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ENVIRONMENTAL HEALTH ABSTRACTS & BIBLIOGRAPHY

September 1979

focus: LEAD POISONING

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE - PUBLIC HEALTH SERIVCE
CENTER FOR DISEASE CONTROL, ATLANTA, GEORGIA 30333

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Prepared by
Center for Disease Control
Bureau of State Services
Technical Information Serivces
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Atlanta, Georgia 30333

Foreword

Environmental Health Abstracts and Bibliography presents a survey of recently published literature in the field. Effort is made to keep the abstracts as current as possible and sufficiently informative to enable the reader to decide whether the original article would be of interest to him or her. The journals in which articles originally appeared should be checked for reprint addresses. The Center for Disease Control is unable to supply reprints of articles which are cited in this publication.

In compiling these abstracts we utilize the National Library of Medicine's interactive retrieval service, MEDLARS II. Under this system, both foreign and domestic biomedical periodicals are searched for material dealing with or related to environmental health. We also utilize the libraries of Emory University, the Center for Disease Control and other federal agencies. Abbreviations of periodical titles are those used by MEDLARS and listed in the National Library of Medicine's *List of Journals Indexed in Index Medicus.*

Future issues of *Environmental Health Abstracts and Bibliography* will be devoted to various environmental health topics. Individuals desiring to be placed on the mailing key to receive future issues as published should write to the Center for Disease Control, Attention: Environmental Health Services Division, Bureau of State Services, Atlanta, Georgia 30333.

Vernon N. Houk, M.D.
Director
Environmental Health Services Division

Contents

GENERAL

Deficits in Psychologic and Classroom Performance of Children with Elevated Dentine Lead Levels

H.L. Needleman, C. Gunnoe, A. Leviton, R. Reed, H. Peresie, C. Maher, and P. Barrett. N ENGL J MED 300(13):689-95, 29 Mar 79.

Authors' abstract: To measure the neuropsychologic effects of unidentified childhood exposure to lead, the performance of 58 children with high and 100 with low dentine lead levels was compared. Children with high lead levels scored significantly less well on the Wechsler Intelligence Scale for Children (Revised) than those with low lead levels. This difference was also apparent on verbal subtests, on three other measures of auditory or speech processing and on a measure of attention. Analysis of variance showed that none of these differences could be explained by any of the 39 other variables studied.

Also evaluated by a teachers' questionnaire was the classroom behavior of all children (2146 in number) whose teeth were analyzed. The frequency of nonadaptive classroom behavior increased in a dose-related fashion to dentine lead level. Lead exposure, at doses below those producing symptoms severe enough to be diagnosed clinically, appears to be associated with neuropsychologic deficits that may interfere with classroom performance.

Lead Exposure among Children—A Reassessment (Editorial)

J.S. Lin-Fu. N ENGL J MED 300(13):731-2, 29 Mar 79.

Health workers in the lead poisoning field have for years been confronted with the crucial question of whether lead can damage the central nervous system of young children even in the absence of overt signs and symptoms referable to that system.

Needleman et al. [see abstract above], using dentine lead content as a marker of previous lead exposure, have found that children with high dentine lead, none of whom had overt lead poisoning, performed significantly less well on IQ tests than their counterparts with low lead content. In addition, according to teachers' evaluations, nonadaptive classroom behavior increased in a dose-related fashion to dentine lead and was not limited to children with the highest lead levels. These clinical findings are supported by recent laboratory data of Silbergeld et al. and Muller et al. [see abstracts in "Research and Evaluation" section].

Data from the Environmental Health Services Division, Center for Disease Control, indicate that in the years 1973-1978, 162,580 among 2,380,942 children screened for lead poisoning had undue lead absorption; 20,994 required chelation for lead poisoning. It is abundantly clear from these figures that undue lead absorption is matched by few other pediatric health problems.

Author concludes: "A re-examination of the concept of lead poisoning based on current knowledge is needed, because what was viewed as undue lead absorption yesterday may have to be considered lead poisoning today. More importantly, future hazardous lead exposure must be prevented. The dissemination of lead in the environment is man-made and controllable. Our concerns over the economic consequences of reducing this dissemination should not cause us to lose sight of the value of intact human life."

The Effects of Inorganic Lead on Behavioral and Neurologic Function

J.D. Repko, C.R. Corum, P.D. Jones, and L.S. Garcia, Jr. DHEW (NIOSH) PUBLICATION NO. 78-128, pp. i-x, 1-92. Washington D.C.: U.S. Government Printing Office, 1978.

Authors' abstract: Fifty-three behavioral measures of sensory and motor functioning, six measures of nerve conduction velocity, five indices of inorganic lead absorption, a clinical electromyogram, a clinical neurological examination, and demographic data were obtained from 85 experimental and 55 comparison subjects. The experimental subjects were paid volunteers from among workers exposed to inorganic lead in the storage battery manufacturing industry. The comparison group consisted of paid volunteers from a light manufacturing industry (manufacture of battery cases), service industries, or were unemployed. The comparison group participants had no known occupational exposure to inorganic lead or other neurotoxic chemical. The data were collected at the authors' laboratory or at a portable field laboratory. Analysis of the data showed that the two study groups were statistically identical in terms of age, height, and weight; a slight, inconsequential difference in educational level was noted, however.

The results of the blood and urine biomedical determinations showed that the experimental group had a mean blood lead of 46μg/100ml; the mean blood lead for the comparison group was 18μg/100ml. The results further indicate that for the experimental subjects, PbB, ALA-D, FEP, PbU, and δ-ALA were intercorrelated and each measure could be predicted from each of the other measures. The greatest intercorrelations were between PbB and the remaining four measures. However, except for a positive relationship between FEP and certain of the pure-tone threshold measures, none of these biomedical indicators bore a significant relationship to NCV or behavioral measures. Results from the clinical electromyogram and neurological examinations indicated that the experimental group was asymptomatic with respect to lead and did not differ clinically from the comparison group.

Differences between the two groups were evident in the NCV and behavioral measures. The lead-exposed workers showed a statistically significant lower conduction velocity in the magnitude of 5 to 9m/sec for the MCV of the median, ulnar, posterior tibial, and deep peroneal nerves. Also, the SCV of the ulnar nerve was significantly slower for the lead workers; no significant differences in the CVSF of the ulnar nerve were noted. The results of the behavioral measures showed that deficits in visual reaction time, under response control of the ulnar nerve, as well as deficits in auditory functioning, in terms of both pure-tone thresholds and tone-decay, were adversely affected by low-level lead absorption. No differences were noted in the grip strength, eye-hand coordination, or other psychological/social measures.

Increased Blood Lead Levels in Mentally Retarded Children in Greece

S. Youroukos, C. Lyberatos, A. Philippidou, C. Gardikas, and A. Tsomi. ARCH ENVIRON HEALTH 33(6):297-300, Nov-Dec 78.

Authors' abstract: In 60 children with mental retardation of unknown etiology, the whole blood lead, as well as the activity of the red cell delta-aminolevulinic acid dehydratase (delta-ALAD), was measured. Thirty normal children and 30 with mental retardation of known etiology were used as controls. The lead values were found significantly higher in the study patients compared with both control groups ($P < 0.001$). The delta-ALAD activity in the 14 patients with blood lead levels $\geq$ 40 μg/dl, was significantly reduced compared with the normal controls ($P < 0.001$) and the mentally retarded controls ($P < 0.01$). In more than 20% of the patients with mental retardation of unknown etiology, indications of significant exposure to lead were found. There was no difference in blood lead values between children from cities and those from rural areas. The possible role of lead in the etiology of mental retardation is discussed.

Behavioral Indicators of Lead Neurotoxicity: Results of a Clinical Field Survey

J.A. Valciukas, R. Lilis, J. Eisinger, W.E. Blumberg, A. Fischbein, and I.J. Selikoff. INT ARCH OCCUP ENVIRON HEALTH 41(4):217-36, 14 Jul 78.

Authors' summary: Central nervous system dysfunction in workers occupationally exposed to lead was investigated by means of performance tests. The test scores of lead-exposed workers were compared with those of control groups (steel workers, papermill workers and farmers). It was found that secondary lead smelter workers showed significantly poorer scores than the nonexposed, control groups. The group differences between steel workers and lead workers in test scores were not attributable to difference in age or education. In the lead-exposed workers correlations between test scores and indicators of lead absorption (particularly blood lead and zinc protoporphyrin levels) were analyzed. Increases in zinc protoporphyrin levels were found to be highly correlated with decreases in test scores. Lower performance test scores were consistent with a sizeable prevalence of central nervous system symptoms among secondary lead smelter workers. Moreover, lead workers without central nervous system symptoms also showed decrements in performance test scores which were also correlated with elevated zinc protoporphyrin levels. The data indicate that certain behavioral tests might be important tools for studying subclinical central nervous system dysfunction due to lead toxicity; significant correlations between zinc protoporphyrin levels and behavioral test scores are considered to be consistent with an etiologic relationship between decrement in performance cores and lead effects on the central nervous system.

Psychological Performance of Subjects with Low Exposure to Lead

H. Haenninen, S. Hernberg, P. Mantere, R. Vesanto, and M. Jalkanen. JOM 20(10):683-9, Oct 78.

Authors' abstract: In a study of the effects of low lead exposure on psychological performance, 49 exposed workers and 24 controls were given a psychological test battery. All the lead workers had been under regular monitoring during their entire exposure time, and only workers whose maximal blood lead concentration had never exceeded 70 μg/100 ml were included in the study. At the time of the examination, the mean blood lead level of the exposed group was 32±11μg/100 ml. Comparisons were made both between exposed and non-exposed workers and within the exposed group. In the latter case, the maximal, the average and the actual blood lead concentrations were used as measures of uptake. The most important finding was a significant relationship between impaired psychological performance and lead uptake within the exposed group. The performances that were most affected by lead depended on visual intelligence and visual-motor functions. Age and neuroticism did not explain these relationships. The impairment of psychological performance correlated better with the average than with the maximal or actual blood lead concentration. Considering that no single blood lead concentration had ever exceeded 70 μg/100 ml, these findings indicate that the threshold for impaired performance lies below that level.

Psychological Dysfunctions in Lead-Exposed Workers. Relation to Biological Parameters of Exposure

P. Grandjean, E. Arnvig, and J. Beckmann. SCAND J WORK ENVIRON HEALTH 4(4):295-303, Dec 78.

Authors' abstract: Insidious neurotoxic effects of lead have been studied in a population of 42 lead-exposed workers and a reference group of 22 comparable workers with no lead exposure. The age of the individuals ranged from 18 to 50 years. The complete Wechsler Adult Intelligence Scale, as well as psychomotor and memory tests, was included in the test battery. The exposure was assessed by means of the lead concentration in blood and hair and the ratio between zinc protoporphyrin and hemoglobin in the blood. Significant differences were found between the two groups of workers, especially concerning long-term memory, verbal and visuospatial abstraction, and psychomotor speed. Decreased performance in these tests was in most cases associated with indices of increased lead exposure, not only in the total population studied, but also within the lead-exposed group alone. Blood lead and zinc protoporphyrin appeared to correlate better with the intellectual impairment than did hair lead, and thus these analyses are probably better

predictors for neurotoxic effects of lead. Age and exposure time were not found to be significant confounding factors in this study.

Lead and Motor Neurone Disease (Editorial)

Anonymous. BR MED J 2(6133):308, 29 Jul 78.

From author's introduction and conclusion: The term "motor neurone disease" describes a progressive degenerative disorder of the central nervous system affecting the motor nuclei of the cranial nerves, the anterior horn cells of the spinal cord, and the descending corticospinal (pyramidal) tracts. Both the etiology and pathogenesis of the condition remain obscure.

In 1970 Campbell and colleagues suggested that chronic lead intoxication might be an important factor, but this view was not widely accepted. Nevertheless, Conradi and colleagues found raised lead concentrations in the cerebrospinal fluid of patients when compared with controls, and more recently they have reported raised plasma lead concentrations in 16 patients compared with 18 control subjects. They postulate that the exposure of the motor end plates to increased amounts of circulating lead in the plasma may result in the uptake of lead by the motor neurones and that this may be conducted by retrograde axoplasmic flow to the cell bodies—as occurs with various injected macromolecules.

While many neurologists will think that it is inherently improbable that lead will prove to be the primary etiological agent in motor neurone disease, the findings of this careful study cannot be ignored or dismissed lightly—especially when, in such a tragic progressive disease, we have no other clues to indicate an alternative, testable, working hypothesis.

Some Biochemical and Clinical Aspects of Lead Intoxication

J.L. Granick, S. Sassa, and A. Kappas. ADV CLIN CHEM 20:287-339, 1978.

This review article is a highly detailed examination of the biochemical and physiological aspects of lead intoxication. The authors consider the action of ALA dehydratase as well as the topics of ferrochelatase, movement of iron into and within bone marrow cells, and protoporphyrin accumulation. They next consider the effects of lead on mental processes and on hyperactivity. They describe lead in cellular fractions and effects on brain enzymes, and the effect on the peripheral and autonomic nervous systems. The effects of lead intoxication on the kidney and on RNA and DNA are also described. Finally, the authors consider the factors that modulate lead absorption and toxicity, and summarize the various biochemical assays for lead exposure.

Threshold Levels and Lead Toxicity

O.J. David, S. Hoffman, and A. Koltun. PSYCHOPHARMACOL BULL 14(3):50-3, Jul 78.

Authors' abstract: The validity of using a threshold level for defining lead poisoning in children is questioned, and a continuum of toxicity is posited instead. This is done via a consideration of how the threshold view is derived; an analysis of the reason(s) for the relative lack of confirmatory evidence substantiating the continuum view (design error); and a review of studies that, avoiding this error, present findings congruent with a continuum view.

Childhood Lead Poisoning: A Re-evaluation

O.J. David, J. Clark, and S. Hoffman. ARCH ENVIRON HEALTH 34(2):106-11, Mar-Apr 79.

Authors' abstract: Long recognized as an environmental toxin of fearsome lethality, lead effects are commonly described as extremely serious, particularly as regards the central nervous system. It is postulated here that this represents only part of the pathologic spectrum. Other lead-related conditions, as yet unrecognized, may include a wide range of central nervous system dysfunctions that although severe, are not so acutely dramatic or widely destructive as the classic encephalopathic or preencephalopathic states. These conditions remain etiologically unrecognized primarily because of (1) the variable nature of onset, (2) the variable nature of the manifestations, (3) the relative subtlety of the dysfunctions, and most

importantly, (4) the absence of consistent, unequivocal evidence demonstrating the relationship of lower blood lead levels with pathologic effects. This last is seen as pivotal, and an extensive examination of the reasons for its absence is presented. It is postulated that biological variability, a concept widely used in medicine but rarely invoked in the researching of lead toxicity, is a crucial ingredient in lead research. It is further asserted that the grevious lack of etiologic recognition will continue until that factor is incorporated into research designs.

Living with Lead

J. Eisinger. NATURE 278(5701):207-8, 15 Mar 79.

From author's discussion: [There is] considerable concern among the public as well as governmental health authorities grappling with the task of defining safe limits for environmental lead exposure.

