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11. BENZENE TOXICITY

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The proper control of benzene in the workplace and the general environment has been a subject of relatively intense interest for at least the past decade. In the United States there have been a series of regulatory actions and ensuing legal battles. including a Supreme Court decision. that have kept a spotlight focused on benzene toxicity and its control. This attention partly reflects the relatively large volume of benzene in commerce, its chemical characteristics allowing it to be both an air and water contaminant. and its ubiquitous presence in modern society. Another major reason for the interest in benzene is that it is the most frequently used and commercially important of the known human carcinogens. Despite ail of the attention this compound has received, many questions remain as to the extent to which it is a hazard. and the appropriate means to protect workers and the general public against the adverse effects of benzene. In this chapter the toxicology and health effects of benzene will be reviewed. as will appropriate means for surveillance and other aspects of workplace protection for which the occupational physician bears responsibility.

Benzene is widely used in industry, particularly in organic synthesis and as a solvent. although the latter use is decreasing due to its potential toxicity to humans. Total U.S. production in 1985 was 9.73 billion tons, up slightly from 1984.[64] Benzene is a common component of many widely distributed substances, particularly gasoline. for which it constitutes about 1% of U.S. gasoline and 5% of European gasoline. NIOSH has estimated that close to 2,000,000 U.S. workers have a potential for benzene exposure.

TOXICOLOGY OF BENZENE

The toxicological properties of benzene are among the most thoroughly studied of all organic compounds. Despite this extensive body of information. there are a number of uncertainties that are crucial to decisions concerning proper protection of workers. The salient features of benzene toxicology are described below. More extensive information is available in review articles.[18-21,37,54,65]

Following inhalation, approximately 50% of benzene is exhaled unmetabolized. Metabolism occurs primarily in the liver, but in other organs as well. including the bone marrow. Quantitatively, the major metabolic product is phenol. There are a large number of metabolites that are formed including glucuronidated and sulfated products. which in essence result in the highly non-polar benzene molecule becoming water soluble and excretable in the urine.[54]

There is ample evidence that it is a metabolite of benzene, rather than benzene itself, that is responsible for its hematological toxicity.[54] Unfortunately there is no agreement at present as to which one or more metabolites of benzene are responsible for this effect. There are three major types of compounds which are candidates: reactive, oxygenated derivatives of benzene such as benzene epoxide; polyhpdroxylated benzene metabolites such as benzoquinone"; or ring opened benzene metabolites such as muconaldehyde.[38] Determination of the hematotoxic metabolites of benzene will be of great practical value in improving our knowledge of the risk assessment for benzene so as to appropriately set workplace standards, and through providing a marker of exposure and ot biological effects."

In addition to inhalation, benzene can also be taken up by ingestion in water or in food and is absorbed through the skin." More information would be ot value as to the capacity for dermal absorption and the extent to which this is of importance in the workplace. Benzene is naturally present in very low concentrations in certain foods. It is also a constituent of cigarette smoke. Further. as our analytical techniques improve and the consequences of leaky underground petroleum storage tanks and careless land disposal practices take effect, more ana more water supplies will be found to contain benzene.

The central nervous system effects of benzene are similar to those observed for alkyl benzenes and are related to the anesthetic-like effects of hydrocarbon solvents of this nature. The central nervous system effects appear to be directly dependent upon the compound itself rather than on a metabolite. Of major concern in the workplace is the drowsiness caused by such compounds. This car lead to industrial accidents and such events as drowning in vats of benzene have occurred. The effect of benzene and the alkyl benzenes on the central nervous system are readily predictable based upon physical properties. In contrast, it is only benzene that has hematological effects.

