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55.62 ± 16 μg/100 ml). There was a significantly increased rate of chromatid aberrations and of unstable chromosome changes in both Groups I and II, when compared to controls, but the differences were not significant for Group III. Culture time was reported 68–70 hours. In a subsequent discussion, Forni stated that they did not find significant differences in rates of unstable chromosome abnormalities between 48–50 hour cultures and 68–70 hour cultures. Lymphocytes from controls as well as lead-exposed workers were both cultured for 68–70 hours.

There is further evidence that women may be more susceptible than male coworkers to the toxic effects of lead. Bell et al reported that when intravenous lead compounds were used during the early part of this century in the therapy of cancer, women exhibited symptoms at 40 mg while 100 mg was necessary to demonstrate the same symptoms in men (45).

Seppalainen found subclinical neuropathy (decreased motor conduction velocity, particularly of the slow conducting fibers of the ulnar nerve) in lead workers with blood leads consistently less than 80 μg/100 ml (46). She noted that women were highly susceptible to these neuropathic effects; for example, three out of four women studied also had fibrillations.

Stuik and Zielhuis administered lead acetate (20 μg/Kg bodyweight/day) for three weeks to human volunteers of both sexes; a significant increase of protoporphyrin IX content of the erythrocytes was noted in female subjects only (47). The blood lead level increased in both groups of volunteers.

Klevay has reported that lead levels in the hair of 242 females were significantly higher than those of 184 males (median 17.9 μg/G vs 11.4 μg/G $p \leq .0001$) (48).

The difference between the sexes may be due to hormonal effects on drug metabolism, for example, testosterone has a stimulatory effect on microsomal drug metabolism. Hepatic microsomes from male rats have been reported to be able to metabolize many drugs three to four times more rapidly than those from females (49). This sex variation in microsomal metabolism is absent in immature animals, and is eliminated by castration or injection of the antagonistic steroid.

Recent reviews of lead have focused on the clinical picture of lead poisoning occasioned by sporadic outbreaks, subclinical effects of lead from occupational exposure, childhood lead poisoning from lead-containing paint in older buildings and environmental contamination leading to an increased body burden of lead (50, 55). The role of lead's toxic effect on pregnancy and reproduction has received little notice. That this is unlikely to continue was emphasized in a recent editorial on lead poisoning and decreased fecundity in men (56).

Conclusion

Biologic evidence is available indicating that women may be more susceptible to toxic effects of lead. In several animal models, lead exerts a profound noxious effect on pregnancy and fetal development. In addition, the older

history of lead's use in the workplace amply documents a deleterious effect on human reproduction. Whether lead is responsible for chromosomal abnormalities in exposed workers remains an unresolved issue. However, there may be no threshold limit at which adverse effects could not occur in the course of development of the human fetus.

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maturity later, and laid significantly fewer eggs than control hens. One-fourth of the eggs laid by the lead-toxic hens had soft and malformed shells.

Chromosomal Aberrations

Muro and Goyer analyzed chromosomes from leukocyte culture of mice fed a diet of 1 % lead acetate (39). They observed an increased number of gap-break type aberrations, largely involving single chromatids. The chromosomal abnormalities included 28 (16.9 %) gaps vs 4 (1.3 %) in the controls, 9 (5.4 %) breaks vs none in the controls, and 20 (12 %) fragments vs none in the controls.

Schwanitz et al reported a three- to fourfold increase in chromosomal aberration in human lymphocytes treated in vitro with lead acetate as compared with control cells exposed to sodium acetate (40). He found an increase in chromosomal aberrations (breaks and gaps) in the peripheral blood lymphocytes of eight male workers in a lead oxide factory; also, he noted a correlation between percentage of abnormal mitoses and excretion of delt-amino-levulinic acid in the urine.

In contrast, O'Riordan and Evans reported the results of chromosomal analysis of 66 shipyard workers, finding no differences in chromosomal aberrations between shipyard workers known to be exposed to lead and other shipyard employees (41). There was no difference in the chromosomal analysis between the groups according to blood lead 40, 40–80, 80–120 and 120 μg/100 ml) or according to job category. Nevertheless, they did find a significant increase in all of the shipyard workers' chromosomal abnormalities (breaks and gaps) compared to individuals in the general population, not employed in shipyards. They emphasized the technical difficulties in chromosomal analysis, and stressed the importance of analyzing the culture after forty-eight hours of growth to prevent the cells from entering a second mitosis which increases the natural occurrence of gaps and chromatid aberrations. Bauchinger and Schmid compared twenty industrial workers with exposure to lead dust and twenty-nine policemen with increased lead absorption to a nonexposed control group, and also found no increase of chromosomal aberration after forty-six hours of culturing lymphocytes (42).

