Anatomy of lead poisoning

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Abstract

Objective: Lead poisoning and lead toxicity is usually often interchangeably used by different Scientists. The Anatomy of lead poisoning encompasses its effects on different organ-systems of different species of organisms. It also includes environmental, functional and biochemical components associated with most heavy metals that enters biological tissues daily through occupational and environmental exposures.
A major outbreak of lead poisoning occurred in Zamfara state Nigeria in 2010, killing over 500 children. Also inMay 2015, Niger state Nigeria was plagued with another outbreak and children were the most affected.Mining activities have increased, oil exploration and pipeline vandalism, have destroyed our ecosystems just to mention a few of the factors responsible for unabated increased levels of heavy metals in our bodies resulting into congenital malformations, infertility, reduced intelligent quotient in children, and cancer.

Methods: Different literature in reputable journals were reviewed in the course of this study. New mechanisms involved in the toxicity of heavy metals were studied. Advances in molecular biology have however tremendously helped in unravelling more mechanisms of lead toxicity.
In this review it is perceived that a population of males or females may surfer adverse reproductive sequelae in future.

Results: The primary form of lead toxicity is by oxidative stress mechanisms, apoptosis and necrosis involving cellular pathways including both mitochondria and cytoplasmic pathways.

Conclusions: Lead and heavy metal toxicities can be ameliorated by synergistic activity of trace elements including selenium, cobalt, zinc and boron.

Keywords: Lead poisoning, anatomy, cellular pathways, trace elements.

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Anatomie d'un empoisonnement au plomb

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Résumé

Objectif: empoisonnement au plomb et la toxicité du plomb est habituellement souvent utilisés de façon interchangeable par différents scientifiques. L'anatomie du saturnisme englobe ses effets sur différents systèmes organiques de différentes espèces d'organismes. Il comprend également des composantes environnementales, fonctionnelles et biochimiques associés à la plupart des métaux lourds qui pénètrent dans les tissus biologiques quotidienne à travers les expositions professionnelles et environnementales.
Une importante épidémie d'empoisonnement au plomb a eu lieu dans l'État de Zamfara Etat du Nigeria en 2010, tuant plus de 500 enfants. Aussi enmai 2015, l'Etat du Niger au Nigeria a été aux prises avec un autre foyer et les enfants étaient les activités les plus affected.Mining ont augmenté, l'exploration pétrolière et oléoduc vandalisme, ont détruit nos écosystèmes pour ne citer que quelques-uns des facteurs responsables de l'augmentation des niveaux sans relâche de métaux lourds dans notre corps qui en résultent dans les malformations congénitales, la stérilité, réduite quotient intelligente chez les enfants, et le cancer.

Méthodes: littérature différente dans des revues de renom ont été examinés dans le cadre de cette étude. De nouveaux mécanismes impliqués dans la toxicité des métaux lourds ont été étudiés. Les progrès de la biologie moléculaire ont cependant énormément aidé à démêler plusieurs mécanismes de la toxicité du plomb.Dans cette revue, il est perçu que la population de mâles ou des femelles peut surfer séquelles néfastes sur la reproduction à l'avenir.

Résultats: La forme primaire de la toxicité du plomb est par des mécanismes oxydatifs de stress, apoptose et nécrose impliquant les voies cellulaires, y compris les deux mitochondries et les voies cytoplasmiques.

Conclusions: plomb et les toxicités de métaux lourds peuvent être atténués par l'activité synergique d'oligo-éléments dont le sélénium, le cobalt, le zinc et le bore

Mots-clés: empoisonnement au plomb, l'anatomie, les voies cellulaires, des oligo-éléments.