A recent report (A.C. Chamberlain et al., *Investigations into Lead from Motor Vehicles,* Harwell: HMSO, 1978) presents the results of a painstaking experimental study of the pathways by which lead enters and leaves our bodies and of the size and fate of the fraction which stays behind. Since the study is primarily concerned with emission from motor vehicles it includes ambient measurements of the concentrations and size distributions of lead aerosols near roadways. [The study] should be useful in constructing kinetic models for lead transport within the body.

The most significant conclusion from the point of view of environmental policy may be that at 1 $\mu g/m^3$, the average air level in British cities, the ratio of air lead to other lead intake is low, between 8 and 20%, and is in substantial agreement with the conclusion of another recent study (*Lead Pollution in Birmingham,* London: HMSO, 1978). The importance of local conditions can be seen from the finding that the mean lead level in the blood of mothers and children in North Wales is doubled if their houses have lead, as opposed to copper, piping (P.C. Elwood et al., "Blood-lead Levels in Mothers and their Children," *Lancet* 1(8078):1363-4, 24 Jun 78). This suggests that the greatest intake among the general population in Britain is caused by lead piping in soft-water areas.

Lead Poisoning

R. Klein. ADV PEDIATR 24:103-32, 1977.

There have been significant changes over the last decade in both the nature of childhood lead poisoning and in our understanding of it. Although illustrations are drawn from the author's experience in Massachusetts, similar observations have been made throughout the country, particularly in the North and East.

First, the clinical character of lead poisoning has changed. Symptomatic lead poisoning is less and less common, but there is a marked increase in the recognition of asymptomatic lead poisoning, whose prevalence is appalling. Secondly, the serious consequences of asymptomatic lead poisoning are now fairly well understood; recent articles suggest that approximately 25 percent of children with asymptomatic lead poisoning develop significant and permanent impairments of the nervous system. The third significant change involves advances in the technical ability to diagnose lead poisoning. Micro-methods of analysis of blood lead and the introduction of the measurement of erythrocyte protoporphyrin as an index of lead poisoning have greatly aided screening efforts. Finally, changes in the country's social consciousness have lead to increased, albeit tenuous and hesitating, efforts at lead poisoning prevention. However, money and manpower from Federal, State, and local sources is still disproportionately minute, and efforts toward removing environmental hazards have been negligible.

Author concludes with an abbreviated list of what is needed to eliminate childhood lead poisoning–including laws, financing, education, and commitment.

Lead Poisoning in Children–What Price Shall We Pay?

J.S. Lin-Fu. CHILDREN TODAY 8(1):9-13, 36, Jan-Feb 79.

To illustrate the thesis that "lead poisoning is a uniquely neglected public health problem of the 20th century," the author reviews the history of lead poisoning in children from the time just before the turn of the century when it began to receive serious attention. Despite the fact that research and data in the years following

indicated the seriousness of the problem, lead poisoning in children was largely ignored for several reasons: (1) there was a misconception that lead poisoning was a problem of the past; (2) the symptoms for lead poisoning are non-specific; (3) lead poisoning is a disease primarily of the socioeconomically deprived; and (4) great problems were encountered in attempts to abate the lead paint hazard in the child's home.

There was finally a general awakening to the problem in the 1960's, which resulted in the Lead-Based Paint Poisoning Prevention Act of 1971 and its later amendments. Recent findings, however, indicate that the problem is not confined to large urban slums and areas east of the Mississippi River as previously thought. Lead paint in dilapidated housing remains the major source of lead poisoning in children, but other important sources, such as dust, dirt, and soil, have been discovered or rediscovered.

Recent technological advances such as the erythrocyte protoporphyrin screening test have made the early discovery of undue lead absorption simpler. This is important because some recent studies have indicated that even children with no clinical signs of lead poisoning may have suffered subtle neuro-psychological damage, and what constitutes "undue lead absorption in young children" is being redefined.

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*Abstracted

SOURCES AND ETIOLOGY

General

Maternal and Cord Blood Metal Concentrations and Low Birth Weight—A Case-Control Study

J.D. Bogden, I.S. Thind, D.B. Louria, and H. Caterini. AM J CLIN NUTR 31(7):1181-7, Jul 78.

Authors' abstract: There has been speculation on the possible role of trace metals in contributing to the occurrence of low birth weight, but few data are available for most metals. Twenty-five women giving birth to infants weighing between 1500 and 2500 g (cases) and 50 women giving birth to infants weighing more than 2500 g (controls) were studied. The cases and controls were matched for age (± 4 years), race, and socioeconomic status. Cord blood and maternal blood collected at delivery were analyzed by atomic absorption spectrophotometry for calcium, magnesiu, copper, lead, and iron. Significant differences between the mean blood metal concentrations of the low birth weight and control groups were found for calcium ($P < 0.001$) and iron ($P < 0.05$) in the maternal blood samples and for calcium ($P < 0.001$) and iron ($P < 0.01$) in the cord blood samples. All concentrations were lower in the low-birth weight group except for the maternal iron level. No significant differences between the low birth weight and control groups were found for copper, lead, and magnesium in either maternal or cord blood.

Maternal Lead Exposure and Blood Lead Concentration in Infancy

J.E. Ryu, E.E. Zigler, and S.J. Fomon. J PEDIATR 93(3):476-8, Sep 78.

From authors' introduction and conclusion: Increased maternal exposure to lead is associated with increased lead content of the fetus and the newborn infant. The following report concerns observations made during pregnancy and lactation in a woman who was exposed to lead before and during most of her pregnancy and in the infant born to this woman. Neither the woman nor infant had evidences of toxicity at any time.

In the absence of important postnatal exposure to lead, it appears that an infant exposed prenatally can substantially reduce the body burden of lead, at least relative to body mass, during the early months of life.

Neonatal Lead Intoxication in a Prenatally Exposed Infant

N. Singh, C.M. Donovan, and J.B. Hanshaw. J PEDIATR 93(6):1019-21, Dec 78.

The following report represents the first example of a liveborn infant with biochemical evidence of lead intoxication due to prenatal exposure to lead.

A 3,200 gm white girl was born after 40 weeks gestation to a 20-year-old mother who, with her husband, had removed paint from her house with a torch and sandpaper during the third trimester. Both father and mother and two siblings were diagnosed as having lead intoxication. Although all the hematologic data were normal, the infant had evidence of asymptomatic increased lead absorption and continued to have elevated lead and erythrocyte protoporphyrin levels at 3 weeks of age. The infant was treated with calcium EDTA and thereafter showed decreasing blood lead and erythrocyte protoporphyrin levels.

The patient showed delayed object permanence skills and delayed language skills at 13 months of age according to the Early Intervention Development Profile. This may have been caused by the prenatal exposure to high lead. The child appears to be at high risk of later learning problems which may become demonstrable during early school years.

Mouthing Activities and Their Relationship to Lead Poisoning

S.M. Marcus, R. Damaso-Diaz, and R. Ziering. J MED SOC NJ 75(12):837-8, Nov 78.

From authors' results and discussion: A study was performed to relate the age at weaning from the bottle with the development of lead poisoning. A significant rise in the incidence of screening levels of over 50 μg/dl was found as the age at weaning increased. This rise was significant at < 0.01 (by chi square). No correlation was found between the presence of pica and the highest level of lead found in chart review or in screening levels. A statistically significant relationship was demonstrated between delayed weaning ($>$ 24 months) and pica ($P < 0.01$). These findings suggest that a method of primary prevention of lead poisoning may be to advise parents to attempt weaning at an age where pica and lead poisoning will be less likely. Our study does not pinpoint such an age.

Sources of Lead in Blood: Identification by Stable Isotopes

W.I. Manton. ARCH ENVIRON HEALTH 32(4):149-59, Jul-Aug 77.

Author's abstract: The isotope ratios of lead in the blood of ten subjects resident in Dallas, Texas, were measured from April 1974 to June 1975. During the same period, the ratios in the city's air changed linearly by 6%. One subject gave erratic results, but the remainder yielded ratios that changed systematically—some linearly, others cyclically with turning points occurring in August to October and February to April. Two South African subjects were 6 months out of phase with their U.S.-born wives and the other U.S.-born subjects. Since the South Africans are presumed to have in their skeletons lead that is isotopically distinct from that in the U.S. environment, the cycles are attributed to the mixing of skeletal and dietary lead. The dietary component is inferred to be greatest in August to October, which correlates with the time at which 25-hydroxyvitamin D is reported to have maximum concentration in blood. On the assumption that the isotope ratios of dietary lead remained constant, the proportion of airborne lead in the blood of those subjects whose ratios changed linearly could be calculated, and values between 7±3% and 41±3% were obtained.

Manganese Pollution in the City Environment and Its Relationship to Traffic Density

M.M. Joselow, E. Tobias, R. Koehler, S. Coleman, J. Bogden, and D. Gause. AM J PUBLIC HEALTH 68(6):557-60, Jun 78.

Authors' abstract: As lead is phased out of gasoline, other additives with anti-knock properties, particularly organic manganese compounds, are being substituted. Unavoidably, such compounds go through the combustion process, are eliminated in exhaust gases, and become part of the city environment. To obtain some indication of the extent of this new pollution, street soils from various locations in a heavily trafficked city (Newark, NJ) were analyzed for manganese and lead by atomic absorption. Highly significant inverse relationships were found between the concentrations of both contaminants and distances from major traffic arteries. Strong circumstantial evidence is thus provided that: 1) manganese pollution is occurring, along with lead, in the city environment; 2) this new pollution is related to traffic density; and 3) the most likely sources are automobile exhausts. This suspicion is further strengthened by the significant correlations observed between manganese and lead contents in children's blood, suggesting a common source for both. Substantiation of the safety of this practice of adding manganese to gasoline is needed.

Bullets, Lead Poisoning and Thyrotoxicosis

C.R. Cagin, M. Diloy-Puray, and M.P. Westerman. ANN INTERN MED 89(4):509-11, Oct 78.

Authors' abstract: A patient with a retained bullet developed lead poisoning in association with thyrotoxicosis. The clinical and laboratory data suggest that lead was mobilized from an increased mobile bone pool during the hypermetabolic period with resultant poisoning. The findings give factual support to earlier concepts that lead poisoning may occur during periods of metabolic change in an individual with an increased body lead burden.

Surma and Lead Poisoning

A.R. Ali, O.R. Smales, and M. Aslam. BR MED J 2(6142):915-6, 30 Sep 78.

Authors' summary and conclusions: Blood lead concentrations were measured in 62 Asian children, of whom 37 had definitely had surma applied to their eyes and 25 were thought not to have done. The mean concentration in those who had not used surma was 0.98±SD 0.42 μmol/l (20.3±8.7 μg/100 ml) compared with 1.65±0.68 μmol/l (34.2±14.1 μg/100 ml) in those who had. Analysis of 29 different samples of surma showed 23 of them to be composed largely of lead sulphide.

We conclude that the use of surma is associated with high blood lead concentrations. In our cases most of it had been obtained abroad, and hence government restrictions might be ineffective in limiting its use: a better method of prevention might be to inform the leaders of Asian communities of the risks.

Occupational and Industrial

Hemoglobin, Serum Iron, and Zinc Protoporphyrin in Lead-Exposed Workers

R. Lilis, J. Eisinger, W. Blumberg, A. Fischbein, and I.J. Selikoff. ENVIRON HEALTH PERSPECT 25:97-102, Aug 78.

Authors' abstract: In a previous study of secondary lead smelter workers (males), a significant prevalence of low hemoglobin levels (< 14 g/100 ml) was found; a statistically significant negative correlation between hemoglobin and zinc protoporphyrin was also detected. In the present study serum iron (Fe) levels and total iron binding capacity (TIBC) were included in the investigation of 111 secondary lead smelter workers and 37 non-exposed controls. The distribution and mean values of serum iron and TIBC were found to be in the normal range in the lead exposed workers; there was no significant difference when compared to the control population. There was no significant correlation between blood lead or zinc protoporphyrin and serum iron, TIBC and Fe/TIBC. A statistically significant negative correlation between hemoglobin and blood lead levels was found; the correlation between hemoglobin and zinc protoporphyrin reached a much higher level of significance. The results support the view that anemia (low hemoglobin levels) in lead exposed male workers is related to the heme synthesis inhibiting effects of lead, as reflected by elevated zinc protoporphyrin levels, and is not due to iron deficiency.

Lead Contamination in the Homes of Employees of Secondary Lead Smelters

C. Rice, A. Fischbein, R. Lilis, L. Sarkozi, S. Kon, and I.J. Selikoff. ENVIRON RES 15(3):375-80, Jun 78.

Authors' abstract: The lead content of particulates in 33 homes of employees of two secondary lead smelters in different geographical areas of the country was investigated. Employees generally showered before going home and work clothes were laundered by the companies. Despite these hygiene measures, the lead content of particulates in the workers' homes was found to be significantly greater than in samples collected in control homes in the same or similar neighborhoods. Samples were collected by the Vostal method. In one area, a geometric mean of 79.3 μg of lead/towel was found in the workers' homes, compared with 28.8 μg/towel in the homes of workers with no history of lead exposure. In the second area studied, a geometric mean of 112.0 μg was determined in the workers' homes, compared with 9.7 μg in the homes of controls. In the latter area, paint chips, particulates from the sidewalk curb, and settled dust were also collected and analyzed for lead content. Elevated zinc protoporphyrin levels were found in some children of lead-exposed workers, but not among children in control homes.

Increased Lead Burden in Children of Battery Workers: Asymptomatic Exposure Resulting from Contaminated Work Clothing

J.L. Dolcourt, H.J. Hamrick, L.A. O'Tuama, J. Wooten, and E.L. Barker, Jr. PEDIATRICS 62(4):563-6, Oct 78.

Authors' abstract: Lead transmitted into the home via contaminated parental work clothing was the probable source of excessive lead exposure among 69% of 58 children whose mothers worked in a battery factory in Raleigh, North Carolina. Blood lead levels were highest in children less than 3 years old, and declined with age. All children were asymptomatic, and all had normal findings on physical examinations. Dust samples from the homes of children with the greatest lead burden demonstrated gross contamination of the home environment. Although maternal employment was short, young children spent a significant portion of their lives exposed to lead. Certain parental occupations can subject children to considerable risk from lead exposure.

Increased Lead Absorption in Children of Workers in a Lead Storage Battery Plant

W.N. Watson, L.E. Witherell, and G.C. Giguere. JOM 20(11):759-61, Nov 78.

Authors' abstract: Exposure to toxic materials originating in the workplace has been recognized in families of workers in several industries. However, to date this problem has not been studied in the storage battery production industry. A total of 27 one- to six-year-old children of 22 workers at a storage battery plant at high risk of exposure to lead oxide were compared with 32 one- to six-year-old children in 22 neighborhood control families for evidence of increased lead absorption. Workers' children had significantly higher blood lead ($P < 0.001$) and erythrocyte protoporphyrin ($P < 0.003$) values than control children. Household exposures to lead in paint and water were similar for the two groups, but workers' homes had significantly higher concentrations of lead in dust ($P < 0.001$). It is postulated that lead is brought home on the skin, hair and clothing of the workers and that their children are ingesting or inhaling the lead in household dust. This is the first report of increased lead absorption in children of workers in this industry.

Urban Lead Mining: Lead Intoxication among Deleaders

R.G. Feldman. N ENGL J MED 298(20): 1143-5, 18 May 78.

From author's introduction and conclusions: Unsafe or carless deleading procedures are resulting in cases of lead intoxication among the deleaders themselves. [Two case reports are outlined.]

