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*Invited Review*

# The problem of benzene in our environment: clinical and molecular considerations

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Benzene has found extensive commercial use in many industries including the leather industry. both artificial and natural: the manufacture of artificial rubber; in gilding. bronzing and silvering. varnish, shellac. and paint removing; in the printing industry including rotogravure, lithography. and photography; and in dry cleaning.[1-6] Benzene is a constituent of high octane gasoline used in airplane and automobile engines.[3,6] In addition, benzene has been used in the manufacture of explosives, pesticides, plastics, synthetic detergents, conditioners. antioxidants, and medicinals.[8] Benzene is also used as a solvent for rubber gums, resins, celluloid. and alkaloids.[1,6]

Although the toxicity of benzene was noted as early as 1897 by Santesson and much work was performed by Selling in-1910-19 16.[9] only recently have the toxic effects of benzene pained nationai attention.[9] This was due *to* an emergency governmental order reducing the permissible levels of benzene exposure to one part per million in rne working atmosphere per eight-hour day from the previous levels of ten parts per million.[9] For most of this century. however. :he acceptable levels have been considerably higher.[10]

## Clinical Toxicity of Benzene

Benzene toxicity has been classified 3s two distinct phenomena. either acute or chronic. The symptoms otacute toxicity have generally been related to the central nervous system. The manifestations include muscle tremors, convulsions. salivation. nystagmus. and phenomena of very intense asphyxiation due to paralysis of the medullary respiratory center.[11-14] Chronic benzene toxicity, on the other hand, is [illegible] hematopoietic system, [illegible] tral nervous system, [illegible] and gastrointestinal[15] effects have been suggested. The most frequently reported findings on history and physical examination include loss of weight, weakness, fatigue, epistaxis, dryness of mucosa, flatulence and/or pyrosis, nausea and or vomiting, colic, palpitations, dyspnea headache, dizziness, insomnia, lethargy, irritability, and rash.[2]

The primary means of entrance of benzene into the body is via inhalation. A study of humans exposed to benzene revealed that it rapidly reaches equilibrium with the alveolar air, and that saturation could be achieved within minutes.[16] In experiments carried out in rats, the concentrations of benzene in the blood were demonstrated to be parallel to the concentration in the inspired air.[17] The human experiments also showed that benzene is retained in the body for many hours after the exposure has been terminated and that elimination of benzene via the lungs accounted for only 12% of the excretion during the first six hours after exposure. The high lipid solubility would lead one to propose that benzene is being stored within the fat deposits of the body. Indeed, it has been suggested that overweight exposed individuals have a higher incidence of hematological changes than those who are normal or below normal weight.[2,19] The high lipid content of the nervous system might be significant in the acute phase of benzene toxicity.

Exposure to benzene can also be by direct contact, although benzene absorption through the skin is not very great.[20-22] When

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direct contact is achieved. the significant toxicity is usually due to inhalation rather than skin absorption.

The principal metabolites of benzene are the phenols, formed by enzymatic hydroxylation.[21,48] The phenols are then further processed by sulfation or glucuronization to give the conjugated end products.[21,49] It has also been proposed that quinones may be produced by oxidation of the phenols.[1]

Based on animal studies it appears that it is a metabolite of benzene that is responsible for hematopoietic toxicity. This subject has been reviewed by Snyder.[52]

The primary effect observed in chronic benzene toxicity is on the bone marrow. Benzene has long been implicated as having many different toxic manifestations including pancytonenia and aplastic anemia. acute myeloblastic leukemia, myeloid metaplasia, and hemolytic anemia. The most common finding is pancytopenia.[1] One problem concerning the relation of benzene to human hematotoxicity is that exposure usually occurs to a mixture of volatile compounds. rather than just to benzene alone. Despite this. the overwhelming evidence points to an association of hematopoietic disease with benzene exposure. The evidence includes the apparent lack of such association with other known volatile agents. epidemiological studies showing outbreaks of hematotoxicity temporally related to the introduction of benzene to an industry which respond to replacement of benzene with other solvents. and the ability to produce bone marrow toxicity in various animal species exposed only to benzene.[11] Much more information is needed. however. concerning the effects of other solvents on hematopoietic tissue and particularly the effects of combined exposures.

Pancytopenia has been clearly identified as a consequence of prolonged benzene exposure. However. no figures are available as to the incidence of this disorder. Although human benzene hematotoxicity is often described as an *aplastic anemia.* bone marrow studies have been variable. Investigators have found the marrow to be hypoplastic,[23-25] normocellular,[23,26] and even hyperplastic.[11,14]

The effects of benzene on the bone marrow is of particular interest when one considers the preferential distribution of benzene to this organ. It was shown in dogs chronically exposed to benzene (blood levels 1-2 mg/dl) that there was an approximately 5fold higher level in the marrow.[1] As the primary entry of benzene is via the lungs. one would expect it to pass through the marrow before being presented to the liver for possible detoxification. One might postulate that the increase in benzene concentration found in the marrow is associated with the high lipid solubility of the agent and the high proportion of fat cells in this location. In considering the effects of benzene toxicity on the hematopoietic system, most studies have focused on the circulating blood. A marked leukopenia is generally associated with benzene toxicity irrespective of the status of the marrow.[5,7,23] In one study benzene was demonstrated to decrease the proliferation of the rabbit myeloid series within the marrow.[11] This was found to occur at the myelocyte stage. The peripheral leukopenia might easily be attributed to the short survival time of these cells within the circulation combined with the decreased entry of new cells.

Abnormalities in leukocyte function have also been reported by a number of investigators. Among the granulocyte abnormalities which occur in mild benezene hematotoxicity, and which may actually precede pancytopenia, are a decrease in phagocytic function,[29] a decrease in leukocyte alkaline phosphatase activity,[30,31] an alteration in granulocyte and monocyte osmotic fragility,[11] an alteration of the fluorescent characteristics of leukocyte nuclei,[11] and the presence of the Pelger-Huet anomaly.[34-37]

Lymphocytopenia has also been reported to be a common finding in benzene toxicity,[11] and Goldwater[38] has suggested that this is more common than leukopenia. Other investigators. though. have failed to observe this

and there have even been some reports of lymphocytosis.[39,40] Animal studies, however. have demonstrated 'effects of benzene on lymphocytes and lymphoid [issues.''''' Snyder et al[42] have recently-shown that lymphocytopenia, was a very early manifestation of toxicity in rats and mice inhaling 100 to 300 ppm benzene. There have also been findings suggesting altered immune function including leukocyte agglutinins,'' altered serum immunoglobulin[44,45] and complement levels,[46] and antibodies against leukocytes. platelets. and red cells in patients chronically exposed to benzene.[47]

An effect of benzene on lymphocytes and the immune response raises the possibility that benzene association with leukemia might result from an altered immune function. based on the theoretical concept of the role of immune surveillance in carcinogenesis. In particular. assessment of whether the effect is specific for B or T lymphocytes and evaluation of the possible effect on suppressor lymphocytes which are postulated to play a role in human aplastic anemia[48,49] should be performed.