The mechanism by which benzene metabolite(s) produce hematologica. toxicity is uncertain. DNA is a likely target and there is ample evidence that benzene exposure produces cytogenetic effects.[16,21,34,58,59] The hematological toxicity of benzene is expressed primarily on bone marrow precursor cells and on lymphocytic cells.[9,12,26,31] The bone marrow production of granulocytic white blood cells, red blood cells. and platelets is linked through the presumed presence of a pluripotential stem cell capable of differentiating to the earliest precursors of each of these cell lines. Identifiable precursor cells, often known as blasts, then progress through a series of stages resulting in mature red cells, granulocytic white blood cells, and platelets. In animal studies, exposure to benzene produce:

aplastic effects similar to those observed in man." At sufficiently high levels. there is complete destruction of bone marrow precursor cells and a resultant decrease in red blood cell count. white blood cell count. and platelet count. The effect follows expected dose response patterns. with lower doses producing lesser extents of aplasia and pancytopenia. As anticipated for an effect of this nature, there is an apparent threshold. i.e., at some benzene dose no overt decrease in blood count is observed. Strain differences in susceptibility to benzene have been reported. including some slight difference in the pattern of response.[40] For instance. CD-1 mice. which are relatively sensitive to benzene, at certain dose levels of benzene tend to have a granulocytic rather than a granulocytopenic response." This is the only mouse strain for which there is some preliminary evidence of benzene-induced granulocytic leukemia."

A decrease in peripheral blood counts has not been observed in any species at exposure doses below the current U.S. Occupational Health Standard of 10 ppm TWA. However, there is good evidence of an effect on bone marrow stem cells. Green et al. have demonstrated a decrease in bone marrow precursor colony forming cells in mice exposed for 6 months, 5 days weekly, 6 hours daily to 10 ppm benzene." No change in peripheral blood counts was observed in this study. These findings can be interpreted as indicating an effect on bone marrow precursor cells that diminishes bone marrow reserve without affecting the ability of the bone marrow to produce normal amounts of circulating cells. This is not inconsistent with what has been observed in humans following treatment with myelotoxic cancer chemotherapeutic agents. In such individuals. despite normal white blood cell counts. there appears to be a decrease in bone marrow reserve as indicated by an impaired ability to increase the white blood cell count in response to infection.

Until recently, benzene was not thought to be carcinogenic in laboratory animals. However, studies from a number of groups have now clearly demonstrated benzene-induced cancer in mice and rats, primarily nonhematological tumors.[42] While hematologic tumors also have been observed" and there is some preliminary evidence of myelogenous leukemia in CD-I mice,[22] a good animal model of benzene-induced acute myelogenous leukemia has yet to be described. The presence of solid tumors in the animal studies has led to suggestions that benzene may be capable of producing nonhematological neoplasia in humans. It should be noted that preliminary evidence has been reported suggesting that in these strains of laboratory animals, similar nonhematological neoplasia may be produced by alkyl benzenes such as toluene, although with lesser potency. Assessment of whether benzene produces nonhematologic neoplasia in humans may be possible by reviewing existing data bases and should be a high priority.

Evaluation of the possible teratogenic effects of benzene has not shown evidence that teratogenesis would occur as a result of workplace exposures.[24,36] However. a recent study notes a decrease in hematologic cells in mice previously exposed in utero to relatively low concentrations of benzene.[35]

HEMATOLOGICAL EFFECTS IN THE HUMAN

Aplastic effects. The production of fatal aplastic anemia in workers exposed to benzene was originally recognized in the 19th century. Benzene can destroy the bone marrow precursors of circulating red blood cells. granulocytic white blood cells. and platelets, leading to anemia, and can produce potentially fatal infections due to granulocytopenia or hemorrhage as a result of thrombocytopenia.[19] The

diagnosis of aplastic anemia is usually made when there is sufficient toxicity produce an overt decrease in bone marrow cellularity. The term pancytopenia often used to denote a milder decrease in blood counts affecting the white blo cell count, platelet count. and red blood cell count. It is important to recogn that it is not just the granulocytes that are affected by benzene exposure but I lymphocytes as well. In fact it appears that a decrease in lymphocyte count is o of the earliest manifestations of benzene toxicity in humans,[23] a finding clea observed in laboratory animals experimentally exposed to benzene." This m account for the apparent effect of benzene on immune function. which has be observed in laboratory animals.[9,66]

Another relatively early manifestation of benzene toxicity is an increase red cell mean corpuscular volume (MCV).[18,28] A variety of other findings altered cell status or function suggests that benzene toxicity results not only it quantitative decrease in cell number but also a qualitative alteration in circulati blood cells of all types. Except perhaps for the decrease in lymphocyte count a increase in MCV, none of these changes as yet appears to be sufficiently w documented for use in surveillance at current levels of benzene exposure in t petrochemical industry."