All workers exposed to lead while deleading houses, even on a single occasion, should follow accepted measures to reduce lead exposure to a minimum: good personal hygiene; use of adequate exhaust ventilation in work areas; use of work clothing, which is not worn home, carefully and frequently washed; use of respirators with appropriate filters changed at appropriate intervals; use of well designed scrapers; and careful handling and disposal of waste materials (especially dust containing lead). Since some exposure to and absorption of lead occur even though these measures are followed, periodic medical surveillance, including monitoring of blood lead levels or a comparable test, must be carried out.

Lead Hazard among Ironworkers. Dismantling Lead-Painted Elevated Subway Line in New York City

A. Fischbein, S.M. Daum, B. Davidow, G. Slavin, A.P. Alvares, S. Sassa, K.E. Anderson, A. Kappas, J. Eisinger, W.E. Blumberg, E.H. Winicow, and I.J. Selikoff. NY STATE J MED 78(8):1250-9, Jul 78.

Authors' abstract: Flame cutting of lead-painted steel structures may be associated with considerable lead exposure. In this study, an outbreak of lead poisoning among ironworkers dismantling an elevated subway line in New York City is described. Industrial hygiene evaluation of the respirators showed that inadequate equipment was the cause of the subsequent occupational disease. In the assessment of the lead-induced effects on the hematopoietic system, a new screening test—erythrocyte zinc protoporphyrin determintion—was employed,

utilizing a portable field device (hematofluorometer) on which an instantaneous reading of ZPP (zinc protoporphyrin) concentration is obtained. Correlative data between ZPP and blood are presented, demonstrating that ZPP determinations may improve and simplify the task of screening and monitoring populations chronically exposed to lead. The effect of lead on the biosynthesis of heme was also assessed in five workers, by investigating the functional capacity of the hepatic cytochrome P-450 system through drug metabolism studies before and after chelation therapy. The effect on this system was considered minimal. Environmental studies showed that very high amounts of lead dusts were generated by the demolition process, but did not present any significant hazard to people residing in the vicinity. It is emphasized that combined medical and industrial hygiene surveillance is essential for the safe management of such work operation, and workers engaged in such operations require proper respiratory equipment to minimize the risk of increased lead absorption.

Urine Delta-Aminolevulinic Acid and Erythropoietic Activity in Human Lead Intoxication

A. Canberk, I. Sehirli, Y. Canberk, and H. Koyuncuoglu. TOXICOL APPL PHARMACOL 44(2):257-61, May 78.

Authors' abstract: A very high blood lead concentration (mean, 97.42 ± 9.85 μg/100 ml; $P < 0.001$) was detected in eight printshop workers. They also had hypochromic anemia and erythrocytosis. There was an increase in erythropoietic activity and urine delta-aminolevulinic acid concentrations were high as well (mean, 1.45 ± 0.18 mg/100 ml; $P < 0.001$). Also various types of large distorted erythrocytes, a few in the shape of four-leaved clovers, were observed in the periphery.

Contact Sensitivity to Lead (German)

N. Czarnecki and P. Fritsch. HAUTARZT 29(8):445-7, Aug 78.

English summary: A case of contact sensitization to lead is described which presented as an acute bullous contact dermatitis after application of an ointment containing lead oxide (unguentum diachylon Hebra). In patch testing, the patient reacted strongly to lead oxide and lead acetate. Further examination revealed a chronic lead intoxication with neurologic and labyrinthine involvement. As a painter, the patient had had professional contact with the lead paints up to 25 years ago for a period of 30 years. He had never noticed any contact allergies to his working materials.

Epidemiologic Investigation of 23 Cases of Lead Poisoning Due to Industrial Cider (French)

J.F. Devars du Mayne, Y.A. Nordmann, N. Phung, and J.P. Hardouin. ANN MED INTERNE (PARIS) 129(8-9):481-5, Aug-Sep 78.

English summary: We report 23 cases of lead poisoning due to industrial cider being contaminated during its manufacture, this being caused by the detergents used to clean the piping. Microscopic examination of the stippled erythrocyte is not effective. On the other hand the elevation of erythrocyte protoporphyrin remains constant, and this is the most reliable, long standing sign of lead poisoning. There is certainly a cumulative effect of toxication but it is the acute increase by ingestion above a certain limit (between 3 and 10 mg of lead daily according to the individual) which provokes clinical signs and symptoms.

Exposure to Lead in Firing Ranges

A. Fischbein, C. Rice, L. Sarkozi, S.H. Kon, M. Petrocci, and I.J. Selikoff. JAMA 241(11):1141-4, 16 Mar 79.

Authors' abstract: Members of law enforcement agencies were examined for adverse health effects caused by their activities in firing ranges and exposure to lead. Central nervous system and gastrointestinal symptoms were prominent and correlated with blood lead and zinc protoporphyrin levels. Half the group had blood lead levels exceeding 40 μg/dL, and four (5%) exceeded 60 μg/dL. Environmental surveys of

three firing ranges indicate that indoor facilities with insufficient ventilation may have considerable air lead concentrations with levels up to 900 μg/cu m or 4.5 times the current Occupational Safety and Health Administration standard for an eight-hour shift. Evaluation of lead effects should be taken into account in medical surveillance programs of firearms instructors. Zinc protoporphyrin determination has proved a suitable and practical way to assess biological effects among exposed persons and should be available at medical facilities responsible for the health of indoor firing range employees.

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*Devars du Mayne JF, Nordmann YA, Phung N, Hardouin JP: Epidemiologic investigation of 23 cases of lead poisoning due to industrial cider (French). ANN MED INTERNE (PARIS) 129(8-9):481-5,Aug-Sep 78.

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DIAGNOSIS AND SCREENING

Clinical

Lead and Hyperactivity: Lead Levels among Hyperactive Children

O.J. David, S.P. Hoffman, J. Sverd, and J. Clark. J ABNORM CHILD PSYCHOL 5(4): 405-16, Dec 77.

Authors' abstract: Previous work has demonstrated an association between hyperactivity and increased body lead burdens in school-age children. In the present study it is shown that within a group of hyperactive children those for whom an organic etiology is present have lead burdens lower than in those for whom no apparent cause could be found. These data lead us to reject the notion that hyperactivity per se is responsible for the acquisition of elevated lead levels, and further strengthen the suspicion that for some children lower lead level absorption may be implicated in the development of the hyperkinetic disorder.

The Pathology and Pathogenesis of Chronic Lead Nephropathy Occurring in Queensland

J.A. Inglis, D.A. Henderson, and B.T. Emmerson. J PATHOL 124(2):65-76, Feb 78.

Authors' abstract: Many children who suffered acute lead poisoning in Queensland eventually died with contracted kidneys. In most cases the kidneys were granular and showed microscopically fibrosis, hypertensive vascular changes and "alterative glomerulitis." Clinically in these patients, hypertension and chronic renal insufficiency had always preceded death which was usually due to uremia. In a minority of cases the kidneys showed the changes of benign hypertension but were unusually small; fibrosis and "alterative glomerulitis" were not present. Clinically these patients had had hypertension but minimal renal insufficiency and death was usually due to cerebral hemorrhage. The evidence indicates that lead caused severe damage to the kidney at the time of the lead intoxication by some mechanism other than hypertension. The sequence of events postulated comprises severe renal damage with destruction of glomeruli during childhood lead poisoning, disappearance of the destroyed tissue during childhood and adolescence, onset of hypertension in adolescence or early adult life, gradual onset and progress of chronic uremia during which fibrosis and granularity developed. In milder cases the sequence is not complete because renal function has remained adequate.

The Neurological Manifestations of Chronic Inhalation of Leaded Gasoline

S.S. Seshia, K.R. Rjani, R.L. Boeckx, and P.N. Chow. DEV MED CHILD NEUROL 20(3):323-34, Jun 78.

Authors' abstract: Abnormal neurological signs were found in 46 of 50 children and adolescents chronically sniffing leaded gasoline. These abnormalities resolved within eight weeks in all but one case. Exaggerated deep reflexes, postural tremor and evidence of cerebellar dysfunction occurred in a highly significant number of patients. Forty-nine had blood lead levels $\geqslant$ 40 μg/dl. The mean blood lead levels were significantly higher in those with (a) abnormally brisk deep reflexes and (b) with evidence of cerebella dysfunction, than in those

without these findings. Five optional treatment regimens were employed and a classification was used, based on clinical findings, initial blood lead levels and the response to the calcium disodium edetate mobilization test. Thirty-nine patients received chelation therapy. These data suggest that neurological manifestations occur frequently in those abusing leaded gasoline and that chelation therapy has an important place in their management.

Laboratory

Studies in Lead Poisoning

S. Sassa, J.L. Granick, S. Granick, A. Kappas, and R.D. Levere. BIOCHEM MED 8(1):135-48, Aug 73.

This study describes the application of a rapid, simple, extremely sensitive new assay for blood protoporphyrin to the detection of lead poisoning in the subclinical range. This protoporphyrin method has proved to be especially useful for the detection of chronic lead intoxication in children because of its precision and the fact that only 2 μl of blood are required for the analysis. Blood protoporphyrin was found to reflect better the level of bone marrow lead existing 2-3 months prior to sampling rather than the circulating blood lead level. The correlation coefficient between log blood protoporphyrin and blood lead was found to be 0.72. Over 95 percent of the population with a blood lead level of 0.06 mg/100 ml had a protoporphyrin concentration of $\geqslant$ 140 μg/100 ml RBC. When a group of children was selected whose blood lead was in equilibrium with bone marrow lead, the correlation coefficient was 0.91.

Several micromethods for the detection of lead poisoning are discussed; using a combination of this new protoporphyrin assay together with either the determination of blood lead, the presence of increased erythrocytic osmotic resistance or the measurement of δ-aminolevulinic acid dehydratase, permits a distinction to be made between acute and chronic lead poisoning and/or iron deficiency anemia.

Zinc Protoporphyrin in the Erythrocytes of Patients with Lead Intoxication and Iron Deficiency Anemia

A.A. Lamola and T. Yamane. SCIENCE 186(4167):936-8, 6 Dec 74.

Authors' abstract: The fluorescent porphyrin in the erythrocytes of patients with lead intoxication or with iron deficiency anemia is zinc protoporphyrin that is bound to globin moieties, probably at heme binding sites.

Zinc Protoporphyrin (ZPP): A Simple, Sensitive, Fluorometric Screening Test for Lead Poisoning

A.A. Lamola, M. Joselow, and T. Yamane. CLIN CHEM 21(1):93-7, Jan 75.

Authors' abstract: The predominant fluorescent porphyrin that appears in erythrocytes as a result of chronic lead absorption or iron deficiency anemia is zinc protoporphyrin. This compound can be fluorometrically assayed in diluted whole blood with high sensitivity. An extremely simple and rapid test for lead absorption is described that is based on this assay. Results of a field trial indicate that this test should be seriously considered as a primary screening test for monitoring the effects of chronic lead absorption.

Response of Free Erythrocyte Porphyrin and Urinary Delta-Aminolevulinic Acid in Men and Women Moderately Exposed to Lead

H.A. Roels, R.R. Lauwerys, J.P. Buchet, and M.-Th. Vrelust. INT ARCH ARBEITSMED 34(2):97-108, 1975.

Authors' summary: The responses of various biological parameters of the heme biosynthesis pathway in a group of adult male and female workers moderately exposed to inorganic lead have been compared. The identical range of blood lead levels in both groups indicates a similar degree of exposure. Women, however, exhibit a larger increase in free erythrocyte porphyrin (FEP) and in urinary δ-aminolevulinic acid (ALA-U) than men.

The earlier response in women is probably not due to a relative degree of anemia (menstrual blood loss) as compared to men, since there is no significant correlation between hemoglobin (Hb) and FEP or ALA-U, and consequently standardization for the same Hb-content does not modify the independent effect of lead on

the FEP and ALA-U responses. A greater susceptibility to Pb of the heme biosynthesis pathway in women has therefore been confirmed by the results of the present epidemiological survey among workers of both sexes.

A preliminary and limited survey on children (11 to 12 years old) of schools situated at less than 1 km from a Pb-processing plant revealed increased FEP and blood lead concentrations and demonstrated that like women children exhibit an earlier biological response to Pb-B than adult men.

Indicators of Internal Dose of Lead in Relation to Derangement in Heme Synthesis

J.J. Chisolm, Jr., M.B. Barrett, and H.V. Harrison. JOHNS HOPKINS MED J 137(1):6-12, Jul 75.

Authors' abstract: Simultaneous measurements of Pb-B, Pb-U, chelatable lead, ALA-U and EP have been made in a group of asymptomatic children with increased lead absorption. Although the group is small, the results are internally consistent and show linear dose-effect relationships between Pb-U and chelatable lead (indicators of dose) and ALA-U and EP (indicators of lead's effect on heme synthesis). The data show, however, that Pb-B in a rather narrow range (48-68 μg Pb) is not a reliable indicator of the internal dose of lead. These results, as well as others, raise questions concerning the validity of relying exclusively on Pb-B in the clinical management of groups such as young children in old houses and lead-exposed workmen who are at increased risk for plumbism. The results suggest that chelatable lead is most closely related to lead's inhibitory effect on heme synthesis and that, biologically, it may serve as the best "chemical biopsy" of soft tissue lead concentration. A simple AAS method for measuring chelatable lead in urine is described. A new wet digestion technique which is compatible with ASV is also described. EP is apparently a better predictor of chelatable lead than Pb-B. Micro tests for EP, especially the zinc protoporphyrin fraction, are simple and highly useful in monitoring long-term trends in soft tissue lead levels in individual patients.

Micro-Scale Photofluorometric Determination of "Free Erythrocyte Porphyrin" (Protoporphyrin IX)

J.J. Chisolm, Jr. and D.H. Brown. CLIN CHEM 21(11):1669-82, Oct 75.

Report describes a simple and reproducible micro-scale fluorometric procedure which can be performed on 20 μl of blood with use of either a filter fluorometer or a spectrophotofluorometer and with standard disposable glassware and commercially available high-purity calibration materials and reagents. It is based on the classical ethyl acetate/acetic acid extraction technique of Schwartz et al., as are other recently published micromethods.

One of the final stages in the biosynthesis of hemoglobin involves the incorporation of iron into protoporphyrin IX to form heme. Unutilized protoporphyrin IX accumulates in circulating erythrocytes if iron is unavailable, as in iron-deficiency states, or if there is disturbance at this stage of metabolism, as in lead poisoning.

Longitudinal Observations of the Relationship between Free Erythrocyte Porphyrins and Whole Blood Lead

J.R. Reigart and N.H. Whitlock. PEDIATRICS 57(1):54-9, Jan 76.

Authors' abstract: Short- and long-term comparison of the variations with time of whole blood lead and free erythrocyte porphyrins (FEP) suggests that changes in FEP are slow and predictable whereas blood lead changes are quite unpredictable. However, when FEP suggests a different clinical category from blood lead, the blood lead is likely to change in the direction predicted by the FEP. Comparison of FEP to blood lead at first contact in 349 children with mild elevation of blood lead reliably predicted which children would still have elevated blood lead six weeks later and which would fall or be normal. The observation of long-term follow-up in four groups of children with various combinations of FEP and blood lead indicated that the follow-up blood lead could be predicted to change in the direction indicated by the FEP measurement. The implications for screening for lead poisoning are discussed.