Still other leukocyte findings have been reported including an absolute eosinophilia[50,51] and monocytosis with the presence of immature and abnormal monocytes'' in the peripheral blood.

A number of investigators have presented evidence of decreased platelet iuncrion associated with benzene toxicity.[53-61] This appears to be due to intrinsic platelet abnormalities which magnify the effect of a decrease in absolute platelet count. Morphological abnormalities of both circulating platelets and their megakaryocytic precursors have also been reported.[14,39-42] In addition. there have been suggestions that abnormalities of coagulation factors might also be present.[54,58]

The most frequently reported erythrocyte abnormality associated with benzene toxicity is macrocytosis.[8,14,38,61-66] It is not known whether this macrocytosis reflects an altered stem cell population. an effect on DNA svnthesis. or is due to some other red cell abnormality. Macroerythroblasts have been noted in the bone marrow by Gornini et al[67] and by Curletto and Ciconali,[68] who also emphasized the marked polymorphism and occasional giant multinuclear forms of megaloblastic ervthrocyte bone marrow precursors. ,Macrocytosis of red cells has been suggested to be of prognostic importance'' and to be an excellent warning signai of hensene-induced hematotoxicity in occupationally exposed individuals.[69] However, macrocytic red cells have not been noted by all authors who have investigated individuals with henzene-induced hematotoxicity.

Significant hemolysis has been occasionally reported in benzene-exposed individuals,[71-76] including a few cases of paroxysmal nocturnal hemoglobinuria.[106,150] Although anemia is usually due primarily to a failure of red cell production. there may be a somewhat shortened red cell life span in many if not most cases of benzene hematotoxicity. This point should he investigated further.

Further evidence that red cells arc qualitatively abnormal in benzene-exposed individuals include the observation of abnormal erythrocyte incubated osmotic fragility despire normal values using the standard osmotic fragility test.[38,77] There are also reports of changes in blood and urine porphyrin levels and aminolevulinic acid, possibly reflecting altered heme synthesis.[78-80] Of note in this regard are the reports of improvement in benzene-poisoned patients with pyridoxine.'' an essential cofactor in heme synthesis.

It is generally accepted that benzene exposure results in an increased incidence of acute myelogenous leukemia and related disorders (eg, erythroleukemia, acute myelomonocytic leukemia). The evidence favoring a causal relationship is not simply the more than 100 case reports which, individually, could be fortuitous. Strong support for the causal role of benzene has been obtained in surveys of areas which have historically had substantial numbers of individuals occupationally exposed to high levels of benzene in

poorly regulated circumstances, most notably in France Italy, and Turkey. The evidence includes the observation by Vigliani and Saita in Italy[87] of a perhaps 20 times greater leukemia risk in benzene-exposed workers than in the general population, and the reports by Girard et al in France revealing a significantly greater positive history of benzene exposure in patients with acute leukemia than in a control group.[83,87] More recently, Turkish investigators have described at least ten cases of acute leukemia,[89,90] mostly myeloblastic. Recently in the United States, Infante and co-workers[143] performed an epidemiological evaluation of workers exposed to low levels of benzene in two factories. These investigators reported at least a fivefold increased risk of total leukemia and a tenfold increased risk of acute myeloblastic leukemia (or its variant myelomonocytic leukemia) in these workers. Accordingly, a causal relationship between benzene exposure and acute myeloblastic leukemia appears proven.

The association of other types of leukemia with benzene exposure is unclear. In some of the larger collections of benzene-induced leukemia, including those of Aksoy et al in Turkey[89] and Vigliani et al in Italy,[87] chronic lymphocytic leukemia has not been reported. In contrast, French investigators[81-83,91-93] have noted a relatively high incidence of chronic lymphocytic leukemia, often exceeding that of acute myelogenous leukemia. Cases of chronic lymphocytic leukemia associated with exposure have also been reported elsewhere, including three from the Soviet Union.[94] Similarly, the French have noted a higher incidence of chronic myelogenous leukemia although not to the extent of chronic lymphocytic leukemia.

The reason for this difference is unclear. It is conceivable that the observed association of chronic lymphocytic leukemia with benzene in France is fortuitous. One possible explanation would be the presence of other solvents specifically in the French workplaces which could possibly alter the expression of benzene hematotoxicity. The observed differences might also be explainable by a longer lag phase for chronic lymphocytic leukemia and the possibly longer benzene exposure of the French patients in contrast to the apparently more defined and recent exposure populations investigated by the Italian and Turkish investigators. These explanations are, of course, speculative. There is also inconclusive evidence suggesting that benzene may produce other lymphoproliferative disorders, including acute lymphoblastic leukemia and lymphoma.[94-100] This would be consistent with an apparent effect of benzene on lymphocyte number and function observed in pancytopenia cases. In addition to chronic myelogenous leukemia, a few cases of myelofibrosis and myeloid metaplasia, another myeloproliferative disorder, have also been reported.[103-109]

Although occupational exposure to benzene appears causally related to acute myelogenous leukemia, a number of important questions persist which are directly pertinent to permissible benzene exposure. Of particular importance is whether leukemogenesis occurs only after high-dose benzene exposure leading to significant bone marrow damage, whether it can result from any degree of cytopenic stem cell toxicity, or, less likely, is totally unrelated to the pancytopenic effect of benzene. It is possible that benzene or its toxic metabolites directly act as a carcinogen on bone marrow hematopoietic cells. Alternately the association with acute leukemia may represent a secondary manifestation of benzene-induced pancytopenia that is expressed through an unrelated bone marrow aberration producing a stem cell that is liable to a further mutagenic event. Such an event might occur many years after discontinuation of exposure. Benzene might therefore act as an initiator or co-carcinogen. Support for these hypotheses, or any other (eg, benzene activates a leukemogenic virus) is conjectural. The lack of an animal model of benzene-induced leukemia hampers study of this issue.