Lehnert in Germany, found an increase in gap-break chromosomal changes in lead workers having a blood lead in the range of 62–89 μg/100 ml (43). He found a positive correlation with an increased urinary ALA and the percent of abnormal mitoses seen. Lead acetate solutions (10^{-4} to 10^{-6}M) added to normal leukocyte cultures produced the same chromosomal abnormalities.

The data of Lehnert and Schwanitz have been corroborated by Forni and Secchi in Italy (44). They analyzed chromosomes from cultures of blood lymphocytes from 65 workers occupationally exposed to lead, and in 65 unexposed controls matched for age. The workers were subdivided into three groups: Group I, 15 workers with preclinical intoxication (blood lead mean 64.07 $\pm$ 16.69 μg/100 ml), Group II, 37 workers with clinical poisoning (blood lead mean 77.73 $\pm$ 24.89 μg/100 ml), and Group III, 13 workers with past lead poisoning, no longer exposed to lead for at least 18 months (blood lead mean

number of pregnancies, number of pups born alive, fertility index, gestation index, viability index, or lactation index (30). The average weight of rats fed the two higher concentrations was slightly decreased. In contrast, Schroeder et al administered 25 ppm lead in the drinking water to pregnant mice and rats, observing runting reproductive failure, and shortened life span.

Weller fed commercial white lead in capsular form to guinea pigs (27). He noted that the offspring from leaded males and nonleaded females had significantly lower birthweights (81.5 gm versus 66.3 gm) compared to those of nonleaded parents. There was also a high rate of mortality of guinea pigs in the first week after birth when the father had been fed lead.

Hilderbrand et al fed lead acetate at doses of 5 and 100 micrograms orally to 80 male and female rats for 30 days (32). At the end of the study period, the blood leads of the females were higher than the males: 30 μgm/100 ml vs 19 μgm/100 ml at 5 μgm lead acetate, and 53 μgm/100 ml vs 30 μgm/100 ml at 100 μgm lead acetate. They noted impotence and prostatic hyperplasia in the males at the lower dose, progressing to testicular damage in those reaching blood leads of 50 μgm/100 ml. In the females, they noted irregularity of the estrus cycle at both doses. They also demonstrated an inhibitory effect by lead upon hepatic microsomes at both doses in both sexes. Electron micrographs of the liver demonstrated a decrease in free ribosomes and smooth endoplasmic reticulum in the treated rats. Sleeping times following 15 mg of pentobarbital per Kilogram were prolonged in both treated groups compared to controls. Thus, they concluded that lead inhibited hepatic detoxification mechanisms in both female and male animals.

Ferm and Carpenter produced specific congenital-skeletal malformations (sacral and tail vertebrae) in hamster embryos following the treatment of the pregnant hamster with various salts of lead (33). They did not evaluate the possible morphologic changes of dead or resorbing embryos, where the very severe developmental anomalies were likely to have occurred. Ferm has also reported that in the presence of cadmium, the teratogenic effect of lead in hamsters is potentiated (34).

Karnofsky and Ridgwey injected lead nitrate into the yolk sac of the chick embryo (35). They found that this produced a severe, characteristic injury to the central nervous system; widespread brain hemorrhage was noted to be followed by necrosis and hydrocephalus. The central nervous system injury occurred after injections from the third to the ninth days of embryogenesis; it was thought that on the earlier days the circulatory system to the brain was less well-developed. Gilani demonstrated congenital cardiac anomalies by studying 8-day-old chick embryos which had been administered lead acetate on the second day of incubation (36). The incidence of cardiac anomalies rose with increasing doses of lead. Other important anomalies were: retardation of body size, micromelia (malformation of the limbs), shortened neck, microphthalmia, ruptured brain, shortened beak, twisted neck and limbs, and everted viscera (37)

Stowe et al fed 1.0 % lead acetate to white leghorn female hens from age four weeks onward (38). The lead-toxic hens grew more slowly, reached sexual

and had a blood lead of 0.240 mg % with signs and symptoms of lead poisoning. She was treated with a seven-day course of intravenous calcium disodium edetate 75 mg/Kg/day. A month later she delivered a normal infant weighing 3200 grams. On a four-year follow up, pediatric, neurologic, and developmental assessments of the boy were normal.