Biochemical Evaluation of Damage Due to Lead: Importance and Significance of Erythrocyte Zinc-Protoporphyrin IX and Urinary Amino Acid Determination (Italian)

F. Sanguinetti, M. Dompe, and G. Ronca. ANN IST SUPER SANITA 13(1-2):399-407, 1977.

English summary: Early detection of lead intoxication requires a practical, simple, reproducible and diagnostically valid screening test. The determination of ALA-D (delta-amino-levulinic acid-dehydratase) in erythrocytes is one of the most reliable tests for the evaluation of occupational exposure to lead. However this test is difficult to standardize and is sensitive to lead contamination of laboratory glassware. Also the activity of enzyme decreases rapidly if stored. The determination of erythrocyte ZPP (zinc-protoporphyrin IX) was proposed as a useful, alternative test. Protoporphyrin IX is a metabolic intermediate in heme biosynthesis; in erythrocytes it is present in free form and in a zinc-bounded compound. The ZPP test gives high values only in lead intoxication and sideropenic anemia. The ALA-D and ZPP in erythrocytes were measured and compared in a group of workers exposed to lead. We have shown a good correlation between these two biochemical parameters. Amino acid excretion in urine from workers exposed to lead was measured and compared with other biochemical parameters of intoxication. All lead workers examined had excessive urinary CP (coproporphyrin) and ALA (delta-amino-levulinic acid) excretion. An abnormal excretion of glycine was present in eight workers (32%), whereas in four others excretion of lysine was present in six workers (21%). The last data appear very interesting because the action of lead in lysine metabolism was not known.

Determination of Porphyrins in Red Blood Cells. Comparison of Two Methods (German)

S. Seubert and A. Seubert. DTSCH MED WOCHENSCHR 102(51):1882-4, 23 Dec 77.

English summary: Two methods for measuring porphyrin concentrations in red blood cells were compared, one by Piomelli in which porphyrin is extracted from the RBCs and then measured fluorometrically, the other in which the blood-porphyrin content is measured directly with the hematofluorometer ZnP 4000. Sample size is the same for both. Results in 59 patients exposed to lead were evaluated: the correlation coefficient between the two tests was 0.99.

A Simplified Method for Rapid Determination of Porphyrins by Thin-Layer Chromatography

T. Okuda, H. Nakajima, K. Yatsuki, M. Amano, and G. Umeda. BR J IND MED 35(1):61-6, Feb 78.

Authors' abstract: Free porphyrins, especially copro-, uro-, and protoporphyrin, were successfully separated by talc thin-layer chromatography (TLC), and were determined from the relationship of the weight and the area of porphyrins in the spot on the thin-layer plate. The results obtained from both the solvent extraction and the simple, rapid TLC method reported in this paper showed good correlation for coproporphyrin levels up to 400 μg/l. The TLC method was applied to the determination of urinary coproporphyrin in lead workers and in rats.

The Influence of Plasma Bilirubin on Zinc Protoporphyrin Measurement by a Hematofluorometer

E. Buhrmann, W.C. Mentzer, and B.H. Lubin. J LAB CLIN MED 91(4):710-6, Apr 78.

Authors' abstract: A fluorometer has recently been developed to detect lead poisoning and iron deficiency by measuring erythrocyte ZPP directly from whole blood. Plasma bilirubin fluorescence has been found to influence this technique. ZPP levels determined by the fluorometer were elevated by artificially increasing the plasma bilirubin concentration, both within and above the normal range, in whole blood samples. A rise in ZPP levels was also observed when the hemoglobin concentration was lowered by dilution with native plasma. When blood samples of patients with hyperbilirubinemia were analyzed, direct measurement of ZPP by this fluorometer yielded significantly higher levels than did an alternate extraction method. Photodegradation of bilirubin in whole blood

samples did not decrease fluorescent interference. Although the bilirubin measurable decreased, fluorescence increased following a 5 hour exposure to light.

Erythrocyte-Zn-Protoporphyrin as an Indicator of Lead Exposure

P. Grandjean and J. Lintrup. SCAND J CLIN LAB INVEST 38(7):669-75, Nov 78.

Authors' abstract: Measurement of erythrocyte-Zn-protoporphyrin with a hematofluorometer on blood samples from eighty-four lead-exposed individuals has been compared with a fluorometric determination of the extracted porphyrins. The results agreed well, and the interference from bilirubin and unchelated protoporphyrin was low. An exponential increase in erythrocyte protoporphyrin and a linear decrease in blood hemoglobin with increased blood lead was found in seventy-nine males with occupational lead exposure. The hematofluorometer is recommended as a useful tool in screening for lead poisoning.

Zinc Protoporphyrin and Blood Lead Levels (Letter)

A. Fischbein and R. Lilis. JOM 20(6):391, Jun 78.

In response to the paper by Barrett and Belk ["Blood Lead Study of Long Term Hand Soldering Operators," *JOM* 19:12, 1977], authors make the following comments on the (demonstrated) relationship between zinc protoporphyrin (ZPP) and blood lead levels. ZPP denotes a slightly delayed and persisting biological effect of lead, while blood lead reflects current and recent lead absorption; thus their plots show a curvilinear, not a linear relationship. A certain ZPP level is not always equivalent to a certain blood lead level because factors such as duration and intensity of lead exposure as well as time from cessation of exposure, if applicable, might account for differences. A recent study by the authors' laboratory showed significant correlations between both duration of exposure and ZPP and between duration of exposure and hemoglobin for a population exposed to low levels of lead (ironworkers repairing an elevated railway). But there was no correlation between duration of exposure and blood lead levels. Actual blood lead measurements would have been much more meaningful in exploring the relationship between ZPP and blood lead levels in the group of hand soldering operators.

Lead-Erythrocyte Protoporphyrin Correlation in Blood of Exposed Workers

F. Peter and R.G. Reynolds. HEALTH LAB SCI 15(3):144-9, Jul 78.

Authors' abstract: A systematic survey of blood samples from 174 industrial workers occupationally exposed to lead fumes and lead dust, revealed some poor correlations between the lead (Pb) level and the free erythrocyte protoporphyrin (FEP) level. In addition to those workers who had an expected correlation (normal Pb-normal FEP or elevated Pb-elevated FEP) there were two groups with atypical correlations. In one group a normal Pb level was associated with an elevated FEP level and in the other group an elevated Pb level was associated with normal FEP level. This shows that neither the Pb nor the FEP test can substitute for the other. Since the individual FEP response to Pb absorption is unpredictable, both tests should be carried out routinely. This would make it possible to determine simultaneously the degree of absorption (Pb level) and the degree of intoxication (FEP level) and would improve significantly the assessment of undue lead absorption of occupationally exposed workers. If, however, only one of these tests is used for screening, the other test should always be carried out as a confirmatory test when the screening detects an elevated Pb or FEP level.

Zinc Protoporphyrin in Blood as a Biological Indicator of Chronic Lead Intoxication

J. Eisinger, W.E. Blumberg, A. Fischbein, R. Lilis, and I.J. Selikoff. J ENVIRON PATHOL TOXICOL 1(6):897-910, Jul-Aug 78.

Authors' abstract: Traditionally, the diagnosis of lead intoxication has relied upon blood lead and urine lead determinations. However, metabolic changes in the biosynthetic pathway of heme as well as damage in other organ systems may occur at blood lead levels hitherto regarded

as "safe." Lead intoxication leads to elevated zinc protoporphyrin (ZPP) levels in the blood which can be measured quickly, inexpensively and conveniently on a drop of unprocessed whole blood by means of a dedicated front face fluorometer, called a hematofluorometer. In the present study, ZPP showed a strong correlation with the lead-in-blood level, as well as with signs and symptoms of lead-related disease. It is concluded that zinc protoporphyrin determination offers a preferred primary screening test for lead-exposed populations.

Fluorometric Determination of Erythrocyte Protoporphyrin in Blood, a Comparison Between Direct (Hematofluorometric) and Indirect (Extraction) Methods

F. Peter, G. Growcock, and G. Strunc. CLIN CHEM 24(9):1515-7, Sep 78.

Authors' abstract: We measured the concentration of erythrocyte protoporphyrin in 43 blood samples by two fluorometric methods. In the indirect method, protoporphyrin was extracted from blood and the fluorescence of the free acid in the extract was determined with a filter-fluorometer. These results were compared with results of direct determination of protoporphyrin in the same samples. In the direct assay the fluorescence of protoporphyrin, present in blood as the zinc salt, was measured without extraction, with the use of a hematofluorometer. Comparison of the results of the direct and indirect methods showed an excellent correlation ($r = 0.986$), but the hematofluorometric values (y) were approximately 9% lower than the fluorometric values ($y = 0.911x$). The slope of the regression line (0.911) is likely to be different for each hematofluorometer-fluorometer combination. Therefore, hematofluorometric values can only be compared with fluorometric values if the slope of the regression line is known and is used as a correction factor.

Interlaboratory Comparison of Results of Erythrocyte Protoporphyrin Analysis

K.W. Jackson. CLIN CHEM 24(12):2135-8, Dec 78.

Author's abstract: Each of 65 laboratories analyzed 10 whole-blood samples for erythrocyte protoporphyrin by one or more of several analytical procedures. These procedures were of two types: (a) extraction of protoporphyrin from the erythrocytes into ethyl acetate/acetic acid, re-extraction into hydrochloric acid, and fluorometric measurement; or (b) direct reading in a portable fluorometer (hematofluorometer), with no pretreatment of the blood sample. Interlaboratory correlation was generally poor, especially between laboratories using extraction procedures. Hematofluorometric results intercorrelated better, but they had a low bias as compared to the extraction approach. Nationwide standardization of the test is required to assure satisfactory interlaboratory performance and to identify laboratories whose results are sufficiently accurate to be used for interpretations according to guidelines set forth by the Center for Disease Control for erythrocyte protoporphyrin testing.

Some Factors Affecting the Utility of Bovine Blood as a Control Material in Lead-Screening Programs

Z. Penton and G. Bissell. CLIN CHEM 24(3): 504-6, Mar 78.

Authors' abstract: Bovine blood is used frequently as control material in interlaboratory comparisons for blood-lead analysis, but an erythrocyte protoporphyrin control material is needed. We present data on the rate of changes in blood lead and erythrocyte protoporphyrin in steers fed lead acetate. We also show, by comparison of fluorescence spectra with those of known compounds, that most of the porphyrin in lead-burdened steers probably exists as free protoporphyrin IX along with some zinc-complexed protoporphyrin IX. Bovine blood is suitable as an erythrocyte protoporphyrin control material for laboratories using acid extraction procedures, but not for the proficiency testing of laboratories using hematofluorometers.

Interlaboratory Comparison of Lead and Cadmium in Blood, Urine, and Aqueous Solutions

P.E. Paulev, P. Solgaard, and J.C. Tjell. CLIN CHEM 24(10):1797-800, Oct 78.

Authors' abstract: Analysis for lead and cadmium in biological liquids (blood and urine)

is difficult. Results of such analyses from five laboratories are compared for samples with known additions of lead and cadmium. The data, evaluated in terms of inter- and intralaboratory reproducibility and accuracy, suggest that laboratories should voluntarily participate in quality control programs. Users of routine laboratories are advised to use their own quality control program.

An Automated System for the Determination of Lead in Blood, Manganese in Urine and Nickel in Waste Water

M. Ikeda, I. Kaneko, T. Watanabe, N. Ishihara, and T. Miura. AM IND HYG ASSOC J 39(3):226-32, Mar 78.

From authors' abstract and conclusions: An automated system has been developed to analyze lead in blood, manganese in urine and nickel in waste water at a rate of 20 to 30 samples per hour. The analysis is based on direct chelation without digestion, extraction into methyl isobutyl ketone and flame atomic absorption spectrophotometry. The applicability of the system in the field of occupational and environmental medicine is discussed.

For determination of lead in blood, it appears reasonable to conclude that the automated system is useful to screen out those with high blood levels by picking up peaks which correspond to more than 30 μg of lead/dl of blood. A preliminary experiment with blood samples containing 50 and 100 μg (as lead)/dl of PbEDTA revealed that the lead could be quantitatively measured without any interference, indicating that the method is applicable also to the samples from a patient treated with Pb-chelating agents.

Analysis for Lead in Undiluted Whole Blood by Tantalum Ribbon Atomic Absorption Spectrophotometry

B.L. Therrell, Jr., J.M. Drosche, and T.W. Dziuk. CLIN CHEM 24(7):1182-5, Jul 78.

Authors' abstract: We describe a modified tantalum ribbon atomic absorption procedure for determining lead in undiluted whole blood. An Instrumentation Laboratory (I.L.) Model 151 atomic absorption spectrophotometer equipped with an I.L. Model 355 Flameless Sampler was used. The Flameless Sampler was slightly modified to include three-cycle operation instead of the normal two cycles. This modified single-beam system, equipped with background correction, allows 5-microliter specimens of whole blood to be quickly and accurately analyzed. No sample preparation other than vortex mixing is involved and method reliability has been demonstrated during an extended period of successful participation in proficiency testing studies conducted by the Center for Disease Control. This tantalum ribbon methodology has further been demonstrated to be effective both as a primary screening procedure and as a confirmatory procedure, when coupled with erythrocyte protoporphyrin determinations, in screening over 300,000 clients during a three-year period of use in the Early and Periodic Screening, Diagnosis and Treatment (EPSDT) Program in Texas.

The Paper Punched Disc Technique for Lead in Blood Samples with Abnormal Hemoglobin Values

G.F. Carter. BR J IND MED 35(3):235-40, Aug 78.

Author's abstract: A series of 15 blood samples with hemoglobin levels ranging from 4.6–16.1 g/dl were spotted on to Whatman No. 4 filter paper. Blood samples with low hemoglobin concentrations spread over a greater area of the filter paper than did those with high hemoglobin concentrations. This was further investigated by studying the performance of laboratory-prepared samples, and any effect on the estimation of blood lead value. Blood lead values assayed by the punched disc method on blood samples with low hemoglobin values were unreliable unless the estimated value was adjusted with respect to the area over which the blood had spread.

Lead in Enamel and Saliva: Dental Caries and the Use of Enamel Biopsies for Measuring Past Exposure to Lead

F. Brudevold, R. Aasenden, B.N. Srinivasian, and Y. Bakhos. J DENT RES 56(10):1165-71, Oct 77.

Authors' abstract: Enamel biopsies taken from schoolchildren in a community where exposure to lead was a health hazard were analyzed for lead and fluoride. The children with high enamel lead had significantly higher caries scores than the children with low enamel lead, in spite of the fact that the high lead group also was higher in enamel fluoride. There was no increase in enamel lead with age. The lead in saliva was only a fraction of that in blood. Infants with lead poisoning showed higher saliva lead than a normal infant. The use of the lead in enamel biopsies and in saliva for measuring exposure to lead is discussed.

Determination of Urinary Lead through Optic Emission Spectrography Using the Double-Arc Method (Italian)

G. Cecchetti and A. Iannoccone. ANN IST SUPER SANITA 13(1-2):367-76, 1977.

English summary: A new method for the determination of urinary lead by means of emission spectroscopy is described. The sample is concentrated by lyophilization and the homogeneous dust obtained is analyzed using the "double-arc" method. The matrix effects and source instability are compensated by the use of the internal standard. The influence of the volatilization of the elements of the analytical pairs is studied and the thallium-lead pair is selected. The method is reproducible and the detection limit is 5 μg/l of urinary lead.