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INTRODUCTION

Lead is a naturally-occurring element found in rock and soil, yet widespread anthropogenic use has resulted in its ubiquitous presence in the environment.it is found in all environmental media in Nigeria as well as in food and drinking water. Lead is associated with risks to human health, and also to the environment. Lead is currently subject to numerous federal risks management initiatives directed toward consumer products, cosmetics, drinking water, food, natural health products, therapeutic products, tobacco, and environmental media including house dust, soil and air. Lead induces a broad range of physiological and behavioural dysfunction in humans. Lead poisoning is associated with several clinical symptoms with limited molecular mechanism underlying its toxicity. Toxic metals increase production of free radicals and decrease availability of antioxidant reserves to respond to the resultant damage. Lead adversely impacts offspring development at maternal blood lead concentrations that do not produce maternal clinical toxicity. Reproductive effects observed in females associated with low level exposure to lead include (i) delays in sexual maturation (ii) risk of spontaneous abortion (iii) effects on birth weight, and pre-term birth.

Several studies have demonstrated an association between delayed puberty in adolescent girls and blood lead concentrations as low as 3 microgram per decilitre. Maternal bone lead burden is inversely related to birth weight.. In males, most reported effects on the reproductive system have been observed at blood lead-levels below 10 microgram per decilitre and have included decreased sperm count, morphological aberrations, and an increased risk of infertility.

BACKGROUND

Endocrine disruptors like lead are estrogen-like chemicals in the environment that have potentially hazardous effects on the male reproductive axis resulting in infertility and on other hormonal dependent reproductive functions causing erectile dysfunction (ED). The chemicals are called “endocrine disruptors” because they (i) mimic natural hormones, (ii) inhibit the action of hormones, and/or (iii) alter the normal regulatory function of the endocrine systems. Besides reduced fertility and ED, testicular and prostate cancers, abnormal sexual development, alteration in pituitary and thyroid gland functions, immune suppression, and neurobehavioral effects are also possible due to such endocrine disruption in the male.

Data collected over the last 30 years have shown disturbing trends in male reproductive health. An earlier report from Scotland revealed that men born after 1970 had a sperm count 25% lower than those born before 1959–an average decline of 2.1% a year [Brake 1992]. Sperm count is also associated with poor semen quality [Lewis 2005]. In contrast, Olsen et al., used several statistical models and found an actual increase in average sperm numbers., while some environmentalists believe that the human species is approaching a fertility crisis, others think that the available data are insufficient to deduce worldwide conclusions [Fisch 1996 , Parvinen 1984]. Newer tools for the detection of Y-chromosome deletions shows that a decline in male reproductive health and fertility is related to the presence of certain toxic chemical compounds in the environment [Neiderberger 2005]. These chemicals mimic or otherwise disrupt androgen balance in the body by binding to hormone receptors during fetal and neonatal development. This has been the subject of a number of reviews, suggesting that etiology, diagnosis, and treatment of male factor infertility remains real challenge Declining semen quality is not the only indicator that

suggests that human reproduction is at risk. An increase in the incidence of testicular cancer in young men has been associated with other abnormalities including undescended testis, Sertoli-cell only pattern, and hypospadias which cause poor gonadal function and low fecundity rates. The human male produces relatively fewer sperm on a daily basis compared with many of the animal species used for toxicity testing.. In fact, in many men over age 30, the lower daily sperm production rate already places them close to the subfertile or infertile range. A less dramatic decrease in sperm numbers, motility, and/or morphology in humans can have serious consequences for reproductive potential, even though it takes only one sperm to fertilize an egg. Problems in the production, maturation, and fertilizing ability of sperm are the single most common cause of male infertility. Although any discussion of gonadal function and toxicity is of special relevance to man, much of this understanding has been obtained from various experimental models and research using animal species. In addition, both intra-testicular and post-testicular events have been postulated and different mechanisms have been proposed to explain the presence of damaged DNA in human spermatozoa.