One possibly pertinent topic is that of

preleukemia. This relatively poorly defined diagnosis has been frequently made in benzene-exposed individuals. There are a number of case reports of benzene-induced pancytopenia in which morphologically abnormal preneoplastic bone marrow precursor cells progressively developed. eventually. resulting in frank acute leukemia.[4,80,101,102] Reported morphological abnormalities include bizarre red cell precursors which often have led to the diagnosis of erythroleukemia. The subject of preleukernia, including the effects of benzene, has been reviewed by Pierre.[103]

The interrelation of idiopathic aplastic anemia, preleukemia, and acute leukemia has been noted by a number of authors. Of interest is the theoretical discussion of Damashek[104] who added paroxysmal nocturnal hemoglobinuria to this group. This rare paraneoplastic condition. in which there is an abnormal population of circulating red cells derived from a single stem cell. may precede or follow frank aplastic anemia. may end as acute leukemia. or may transiently occur during leukemia states. Its reported occurrence in association with benzene exposure is further suggestive evidence of benzene-induced pancytopenia being linked to acute leukemia.[5,98,150]

## Molecular Considerations

Investigators have tried to locate a nuclear lesion within the precursor cells of animals and humans exposed to benzene.[105,106,107] Chromosome abnormalities associated with benzene exposure in humans include ring chromosomes.[108] dicentric or tricentric chrornosomcs.[109] and an erythroleukemic line with a pseudodiploid karyotype where the two E chromosomes were replaced with markers.[111] However, it should be pointed out that even though studies have shown statistically significant increases in chromosomal structural alterations in humans exposed to benzene. most of these people had no detectable clinical abnormalities. When peripheral blood lymphocytes of individuals exposed to benzene were stimulated by phytohemagglutinin (PHA). chromosome alterations were noted even though there were no detectable changes in the marrow.[110] The chromosome aberrations included qualitative changes of both a stable and unstable nature (breaks. gaps) as well as frequently reported quantitative changes (aneuploidy. polyploidy). Individual variation was considerable. In studies by Girard[10] and Forni.[110] the significantly higher average chromosome breakage rates of the exposed groups were attributable to a few individuals. It should be noted that although the chromosome alterations were more evident in those who showed initial clinical evidence of the benzene exposure. the changes had persisted both in the symptomatic and nonsymptomatic groups for many years after exposure.

Recently. the etfects of benzene on DNA and RNA synthesis have been studied.[112]It was shown that in those animals which developed a pancytopenia. there was an associated disturbance of the DNA and RNA synthesis as well as chromosome aberrations.[112] Evaluation of RNA synthesis in rabbits using $^{3}$H-cytidine showed a benzene effect on the RNA synthesis of the basophilic iiorrnoblast but not the pronormoblast.[112] This may indicate a maturation arrest between these stages. It was further shown in mice that the hemopoietic stem cell was intact as determined by in vivo colony forming assay.[112] However. the nuclear integrity of this cell could not be determined by this technique.

Experiments in rabbits using $^{3}$H-thymidine showed a marked inhibition of DNA synthesis with chronic benzene administration.[24] This was attributed primarily to an arrest of the metaphase sequence at the pronormoblast stage preventing differentiation of the basophilic normoblast. These staging results are in accordance with the information available on RNA synthesis discussed earlier.

Recentlv, studies in this laboratory have looked to the effect of benzene directly on the translational level. Lee et al[112] had shown that the incorporation of radioactive iron into

mouse bone marrow was decreased after a single subcutaneous injection of benzene. This experiment raises the question of whether or not benzene could directly affect heme svnthesis. As heme is necessary for initiation of protein synthesis in most. if not all. cells (see below) this could he a site of toxicity to explain what is seen with benzene exposure.

Forte et al[111] have shown that benzene inhibits both human and rabbit reticulocyte protein synthesis *in vitro*. The reticulocyte is an anucleate cell. and there is no transcription occurring in this system. The effect on prorein synthesis in reticulocytes, therefore, is due to an inhibition of translation. The minimum concentration of benzene necessary to consistently inhibit protein synthesis in these studies was 438 mg/100 ml (0.056 M). Hemin (50 μM) prevented and reversed this inhibition. This concentration of hemin has previously been show to maintain protein synthesis in the absence of added iron-transferrin far heme synthesis.[112] Benzene inhibition also occurred when iron-transferrin for maximum endogenous heme synthesis was present. On the basis of these experiments it appears that benzene is interfering with endogenous heme synthesis, at a site other than incorporation of iron into the cell.

The effect of benzene also was associated with a reversible conversion of polyribosomes to smaller aggregates. predominantly monoribosomes. These findings are in agreement with those of Tryfiates[113,114] who found that rat liver polyribosomes disaggregated after injection of the animals with benzene at a dose of 0.52 to 5.63 mM. The number of ribosomes on messenger RNA is directly proportional to the rate of initiation and inversely proportional to the rate of release of ribosomes from mRSA. Thus, benzene polyribosomal disaggregation is consistent with an inhibition of initiation with normal elongation and release. as occurs with heme deficiency.[111] This conclusion is supported by experiments showing that hemin both prevents and reverses benzene-induced polyribosomal disaggregation. as well as by experiments where benzene failed *to* disaggregate polyribosomes when elongation was prevented by cycloheximide.

Direct demonstration of benzene inhibition of heme synthesis was also presented *in* this study. It was observed that benzene inhibition occurred more rapidly when either hemin was omitted from the incubation medium. or when the cells were made iron deficient with an iron-chelating agent. Possible interpretations *of* this finding include rapid uptake of benzene into the cells and direct inhibition of an enzyme rather than depletion of endogenous iron. The interpretation that iron was not depleted was supported further by the reversal of polyribosomal disaggregation when benzene was removed and the cells incubated in the absence of either iron-transferrin or hemin.