Leukemic Effects. Association of exposure and acute myelogenous le kemia has been noted for more than 50 years. However, it has not been un recent decades that a causal relationship between benzene exposure and tl form of leukemia and its variants has been accepted by the scientific co1 munity as a whole.[21,65] Review of the hematological literature suggests th; based upon case reports. hematologists were among the first to accept tl causal relationship. These case reports were notable for being from differe countries and having different work circumstances, often with other chemic:. present. but with a common denominator of benzene exposure." There a also reports of work forces containing many individuals with varying degre of pancytopenia clearly due to benzene exposure, among whom occasiona: one would be observed to go from aplastic anemia through a preleukem phase into the development of acute myeloblastic leukemia. As in these situ tions benzene was clearly the antecedent for the aplastic anemia. and aplastic anemia from apparently any cause is believed to enhance the risk development of acute myelogenous leukemia, benzene was relatively readi accepted by hematologists as being a causal instigator of acute myelogeno leukemia. Further lending biomedical plausibility to this relationship was ti observation that individuals with hematological abnormalities secondary benzene exposure often had marked chromosomal changes in their circulati lymphocytes and in bone marrow cells not dissimilar to those observed follow radiation.[16]

Aggregations of cases of acute myelogenous leukemia following benze: exposure have been reported from a number of industries. One of the first to t thoroughly studied was that of shoe workers in Italy, evaluated by Vigliani a r his colleagues.[62,63] More recently, Aksoy has studied an epidemic of hemat logical disorders due to benzene occurring in the tanning handcraft leath industry? Cases of aplastic anemia were observed within a short time followin introduction of a new benzene-based glue. Subsequently, an increased incidenc of acute myelogenous leukemia and related disorders was noted in the: workers. Measurement of ambient levels of benzene, only rarely obtaine exceeded 200 ppm. Replacement of the glue has apparently put an end to th outbreak of overt hematological consequences due to benzene exposure. Durir

this period Aksoy et al. also reported a number of other hematological disorders. including paroxysmal nocturnal hemoglobinuria.' This rare hematological disorder. which is related both to aplastic anemia and acute myelogenous leukemia, and can be understood to be a premalignant condition. has been reported in other benzene exposed workers. More recently. Aksoy has noted Hodgkin's disease and lung cancer in benzene exposed workers in Turkey.' The causal relationships have not been established.

There are a number of variants of acute myelogenous leukemia, including myelomonocytic leukemia. promyelocytic leukemia and erythroleukemia. It is notable how often erythroleukemia, which is otherwise relatively rare, has been reported in benzene exposed workers. Benzene has also been relatively frequently associated with the myeloproliferative disorders chronic myelogenous leukemia and myelofibrosis, and myeloid metaplasia. However. in my judgment the evidence **of** a causal relationship, while plausible. is less than certain.

There are a number of reports relating benzene exposure to a variety of lymphatic tumors. including Hodgkin's and non-Hodgkin's lymphoma. *to* acute lymphatic leukemia. and to multiple **myeloma**.[15,61] This would not be surprising in view of the propensity of benzene to affect the lymphatic system in animals and **man**,[23,52] and the production of benzene-induced lymphoma in mice." However. in no case does the evidence appear to be sufficiently clear-cut to overwhelmingly demonstrate a causal relationship between benzene and one or more human lymphatic tumors. One study of interest was performed by Girard and his colleagues.'' who started with patients diagnosed as having hematological diseases and searched for previous history suggestive of benzene exposure. In addition to the expected association with acute leukemia and aplastic anemia. there was also a statistically significant increase in history of benzene exposure among those with chronic lymphocytic leukemia. This may reflect a long latency period for benzene-induced chronic lymphocytic leukemia, which is a disease almost totally limited to the elderly. Therefore, the studies in Turkey and Italy evaluating recently exposed workers might not yet be expected to observe benzene-induced chronic lymphocytic leukemia.

