary to differentiate among the various types of asthmatics with respect to ozone sensitivity.

Dr Von Neiding of the Federal Republic of Germany examined the effects of NO_2 on 111 chronic bronchitics aged 25 to 74 years over a range of

concentrations of 0.5 to 8.0 ppm for 15 minutes up to 1 hour. Of significance were observations that at 4 ppm a significant decrease of arterial oxygen tension occurred while at the concentration of 1.5 ppm there was a significant increase of airway resistance.

POLICY ISSUES

In addition to biomedical research on high risk groups, the conference devoted considerable time toward elucidating the role that the knowledge of high risk groups should have in occupational health policies and practices as well as standard setting in the United States. The conference provided a framework whereby different interest groups such as industrial management, labor unions and government regulatory agencies such as the Occupational Health and Safety Administration had the opportunity to present their view points and to further explore areas of agreement and of course, disagreement.

In a major address at the conference, Dr Paul Kotin, Vice President of Environmental Health and Safety of Johns Manville Co., a leading producer of asbestos products in the United States, indicated that high risk groups are not just an insignificant segment of the population. Increased risk to toxic and/or carcinogenic effects are not only a function of one's age, and genetic background but also of one's cultural and personal habits. He stated that there is little question that variability is the hallmark of all biological systems including humans and susceptibility is the generic term for differentiating the level of intensity of response to external stimuli. In fact, susceptibility has a special significance to the principal objective of industrial hygiene programs which is to maintain an acceptable non-hazardous workplace. In order to achieve this goal of an acceptable non-hazardous workplace, hypersusceptibility is one of several factors considered in worker selection. Dr Kotin emphasized that union arguments which claim that screening of hypersusceptible workers is only a ploy to avoid environmental controls, work practices or maintaining performance standards is no longer a persuasive argument.

Biological predispositions to toxic and carcinogenic responses cannot be legislated away by any governmental law designed to equalize opportunities. The real worlds of biology and medicine do not cooperate. For example, consider the increased susceptibility of asbestos related cancer in smokers. Dr Kotin mentioned that Johns Manville will not hire any individual who smokes for a position which will encounter exposure to asbestos. The risks and the responsibility are too great. If they do hire such a person how can they comply with the general relief laws of the Occupational Safety and Health Act of 1970 which states in Section 5-A that "each employer shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or likely to cause death or serious physical harm to his employees". According to Dr Kotin, employees at increased risk to specific industrial agents should be provided employment for which their biological predispositions would not place them at enhanced risk. Although many may claim that industry should eliminate all potential hazards especially the

carcinogens, mutagens and teratogens, instead of selective screening out of high risk groups, the social consequences of such an act which would probably criple industries as a steel, petro-chemical, automobile manufacturing and others is probably unacceptable to socicty.

Dr Kotin noted that the result of these difficult management-labor-societal decisions demands that management and labor accept a joint responsibility to reduce risk in the industrial environment. The fact that labor has challenged, in the courts, Johns Manville's non-hiring policy for smokers strongly suggests that this joint cooperative relationship is more a goal than reality. Dr Kotin finally concluded that "the recognition of the hypersusceptible worker in no way negates or challenges the right of anybody to a job and anybody who says that it does either is uninformed or is distorting reality. Everybody has a right to a job. Not everybody has a right to every job."

A perspective from labor was given by Michael Wright, of the Steel Workers Union who felt that there were several major issues with which labor should be concerned with respect to the increased sensitivity to toxic and carcinogenic agents in the workplace. First, to what extent will industry honestly consider eliminating the risk to so-called non-susceptibles. For example, if you are a woman of childbearing age you are not allowed to work around lead and other potentially embryo-toxic chemicals. Thus, certain industries are screening out women while ignoring possible reproductive effects in men. Second, to what extent will the negative aspects of screening be considered. For example, what would be the effect of a screening out program on a plant manager who may now conclude that since we have eliminated those at increased risk we don't have to be as concerned with environmental controls. In an utopian world Dr Kotin's views on this matter may be fine but in the real world it is often quite to the contrary. Third, to what extent do we consider the elimination of risk factors rather than the elimination of high risk workers. And fourth, to what extent will companies such as Johns Manville absolutely guarantee a job to people removed by screening programs and that these new jobs bring with them the seniority and other benefits. According to Mr Wright, if industry is not willing to make such guarantees, then the fears of labor are legitimate.

The sentiments of Mr Wright were, in general, strongly supported by Dr Nicholas Ashford of Massachusetts Institute of Technology who emphasized that economic incentives encourage management to remove the high risk groups from certain jobs thereby reducing potential workman's compensation claims. Of course, management could apt for removing the hazard but it is cheaper to remove the potential claimant.

According to Dr Bertram Dinman, Corporate Medical Director of Alcoa in the United States, excellent progress has been made in his company, at least, to achieve the goal of joint management-labor cooperation on health and safety issues. Through their joint Safety and Health Committee both management and labor become aware of each other's concerns including the health and economic realities. As a result of such open lines of communications, workers realize that it is not possible for management to guarantee a hazard free workplace while

management has recognized the issues raised by Mr. Wright, and does recognize that workers will not lose any salary because of job transfers on the basis of hypersusceptibility.

CONCLUSIONS

The concept of increased susceptibility to environmental stressor agents must be seen in a broad context. Individuals may be at increased risk because of their age, genetic background, nutritional status, a preexisting disease condition, as well as their personal habits and lifestyle. The precise mechanistic explanation of differential susceptibility to toxic and/or carcinogenic agents is known for only a few agents and predisposing conditions with most explanations awaiting discovery. This is why it is difficult to truly evaluate the role of high risk groups knowledge in policy matters. Future explanations may hopefully further clarify why certain individuals may be predisposed to developing environmentally induced cancers while others are not. How this knowledge should affect occupational health standards, job placement, workmen's compensation, management-labor relationships, etc. is difficult to define. However, the general concensus is:

1. that industries must remain competitive;
2. that industrial management and labor must work together in solving health and economic issues;
3. that industry must adopt a strong effort to reduce the level of stressor agents in the environment;
4. that if high risk workers can not be protected and strict standards are not possible then a job replacement with similar salary and benefits should be given;
5. that a screening out of hypersusceptibles program should not encourage a diminished concern for the health and safety of the so-called non--susceptibles.

REFERENCE

1. *Kellermann, G., Shaw, C. R. and Luyten–Kellermann, M.* Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. N. Engl. J. Med., **289** (1973) 934–937.