In order to more definitively determine the site of benzene inhibition of heme synthesis. the following experiments were performed by Freedman et al.[111] Benzene (0.113 M) was added to rabbit reticulocyte incubations and both heme synthesis (L-2-$^{14}$C glycine incorporation) and protein synthesis (L-$^{14}$C leucine incorporation, were found to be inhibited by approximately 50%. However, when the radioactive precurcor used was 4-$^{14}$C aminolevulinic acid (ALA), there was no significant inhibition of heme synthesis. Since ALA measures heme synthesis beyond the enzyme ALA-synthetase. it was concluded that benzene is inhibiting heme synthesis at or before this enzymatic step. Similarly. 1 mM ALA both protcctcd against and reversed the benzene inhibition of protein synthesis. This confirmed both the interdependence of heme and globin synthesis as well as the inhibition of the enzyme ALA-synthetase.

When pyridoxine (1 mM) was added to the incubation mixture. there was also protection against the benzene inhibition of both heme and protein synthesis.[111] The active form of pyridoxine in cells, is pyridoxal phosphate. Therefore. in this system at least a portion of the pyridoxine has to be phosphorylated by the enzyme pyridoxal phosphokinase. Since pyridoxine was added in great excess. this

study did not differentiate between benzene competition with pyridoxal phosphate at the site of ALA-synthetase, or benzene competition with pyridoxine for pyridoxine phosphokinase. Of note in this regard are the uncontrolled observations suggesting that pyridoxine may be of therapeutic value in human benzene hematoxicity.[41]

More recently it has been shown that elevated levels of intracellular cyclic AMP also prevent and reverse benzene inhibition of heme synthesis (and secondarily protein synthesis).[41] Cyclic AMP has been shown to exert its protective effect against inhibition of heme synthesis at the level of ALA-synthetase.[41]

On the basis of these studies, Freedman et al[117] have postulated that the primary toxic effect of benzene might conceivably be inhibition of heme synthesis at or before ALA-synthetase. Intracellular hemin has been shown to control globin synthesis by preventing the formation and/or reversing the activity of a hemin-controlled repressor (HCR) of initiation of globin chain synthesis.[114,120-132] Hemin has also been shown to be necessary for the synthesis of globin as well as a large variety of nonglobin proteins in many cell types.[133-141] It appears that hemin is necessary for translation of most, if not all, proteins. The reported effects on DNA and RNA synthesis might then conceivably reflect a decreased production of the enzymes for DNA and RNA synthesis. The effect on marrow precursors other than erythroid cells could then result from a universal requirement for hemin in the initiation of protein synthesis.

In the past few years various investigators have suggested that ALA-synthetase plays a central role in erythropoiesis. Levere and Gidari[142] in a recent review, summarized the data showing that erythropoietin and the 5-$\beta$-H steroids stimulate erythropoiesis, heme and globin synthesis in bone marrow cells, These hormones appear to exert a major part of their action by primarily inducing the synthesis of ALA-synthetase. Glass et al[143] in a murine bone marrow erythroid precursor system showed that erythrapoietin stimulated ALA-synthetase and heme synthesis before any stimulatory effect on globin synthesis. These investigators also showed that heme synthesis is maximal in the earliest precursor cells and decreases with cell maturity, while globin synthesis increases with cell maturity. These results are compatible with the theory that there must first be sufficient hemesynthesis to elevate intracellular hemin concentration. Sufficient intracellular hemin might then reverse preformed HCR which would allow protein synthesis and erythropoiesis to proceed. One possibility to explain this data is that benzene by its action at or before ALA-synthetase. prevents hormonal activation of heme synthesis and derepression of HCR, which in turn is necessary for globin synthesis and erythropoicsis. Furthermore. the hemin requirement in other cell types might explain why there is involvement of the entire marrow.

An inhibition of ALA-synthetase might also explain the apparent differential of benzene toxicity between the sexes. In both animal and human studies, females were shown to he more sensitive to the effects of benzene.[9,19,21,26,28] ALA-synthetase is an inducible enzyme whose activity is reiated to the presence of various steroids.[142] Etiocholanolone, a metabolite of testosterone. in the presence of glucocorticoids, greatly increases the activity of ALA-synthetase.[142]

This theory is also consistent with the view that toxicity with any inhibitor of heme synthesis might not necessarily lead to aplastic anemia. In order to develop aplastic anemia it would he necessary to prevent heme synthesis in very early marrow precursor cells. Since ALA-synthetase is the rate-limiting enzyme, an inhibitor would have to either affect this enzyme or decrease the other enzymes in the pathway below the activity of ALA-synthetase. Benzene is a likely candidate to affect early marrow cells as it is highly lipid soluble with a pronounced affinity for the bone marrow.[47]

It should be emphasized, however, that what was investigated in our studies was acute benzene exposure *in vitro* and that most cases of benzene aplastic anemia follow prolonged and continuous exposure. These *in vitro* experiments in reticulocytes must, therefore, still be interpreted with caution before applying this data to clinical situations. Much more work needs to be done to ascertain if indeed it is benzene or a metabolite which is toxic, the dose at which benzene toxicity occurs, the mechanisms of concentration in the marrow, and the mechanism of development of aplastic anemia and other clinical hematological conditions. Furthermore, the interaction with other environmental pollutants, such as lead[145] and alcohol,[146] might accelerate the development of benzene toxicity. There Lire still many questions to he answered concerning benzene toxicity. What we have discussed in this review is a speculative theory that hopefully will stimulate further research in this very important area.