Abendroth described a similar case in Germany of a woman in her fifth month of pregnancy who took approximately 25 grams of an inorganic lead compound (probably lead oxide) over a period of about three weeks (22). Following aggressive chelation therapy, a healthy baby was born and was reportedly doing well after four years of followup.

The reproduction ability of men occupationally exposed to lead is interfered with by altered spermatogenesis. Lancranjan et al reported a significant increase in teratospermia amongst lead-poisoned workmen (blood lead mean 74.5 μg/100 ml) and workmen with moderately increased absorption (blood lead 52.8 μgm/100 ml) (23). Hypospermia and asthenospermia were increased not only in both preceding groups, but also those with only slightly increased absorption (blood lead mean 41 μgm/100 ml). They also determined urinary gonadotropins and 17-ketosteroids which did not differ from controls. Thus, they concluded that lead has a direct toxic effect upon the male gonads. Abnormal spermatogenesis may be the cause of the high fetal wastage rate amongst the wives of lead workers.

Soviet investigators had previously demonstrated the effects of lead in causing sperm damage in animals (24). They also stated that among the effects of a parental poison burden in children, functional disturbances prevail by far, ahead of mutations and malformations.

Pregnancy is a stress which may mobilize lead from skeletal storage sites. Both iron deficiency and calcium deficiency increase the susceptibility to lead toxicity; women have an increased risk of both deficiencies during pregnancy, and postpartum. The cause of the increased perinatal mortality may be lead's mutagenic and teratogenic effects (25–28). Important genetic effects may be latent for several generations and, in addition, the damage may be permanent. Experimental animal studies with lead have demonstrated increased rates of developmental anomalies, chromosomal damage, and decreased rates of pregnancy.

Experimental Investigations

Varma et al fed 2 % lead acetate to 14 male Swiss mice for four weeks (29). He then allowed each to mate for one week with three virgin untreated females. The overall incidence of pregnancy, indicative of fertility, was 52.7 % in the control group, as compared to 27.6 % in the treated group. The fertility of the treated males was reduced by 50 %. He calculated the mutagenicity index (number of early fetal deaths/total implants) to be 10.4 for lead-treated mice versus 2.9 for controls ($x^2 = 10.4$ $p \geq .05$).

A three-generation, six-litter rat reproductive study showed no effect of dietary lead at concentrations of 0,10,50,100,1,000 and 2,000 ppm on the

1. Intrauterine deaths of fetus at 33 weeks. Maternal blood leads were 55, 34 and 72 μg/100 ml at weekly intervals after fetal death, and 51 μg/100 ml two months later. Analysis of fetal tissues for lead were: 1) Kidney 0.2 mg/100 G (normal 0.01-0.16 for normal adults by Kehoe) and liver 0.53 mg/100 G (normal 0.04-.28 mg/100 G for normal adults); 2) Congenital defects (nystagmus, albinism, and hemangioma). Maternal blood lead was 31 μg/100 ml; 3) Congenital defects (multiple hemangiomata). The mother had been sterile for six years previous to this pregnancy which had a threatened miscarriage at 11 weeks and subsequently delivered prematurely; and 4) Two abnormal pregnancies occurred in a woman with four previous miscarriages and two surviving children. The first included a threatened miscarriage at seven weeks with a maternal blood lead of 53 μg/100 ml and subsequently an antepartum hemorrhage occurred at 36 weeks with premature delivery.

Lead has been found in concentrations in umbilical cord blood of newborns parelleling that of the mother (15, 16). Gershanik et al in examining 98 cord blood pair samples found a coefficient of correlation of 0.6377 with maternal samples ($\bar{x}$ 10.1 μg/100 ml newborns and 10.3 μg/100 ml mother) (16). Lead has also been found to be transported into maternal milk during lactation.