Interactive effects of benzene with other agents have been **reported**.[8,11,51,67] The most significant potential workplace interactions are those noted with toluene and with ethanol. Exposure of laboratory animals to both benzene and toluene has previously been reported to decrease the hematological toxicity of **benzene**.[8] However. more recent studies have shown that this protective effect of toluene occurs only a relatively high levels. At lower levels. in the range encountered in the workplace. no interaction in hematological toxicity or metabolism was observed in the rat or in metabolism in a human.'' Laboratory studies have shown that ethanol in the drinking water of mice exposed 6 hours a day five days weekly to ***300*** ppm benzene potentiates hematological toxicity.'' Also of potential interest **Is** a report by Ishimaru et al.,[33] who noted that those Japanese atom bomb survivors who developed leukemia were more likely to also have had exposure to benzene or to x-ray.

In the past decade there have been a number of studies of workers occupationally exposed to benzene that have clearly demonstrated a substantially increased risk of acute myelogenous leukemia. Perhaps the most notable of these. and one of the most thoroughly studied cohorts of American workers. has been the group of rubber industry worhers under evaluation by investigators from NIOSH since **1976**.[29,47,48] The expected number of deaths due to leukemia in a cohort of white males was **1.38** or 1.48, depending upon the control group in

use. However, seven deaths were observed.[29] This observation was the initiating factor of changing the 10 ppm TWA standard for benzene to 1 ppm as an emergency temporary standard in 1976. Following an unsuccessful court defense of this approach, OSHA went to formal rule-making and again proposed a 1 ppm standard, but in 1980this also was overturned by the Supreme Court. More recently, OSHA has announced the promulgation of a 1 ppm standard.[1]

A number of other studies in benzeneexposed populations have tended to show a statistically significant increased risk of leukemia. Among these are: studies in the chemical industry; the observation of increased deaths due to hematopoietic and lymphatic tumors among workers at four tire manufacturing plants; and a statistically significant increase in deaths due to leukemia and lymphatic tumors, including myeloma, in rubber industry workers.[7,10,14,27,44,46,50,55,56,57,68] Tumors of the hematopoietic system have been found to occur at statistically significant high levels in members of the American Chemical Society and, in a study in Britain, in the occupational classification including professional and technical workers.[2,39] If one evaluates the mortality of potentially exposed groups. such as workers in the chemical, rubber and petrochemical industries, in almost all cases a standard mortality ratio above 100 for hematopoietic tumors or leukemia is observed, even though the number of individuals is usually too small to make the difference statistically significant in any one study. An interesting example was reported in Britain, where the overall SMR was only 94.50 However. a follow-up case control study of those individuals with leukemia revealed a statistically significant likelihood of exposure to moderate or high levels of benzene.[50] In contrast, a recent case control study of an oil refinery workgroup that had previously been shown to have an increased mortality rate due to leukemia could not identify a greater likelihood of exposure to benzene.[10]

The risk of acute myelogenous leukemia due to benzene has been calculated by a number of different groups.[19,30,47] In general, there is surprisingly good agreement among these estimated unit risk numbers for the carcinogenicity of benzene, despite major differences in starting points and assumptions. Of particular note is the exceptionally close agreement in two risk assessments done by EPA. one beginning with data in human epidemiological studies and one with data from animal bioassays.[19] This resulted in a unit risk of 7 in one million for death due to leukemia as a result of lifetime exposure to 1 $\mu g/m^3$ (0.3 ppb) benzene. The presumed linearity of dose response for carcinogens implies that for an average lifetime exposure of a mg/m^3 (1,000-fold higher) there would be a corresponding 1,000-fold higher leukemia rise of 7 in 1,000 lifetime. The risk for a working lifetime has been estimated by OSHA as 10 excess leukemia deaths per 1.000 employees exposed for a working lifetime to 1 ppm benzene, the new OSHA standard.' This is a relatively high risk in comparison to other workplace standards. All of these risk estimates assume no threshold.