Red-Cell Pyrimidine 5'-Nucleotidase and Lead Poisoning

H.A. Buc and J.C. Kaplan. CLIN CHIM ACTA 87(1):49-55, 1 Jul 78.

Authors' abstract: In an effort to determine its value as a biological index of lead poisoning, we investigated the red-cell pyrimidine 5'-nucleotidase (Py5N) activity, along with the classical parameters, in 22 subjects with varying degrees of lead intoxication. In all cases, the red-cell Py5N activity was found to be decreased, even when most of the other biological tests of lead intoxication remained negative. Below the level of 150 micrograms of lead per 100 ml of blood, the magnitude of the red-cell Py5N decrease was roughly proportional to the level of lead in peripheral blood. We conclude that red-cell Py5N is a convenient, reliable and sensitive index of lead exposure.

Heme Metabolites in Blood and Urine in Relation to Lead Toxicity and Their Determination

J.J. Chisolm, Jr. ADV CLIN CHEM 20:225-65, 1978.

This review article opens with a general discussion of the disturbances in the biosynthesis of heme due to lead. A detailed consideration of the dose-response relationships of lead in man follows. Experimental data on the interactions between lead and other trace metals affecting heme synthesis are reviewed. The clinical factors involved in the laboratory diagnosis of lead poisoning are considered, as well as the monitoring of populations with a high risk of lead poisoning and the monitoring of therapeutic responses in such populations. Finally the methods of biochemical analysis involved in these clinical problems are discussed.

Iron Deficiency

The Measurement of Free Erythrocyte Porphyrin (FEP) as a Simple Means of Distinguishing Iron Deficiency from Beta-Thalassemia Trait in Subjects with Microcytosis

J.A. Stockman III, L.S. Weiner, G.E. Simon, M.J. Stuart, and F.A. Oski. J LAB CLIN MED 85(1):113-9, Jan 75.

Authors' abstract: Assay of free erythrocyte porphyrin (FEP) and measurement of red cell indices were obtained in a group of subjects with iron deficiency and beta-thalassemia trait to determine if these studies could detect these disorders and discriminate between them. FEP values were increased in 90.2 percent of subjects with iron deficiency but were within the normal range in 96.6 percent of subjects with beta-thalassemia trait. Mean FEP values increased slightly as transferrin saturation fell but became abnormally elevated when the transferrin saturation was less than 15 percent. Unlike subjects with iron deficiency in whom the mean corpuscular volume varied from 46 to 84, all individuals with beta-thalassemia trait

exhibited microcytosis. In most instances, determination of FEP appears to distinguish beta-thalassemia trait from iron deficiency in patients with microcytosis.

The Micromeasurement of Free Erythrocyte Protoporphyrin as a Means of Differentiating Alpha Thalassemia Trait from Iron Deficiency Anemia

H.M. Koenig, A.L. Lightsey, Jr., and J.E. Schanberber. J PEDIATR 86(4):539-41, Apr 75.

Free erythrocyte protoporphyrin (FEP) levels were measured in 29 individuals with alpha thalassemia trait, 19 with proved iron deficiency anemia, and 25 normal control subjects. Individuals with alpha thalassemia trait and normal iron studies had FEP levels in the normal range despite marked degrees of microcytosis. In contrast, individuals with iron deficiency anemia had marked elevation of FEP levels with similar degrees of microcytosis. Measurement of FEP levels appears to be a useful tool in differentiating alpha thalassemia trait from iron deficiency anemia.

Erythrocyte Protoporphyrin in the Detection of Iron Deficiency

G.D. McLaren, J.T. Carpenter, Jr., and H.V. Nino. CLIN CHEM 21(8):1121-7, Jul 75.

Any decrease in the availability of iron for incorporation into the heme moieties of hemoglobin results in an increase in the erythrocyte protoporphyrin concentration. Authors compared protoporphyrin concentrations, determined spectrophotometrically, with body iron stores, as assessed from the amount of iron demonstrable by Prussian blue staining of bone marrow aspirates. The mean protoporphyrin concentration (175 μg/dl) in the erythrocytes of a group of patients with markedly decreased stainable marrow iron or no iron was significantly greater ($P < .001$) than the mean concentration (76 μg/dl) in a comparable group with adequate bone marrow iron stores, except in the presence of certain interfering conditions. These results suggest that the erythrocyte protoporphyrin test may be a useful addition to the methods now available for assessing disorders of heme synthesis, the most common of which is iron deficiency.

The Diagnosis of Iron Deficiency by Erythrocyte Protoporphyrin and Serum Ferritin Analyses

M.E. Koller, I. Romslo, P.H. Finne, F. Brockmeier, and I. Tyssebotn. ACTA PAEDIATR SCAND 67(3):361-6, May 78.

Authors' abstract: Free erythrocyte protoporphyrin (FEP) and serum ferritin have been determined in 57 healthy children and in 25 children with varying degrees of iron deficiency. FEP was found to be inversely correlated to the concentration of hemoglobin ($r = -0.80$) as well as to serum ferritin ($r = -0.64$). Elevated FEP was found in children with hemoglobin less than 12.5 g/dl, or serum ferritin less than 8 μg/l. In a group of apparently hematologically normal children between the age of 10–14 years (hemoglobin greater than 12.5 g/dl), a 2-month trial of iron medication resulted in an increase in hemoglobin and ferritin, and a decrease in FEP, indicating suboptimal supply of iron for hemoglobin synthesis before iron medication. In a patient with iron deficiency (FEP 15.3 μmole/l, hemoglobin 5.2 g/dl), iron therapy was followed by a rapid fall in FEP before any changes in hemoglobin, serum iron transferrin saturation and ferritin could be detected. The rapid fall in FEP during start of treatment in iron deficiency makes FEP a sensitive biochemical parameter on iron homeostasis in iron deficiency anemia.

Studies of Erythrocyte Protoporphyrin in Anemic Mutant Mice: Use of a Modified Hematofluorometer for the Detection of Heterozygoes for Hemolytic Disease

S. Sassa and S.E. Bernstein. EXP HEMATOL 6(5):479-87, May 78.

Authors' abstract: Erythrocyte protoporphyrin concentration was determined on a single drop of blood from normal and anemic mutant mice using a modified hematofluorometer. Mice showed age- and sex-dependent changes in protoporphyrin concentrations. Mice with hypoplastic anemias had a slight elevation and mice with iron deficiency anemia had a moderate

increase in red cell protoporphyrin. Those with inherited hemolytic anemias had a marked elevation of erythrocyte protoporphyrin. Mice heterozygous for hemolytic anemias had no overt hemolysis and reticulocytosis, yet their erythrocyte protoporphyrin concentrations were distinctly higher than their littermate controls. Previously these heterozygotes were differentiated only by laborious and expensive progeny testing. This paper is the first demonstration of a quick and practical way of detecting mice heterozygous for hemolytic anemias by erythrocyte protoporphyrin determination. The data of this study demonstrate not only the usefulness of the hematofluorometer for protoporphyrin determination in the diagnosis of mouse anemias, but also the significance of elevated erythrocyte protoporphyrin as a very sensitive indicator of increased erythropoiesis, or of iron deficiency.

Free Erythrocyte Porphyrins in Cord Blood

M.A. Gottuso, B.F. Oski, and F.A. Oski. J PEDIATR 92(5):810-2, May 78.

Authors' abstract: Red cell free erythrocyte porphyrin determinations were performed on cord blood specimens from 236 term infants and on capillary blood specimens from 63 preterm infants weighing less than 1,500 gm, during the first week of life. These results were contrasted with those obtained from 398 normal infants and children ages 1 to 6 years. The mean FEP value for the infants was significantly higher than that observed in the normal control subjects. In 10.5% of the term infants and 15.9% of the preterm infants, values in excess of 120 μg/dl RBCs, the highest value recorded in the normal subjects, were observed. Elevations in FEP values were not related to either blood lead concentration or hematocrit levels in the infants. Infants with elevated FEP values were found to have lower serum iron and transferrin saturation values than did infants with low FEP values. These findings suggest that elevations in cord blood FEP values may indicate a state of relative iron deficiency present at birth.

Predictive Values of Erythrocyte Indices for Tests of Iron, Folic Acid, and Vitamin B12 Deficiency

P.F. Griner and P.R. Oranburg. AM J CLIN PATHOL 70(5):748-52, Nov 78.

Authors' abstract: The probabilities of low transferrin saturation, folic acid, or vitamin B12 levels in association with various erythrocyte indices was determined from the prevalences of these abnormalities and the distributions of the indices among 206 hospitalized and 1,000 ambulatory anemic patients. At mean corpuscular hemoglobin (MCH) greater than 30 pg, the probability of low transferrin saturation was 0.04 for hospitalized patients and 0.14 for ambulatory anemic patients. For MCH less than 27 pg, the corresponding probabilities were 0.52 and 0.67. The probabilities of low vitamin B12 or folic acid levels among hospitalized anemic patients were 0.0011 for mean corpuscular volume (MCV) less than 95 cu micron and 0.18 for MCV greater than or equal to 95 cu micron, indicating that measurements of these vitamins are of very limited value in most cases of anemia. These findings indicate that in some patients, the erythrocyte indices are sufficiently predictive for or against deficiency states to facilitate decisions regarding further diagnostic tests, as opposed to the increasing tendency to order such tests regardless of the indices.

Serum Ferritin in Assessment of Iron Nutrition in Healthy Infants

U.M. Saarinen and M.A. Siimes. ACTA PAEDIATR SCAND 67(6):745-51, Nov 78.

Authors' abstract: We followed up 238 infants on 7 occasions during their first year of life. The diets of the infants were systematically either supplemented or not supplemented with iron. Developmental changes in serum ferritin were determined from a group with adequate intake of iron and without evidence of iron deficiency by three laboratory criteria: hemoglobin, mean corpuscular volume, and transferrin saturation. The data indicate that the average level of serum ferritin correlates well with iron nutrition within groups of infants since the developmental changes are in accordance with the known changes in storage iron, the level of serum ferritin correlates with iron intake, and low ferritin levels are associated with lower transferrin saturation. The usefulness of

serum ferritin as the sole criterion of iron deficiency in individual infants is limited, suggesting the use of more than one indicator to refine the diagnosis of iron deficiency without anemia.

Erythrocyte Protoporphyrin/Heme Ratio in the Assessment of Iron Status

R.F. Labbe, C.A. Finch, N.J. Smith, R.N. Doan, S.K. Sood, and N. Madan. CLIN CHEM 25(1):87-92, Jan 79.

Authors' abstract: The protoporphyrinemia of iron deficiency is well recognized. Clinically, information on the protoporphyrin/heme molar ratio in whole blood offers certain advantages over protoporphyrin measurement alone. A procedure for determining this ratio is reported. Protoporphyrin is extracted, solubilized, and measured fluorometrically. Heme (as hemin chloride) is precipitated with the blood proteins, the precipitate is dissolved in an alkaline/pyridine solvent, and the resulting bispyridine ferriprotoporphyrin is measured spectrophotometrically. The molar ratio of these two metabolites correlates well with values for plasma ferritin, plasma iron, transferrin saturation, hemoglobin, and hematocrit. In some cases the ratio increases detectably while the other variables, especially hematocrit and hemoglobin, remain normal. Evidently it is a more sensitive index to iron status. For healthy men and women, the mean ratio is 16.0 (SD, 5.3). The mean + 3 SD, or a ratio of 32, is distinctly abnormal, as shown by a confirmatory test. We validated the test by surveying routine blood specimens obtained from several population groups.

Percentile Curves for Hemoglobin and Red Cell Volume in Infancy and Childhood

P.R. Dallman and M.A. Siimes. J PEDIATR 94(1):26-31, Jan 79.

Authors' abstract: Percentile curves were calculated for hemoglobin and mean corpuscular volume in children between 0.5 and 16 years of age. The curves were derived from several populations of non-indigent white children who lived near sea level. Subjects were excluded from the reference population if they had laboratory evidence of iron deficiency, thalassemia minor, and/or hemoglobinopathy. The final reference populations included 9,946 children for the derivation of the hemoglobin curves and 2,314 for the MCV curves. The percentile curves should be particularly applicable to the diagnosis and screening of iron deficiency and thalassemia minor.

Anemia in Patients with Juvenile Rheumatoid Arthritis

M.A. Koerper, D.A. Stempel, and P.R. Dallman. J PEDIATR 92(6):930-3, Jun 78.

Authors' abstract: Patients with juvenile rheumatoid arthritis may have an anemia attributable to the chronic disease, to iron deficiency, or to a combination of the two. The contribution of iron deficiency is often difficult to determine by routine laboratory studies. We studied 51 patients with pauciarticular and polyarticular juvenile rheumatoid arthritis with red blood cell counts, indices, free erythrocyte protoporphyrin, and serum ferritin. Fifteen of the 18 who were anemic were restudied after a 3- to 6-month period of iron therapy. Thirteen of the 15 responded by these criteria: a rise in hemoglobin of 1.0 gm/dl or more and an increase in mean corpuscular volume of 3 fl or more; in 11 of these 13, hemoglobin values returned to the normal range for age. These findings indicate that iron deficiency can be a major component of the anemia that is commonly found in patients with active juvenile rheumatoid arthritis.

Heme Biosynthesis in Rheumatoid Disease

B.C. Campbell, N. Rennie, G.G. Thompson, M.R. Moore, and A. Goldberg. BR J HAEMATOL 40(4):563-9, Dec 78.

Authors' abstract: The activities in blood of six enzymes of the heme biosynthetic pathway have been determined in 12 patients with rheumatoid disease, six of whom were anemic. The porphyrin and porphyrin-precursor intermediary products of heme biosynthesis were also determined in blood, urine and feces. No significant differences were found between anemic and non-anemic subjects. Failure of delta-amino-levulinate synthase activity to in-

crease in response to anemia may be the nature of the marrow unresponsiveness suggested as one factor in the causation of the anemia. Normal ferrochelatase activity and normal concentrations of free protoporphyrin support the view that iron is effectively unavailable although present in normal amounts. Coproporphyrinogen oxidase activity was significantly depressed.

Effects of Iron Deficiency Exclusive of Anemia

P.R. Dallman, E. Beutler, and C.A. Finch. BR J HAEMATOL 40(2):179-84, Oct 78.

Authors' conclusions: Despite the high incidence of iron deficiency, research in this area has been limited, perhaps because iron deficiency is accepted as a relatively benign condition. However, improved understanding of food-iron absorption and the feasibility of more effective fortification now makes it important to know the cost of iron deficiency in respect to ill health. Our understanding of the tissue effect of iron deficiency is particularly incomplete. With the development of experimental animal models one can now evaluate, under carefully controlled conditions, the functional abnormalities produced by iron deficiency and their biochemical basis. Once a specific abnormality and its effects are defined, it can be evaluated to the extent that is possible in man. The pathophysiology of iron deficiency clearly involves more than the roles of hemoglobin and storage iron. A better understanding of the effects of iron deficiency on tissues may add impetus to the development of sound strategies for the prevention and treatment of this common disorder.