Fahim et al compared the course and lead values in 249 pregnancies in Columbia, Missouri, with 253 occurring in the center of America's lead belt at Rolla, Missouri (18). At Columbia, greater than 96 % delivered normally at term, 3 % were preterm (defined as a neonate born before 37 weeks of gestation and weighing less than 2500 grams), and less than 1 % had premature rupture of the membrane (occurring in an insulin-dependent diabetic). At Rolla, only 70 % were term, 17 % had premature membrane rupture (defined as spontaneous rupture of the membrane before the onset of labor and when labor does not begin within 12 hours), and 13 % were preterm. The striking blood lead findings from the Rolla lead belt area were a doubling of maternal blood lead in the premature membrane rupture and preterm groups (4.6±0.08 μgm/100 gm to 14.2±0.78 and 17.5±1.06 respectively). There also was a three- to fourfold increase of fetal blood lead in the premature membrane and preterm groups.

Palmisano et al reported a case of a ten-week-old infant with evidence of neurologic defects, intrauterine growth retardation and postnatal failure to thrive which was the conceptus of a 33-year-old woman with a history of long-term ingestion of "moonshine" whiskey (19). After challenge doses of calcium EDTA, the infant and the mother each excreted an abnormally large amount of lead in the urine. A recent survey based on chemical analyses of untaxed "moonshine" whiskey samples disclosed that 53 percent contained concentrations of lead above 1000 μg per liter.

Greenfield reported a patient with plumbism in 1957 who subsequently became pregnant and had a normal pregnancy productive of a seven-pound normal infant (20). During the pregnancy, the blood and urine tests for lead were normal (less than 10 μg/100 gm. and 0.11/mg/liter respectively).

A family lead-poisoned by heating their home with lead battery casings was described by Angle and McIntire (21). The mother was eight months pregnant,

abortifacient (3). Sixty percent of the pregnancies in the first trimester ended in abortion. Four pregnancies of five or more months duration resulted in one abortion and three normal infants.

Rennert in 1881 found a high prevalence of convulsions and a peculiar form of macrocephaly in the German village of Almerode where pottery glazing was a home industry (5). He gave the following record of 79 children:

	# Children	Macrocephaly	Convulsions	Stillbirths
Both parents leaded	19	18	17	1
Father leaded, mother slightly	27	17	9	6
Father leaded, mother normal	33	19	13	0
TOTAL	79	54	39	7

Seventy one percent of the children had either macrocephaly or convulsions with a mortality rate of over fifty percent.

In 1908, Chyzzer published an account of a Hungarian village engaged in home pottery glazing where the same peculiar form of macrocephaly prevailed (6). This was confirmed by Oliver (British Inspector of Factories) who made a special journey to Hungary (7).

Torelli in 1930 studied the influence of chronic lead poisoning on offspring of parents in the printing trade in Milan, Italy (3). He found the abortion rate for Milan in general to be 4–4.5%, but among the wives of printers the rate was 14% and among the women printers 24%. The average death rate in 1930 in all Italy for children during the first year was 150/1,000 births, but for this group it was 320/1,000.

Teleky analyzed German female workers in the printing industry, and stated that spontaneous abortions were three times as common among those exposed to lead as those not exposed (8).

Arlidge in England, reporting on 71 females working with lead after marriage, found that 11 percent of pregnancies ended in miscarriage (9). The neonatal mortality was almost 40 percent.

Tardieu reported to the French government in 1905 that 608 out of 1,000 pregnancies in lead workers ended in abortion (9).

Legge, in summarizing the reports of 11 English factory inspectors in 1897, found that of 212 pregnancies in 77 females working with lead, only 61 living children were produced (10). Fifteen had never become pregnant; there were 21 stillbirths; miscarriages occurred ninety times; and of 101 children born, 40 died in their first year. Legge also noted that when pregnant animals were fed lead, they always aborted. Legge felt that lead affected pregnancy directly through the female's exposure to lead; he found little evidence to suggest any adverse effect on pregnancy or the health of the offspring if only the male were exposed to lead.

However, in 1905 Rudeaux analyzed 442 pregnancies in women married to lead workers; 66 ended in abortion, and 241 in premature birth (3). Also in 1905, Deneufbourg noted 23 abortions and stillbirths amongst 134 pregnant females exposed to lead (11). He found a 25.5 % (113 in 442 pregnancies) abortion and stillbirth rate in the wives of male lead workers. He also noted

that in animal experiments, offspring of leaded parents had lead far more evenly distributed in the various bodily organs than in mature individuals.