MEASUREMENT OF BENZENE EXPOSURE

There basically are three ways in which one can estimate workplace exposure: modelling, ambient monitoring, and biological monitoring. It is possible to model benzene exposure based upon known benzene volume, dispersion values, temperature, etc. Modelling can be useful in engineering design and in retrospective assessment in a tort case. However, where there is a possibility of significant benzene exposure. ambient monitoring is the preferred approach, with biological monitoring (ie., hematological surveillance) being a valuable and necessary supplement.20

The success of an ambient monitoring program in protecting workers is dependent upon the ability of the monitoring approach to detect fluctuations in benzene levels pertinent to each worker. Each site and work regimen will present different challenges. For work forces with a homogenous job pattern, operating in an uncluttered building with good air mixing, a single benzene sampling station will better typify worker benzene exposure than in a building with different tasks being performed, localized benzene sources. and obstructed air flow patterns. While the industrial hygienist is the professional primarily involved in making decisions concerning location and frequency of sampling, it is important that the occupational medicine physician be aware of this sampling program and its implications to potential exposure. One must also keep in mind that standard sampling approaches are of little value in detecting highly localized exposures, e.g., around a valve located near a worker's breathing zone or in situations where an individual is engaging in sloppy work practices. There are many techniques that can accurately assay benzene in air or other media at levels less than 1 ppm. Newer experimental approaches, suitable for personal monitoring, can integrate ambient benzene exposure in the range of 1 ppb over a workday period.

The extent of benzene exposure in the U.S. petroleum industry 1978-1983 has been reviewed by Runion and Scott. They reported that 87% of exposures were below I ppm TWA and 98% below 10 ppm TWA.[49]

Rationale for Surveillance

When considering the rationale for biological monitoring at the workplace, it should be emphasized that the primary defenses against benzene exposure are engineering and work practices designed to avoid any possibility of human exposure. This is no different than for any potentially hazardous substance. If engineering and human work practice approaches were perfect, there would be no need for biological monitoring. Unfortunately, engineering design is not perfect, and human carelessness and callousness must be assumed. Accordingly, there is clearly a role for biological monitoring in occupational health.

In general. there are three types of biological markers: markers of exposure. markers of effect. and markers of susceptibility. Currently, biological monitoring for benzene primarily aims at quantitating markers of effect. These hematological parameters indicative of benzene toxicity will be discussed in detail below.

Exposure markers are also potentially available for benzene. Measurement of benzene in blood or expired air is technically feasible at relatively low concentrations. However. the relatively rapid half-life of benzene which. theoretically. may well differ greatly from person to person and from time to time. limits the value of measurement of benzene in the body. Although momentary body burden can be obtained, blood benzene levels give a poor indication of the integration of benzene exposure over time. The marker of benzene exposure most frequently used has been urinary phenol. Unfortunately. there are other sources of phenol, particularly in the diet. which result in variable amounts of urinary phenol unrelated to benzene exposure. Such variations in urinary phenol will obscure phenol formed from low levels of benzene. The measurement of urinary phenol is still useful if there is a question as to whether or not an individual has been exposed to substantial levels of benzene. However, for situations within the current 1 ppm workplace standard. urinary phenol is an inadequate assay to determine extent of benzene exposure. While other metabolites of benzene can be measured in our body fluids. it is not clear which of these will provide an accurate linkage with either exposure or response. Mechanistic studies

aimed at unravelling the metabolite of benzene responsible for its hematotoxicit may well help find an exposure marker that is related to an effect marker. Suc studies must be pursued vigorously.