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EPIDEMIOLOGY

Levels of Lead and Other Metals in Human Blood: Suggestive Relationships, Determining Factors

R.L. Zielhuis, P. del Castilho, R.F. Herber, and A.A. Wibowo. ENVIRON HEALTH PERSPECT 25:103-9, Aug 78.

Authors' abstract: Epidemiological studies on metal levels in blood were carried out. Evidence suggested the existence of a different trend in serum-iron levels in relation to blood lead levels in nonoccupationally exposed males (negative trend) and females (positive trend). There was a positive relation between blood lead levels and blood manganese levels in children and occupationally exposed male workers. Blood metal levels increased with age in young children. There was evidence for an influence of socioeconomic class on blood lead levels in children. A direct and an indirect effect of smoking was found on blood lead levels and on the activity of delta-aminolevulinic acid dehydratase activity in erythrocytes in adult nonoccupationally exposed females.

Absorption and Retention of Lead by Infants

E.E. Ziegler, B.B. Edwards, R.L. Jensen, K.R. Mahaffey, and S.J. Fomon. PEDIATR RES 12(1):29-34, Jan 78.

Authors' summary: Eighty-nine metabolic balance studies were performed with 12 normal infants ranging in age from 14-746 days. Intake and fecal and urinary excretions of lead were determined and net absorption and net retention were calculated. Subjects were fed milk or formula and commercially prepared strained foods. Intakes of lead ranged from 0.83-22.61 μg/kg/day with a mean of 9.43 μg/kg/day. Urinary excretion averaged 1.02 (SD 0.68) μg/kg/day and was positively correlated with lead intake. Fecal excretion was highly correlated with intake of lead; fecal excretion exceeded intake in 10 studies. In 61 balance studies with lead intakes greater than 5 μg/kg/day, net absorption averaged 41.5% of lead intake and net retention averaged 31.7% of intake.

Retention of lead was highly correlated with lead intake. Urinary plus fecal excretion of lead exceeded intake in 19 of 28 balances in which lead intakes were less than 5 μg/kg/day. Absorption and retention of lead were inversely correlated with intake of calcium. Absorption and retention of lead accounted for greater percentages of intake of lead in this study of infants and young children than have been reported in studies of older subjects.

Highly efficient absorption and retention of ingested lead by young children may be partly responsible for the high prevalence of lead intoxication in this age group.

Placental Transfer of Lead, Mercury, Cadmium, and Carbon Monoxide in Women. I. Comparison of the Frequency Distributions of the Biological Indices in Maternal and Umbilical Cord Blood

R. Lauwerys, J.P. Buchet, H. Roels, and G. Hubermont. ENVIRON RES 15(2):278-89, Apr 78.

Authors' abstract: In 1975 and 1976 we have undertaken a survey among 500 pregnant women living in different areas of Belgium in order to evaluate the extent of exposure to heavy metals (lead, mercury, cadmium) during

fetal life, their possible biological effects, and the epidemiological factors which may influence the intensity of exposure.

Carboxyhemoglobin level was also determined. Comparison of the frequency distributions of the various hematological indices in maternal and umbilical cord blood indicates that the three heavy metals are transferred from the mother to the fetus but the barrier role of the placenta is different for the three metals. There is no barrier for the transfer of mercury, a slight one for lead, and a more important one for cadmium. This explains why the correlation found between the cadmium concentration in maternal (Cd-B) and fetal blood is much lower (although statistically significant; $r = +0.38$) than that found for lead and mercury ($r > 0.6$). For the range of blood lead concentrations (Pb-B) observed in the mothers and their newborns, there is no significant correlation between Pb-B and erythrocyte porphyrin level. On the contrary, because of its high sensitivity to lead, the erythrocyte enzyme δ-aminolevulinate dehydratase (ALAD) is negatively correlated with Pb-B in mother and newborn. The correlation is higher when ALAD activity is expressed in percent of its activity found in presence of the reactivator dithiothreitol rather than in absolute values. Carboxyhemoglobin levels (HbCO) of mother and newborn are highly correlated ($r = +0.81$, $P < 0.001$). In mother, HbCO is also slightly correlated with Cd-B ($r = +0.29$, $P < 0.001$) which suggests that both pollutants come at least partly from a similar source (smoking).

Because of the different barrier effect of the placenta for CO and Cd no significant correlation between both parameters is found in newborns.

Placental Transfer of Lead, Mercury, Cadmium, and Carbon Monoxide in Women. II. Influence of Some Epidemiological Factors on the Frequency Distributions of the Biological Indices in Maternal and Umbilical Cord Blood

J.P. Buchet, H. Roels, G. Hubermont, and R. Lauwerys. ENVIRON RES 15(3):494-503, Jun 78.

Authors' abstract: We have investigated the influence of various epidemiological factors (smoking habits, residence, age, occupation, drinking habits, duration of pregnancy, number of previous pregnancies) in the exposure of 474 European pregnant women and their newborns to lead, mercury, cadmium, and carbon monoxide. Smoking has a statistically significant influence on carboxyhemoglobin level in mothers and newborns and on cadmium concentration in maternal blood. The association of smoking with a reduction of fetal weight was confirmed. A slight but statistically significant effect of environmental pollution by lead (urban and industrial > semirural > rural area) on lead uptake by the pregnant mothers and its transfer to their fetuses was demonstrated. Some results suggest that during pregnancy lead could be mobilized from maternal tissue depots, but further investigations are required to confirm this tentative conclusion. No significant relationships were found between the other epidemiological parameters and the various biological measurements performed on mother and cord blood.

Placental Transfer of Lead, Mercury, Cadmium, and Carbon Monoxide in Women. III. Factors Influencing the Accumulation of Heavy Metals in the Placenta and the Relationship between Metal Concentration in the Placenta and in Maternal and Cord Blood

H. Roels, G. Hubermont, J.P. Buchet, and R. Lauwerys. ENVIRON RES 16(1-3):236-47, Jul 78.

Authors' abstract: The concentration of lead, mercury, and cadmium was determined in placenta from 474 European women and was compared with the level found in maternal and newborn blood. The influence of some epidemiological factors (residence, smoking, drinking habit, age, occupation, previous pregnancies) on heavy metal accumulation in the placenta was also investigated. The median values of the three heavy metals in placenta were 7.5, 1.06, and 1.08 μg/100 g (wet weight) for lead, mercury, and cadmium, respectively. In comparison with maternal blood, the placenta does not concentrate lead nor mercury but concentrates cadmium about 10-fold. Cadmium concentration in placenta was significantly correlated with that in maternal blood ($r = +0.38$); for lead the correlation was lower although still statistically

significant (r = +0.22); for mercury the level in placenta was not significantly correlated with the metal concentration in maternal blood. Among the three heavy metals, only cadmium shows an increased accumulation in placenta of smokers. No significant effect of current residence, maternal age, and occupation on the accumulation of the heavy metals in placenta was observed.

Interactions of Lead Poisoning and Vitamin E Deficiency

O.A. Levander, V.C. Morris, and R.J. Ferretti. CLINICAL CHEMISTRY AND CHEMICAL TOXICOLOGY OF METALS, pp. 23-6. Amsterdam: Elseveier/North-Holland, 1977.

From authors' results and conclusions: Lead poisoning caused a 140% increase in spleen size and a 19% decrease in hematocrit value in vitamin E-deficient rats. On the other hand, lead poisoning caused only a 40% increase in spleen size and a 10% decrease in hematocrit value in vitamin E-supplemented rats. Vitamin E deficiency per se had little or no effect on the spleen size or hematocrit value of rats not poisoned with lead. The anemia observed in the E-deficient lead-poisoned rats was due to a defect in the circulating red cells rather than to a defect in red cell production.

These results demonstrate that the nutritional status with regard to vitamin E is an important factor in determining the response to lead poisoning. The data are consistent with the hypothesis that red cells from E-deficient lead-poisoned rats tend to undergo the discocyte-spherocyte transition readily as a result of membrane loss due to lipid peroxidation. The spherocytes formed thereby are rigid bodies which are unable to negotiate the microvasculature of the splenic filter bed. This hypothesis accounts for the increased splenomegaly and red cell mechanical fragility and decreased erythrocyte deformability observed in E-deficient lead-poisoned rats. An assessment of vitamin E nutriture should be part of any epidemiological study of the hematological aspects of lead poisoning.

Interactions of Lead, Calcium, Vitamin D, and Nutrition in Lead-Burdened Children

M. Sorrell and J.F. Rosen. ARCH ENVIRON HEALTH 32(4):160-4, Jul-Aug 1977.

Authors' abstract: This study was undertaken to evaluate relationships between blood or serum levels of lead (Pb), calcium, and 25-hydroxyvitamin D (25-OHD), within the framework of a nutritional survey of lead-burdened children. The results demonstrate that: regardless of blood Pb concentration and season of the year, serum 25-OHD concentration reflects vitamin D intake; high blood Pb ($\geq$ 60 μg/dl) was associated with decreased levels of 25-OHD (18±1 ng/ml vs. 32±1 in controls, $P < .001$); concentrations of Pb and calcium were inversely correlated in control and lead-burdened children; and children in the high blood Pb group ($\geq$ 60 μg/dl) had lower mean daily intakes of both calcium (610±20 mg vs. 770±20 in controls, $P < .001$) and vitamin D (210±17 IU vs. 325±20 in controls, $P < .001$). These data indicate that, in Pb-burdened children, multiple factors modify the absorption and toxicity of Pb, and relative vitamin D deficiency, not excess, is associated with high blood Pb levels. Assessment of nutrition, calcium metabolism and vitamin D status is recommended in evaluating children known to have undue absorption of Pb.

Monitoring of Lead in the Environment

I.B. Millar. J EPIDEMIOL COMMUNITY HEALTH 32(2):111-6, Jun 78.

Autnor's abstract: Children living near a lead works and children of employees at the works were selected in order to analyze the lead content of their blood as the biological counterpart of a monitoring exercise for lead in the environment. The overall mean for the 262 children in the survey was 0.91 μmol/l and results were within the normal reference range of 0.3 to 1.8 for all except two children. The results compared favorably with similar areas, and with a survey in the same area in 1972. The mean for the 71 children of employees at the lead works was 1.02 μmol/l, significantly higher than the mean for the other children in the

survey (0.88 μmol/l). No appreciable differences were found in housing or wind direction. The means for all groups were unexceptional, but some of the differences were significant. Younger children had significantly higher blood lead levels than older children, and the group of 26 children with levels of 1.3 μmol/l or more was doubly weighted with the youngest age group. After careful investigation, no deviations from normal health were found in this group. The weighting of younger children also contributed to the significance of the higher mean found for children living in the central half of the area.

The Summer Disease. Some Field Evidence on Seasonality in Childhood Lead Poisoning

J.M. Hunter. SOC SCI MED 12(2D):85-94, Jun 78.

Author's abstract: Blood leads of 32 well children measured before and after the summer show a significant elevation indicating that circulating lead is seasonally mobilized from the body burden. In a larger sample of 243 well children, white, black and chicano, of mean age 36 ± 16 months, tested for blood leads, analysis reveals a close correlation between month of birth and lead level; spring-born and summer-born children constitute low and high blood-lead groups, respectively. Seasonal variations of placental transfer of lead to the fetus is implicated, as are other factors. Density of skin pigments affecting biosynthesis of vitamin D apparently causes seasonality variations among the three ethnic groups. The seasonality factor accounts for 16% of explained variance of blood-leads of black children, 12% for chicano, and 4% for white children. Public health screening programs should ideally be conducted in summer to identify the maximum number of children at risk. Where year-round readings are taken, proportional adjustments should be made in the order of 30-50% to allow for summer elevations. Physicians should be particularly alerted to summer elevations in black children.

Tooth Lead Levels in Birmingham

A.C. Mackie, R. Stephens, and A. Townsend. ARCH ENVIRON HEALTH 32(4):175-85, Jul-Aug 77.

Authors' abstract: The mean lead content of deciduous teeth from children living in the city of Birmingham (U.K.) has been shown to be 11.8 ppm dry weight, irrespective of the sex of the donor. Lead content varies according to type of tooth, and there is a gradient from incisors, with the highest level, to second molars, with the lowest. A relationship was shown between age of donor and lead content of canines and (when lognormalized data were considered) first molars. We were not able to demonstrate a correlation between tooth lead levels and residence near a potential industrial lead source, and we conclude that pollution from a general source is responsible for the body burdens we found.

Lead in Deciduous Teeth of Norwegian Children

G. Fosse and N.P. Justesen. ARCH ENVIRON HEALTH 33(4):166-75, Jul-Aug 78.

Authors' abstract: Two thousand two-hundred and thirty-three deciduous teeth were collected from cities, industrialized areas, and rural and fishing communities in several Norwegian counties. Teeth from Medieval Bergen were also included. Lead analysis of whole teeth revealed that in Norway there are many communities where lead absorption is minimal and comparable to background absorption in ancient societies. Such conditions are reflected in a lead level of 2.92 μg/g in deciduous teeth. However, the analysis also revealed that urbanization and industrialization increased lead absorption, although the mean level recorded in Norway of 3.73 μg/g was far lower than normal levels found in other countries. Automobile exhaust was reflected as an important source of undue lead absorption. This study indicated that 0.18% of Norwegian children from the ages of 7 to 12 years may have been victims of undue absorption, reflected in a tooth lead level of about 70 μg/g.

The Investigation of Lead Levels in Vertebra and Rib Samples (German)

L. Ulrich. ARCH TOXICOL 41(2):133-48, 11 Dec 78.

English summary: The dithizone extraction method has been applied in the determination of

lead content in human bones. The lead in 21 samples of fresh vertebrae and ribs from autopsies is compared with the lead content of historical bones of 17 skeletons from 600-800 A.D. The preparation and the direct mineralization of the bones are presented. The lead content detected in the ash of bones is too low compared with the value found by direct wet mineralization of the bones. During the dry ashing process with temperatures of 500°C or higher, lead may be lost. For the same person the lead content of rib is always lower than the value found in vertebra. The difference of the lead content of fresh bones and the historical bones is small. In both groups the lead content in the bones increased with age. Compared with studies of other authors in the period 1930-1970, the results would suggest that the present intake of lead in randomly selected bones among a population situated in an appointed area is not greater than in the past.

Lead Retention in Ancient Nubian and Contemporary Populations

P. Grandjean, O.V. Nielsen, and I.M. Shapiro. J ENVIRON PATHOL TOXICOL 2(3):781-7, Jan-Feb 79.

Authors' abstract: The lead concentration in bone and tooth has been determined in 105 well-preserved Nubian skeletons from the period 3300 B.C.-750 A.D., as well as in 17 individuals from present-day Denmark. The analyses were performed blind in two different laboratories, and the results were in close agreement. Compared to contemporary lead levels in Denmark, the oldest Nubian bones contained about 10 times less lead, while the teeth contained about 30 times less lead. Small increases in lead retention of Nubians during historical time periods were associated with early uses of lead.

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RESEARCH AND EVALUATION

Factors Influencing Metabolism and Toxicity of Metals: A Consensus Report

G.F. Nordberg, B.A. Fowler, L. Friberg, A. Jernelov, N. Nelson, M. Piscator, H.H. Sandstead, J. Vostal, and V.B. Vouk. ENVIRON HEALTH PERSPECT 25:3-41, Aug 78.