An endocrine disruptor effects several potential target sites in the male reproductive tract. The most important sites is the testes which usually exist in pairs and are the sites of spermatogenesis and androgen production Paracrine and autocrine regulations in various compartments of the testis under endocrine influences from the pituitary and hypothalamus. Sertoli cells, form a continuous and complete lining within the tubular walls which envelope the developing sperm during spermatogenesis. These cells establish the blood-testis barrier by virtue of tight junctions. The luminal environment as controlled by these Sertoli cells is under the influence of follicle stimulating hormone (FSH) and inhibin. These Sertoli cells: (1) provide nourishment for the developing sperm cells; (2) destroy defective sperm cells; (3) secrete fluid that helps in the transport of sperm into the epididymis; (4) release the hormone inhibin that helps regulate sperm production. The differentiation of Sertoli cells and the formation of a competent blood-testis barrier are essential to the establishment of normal spermatogenesis during puberty. Leydig cells are the endocrine cells in the testis that produce testosterone from cholesterol via a series of enzymatic pathways and steroidal intermediates under the control of luteinizing hormone (LH) from the pituitary. These cells arise from interstitial mesenchymal tissue between the tubules during the eighth week of human embryonic development. They are located in the connective tissue between the seminiferous tubules.

Spermatogenesis is a chronological process spanning about 80 days in man and 40–50 days in the rodent (depending upon species). During this period, the immature germ cells (relatively undifferentiated spermatogonia), develop into highly specialized spermatozoa in a cyclic manner. Spermatogonia undergo several mitotic divisions to generate a large population of primary spermatocytes, which produce haploid spermatids by two meiotic cell divisions. Spermiogenesis is the transformation of spermatids into elongated flagellar germ cells capable of motility. The release of mature germ cells is known as spermiation. Most of the testicular volume, which diminishes if testicular damage has occurred, consists of these germ cells, During mitotic arrest, the gonocyte becomes acutely sensitive to toxic agents. Low-dose irradiation, completely eradicates germ cells while causing little damage to developing Sertoli cells, thus creating a Sertoli-cell-only testes [Mandl 1964].

Many estrogenic pollutants including agricultural products industrial chemicals and heavy metals have significant

reproductive consequences due to their multiple routes of exposure, their widespread presence in the environment, and their ability to bioaccumulate and resist biodegradation. In addition, many pharmacological and biological agents including radiation therapy affect male reproduction by disrupting hormonal balance. A detrimental effect of agricultural and industrial chemicals on sperm concentration, motility, and morphology is caused by impaired spermatogenesis secondary to various hormonal alterations [Whorton 1977; [Mattisson 1983].

Heavy metals (e.g., arsenic, lead, boron, mercury, cadmium, antimony, aluminum, cobalt, chromium, lithium) exert adverse effects on the reproductive axis of human and experimental animals. More reports are available on lead-induced toxicity than any other heavy metal. Historically, the fall of the Roman Empire has been attributed to lead poisoning [Gilfillan 1965]. Men working in battery plants and exposed to toxic levels of lead demonstrated adverse effects on their reproductive capacity [Lancranjan, 1975; Gilfillan, 1995].