No susceptibility marker for benzene is available. Based on general toxicc logical principles. some variation in human susceptibility to benzene would b anticipated. There are suggestions in the literature of heightened sensitivity t benzene depending upon age. sex. stature. and familial factors." Aksoy describe a husband and wife engaged in manufacturing whistles by dipping plastic materi in a solution of benzene. The wife developed severe aplastic anemia after months of work. whereas the husband had normal hematological findings aftt 14 years of exposure.' However, there is no conclusive evidence that any particula factor will have a major impact. It also is not unreasonable that a situatio leading to increased bone marrow turnover might lead to increased susceptibilit to benzene. For example. a potential interaction between thalassemia minor an benzene toxicity has been suggested, but again there is a lack of convincing dat. Most importantly. there is no clear evidence of the type of exquisite sensitivity f the development of aplasia observed in the small subset of individuals susceptib to chloramphenicol.

Due to its drastic effects on the bone marrow. there are numerous hemat logical tests that can be used as markers of benzene hematotoxicity. Howeve there is no simple laboratory test specific for benzene hematotoxicity. While number of ancillary laboratory approaches have been reported to be helpfu reliance for surveillance and early diagnosis of benzene hematotoxicity is primari based on the complete blood count (CBC). including the red blood cell coun hemoglobin. hematocrit. red cell indices. white blood cell count. differential. an platelet count." Although benzene classically produces a pancytopenia. there no pattern or constellation of findings that clearly distinguishes benzene toxici from all other causes. Laboratory tests should never fully replace a comple medical evaluation and the use of medical judgment.

There are two aims for the biological monitoring of benzene which ca broadly be described as a clinical and a public health aim. The clinical aim can b defined as detection of an individual. or individuals. with overt benzene-induct. hematological toxicity. Such an individual would then be removed from th workplace and treated appropriately. The public health aim is to detect subt changes in larger groups of individuals. or in the work force as a whole. in ord to act preventively before there are overt effects. Obviously. depending upon tt type of exposure episode. finding a single individual with clear-cut hematologic toxicity can be a sentinel event leading to detection of more subtle effects in oth workers.

Complicating Factors in Surveillance

Two complicating factors must be kept in mind when interpreting routi laboratory tests used in an occupational medicine surveillance program. The fir is that these tests have been developed primarily for the clinical setting with th aim of detecting overt disease. The routine laboratory test procedure is designc to readily distinguish clinically normal from clinically abnormal. but is not qui as adept at finding preclinical disease or the subtle changes that are early signs a workplace toxin. The second complicating factor with the use of the CBC as a early indicator of benzene hematotoxicity is that each CBC component has wide range of normal. For example. the typical normal range for a white bloc count is a factor of two (5,000-10,000/cu mm); although the platelet cou

typically has a factor of 2.3 (150,000–350,000/cu mm), the red blood cell range of normal is somewhat narrower and differs between males and females. Widely differing blood counts thus can be considered to be normal, conceivably obscuring a major degree of bone marrow toxicity if only absolute blood counts are evaluated. In addition. it is not always clear how to interpret findings just beyond the published range of normal. Assuming that there is a typical bell-shaped distribution of normal values. and that the range of normal is set at 95% of the population value. there is about 2.5% of the healthy population who will have less than statistically normal blood counts. i.e. individuals who might be falsely identified as having a low blood count due to benzene exposure. As there are three reasonably independent blood cells being tested (platelets, white cells and red cells), surveillance of even a relatively small work force is likely to find at least one blood count below the statistically normal range. Obviously, the lower the count, the less likely that the finding represents the tail end of a normal distribution curve. One must also be alert to the fact that females may have a lower red blood cell count than males.