From authors' summary, general conclusions, and recommendations: The present meeting [organized by the Scientific Committee on the Toxicology of Metals under the Permanent Commission and International Association on Occupational Health] was organized to examine relationships between metals like lead, cadmium, and mercury and other factors which quantitatively and qualitatively modify their metabolism and toxicity. The necessity of such considerations is partly due to the fact that man is simultaneously exposed to a number of toxic elements and previous experience indicating that interactions of possible health significance do occur.

General conclusions reached at the meeting were that there was ample evidence from animal experiments that a number of interactions occur, and that it is not realistic to consider the toxicology of a single metal by itself without considering such modifying factors. The available data made it obvious that the effects of these major toxic elements could be influenced by interactions with each other and with essential elements. In addition to the above considerations, the effects of various other factors (age, sex, certain nutrients, irritating substances, smoking, etc.) on the toxicity of these specific metals were discussed. From the data available to the group, it seemed the age factor was of particularly great importance.

Long-term, low-level exposure studies employing many different animal species should be conducted to evaluate interactions among the metals discussed (arsenic, cadmium, lead, and mercury). Routes of administration should include exposures similar to those encountered by human population. The effects of essential elements and other nutrient intake at deficient, marginal and nutritionally adequate levels should be studied in relation to the metabolism and toxic manifestations of arsenic, cadmium, lead and mercury. Lead and iron interactions, for example, should be further studied with regard to nutritional status, age, sex, and body iron stores (tissue and serum ferritin and serum iron). [Other areas for study and consideration are outlined.]

Investigations of Factors Influencing Exposure and Response to Lead, Mercury, and Cadmium in Man and in Animals

H.A. Roels, J.P. Buchet, A. Bernard, G. Hubermont, R.R. Lauwerys, and P. Masson. ENVIRON HEALTH PERSPECT 25:91-6, Aug 78.

Authors' abstract: The susceptibility of the heme biosynthetic pathway to lead, as reflected by increased free erythrocyte porphyrin (FEP) concentration, is in humans as well as in rats in the order of young greater than or equal to female greater than male. The difference between adult male and female rats can be explained at least partially by the interaction of estradiol and progesterone with the FEP response to lead; the hormonal influence of FEP does not seem to be mediated through changes in plasma iron. The classical "tubular

type" proteinuria in workers chronically exposed to cadmium has two not necessarily concomitant components, namely, a tubular type and glomerular type component characterized by increased excretion of low and high molecular weight proteins, respectively. No synergistic effect of cadmium and lead on the proteinuria of workers simultaneously exposed to both metals was observed. Mercury (most likely methylmercury) is freely transferred from the mother to the fetus; there is only a slight placental barrier for lead and a rather strong one for cadmium. Compared to maternal blood, placenta does not accumulate lead or mercury but concentrates cadmium about 10-fold.

Effects of Calcium on the Absorption and Retention of Lead

J.L. Barton, M.E. Conrad, L. Harrison, and S. Nuby. J LAB CLIN MED 91(3):366-76, Mar 78.

Authors' abstract: An inverse relationship between lead retention and dietary calcium content has been known to exist for many years, but the reasons for this association remained unknown. In rats, the manipulation of dietary calcium had no significant effect upon the absorption of lead, but calcium-deprived animals had decreased excretion and thus increased body retention of lead. Intraluminal calcium decreased the absorption of test doses of lead from the small intestine in a dose-related manner. We postulated that this occurred because the two metals competed for similar binding sites on intestinal mucosal proteins which were important in the absorptive process. In vivo, lead bound to two heat-stable intestinal mucosal fractions which have been shown to bind calcium. Although more lead bound to the higher molecular weight fraction and more calcium bound to the lower molecular weight vitamin D-induced CaBP, substantial amounts of lead and calcium were found in both fractions. Further, the addition of calcium to test doses of lead markedly diminished the amount of lead bound by both fractions. Shared binding sites on absorptive proteins would explain why dietary calcium decreases lead absorption.

Copper, Manganese, Zinc, Nickel, Cadmium and Lead in Human Fetal Tissues

C.E. Casey and M.F. Robinson. BR J NUTR 39(3):639-46, May 78.

Authors' abstract: Concentrations of copper, manganese, zinc, nickel, cadmium and lead were measured in samples of liver, kidney, brain, heart, lung, skeletal muscle and vertebral bone from forty fetuses of 23-43 weeks gestation. Copper concentrations in the liver were up to 100 times those in other tissues, but only those in the brain showed a significant increase with gestational age. Manganese concentrations were similar in all tissues; the over-all range was 0.35-9.27 μg/g dry matter (DM). Concentrations of zinc in the liver were much higher than in other tissues and decreased with gestational age, whereas levels in skeletal muscle increased. In all tissues nickel concentrations were within the range 0.04-2.8 μg/g DM and levels in kidney and muscle decreased significantly with age. Cadmium was detected in most of the tissue samples and concentrations were within the range 0.01-0.58 μg/g DM. Concentrations of lead, where it was detected, varied from 0.1 to 2.4 μg/g DM in the soft tissues and from 0.4 to 4.3 μg/g DM in the bone samples.

Interrelationships among Zinc, Copper, Lead, and Cadmium in Food, Feces, and Organs of Humans

K. Tsuchiya and S. Iwao. ENVIRON HEALTH PERSPECT 25:119-24, Aug 78.

Authors' abstract: Concentrations of zinc, copper, lead, and cadmium were determined in 20 samples of food collected over a period of 20 days, 221 samples of feces collected over a period of 5 days from 19 males, 17 females, and 11 children and 85 samples each of renal cortex and liver from autopsied human cadavers in order to investigate the relationships among the four metals and among the various matrices. In food the highest correlation was observed between copper and zinc (0.34). In feces the highest correlation was also between copper and zinc (0.45). In the liver the highest correlation was between cadmium and zinc (0.33), but that in the renal cortex was between copper and

cadmium (0.52). These findings suggest that the relationships among the concentrations of the four metals in food and feces are almost equal to each other, but differ greatly from the concentrations in human organs due to the differing metabolic actions of the metals once they are absorbed into the body. In addition, it was observed that zinc and cadmium concentrations in the renal cortex increase with age, but copper and lead concentrations do not show much variation with age.

Metabolic Interactions between Metals and Metalloids

O.A. Levander. ENVIRON HEALTH PERSPECT 25:77-80, Aug 78.

Author's abstract: The experimental evidence obtained with laboratory animals which shows that the toxicities of lead, cadmium, and mercury can be increased by deficiencies of certain essential nutrients such as calcium, iron, zinc, and selenium is briefly reviewed. An idealized theoretical model which indicates the possible influence of multiple nutritional deficiencies on the toxicity of a heavy metal is presented. It is suggested that multiple marginal nutritional deficiencies may be of importance in determining the response of humans to the toxic effects of various heavy metal pollutants.

Interactions among Lead, Cadmium, and Arsenic in Relation to Porphyrin Excretion Patterns

B.A. Fowler and K.R. Mahaffey. ENVIRON HEALTH PERSPECT 25:87-90, Aug 78.

Authors' abstract: This paper reviews the effects of lead (Pb), cadmium (Cd), and arsenic (As) on the mitrochondrion with emphasis on alteration of mitochondrial heme biosynthetic pathway. The information was used to examine results of a Pb *X* Cd *X* As interaction study which employed urinary porphyrin excretion patterns as one assessment criterion. Data from the study showed that dietary Pb produced increased urinary excretion of aminolevulinic acid (ALA) and coproporphyrin. Dietary exposure to organic or inorganic As caused increased excretion of uroporphyrin and to a lesser extent coproporphyrin, while dietary Cd caused no significant changes in urinary levels of any of the porphyrins measured. The combination of Pb plus As produced an additive effect of coproporphyrin excretion but not that of either ALA or uroporphyrin. These data are discussed in relation to utilization of urinary porphyrins for assessing toxicity and elemental interactions.

Some Observations on the Interaction of Zinc, Copper, and Iron Metabolism in Lead and Cadmium Toxicity

H.G. Petering. ENVIRON HEALTH PERSPECT 25:141-5, Aug 78.

Author's abstract: A brief review of the literature indicates that nutritional deficiencies have been shown to increase the absorption and toxicity of orally ingested lead and cadmium. Results from recent studies indicate that low level oral ingestion of cadmium and lead perturbs the metabolism of zinc, copper, and iron and that these changes may be the earliest manifestation of the toxicity of lead and cadmium. The significance of these findings reveals itself in two ways: namely, the toxicologic investigations of lead and cadmium, whether experimental or clinical, must be based on a definitive consideration of the nutritional status of animals or people, and, secondly, that the preventive role of nutrition, especially that of trace metal intakes, must be taken seriously when establishing measures for reducing, eliminating, or combatting the toxic effects of widespread exposure to lead and cadmium in humans.

Research Review. Interactions Between Environmental Chemicals and Drug Biotransformation in Man

A.P. Alvares. CLIN PHARMACOKINET 3(6):462-77, Nov-Dec 78.

From author's abstract: Many factors influence the metabolism of drugs in man. Besides genetic factors, environmental factors may play a significant role in explaining the variation observed in the rates of drug metabolism between different individuals. Intentional or unintentional exposure to environmental chemicals could enhance or inhibit the activity of hepatic mixed function oxidases that metabolize drugs and other foreign chemicals, as well as

endogenous substrates such as steroid hormones. A major source of such exposure may be occupational. Exposure to the heavy metal, lead, has been shown to inhibit drug metabolism; whereas intensive exposure to chlorinated insecticides, and other halogenated hydrocarbons such as polychlorinated biphenyls, has been shown to enhance the metabolism of test drugs such as antipyrine and phenylbutazone. Such intentional or unintentional exposure to environmental chemicals which may alter the rates of drug metabolism in man indicates the importance of individualization of drug therapy.

The Porphyrins (7 Volumes)

D. Dolphin, ed. New York: Academic Press, 1978.

From editor's general preface: It is the objective of "The Porphyrins" to present a full and critical coverage of all the major fields relating to porphyrins, their precursors, catabolic derivatives, and related systems in a manner that we trust will be useful to those in physics, chemistry, biochemistry, and medicine.

The treatise consists of seven volumes. Volumes I and II (Structure and Synthesis, Parts A and B) cover nomenclature, history, geochemistry, synthesis, purification, and structural determination of porphyrins, metalloporphyrins, and mono- and polypyrrolic compounds and related systems. Volumes III, IV, and V (Physical Chemistry, Parts A, B, and C) cover electronic structure and spectroscopy including uv-vis, ORD, CD, MCD, mass, ir, resonance Raman, Mossbauer, Zeeman, nmr (diamagnetic, paramagnetic), esr, and X-ray crystallography. In addition, redox chemistry, electron transfer, aggregation, oxygenation, and solid state phenomena are included. Volumes VI and VII (Biochemistry, Parts A and B) cover the biosynthesis and enzymatic synthesis of porphyrins, chlorophylls and their precursors, and the chemistry and biochemistry of the bile pigments and the roles of porphyrins and bile pigments in clinical chemistry. The structure and function of the major hemoproteins are also covered.

Delta-Aminolevulinic Acid: Influences on Synaptic GABA Receptor Binding May Explain CNS Symptoms of Porphyria

W.E. Muller and S.H. Snyder. ANN NEUROL 2(4):340-2, Oct 77.

Authors' abstract: Symptoms of acute porphyria have been attributed to effects of delta-aminolevulinic acid (ALA). We report that ALA selectively competes for the binding of tritiated gamma-aminobutyric acid ([^{3}H]GABA) associated with synaptic GABA receptors in central nervous system membranes. Concentrations of ALA that inhibit GABA receptor binding are consistent with levels of ALA thought to exist in the central nervous system of porphyric patients. Some of the symptoms of acute porphyria resemble those elicited by muscimol, a potent GABA agonist drug. Barbituates, which exacerbate porphyric symptoms are potent facilitators of the synaptic actions of GABA. The results suggest that some symptoms of acute porphyria might be attributable to a mimicking by ALA of GABA at its central nervous system receptor sites.

Morphologic Features of Erythrocytes in Normal Subjects and in Anemia Caused by Lead Poisoning (Electron Microscopic Study) (Russian)

Iu.D. Batsura, G.G. Kruglikov, V.D. Arutiunov, and I.A. Gribova. ARKH PATOL 40(5):41-8, 1978.

English summary: The methods of scanning and transmission electron microscopy were used to study erythrocytes from normal subjects and those suffering from anemia of lead poisoning genesis. Erythrocytes from normal subjects were shown to have predominantly convex-concave and biconcave shapes. An insignificant portion of aging erythrocytes of spherical shape and decreased volume had granular surface and consolidated hemoglobin. Normally, in addition to the above-mentioned cells, erythrocytes with an abnormal relief occur: with perforating openings, crypt-like recesses, tubercles and processes. In anemia, the number of atypical erythrocytes increases many-fold. The process of sequestration and fragmentation of hemoglobin-containing particles is one of the mechanisms of anemia development.

General Subcellular Effects of Lead, Mercury, Cadmium, and Arsenic

B.A. Fowler. ENVIRON HEALTH PERSPECT 22:37-41, Feb 78.

Author's abstract: Documented metal-induced alterations in nuclear, mitochondrial, microsomal, and lysosomal functions are discussed in relation to their potential impact on cellular responses to other environmental agents. Each of the above elements has been found to interfere with normal cellular replication and genetic processes. Mitochondrial swelling and depression of respiratory function are discussed in relation to known metal-specific perturbations of mitochondrial heme biosynthetic pathway enzymes. Inhibition of microsomal enzyme activities and protein synthesis by lead and mercury is compared to the apparent absence of such effects following arsenic or cadmium exposure. Lysosomal uptake of all the metals is documented, but biochemical alterations in these structures have been reported for only mercury and cadmium. It is concluded that these toxic metals are capable of interacting with, and biochemically altering major cellular systems at dose levels below those required to produce signs of overt metal toxicity. The impact of these effects on cellular response to other metals and xenobiotics in complex exposure situations is presently unknown, and further research is urgently needed in this area.

Subcellular Mechanisms of Lead Neurotoxicity

E.K. Silbergeld and H.S. Adler. BRAIN RES 148(2):451-67, 16 Jun 78.

Authors' summary: The neurotoxic effects of inorganic lead (Pb) involve inhibition of calcium-dependent acetylcholine release and increases in calcium-dependent dopamine release. These apparently differential effects of Pb are associated with differing Pb-calcium (Ca) interactions: Pb blocks ^{45}Ca binding to peripheral cholinergic ganglia and increases ^{45}Ca binding to synaptosomes prepared from caudate nucleus (CN). Pb-induced increases in CN ^{45}Ca binding did not result from non-specific disruption of selective ion permeability of the membrane. Also, the Na-K ATPase-linked Ca extrusion system of synaptosomes was not affected by Pb. A Pb-sodium (Na) interaction was found such that elevation of intrasynaptosomal Na reversed effects of Pb on ^{45}Ca binding. The intracellular localization of this effect appeared to be primarily at the mitochondrial level. Pb inhibited Na-induced release of ^{45}Ca from preloaded mitochondria. This action may be translated into increased transmembrane flux of exogenous Ca, and thence into increased exocytotic events at the synapse. The apparently neurotransmitter-specific effects of Pb, cholinergic inhibition and dopaminergic augmentation, are hypothesized to result from different Pb-Ca interactions which are determined by the specific localization of Pb within nerve endings.