## References


1. Wilson RH: Benzene poisoning in industry. J Lab Clin Med 27:1517-1521, 1942.
2. Greenberg L, Mayers MR, Goldwater L, et al: Benzene (benzol) poisoning in the rotogravure printing industry in New York City. J Indust Hyg Toxicol 21:395-420, 1939.
3. Hardy HL, Elkins HB: Medical aspects of maximum allowable concentrations. Benzene. J Indust Hyg Toxicol 30:196-200, 1948.
4. Gerarde HW: Toxicological studies on hydrocarbons II. A comparative study of the effect of benzene and certain mono-n-alkylbenzenes on hemopoiesis and bone marrow metabolism in rats. AMA Arch Indust Health 17:468-473, 1956.
5. Tammers MA: Total synthesis benzene and its derivatives as major gasoline extenders. Science 193:231-232, 1976.
6. Wintrobe MM, Lee GR, Boggs DR: Clinical Hematology, ed 7. Philadelphia, Lea & Febiger, 1974, p 1745.
7. Wolf MA, Kowe VK, McCollister DD, et al: Toxicological studies of certain alkylated benzenes and benzene. AMA Arch Indust Health 14:387-398, 1956.
8. Erf LA, Rhoads CP: The hematological effects of benzene (benzol) poisoning. J Indust Hyg Toxicol 21:421-433, 1939.
9. US limits benzene—permitted. The New York Post, April 29, 1977.
10. Bowditch M, Elkins HB: Chronic exposure to benzene (benzol). I. The industrial aspects. J Indust Hyg Toxicol 21:321-330, 1939.
11. Braier L, Francone M: Phenomenes hemolytiques dus au benzene et ses homologues. Arch Mal Prof 11:367-369, 1950.
12. Monaenkova AM, Snegov GV: Cerebral circulation in some occupational poisonings: Lead, carbon disulfide, benzene. Gig Tr Prof Zabol 17(4):33-37, 1973.
13. Sobczyk W, Siedlecka B, Gajewska Z: EEG recordings in workers exposed to benzene compounds. Med Prac 24:273-283, 1973.
14. Monaenkova AM, Zorina LA: Hemodynamics and heart muscle changes in chronic benzene poisoning. Gig Tr Prof Zabol 19(4):30-34, 1975.
15. Thienes CH, Haley TJ: Cardiac poisons. *in* Clinical Toxicology, ed 5. Philadelphia, Lea & Febiger, 1972, chap 5.
16. Bazenova KV: The functional condition of the stomach, pancreas and liver of workers employed in undertakings using benzene. Gig Tr Prof Zabol 6(5):35-39, 1962.
17. Caprotti M, Colombi R, Corsico R: Ulcers in the mucous membrane of the colon in benzene poisoning—clinical and radiological study. Lav Um 14(9):445-452, 1962.
18. Hunter CG, Blair D: Benzene: Pharmacokinetic studies in man. Ann Occup Hyg 15:193-199, 1972.
19. Deichmann WH, MacDonald WE, Bernal E: The hemopoietic tissue toxicity of benzene vapors. Toxicol Appl Pharmacol 5:201-224, 1963.
20. Conca GL, Maltagliata A: Study on the absorption of benzene through the skin. Med Lav 46:194-198, 1955, abstracted Indust Hyg Digest 20:13, 1956.
21. Ikeda M: Enzymatic studies on benzene intoxification. J Riochem 55:231-243, 1963.
22. Goldstein BD: Hematotoxicity in man. *In* Laskin S, Goldstein BD (eds): Benzene toxicity, a critical evaluation. J Toxicol Environ Health (suppl 2): 69-105, 1977.
23. Kissling M, Speck B: Further studies nn experimental benzene-induced aplastic anemia. Blut Band 25:97-103, 1972.
24. Moeschlin S, Speck B: Experimental studies on the mechanism of action of benzene on the bone marrow (radioautographic studies using $^{3}$H-thymidine). Acta Haematol 38:104-111, 1967.
25. Kissling M, Speck B: Chromosome aberrations in experimental benzene intoxication. Helv Med Acta 36:59-66, 1972.
26. Hunter FT: Chronic exposure to benzene (benzol). II. The clinical effects. J Indust Hyg Toxicol 21:331-354, 1939.
27. Schrenk HH, Yant WP, Pearce SJ, et al:

Absorption. distribution and elimination of benzene by body tissues and fluids of dogs exposed to benzene vapor. J lndust Hyg Toxicol 23:20-34. 1941.

28. Mallory TB. Gall EA. Brickley WJ: Chronic exposure to benzene (benzol) 111. The pathologic results. J lndust Hyg Toxicol 21:355-393. 1939.
29. Kosiova TA. Volkova AP: Blood picture and phagocytic activity of leukocytes in workers having contact with benzene. Gig Sanit 25:29-34. 1960.
30. Girard R. Mallein ML. Bertholon J et al: Etude de la phosphatase alcaline leucoytaire et du caryotype des ouvriers exposes au benzene. .Arch Mal Prof 31(1-2):31-38. 1970.
31. Girard R. Mallein ML. Bertholon J et ai Leucocyte alkaline phosphatase and benzene exposure. Med Lav 61:502-508. 1970.
32. Pollini G. Colombi R: Changes in the osmotic resistance of the leucoytes in persons exposed to benzene. Lav Um 16(4):177-184. 1964.
33. Kolesar D, Ballog O: Studies by fluorescenc microscopy of the effect of occupational benzene exposure on leucocyte nuclei changes. Bratislavske Lakarske Listy 40 II (4):212-219. 1965.
34. Aksoy M, Dincol K. Akgun T et ai: Haematological effects of chronic benzene poisoning in 217 workers. Br J lndusi Med 28:296-302. 1371.
35. Saita G. Moreo L: A case of chronic benzene poisoning with a Pelger-Huët type leucocyte anomaly. Med Lav 57(5):331-335. 1966.
36. Sellyei M, Kelemen E: Chromosome study in a case of granulocytic leukemia with "pelgerisation" 7 years after benzene pancytopenia. Eur J Cancer 7 83-85. 1971.
37. Zini C, Alessandri M: Anomalia leucocitoria pseudopelgeriana in un caso di emopatia benzolica con leucosi acuta terminale. Haemotologica 52:258-266. 1967.
38. Goldwater LJ: Disturbances in the blood following exposure to benzol. J Lab Clin Med 26:957-973, 1941.
39. Bernard J: La lymphocytose benzenique. Sangre 15:501-505. 1942.
40. Doskin TA: Effect of age on the reaction to a combination of hydrocarbons. Hyg Sanit 36:379-384. 1971.
41. Latta JS. Davies LT: Effects on the blood and hemopoietic organs of the albino rat oi repeated administration of benzene. Arch Pathol 31:55-67. 1941.
42. Snyder CA, Goldstein BD. Laskin S: Chronic inhalation studies of benzene with rats and AKR mice. Am Indust Hyg conf, May 1976. p 75. (abst).
43. Lange A. Smolik R, Zatonski W et al: Leukocyte agglutinins in workers exposed to benzene, toluene and xylene. Int Arch Arbeitsmed 31:45-50, 1972.
44. Lange A. Smolik R. Zaionski W et al: Serum immunoglobulin levels in workers exposed to benzene, toluene and xylene. Int Arch Arbeitsmed 31:37-44. 1971.
45. Roih L. Dinu IV. Turcanu P et al: Cytologic and immunochemical features of benzene-induced reticulosis. Timisoara Med 17:29-38. 1972.
46. Smolik R. Grzybek-Nryncewicz K. Lange A et al: Serum complement level in workers exposed to knzene. toluene and xylene. Int Arch Arbeitsmed 31:243-247. 1973.
47. Revnova NV: Concerning auto-immunity shifts in chronic occupational benzene poisoning Gig Tr Prof Zabol 6(7):38-42. 1962.
48. Hoffman K. Zanjani ES. Lutton JD et al: Suppression of erythroid-colony formation bv lymphocytes from patients with aplastic anemia. N Engl J Med 296:10-13. 1977.
49 Kagan WA. Ascensao JA, Pahwa RN et al: Aplastic anemia: Presence in human hone marrow of cells that suppress myelopoiesis. Proc Natl Acad Sci USA 73:2890-2894. 1976.
50. Hernberg S. Savilahti M, Ahlman K et al: Prognostic aspects of benzene poisoning. Br J Indust Med 23:204-209. 1966.
51. Savilahti M: Over 100 cases of benzene poisoning in a shoe factory. Arch fur Gewerbepathol Gewerbehyg 15:147-157. 1956.
52. Roth L, Turcanu P. Dinu J et al: Monocytosis in those who work with benzene and chronic henrcnc poisoning. Folia Haematoi 100:213-224. 1973
53. Rinci L, Conte M, Bourliere F: Intoxification benzolique mortelle chex une femme vendant des sacs cn cuir synthetique. Presence de benzene dans le sang. Hull Mem Soc Med Hop Paris 61:118. 1945.
54. Craveri A: Fibrinolysis, blood platelets. fibrinogen and other blood coagulation tests in clinical henzcne poisoning. Med Lav 53(1):722-721. 1962.
55. Favre-Gilly M, Bruci M: Syndrome hemarragique benzolique nvec simple alteration morphologique des plaquettes. . l'utilite Je'cxarnen 'ps-tematique des plaquettes sur lame chez les ou\riers exposes au benzol. Arch Mol Prof 91:274-277. 1948.
56. Inceman S, Tangun Y: Impaired platelet-collagen reaction in a case of acute myeloblastic leukemia due to chronic benzene intoxication. Turk Tip Cemiy Mecmuasi 35:417-424. 1969.
57. Kliche N, Meubrink H, Wohl F Chronische benzolschaden bu dachdeckern. Z Gesamte Hyg 15:310-316. 1969.
58. Monteverde A, Grazioli C, Fumagalli E: The effect of fibrinogen and platelets on the thromboelastopram in benzene poisoning. Med Lav 54(2):95-102. 1963.
59. Saita G, Sbertoli G: L'agglutins gramma nul intossicazione crontca da benzolo. Med Lav 45:250-253. 1954.