Observation of a cytopenic or pancytopenic individual in the work force provides the occupational medicine physician with a challenge to determine whether or not the observed effect is due to benzene. Obviously. in the face of benzene exposure one must protect the worker. In considering the differential diagnosis one should start with a review of the extent of benzene exposure. Evidence of a recent spill or other untoward event should be contrasted with situations where a worker may have had only minimal exposure out-ofdoors to a benzene-containing solvent. The differential diagnosis of anemia is extensive. The most common form of anemia. that of iron deficiency, produces microcytosis as opposed to the macrocytosis usually observed in benzene exposure. Accordingly, benzene should not be considered to be a likely cause of microcytic anemias. However. discovery of a microcytic anemia does not necessarily rule out benzene as at least a partial cause of the problem. Helping in the differential is that mild iron deficiency would not usually result in a decrease in the platelet count or white count. Parenthetically. but perhaps of greater importance. observation of iron deficiency in a male. or in a non-menstruating female, requires further work-up to determine the cause of the iron deficiency which. for example. might be the first indication of an early treatable colon cancer.

Low white blood counts can occur as part of an intercurrent infection. particularly viral infections. A history of a recent such infection, coupled with a minimal decrease in the white blood cell count, can be considered grounds to repeat the blood count before other action is taken. When macrocytic red cells are observed. particularly in association with low platelet and white blood cell counts, there is a much greater likelihood that benzene is a causal factor. However, macrocytic red cells are a relatively early indicator of alcoholism. even in the absence of overt folic acid deficiency.[80] It is unclear whether this effect of alcohol is due to direct bone marrow toxicity. Animal studies demonstrate that ethanol intake potentiates benzene hematotoxicity.[81] Further complicating the differential diagnosis is the fact that higher levels of alcohol intake can lead to pancytopenia on the basis of folic acid deficiency or hypersplenism.

One possible approach to the differential diagnosis of a persistently low white blood count is to evaluate bone marrow reserve. which would be expected to be low in benzene toxicity. Less than half of mature neutrophils are actually in the circulation. much of the total pool residing within the bone marrow. A number of agents have been used, including etiocholanolone. endotoxin and

glucocorticoids, to stimulate the release of mature neutrophils into the circulation.'' The response of the white cell count to a stimulus of this nature could conceivably be a useful tool in situation in which there is a question concerning whether a persistently low white blood cell count is due to benzene-induced bone marrow toxicity.

Evaluating slight but persistent elevations in the white blood count also present a problem. Presuming a medical evaluation finds no nonhematological acute or chronic disease process responsible for the leukocytosis, there is always the possibility that a mild leukocytosis represents an early marker of a myeloproliferative syndrome, perhaps indicative of a benzene-related disorder. Much more common. however, is the likelihood that a borderline high white blood cell count is a stress-related phenomenon reflecting a demargination of leukocytes from blood vessel walls into the circulating pool. **An** indirect approach of some help in differentiating an early myeloproliferative syndrome from stress is the old-fashioned eosinophil count, or, if there are many differential counts available. simply reviewing the eosinophil percent. In myeloproliferative disorders there is **a** tendency toward an increase in the percentage of eosinophils, whereas stress-induced adrenal-corticosteroids tend to decrease the total eosinophils. A more specialized test that can be used in this differential is the leukocyte alkaline phosphatase level which is often abnormal in myeloproliferative syndromes Splenomegaly should be searched for carefully as it is a hallmark of myeloproliferative syndromes. A slightly elevated platelet count along with an increased white blood cell count would also suggest a myeloproliferative syndrome. I! clinically indicated. a bone marrow evaluation accompanied by a cytogenetic analysis should be performed.

It must be emphasized that there is no reasonable role for hematologica. surveillance in the detection of early acute myelogenous leukemia. The relatively explosive development and significant clinical symptomatology of most cases o1 acute leukemia make it highly unlikely that routine blood surveillance woulc detect this disease before the individual sought medical attention. Accordingly. a surveillance program should not be said to protect workers by finding early evidence of acute leukemia.