In an excellent study from Japan using an unexposed control group, Koinuma compared the marital life records of workmen exposed to lead in storage battery plants with the records of those working in nonleaded occupations (1). The sterile marriages constituted 24.7 % for the lead group and only 14.8 % for the nonlead group. The percentage of pregnancies ending prematurely or in stillbirth was 8.2 for the lead group and 0.2 for the control group.

In 1911, Oliver published statistics on the effect of lead on pregnancy:

	# abortions and stillbirths per 100 females	# neonatal deaths (first year) per 100 females
Housewives	43.2	150
Female workers (mill work)	47.6	214
Female exposed to lead premaritally	86.0	157
Female exposed to lead after marriage	133.5	271

A more recent report on occupational lead exposure and pregnancy comes from Nogaki in Japan (12). A detailed study of the pregnancies of 104 Japanese women before and after beginning lead work showed an increase in miscarriages to 84.2/1,000 pregnancies from a prelead rate of 45.6/1,000. The miscarriage rate for 75 comparable employees not exposed to lead was 59.1/1,000 pregnancies. The maternal blood leads ranged from 0.110 mg % to 0.317 mg %.

Gilfillan (1965) has presented an interesting hypothesis that the fall of Rome was caused by sterility in the ruling class due to their consumption of wine sweetened with lead (13).

Thus, it was reported as early as the 19th century, that lead had a damaging effect on fertility, the course of pregnancy and the development of the fetus. It was also apparent that exposure to lead by either sex could lead to reproductive failure. Certainly, in these early reports, the lead exposures were uncontrolled, and may have been very high.

Recent Studies

More recently, A. T. Wilson in Scotland reported the effects of abnormal lead content of water supplies on maternity patients (14). He noted that the water supplies of his district often exceeded the World Health Organization standard limit for the lead content of drinking water (0.05 mg/l) due to the soft water's corrosive action on lead piping. He analyzed routine prenatal urine specimens for coproporphyrin in 72 patients during 75 pregnancies over a two-year period. He divided his patients into two groups: one with unrestricted access to the water supplies, and one encouraged to drink milk and restrict water. Thirty-one percent (11 of 35) in the unrestricted group reached a level of coproporphyrinuria exceeding 100 μg/l versus one out of forty in the restricted group. Five pregnancies in four patients in the former group were abnormal:

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Effects of Lead on the Female and Reproduction: A Review

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Introduction

With increasing numbers of women entering the workplace, attention is being focused on hazards that may have special effects on their health. Lead, especially in relation to the development of an Occupational Safety and Health Administration standard, has received recent attention because of its history of acting as an abortifacient. A survey of the literature has been undertaken: first, to summarize the reported data on lead's effect on human pregnancy; second, to review experimental animal studies of lead's effects on pregnancy; and third, to evaluate the published evidence that women may be more susceptible to toxic effects of lead than men.

Lead has been known to affect women during pregnancy for more than a century. Teratogenesis has been reported and documented by animal experimentation. In addition to lead's direct adverse effect on the course of pregnancy, it has an indirect effect by its toxic action on the male germ cell. There is evidence that women, particularly during specific periods, i.e., adolescence, pregnancy, etc., are more susceptible to toxic effects of lead. Oliver has noted that women are more susceptible to lead poisoning between ages of 18 and 23, and after shorter exposure (1). He noted that women poisoned by lead have a higher incidence of encephalopathy, and a lower incidence of paralysis and colic, than males.

Early Reports

During the late nineteenth and early twentieth centuries, women in the pottery and white lead industries felt lead was an abortifacient. In 1860, Constantin Paul published figures indicating a profound effect of paternal plumbism on sterility and on the viability of the offspring (2). Reid gathered statistics on women in the English potteries and white lead works, reporting that women in lead work, as compared to ones not employed in this work, were more likely to be sterile; and if they became pregnant, to miscarry. If the pregnancy went to term, it was more likely to end in stillbirth; and if the child was born living, death was more likely to come in the first year of life (3).

Pindborg reviewed 25 well-documented cases of mild to moderately severe lead poisoning in Danish women who had ingested lead oxide as an

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