60. Saita G. Sbertoli G. Farina GF: Thromboelastographie investigations in benzene haemopathv. Med Lav 55(11):655-664, 1964.
61. Sroczynski J. Kossmann S, Wegiel A: Coagulation system in experimental poisoning with benzene vapors. Bull Slezby Sanit Epidemiol Vojewodztwa Katowickiego 15:131-134, 1971.
62. Solov'eva EA: Morphological changes of blood platelets and of megakaryocytes in chronic benzene poisoning. Gig Tr Prof Zabol 7(11):57-60, 1963.
63. Aksoy M, Dincol K. Erdem S et al: Details of blood changes in 32 patients with pancytopenia associated with long-termexposure to benzene. Br J Indusi Med 29:56-64. 1972.
64. Hutchings M, Drescher S. McGovern FB et al: Investigations of benzol and toluol poisoning in Royal Australian Air Force workshops. Yed J Aust 2(23):681-693, 1947.
65. Kauppila O. Setala A: Chronic benzene poisoning: Report of 5 cases. Ann Med Int Fenniae 45:49-51, 1956.
66. Vilter KW. Janold T. Will JJ et al: Reiractorv anemia uith hyperplastic Sone marrow. Blood 15:1-29. 1960.
67. Gorini P. Colombi R. Pecorari D: Investigation on the origin of the macrocytosis in the cytoplasmic anemia from chronic benzene poisoning. Lav Um 11:121-133, 1959.
68. Curletto R. Ciconali M: Haematological disorders in benzene poisoning. Med Lav 53(8, 9):505-546, 1962.
69. Corsico R. Biscaldi GP. Lalli M: Benzene-induced changes in the size of haemopoietic and haematic cells. Lav Um 19(1):16-27, 1967.
70. Esteban JM: Benzene poisoning--review of some cases—the warning signal. Med Segundad de Trabago 12(45):11-23, 1964.
71. Andre R, Dreyfus B: Anemic hemolytique grave associee a un purpura h norragique thrombopenique. Role probable due benzol transfusion massif splenectomie guerison. Sangre 22:57-65, 1951.
72. Ferrara A, Balbo W: Malattia hemlitica in soggetto esposto a rischio prof di tipo benzolico. Riv Infart Mol Proi 44:713, 1957.
73. Marchal G. Duhamel G: L-anemic hemolytique dans les leucemies. Sangre 21:254-261, 1950.
74. Nissen NI, Ohlsen AS: Erytromyelosis. Oversigt og et tilfuelde hos en benzolarbegder. Ugeskr Laeger 114:737-742, 1952.
75. Koth L. Dinu IV, Turcanu P et al: Cytologic and immunochemical features of benzene-induced reticuloses. Timisoara Med 17:29-38, 1972.
76. Saita G. Moreo L: Hacmolytic attack following inhalation of a single massive dose of benzol. Med Lav 52(11):713-716, 1961.
77. Aksoy M, Erdem S. Akgun T et al: Osmotic fragility studies in three patients with aplastic anemia due to chronic benzene poisoning. Blut 13:85-90. 1966.
78. Kahn H, Muzyka V: The chronic effect of benzene on porphyrin metabolism. Work Environ Health 10:140-143, 1973.
79. Kahn ti. Muzyka VI: The effect of benzene on the δ-aminolevulinic acid and porphvrin content in the cerebral cortex and in the blood. Indust Hyg Prof Assoc Disorders 3:59-60, 1970.
80. Wakiska I. Ito T. Nagai H: Influence of environmental concentration upon the health of benzene workers. Showa Igokukai Zasshi 22:291-297, 1962.
81. Browning E: Vitamins in the treatment of chronic benzene poisoning. J Occup Med 7(11):291-297, 1962.
82. Vigliani EC. Saita G: Leucemia emocitoblastica da benzolo. Med Lav 34:182-191, 1943.
83. Girard R. Prost G, Tolot F: Comments on indemnification for benzene-induced leukemia and aplasia Arch Mol Prof 32(9):581-583, 1971.
84. Girard R. Revol L: La frequence d'une exposition benzenique au cours des hemopathies graves. Nouv Rev Fr Hematol 10:477-484, 1970.
85. Girard R. Rigout P. Bertholon J et al: Les expositions benzeniques meconnues. Leur recherche systematique au cours des hemopathies graves. Enquetes chez 200 hemopathiques hop italises. Arch Mol Prof 29:723-726, 1968.
86. Girard R, Tolot F. Bourret J: Hydrocarbures benzeniques et hemopathies graves. Arch Mol Prof 31(12):625-636, 1970.
87. Girard R. Tolot F. Bourret J; Malignant hemopathies and benzene poisoning. Med Lav 62.71-76. 1971.
88. Aksov M. Erdem S. Dincol G: Leukemia in shoe workers exposed chronicailv to benzene. Blood 44(6):837-841, 1974.
89. Aksov M. Erdem S. Dincol G. Types of leukemia in chronic benzene poisoning. A study in thirty-lour patients. Acta Haematol 55:65-72, 1976.
90. Aksov M. Erdem S. Erdogan G et al: Combination of genetic factors and chronic exposure io benzene in the aetiology of leukaemia. Hum Hered 26:149-153, 1976.
91. Revol L, Cl Millet. Thivollet: A propos de l'etiologie de la leucose argue. Etude de 193 cas. Sangre 25:825-840, 1950.
92. Goguel A. Covigneaux A, Bernard J: Benzene leukaemia. Inst Natl Sante Recherche Med 22(3):421-441, 1967.
93. Goguel A, Covigneaux A. Bernard J: Benzene leukemias in the Paris region frnm 1950 to 1965. Nouv Rev Fr Hematol 7:465-480, 1967.
94. Tareeff EM, Kontchalovskaya NM. Zorina LA: Benzene leukemias. Acta Unio Intl Contra Can Crum 19:751-755, 1963.