A variety of other laboratory tests have been proposed to be of value ir detecting early benzene toxicity. Two are part of the routine **CBC.** As discussec above. an elevation of red cell mean corpuscular volume (MCV) has been notec as a relatively early finding in benzene-exposed workers. as has a decrease in thc absolute lymphocyte count. More attention should be placed on a fall in th absolute lymphocyte count **now** that automated white cell differential countin: equipment is available. In the past. when only 100 cells were counted by a tech nician. the inherent sampling variability was too broad to rely on a measuremrn of the absolute lymphocyte count. However, this variability is greatly minimizec by counting 1,000 cells. Chromosomal abnormalities are frequently observed wit: overt benzene hematotoxicity in humans and in laboratory animals. Although t(date cytogenetic testing has not as a rule been a useful tool for workplace screening newer advances in techniques are promising and warrant exploration. Standarc cytogenetic assays may be useful in situations where the question is whether a patient's overt hematological abnormalities are due to benzene or to some othe cause. In a situation with a significantly compromised bone marrow. the absenc of chromosomal changes would argue against benzene **as** a causal agent.

Other suggested assays for benzene toxicity include serum immunoglobuli levels, porphyrin levels, leukocyte alkaline phosphatase activity, and red ce.

glycerol hemolysis time.[18,20,45] In my judgment, there is insufficient data at present to include any of these in routine surveillance of workers in a modern chemical or petrochemical industrial location.

A perhaps greater challenge to the occupational medicine physician than the differential diagnosis of an individual with an overt decrease in blood count is to determine whether a slight decrease in an average blood count for an entire potentially exposed work force is an indicator of a benzene effect. For example, suppose a work force has a statistically significant decrease in white blood count from a previous mean of 7,500/cu mm to a mean of 7,000/cu mm, but yet there is no one individual with a count clearly below the normal range. The question as to whether this reflects a mild effect of benzene. requiring a vigorous approach by industrial hygienists to discover the source, can be difficult to answer. A major cause of such a change over time can simply be laboratory variability, particularly as a small change of such a nature is not of clinical pertinence and thus unlikely to be of concern to a routine clinical laboratory. However, if appropriate arrangements are made, information can often be obtained as to normal values and instrument standardization for a particular day. Similarly, if the laboratory tests are done on site, it is important that careful attention be given to standardization and quality control consistent with the aim of the surveillance approach. This is true whether the intentionally exposed workers are tested in batches, e.g., on the same day every 6 months. or on different days throughout a cycle. When workers are tested in batches. one can use the data on a control group of individuals with no potential for benzene exposure as a means to distinguish between laboratory variability rather than that due to an actual change in the population. For example. if a control group of company executives and office workers has a decrease in white blood cell count similar to that observed in workers potentially exposed to benzene. laboratory variability would be the likely cause.

Interpretation of the likelihood that benzene is responsible for a decrease in a sample blood count is greatly assisted by review of all of the laboratory findings. This highly valuable approach is often overlooked. Benzene can be expected to decrease each blood cell count and increase the MCV. An isolated finding of a slight decrease in one blood cell count is much more likely to be a result of benzene if the other blood cell counts are in the lower range of normal and. conversely. unlikely to be due to benzene if the other blood cell counts are in the higher range of normal. In a large scale biological monitoring program. in which a group of individuals has. for example. a white blood cell count just below the normal range. the data can be analyzed to assess whether the mean platelet count. red blood cell count or MCV of these individuals are different from the mean of individuals with white blood cell counts in the normal range.

When a question remains as to whether an abnormal blood count is due to benzene. further assessment is necessary. Repeat of the blood counts is the simplest approach. Spurious findings are unlikely to be repeatable. Review of the findings by a hematologist or other physician with specialized knowledge can be useful. More specialized studies, such as bone marrow evaluation, will depend upon the findings in individual cases. It is imperative that the identification of a potential case of benzene hematotoxicity be considered not only as a reason for further investigation of the individual but also as a possible sentinel case indicating a problem at the workplace requiring aggressive action.

The appropriate medical surveillance approach has been one of the major areas of consideration by OSHA in its proposal to revise the occupational standard. To this reviewer it would seem not unreasonable to obtain a complete

CBC. including a white cell differential and platelet count. every *6* months. T first set of laboratory tests might **also** include a broader range of hematologic tests. including a reticulocyte count and serum iron and total iron bindi capacity. as a baseline in case hematological evaluation be needed in the futur

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