Neuropathology of Heavy Metal Intoxication

M.R. Krigman. ENVIRON HEALTH PERSPECT 26:117-20, Oct 78.

From author's introduction and conclusion: Neurotoxicity may be an important feature of heavy metal intoxication. This report will be confined to a consideration of the morphologic changes, or so-called pathology of heavy metal [lead, cadmium, arsenic, alkylmercury, and manganese] neurotoxicity.

Neuropathologic studies of toxicants such as heavy metals are dependent upon recognition of cellular changes and altered ultrastructure. Traditionally, these studies have been based upon recognizing qualitative differences; however, few studies have attempted to define in a quantitative manner these differences. Contemporary neuropathologic studies, particularly those related to neurotoxicology, will have to include objective quantitative structural analyses which can be subjected to statistical analysis. Such morphometric studies are necessary not only for demonstrating and defining the subtle undue burdens of toxicants but for demonstrating the full range of effects. Quantitative base-line date are needed for determining the potential for regeneration and distinguishing between aging and toxic effects.

Potential Uses of Lead Isotope Ratios in Gunshot Cases

B. Keisch and R.C. Callahan. J ASSOC OFF ANAL CHEM 61(3):520-5,May 78.

Authors' abstract: The determination of lead isotope ratios in 14 bullets, and in material taken from 9 hand swabs and 5 primers shows that there are potentially valuable forensic uses for such a method. While a more complete study is required, this method could possibly be used to prove (or disprove) relationships between bullets and manufacturers, weapons, or persons firing the weapons. Sample size requirement (1 microgram or less) are such that damaged or fragmented bullets, or minute particles therefrom, may be used for the required analyses. An experiment showed that gunshot residue from a test-fired weapon was detectable even after washing the hands.

Atomic Absorption Spectroscopic Determination of Lead Extracted from Acid-Solubilized Tissues

F.F. Farris, A. Poklis, and G.E. Griesmann. J ASSOC OFF ANAL CHEM 61(3):660-3,May 78.

Authors' abstract: A method is presented for determining lead in a variety of tissues. Lyophilized samples are solubilized with nitric acid at room temperature in glass screw-cap culture tubes. Following neutralization with sodium hydroxide and sodium bicarbonate, the lead is extracted into methyl isobutyl ketone as the pyrrolidine dithiocarbamate complex and analyzed by flame atomic absorption spectrophotometry. Brain, heart, liver, lung, and spleen gave recoveries ranging from 92 to 102% with standard deviations of less than 8%. Aorta, kidney, and rib were unsuitable for analysis by this method. A large number of samples can be analyzed without specialized equipment or intricate experimental steps. The detection limit is 35 ng/g tissue (wet weight) and sensitivity is approximately 140 ng/g tissue (wet weight).

Microprobe Analysis of Lead in Human Femur by Proton Induced X-Ray Emission (PIXE)

U. Lindh, D. Brune, and G. Nordberg. SCI TOTAL ENVIRON 10(1):31-7,Jul 78.

Authors' abstract: A method is described for the measurement of the distribution of lead in bone tissue. Two cases of human femur have been analyzed; one worker was exposed to lead in heavy metal industry, the other case presents a reference worker from the same environment not excessively exposed to lead. Lead was determined through proton induced X-ray emission using microprobe technique. The mean lead concentration in the poisoned and the reference case was 70 and 30 ppm, respectively. The reference case showed an even lead distribution in the femur, while the poisoned case exhibited peaks in the distribution indicating that exposure to lead was not evenly distributed. The described technique has potential for microanalysis within the Haversian system for recording the history of exposure.

Variation of Trace Element Contents in a Single Human Liver

W. Koenig, F.W. Richter, B. Meinel, and J.C. Bode. J CLIN CHEM CLIN BIOCHEM 17(1): 23-7, Jan 79.

Authors' abstract: Multi-element analysis of homogenized samples taken from three different areas of a single human liver was performed for 18 elements by proton induced x-ray emission (PIXE). Small (10–20%) but statistically significant variations between the element contents of these areas were found for C1, K, Ca, Fe, Cu, Zn, Br, Rb and Mo. These differences are not parallel to each other. The variation of element content within one area of this single liver did not show any distinct correlation between different elements, nor did it significantly exceed the methodical errors of 3–10% except for lead. Thus we conclude from our measurements that the trace element analysis of small liver samples by PIXE is, with the exception of lead, fairly representative for the whole organ.

Increased Plasma Levels of Lead in Patients with Amyotrophic Lateral Sclerosis Compared with Control Subjects as Determined by Flameless Atomic Absorption Spectrophotometry

S. Conradi, L.-O. Ronnevi, and O. Vesterberg. J NEUROL NEUROSURG PSYCHIATRY 41 (5):389-93, May 78.

Authors' summary: The levels of lead in plasma were determined in 16 cases of amyotrophic lateral sclerosis (ALS) and 18 control

subjects, using flameless atomic absorption spectrophotometry. The mean values were 0.52± 0.22 μg/100 ml (ALS) and 0.37±0.13 μg/100 ml (controls); the difference is statistically significant (5% level). The values in both groups are lower than reported earlier for normal subjects. The findings are discussed against the background of the possible pathogenetic significance of retrograde axoplasmic flow in ALS.

Study of Blood Levels of a Number of Metals (Al, Mn, Cd, Pb, Cu, Zn) in Chronic Hemodialysis Patients before and after Dialysis (French)

P. Allain, H.E. Thebaud, L. Dupouet, P. Coville, M. Pisant, J. Spiesser, and P. Alquier. NOUV PRESSE MED 7(2):92-6, 14 Jan 78.

English summary: Blood levels of Al, Mn, Pb, Cd, Cu and Zn were measured in the chronic hemodialysis patients of three centers, at the beginning and end of treatment sessions.

The results obtained showed the following:

That blood levels of Al were higher in chronic hemodialysis patients than in controls and that, during the hemodialysis session, Al levels increased when the water in the bath was rich in Al and fell when the opposite applied. These changes may be explained by internal redistribution of the metal and passive diffusion across the hemodialysis membrane. This increase in blood Al would appear to be the consequence rather of the presence of excessive quantities of Al in the dialysis fluid than of the ingestion of Al salts per os.

In certain centers, blood levels of Mn were markedly higher in hemodialysis patients than in controls and the increase in Mn also appeared to be related to the dialysate content of the metal, the neurotoxicity of which is well known.

Cd levels were higher in hemodialysis patients than in the controls, but there was no variation during sessions of treatment. Pb levels, expressed per liter of blood, were essentially normal, though this corresponded to an increase in erythrocyte level by virtue of the lowered hematocrit. Plasma Zn increased during dialysis sessions, though remaining below normal values.

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TREATMENT AND PREVENTION

Lead Poisoning Treated with Hemodialysis

R.S. Pedersen. SCAND J UROL NEPHROL 12(2):189-90, 1978.

Author's abstract: A 27-year-old woman ingested as an abortifacient 40 grams of litharge (PbO). She was treated with EDTA infusion and hemodialysis. The half-life of lead in the blood was 9 hours during combined hemodialysis and EDTA infusion and 96 hours when EDTA was given alone. Signs and symptoms attributable to acute lead intoxication were mild.

Treatment of Lead Poisoning by 2,3-Dimercaptosuccinic Acid

E. Friedheim, J.H. Graziano, D. Popovac, D. Dragovic, and B. Kaul. LANCET 2(8102): 1234-6, 9 Dec 78.

Authors' abstract: 2,3-Dimercaptosuccinic acid (D.M.S.), a new orally effective agent for the treatment of heavy-metal intoxication, was administered to five lead-poisoned smelter workers for six days at dosages ranging from 8.4–12.7 mg/kg/day on the first day to 28.1–42.2 mg/kg/day on the last day. Mean blood-lead concentration decreased significantly from an initial value of 97 ± 6 μg/dl to 43 ± 4 μg/dl on the last day. Urinary lead excretion was significantly raised. D.M.S. was very well tolerated with no signs of toxicity and no effect on urinary zinc, calcium, magnesium, or iron excretion. Urinary copper excretion was significantly increased, but the magnitude of that effect was not clinically important. D.M.S. seems to be safe and effective for the treatment of lead poisoning.

Occupational Exposure to Inorganic Lead: Revised Criteria - 1978

National Institute for Occupational Safety and Health. DHEW (NIOSH) PUBLICATION NO. 78-158. Washington, D.C.: U.S. Government Printing Office, 1978.

This document revises the criteria for occupational exposure to inorganic lead originally published in January 1973. The revised criteria are based on an evaluation of the scientific literature published since the date of the original document, and on testimony presented by NIOSH at hearings held by the Occupational Safety and Health Administration in July 1977.

The primary changes in the recommended standards are a lowering of the permissible exposure level from 150 to 100 $\mu g/m^3$, lowering of the maximum permissible blood lead level from 80 to 60 μg/100 g, revised recommendations for respiratory protection, and more up-to-date recommendations regarding work practices and sanitation.

New information on the biologic effect of lead exposure, sampling and analysis of lead in air, work practices and sanitation is included. A review of the scientific literature and a transcript of NIOSH's testimony at the OSHA's hearings are also included.

Health Assessment of Employees with Different Body Burdens of Lead

B. Ramirez-Cervantes, J.W. Embree, C.H. Hine, K.W. Nelson, M.O. Varner, and R.D. Putnam. JOM 20(9):610-7, Sep 78.

From authors' introduction and conclusions: Proposed rulemaking by the Department of

Labor, OSHA, with regard to occupational exposure to lead was set forth in the *Federal Register* of October 3, 1975. Since the recommended frequency of examination appeared to us to be unnecessarily demanding, we undertook a review of our experience to determine whether a program of health approval which was based on less critical assessment would be protective of employees' health. Biological monitoring of the concentration of lead in the blood of all workers has been a routine procedure carried out by the ASARCO Department of Environmental Sciences for a number of years. Results of the study have been used to evaluate the OSHA proposal.

The results of this study demonstrated that there were no significant differences in the health of workers with blood lead concentrations between 60 and 80 μg/dl and those whose blood lead concentrations were lower than 60 μg/dl. Even though the population studied has been substantially exposed above the newly proposed TLV of 0.10 mg/m^3, there have been only a few cases of clinical problems related to the lead exposure, and few, in the opinion of the attending physician, have required chelation therapy for the reduction of the body burden of lead.

Based on these findings, it is our opinion that the current blood lead standard of 80 μg/dl can be kept, unless more new data will support the OSHA proposal. Also, the OSHA recommendation of monthly medical examinations appears to be too rigid. Our data indicate that it is possible to maintain a high degree of employee health with much less frequent examinations, with the frequency increased only if the blood lead concentration is found to be elevated beyond 80 μg/dl. We believe that implementation of this proposal of OSHA would not add any further dimension to the less rigorous protection program employed by ASARCO.

Occupational Lead Exposure and Women

K. Bridbord. PREV MED 7(3):311-21, Sep 78.

From author's summary and conclusions: The toxicity of lead has been known for approximately 2000 years, but the issue of women exposed to lead in the workplace has received relatively little attention until recent years. The major thesis of this paper is that the fetus represents an organism which is sensitive to lead and that the fetus is exposed to lead through the mother by the fact that lead crosses the placental barrier. Fetal exposure to lead is, in the author's opinion, the critical issue involved in assessing occupational exposure to lead among women of childbearing age. Multiple studies have demonstrated that concentrations of lead in the mother's blood are comparable to concentrations of lead in umbilical cord blood at birth. Many investigators consider the demonstrated effects of lead upon the hematopoietic system to be the earliest effect associated with lead exposure. Control strategies which prevent significant alterations in the heme synthetic pathway of the mother should prevent such changes in the fetus and thus protect against the more serious adverse effects of fetal lead exposure.

Available data indicate significant alteration in heme synthesis at blood lead levels of 30 μg/100 ml and above in children. Further, a number of studies suggest adverse effects on the neurologic system in children at blood lead levels above 30 to 40 μg/100 ml. Accordingly, it would seem prudent to keep blood lead levels of newborn infants, and thus blood lead levels of their mothers, below 30 μg/100 ml. If one assumes that women entering the work force have blood lead levels about 5 μg/100 g lower than men due to differences in general environmental exposure, an air lead exposure of about 50 μg/m^3 in the workplace would result in blood lead levels in female workers in the range of 30 to 40 μg/100 g. On this basis, it is concluded that, to keep blood lead levels of women workers below 30 μg/100 g, 40-hr time-weighted average, weekly air lead exposures would have to be no higher than 50 μg/m^3.

National Standard for Airborne Lead

Committee on Environmental Hazards, American Academy of Pediatrics. PEDIATRICS 62(6):1070-1, Dec 78.

From authors' discussion and conclusions: The Environmental Protection Agency (EPA) decision to establish a 1.5 μg/m^3 air lead standard has been criticized on the grounds that (1) the relative contribution of airborne lead to children's lead absorption has not been fully quanti-

fied; and (2) EP level elevation is a nonspecific phenomenon that may be caused by factors other than lead (iron deficiency, in particular) that interfere with heme biosyntheses. It has been argued that because iron deficiency is so highly prevalent in young children, it is difficult to specify a precise threshold at which EP level elevation induced purely by lead first becomes evident. It has been noted also that other deliberative bodies, including the World Health Organization, have estimated the threshold whole blood lead level for EP level elevation in children to be between 20 and 25 μg/dl.

The Committee on Environmental Hazards has reviewed these arguments and has concluded that further work may be required to confirm the precise blood lead-EP threshold. However, the Committee is in agreement with the EPA's calculation that a reduction in the mean blood lead level to 15 μg/dl would lower to less than 1% the prevalence of increased lead absorption in U.S. children. Also the Committee considers that EPA's estimates on the contribution of airborne lead to blood lead are reasonable extrapolations from existing data. Thus the Committee on Environmental Hazards lauds the efforts of the EPA to reduce the exposure of young children to lead. A reduction of air lead levels to 1.5 $\mu g/m^3$ may be of particular benefit to children in inner cities, where total exposure to lead from many sources, including air, is higher than the average, and where the adverse hematological and neurological effects of lead may be enhanced by a high prevalence of iron and calcium deficiency. A strictly enforced reduction in air lead levels will also be of great benefit to children who live in communities near lead smelters.

Fouling One's Own Nest

J.J. Chisolm, Jr. PEDIATRICS 62(4):614-7, Oct 78.

Children living near smelters and other industrial plants are sometimes vulnerable to increased assimilation of chemicals (including lead) both directly, and indirectly due to occupational exposure of parents. Adults may transport the chemicals home on their person or clothing, especially work clothing. NIOSH lists 111 occupations with a potential for increased exposure to inorganic lead, and there are also many dusty trades and hobbies besides those involving lead exposure.

Pediatricians would do well to include a careful occupational history—past and present—of adults with whom the children live. This should include a clear description of the adult's work, ascertaining whether the adults are exposed to substances that impregnate or adhere to their clothing, and if so, whether they shower at the plant or wear or bring their clothing home for laundering.

When the pediatrician does detect adverse health effects in children and suspects that they are secondary to parental occupational exposure or industial or environmental accident, he must report index cases to appropriate local health authorities, so that careful epidemiological studies can be initiated to establish whether a cause-and-effect relationship exists and, if so, to identify effective preventive measures.

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