95. Aksoy M, Erdem S. Dincol K et al: Chronic exposure to benzene as a possible contributory factor in Hodgkin's disease. Blut 38:293-298, 1974.
96. Bousser J. Neyde R, Fabre A: Un cas d'hemopathie benzolique tres retardee a type de lymphosarcome. Arch Mol Prof 9:130, 1948.
97. Casirola G, Santagati G: Considerazioni su due casi clinicamente primitivi di linfomi maligni a sede splenica. Haematologica 54:85-96, 1969.
98. Mallory TB, Gall EA, Brickley WJ: Chronic exposure to benzene (benzol) 111. The pathologic results. J Indust Hyg Toxicol 21(8):355-377, 1939.
99. Patcrni L, Sarnari V: Involutional myelopathy due io benzene poisoning with the appearance of a mediastinal reticulosarcoma at an advanced stage. Sccuritas 50(10):55-59, 1965.
100. Torres A, Giralt W, Raichs A: Coexistencia de antecedentes benzolicos cronicas y plasmocitoma multiple. Presentacion de los casos. Sangre 15:275-279, 1970.
101. Aksoy M, Dincol K, Erdem Setal: Acuteleukemia due to chronic exposure of benzene. Am J Med 52:160-166, 1972.
102. Mallein ML, Bryan PA, Fiere D et al: Cryptoleucose aigue ou "anemie refractoire" benzenique (deux nouveaux cas). Arch Mol Prof 32:577-579, 1971.
103. Pierre RV: Preleukemic stata. Semin Hematol 11:73-92, 1974.
104. Damashek W: What do aplastic anemia, PNH and hypoplastic leukemia have in common! Blood 30:251, 1967
105. Gall EA: Benzene poisoning with bizarre extramedullary hematopoiesis. Arch Pathol 25:315-326. 1938.
106. Aksoy M, Erdem S, Dincol ti: Two rare complications of chronic benzene poisoning: Myeloid metaplasia and paroxysmal nocturnal hemoglobinuria. Report of two cases. Blut 30:255-260, 1975.
107. McLean JA: Blood dyscrasia alter contact with petrol containing benzol. Med J Aust 47(11):845-849, 1960.
108. Rawson R. Parker F, Jackson H: Industrial solvents as possible etiological agents in myeloid metaplasia. Science 6:541-542, 1941.
109. Wurster-Hill DH, Cornwell GG, Mclntyre OR: Chromosomal aberrations and neoplasm — a family study. Cancer 33(1):72-81, 1974.
110. Tough I, Court-Brown WM: Chromosome aberrations and exposure to ambient benzene. Lancet 1:684, 1965.
111. Forni A, Moreo L: Chromosome studies in a case of benzene-induced erythroleukaemia. Eur J Cancer 5:459-463, 1969.
112. Lee EW, Kocsis J, Snyder R: Dose dependent inhibition of $^{59}Fe$ incorporation into erythrocytes after a single dose of benzene. Res Commun Chem Pathol Pharmacol 5:547-550, 1973.
113. Force FJ, Cohen HS, Rosman J et al: Hemin reversal of benzene-induced inhibition of reticulocyte protein synthau. Blood 47:145-154, 1976.
114. Rabinovitz M, Freedman ML, Fisher JM et al: Translational control in hemoglobin synthesis. Cold Spring Harbor Symp Quant Biol 34:567-578, 1969.
115. Tryfiates GP, Choulis NH: Effects of benzene on rat liver ribonucleic acid. J Pharm Sci 61:465-466, 1972.
116. Tryfiates GP: Effect of benzene on rat liver polyribosomes. Biochem Pharmcol 20:1669. 1677, 1971.
117. Freedman ML, Wildman JM, Rosman J et al: Benzene inhibition of *in vitro* rabbit reticulocyte haem synthesis at delta-aminolevulinic acid synthetase: Reversal oi benzene toxicity by pyridoxine. Rr J Haematol 35:49-60, 1977.
118. Freedman ML, Spieler PJ, Rosman J et al: Cyclic AMP maintenance of rabbit reticulocyte haem and protein synthesis in the presence of ethanol and benzene. Br J Haematol 37:179-194, 1977
119. Ibrahim SG, Spieler PJ, Freedman, ML: Ethanol inhibition of rabbit reticulocyte heme synthesis at the level of delta-aminolevulinic acid synthetase. Rr J Haematol, 1978, in press.
120. Kruh J, Borsook H: Hemoglobin synthesis in rabbit reticulocytes *in vitro*. J Biol Chem 220:905-915. 1956.
121. Bruns GP, London IM: Theeffectofheminonthe synthesis of globin. Biochem Biophys Res Commun 18:236-242, 1965.
122. Waxman HS, Rabinovitz M: Iron supplementation *in vitro* and the state of aggregation and function of reticulocyte ribosomes in hemoglobin synthesis. Biochcm Biophys Res Commun 19:538-545, 1965.
123. Grayzel AP, Horchna P, London IM: The stimulation of globin synthesis by heme. Proc Natl Acad Sci USA 55:650-655, 1966.
124. Waxman HS, Rabinovitz M: Control of reticulocyte polyribosome formation in rabbit reticulocytes. Biochem Biophys Acta 129:369-379, 1966.
125. Waxman HS, Freedman ML, Rabinovitz M: Studies with $^{59}Fe$-labeled hemin on the control of polyribosome formation in rabbit reticulocytes. Biochim Biophyr Acta 145:353-360, 1967.
126. Maxwell CR, Kamper CS, Rabinovitz M: Hemin control of globin synthesis: An assay for the inhibitor formed in the absence of hemin and some characteristics of its formation. J Mol Biol 58:317-327. 1971.
127. Hunt T, Vanderhoff G, London IM: Control of globin synthesis: The role of heme. J Mol Bioi 66:471-481, 1972.
128. Gross M, Rabinoviu M: Control of globin synthesis in cell-free preparations of reticulocytes

bv formation of translational repressor that is inactivated by hemin. Proc Natl A a d Sci USA 69:1565-1568, 1372.

129. Gross M, Rabinoviu M: Control of globin synthesis bv hcmm: Factors influencing formation of an inhibitor of globin chain initation in reticulocyte lysates. Biochim Biophys Acta 287:340-352, 1972.

130. Adamson SD, Yau E, Herbert E et al: Involvement of hemin. a stimulatory fraction from ribosomes and a protein synthesis inhibitor in the regulation of hemoglobin synthesis. J Mol Biol 63:247-264, 1972.

131. Legon S, Jackson RJ, Hunt T: Control of protein synthesis in reticulocyte lysates by haemin. Nature New Biol 241:150-152, 1973.

132. Freedman ML, Geraghty M, Rosman J: Hemin control of globin synthesis. Isolation of a hemin-reversible translational repressor from human mature erythrocytes. J Biol Chem 249:7290-7294, 1974.

133. Freedman ML, Rosman J: A rabbit reticulocyte model for the role of hemin-controlled repressor in hypochromic anemias. J Clin Invest 57:594-603, 1976.

134. Balkow K, Mizuno S, Rabinovitz M: Inhibition of an initiation codon function by hemin deficiency and the hemin-controlled translational repressor in the reticulocyte cell-free system Biochem Biophys Res Commun 54:3 15-323, 1973.

135. Beuzard Y, Rodvien R, London IM: Effect of hemin in the synthesis of hemoglobin and other proteins in mammalian cells. Proc Natl Acad Sci USA 70:1022-1026, 1973.

136. Lodish HF, Daalu O: Regulation of synthesis of nonglobin proteins in cell-free extracts of rabbit reticulocytes. J Biol Chem 248:3520-3527, 1973.

137. Freedman ML, Karpatkin S: Requirement of iron for platelet protein synthesis. Biochem Biophys Res Commun 54:475-481, 1973.

138. Karpatkin S, Garg SK, Freedman ML: The role of iron in thrombopoiesis. Am J Med 57:521-525, 1974.

139. Raffel C, Stan S, Kacmpfer R: Role oi heme in mammalian protein synthesis: Activation of an initiation factor. Proc Natl Acad Sci USA 71:4020-4024, 1974.

140. Matthews MB, Hunt T, Brayley A: Specificity of the control of proteinsynthesis by haemin. Nature New Biol 243:230-233, 1973.

141. Rhoads RE, McKnight GS, Schimke RT: Quantitative measurement of ovalbumin messenger ribonucleic acid activity. J Biol Chem 248:2031-2039, 1973.

142. Levere RD, Gidari AS: Steroid metabolites and the control of hemoglobin synthesis. Bull NY Acad Med 50:563-579, 1974.

143. Glass J, Lavidor LM, Robinson SH: Studies of murine erythroid cell development. J Cell Biol 65:298-304, 1975.

144. Gidari AS, Levere RD: Enzymatic formation and cellular regulation of heme synthesis Semin Hematol 14:145-168, 1977.

145. Wildman JM, Freedman ML, Rosman J et al: Benzene and lead inhibition of rabbit reticulocyte heme and protein synthesis: Evidence for additive toxicity of these two components of commercial gasoline. Res Commun Chem Pathol Pharmacol 13:473-487, 1976.

146. Greenblatt DR, Rosman J, Freedman ML: Benzene and ethanol additive inhibition of rahhit reticulocyte heme and protein synthesis. Environ Res 13:425-431, 1977.

147. Forni A, Pacifico D, Limonta A: Chromosome studies in workers exposed to benzene or toluene or both Arch Environ Health 22:373-378, 1971.

148. Snyder CA: Analytical techniques. *In* Laskin S, Goldstein BD (eds): Benzene toxicity. a critical evaluation. J Toxicol Environ Health (suppl 2): 5-22, 1977.

149. Rusch GM, Leong BKJ, Laskin S: Benzene metabolism: *In* Laskin S, Goldstein BD (eds): Benzene toxicity, a critical evaluation. J Toxicol Environ Health (suppl 2):23-36, 1977.

150. Croizat P, Guichard A, Revol L et al: Etude anatomo-clinique et chimique d'un cas de maladie de Marchiafava-Micheli. Sangre 19:218, 1948.

151. Wolman S: Cyiologic and cytogenic effects of benzene. *In* Laskin S, Goldstein BD (eds): Benzene toxicity. a critical evaluation. J Toxicol Environ Health (suppl 2):63-68, 1977.

152. Snyder R, Kocsis JJ: Current concepir of chronic benzene toxicity. CRC Crit Rev Toxicol June 1975, pp 265-288.

153. Infante PF, Rinsky RA, Wagoner JK et al: Leukaemia in benzene workers. Lancet 2:76-78, 1977.