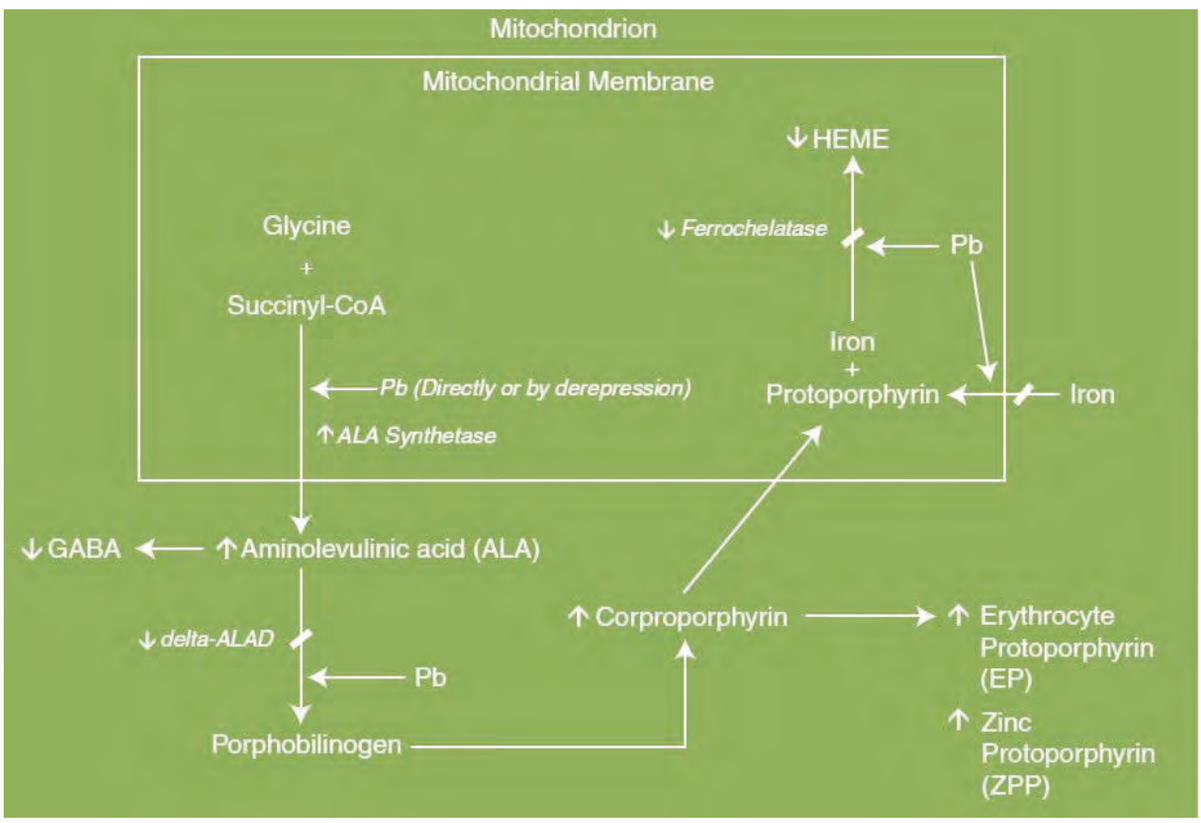
In animals, lead exposure results in a dose-dependent suppression of serum testosterone and spermatogenesis [Ewing, 1981; Foster 1993]. Although testicular biopsies reveal peritubular fibrosis, vacuolation, and oligospermia, suggesting that lead is a direct testicular toxicant [Weir, 1972], recent studies have shown that lead exposure disrupts the hormonal feed-back mechanism at the hypothalamic-pituitary level [Sokol, 1987].

Animal studies suggests that these effects can be reversed when lead is removed from the system. Such detailed evaluations in humans need further investigations. Boron is extensively used in the manufacture of glass, cements, soaps, carpets, crockery, and leather products. Oligospermia and decreased libido were reported in men working in boric acid-producing factories [Weir, 1972]. Boron has a major adverse reproductive effect on the testes and the hypothalamic-pituitary axis in a manner similar to lead toxicity. Cadmium, another heavy metal, is a testicular toxicant that is used widely in industries like electroplating, battery electrode production, galvanizing, plastics, alloys, paint pigments [Friberg,, 1974]. It is also present in soil, coal, water, and cigarette smoke. Animal studies have shown that cadmium causes severe testicular necrosis in mice that is also strain-dependent [King, 1998]. Cadmium-DNA binding and inhibition of sulfhydryl-containing proteins mediate cadmium toxicity directly or through transcription mechanisms. Cadmium induces the expression of heat shock proteins, oxidative stress response genes, and heme oxygenase induction mechanisms [Snow, 1992.]. Clinical studies have associated cadmium exposure with testicular toxicity, altered libido, and infertility.

Mercury exposure can happen during the manufacture of thermometers, thermostats, mercury vapor lamps, paint, electrical appliances, and in mining. Such exposure can alter spermatogenesis and has been found to decrease fertility in experimental animals.

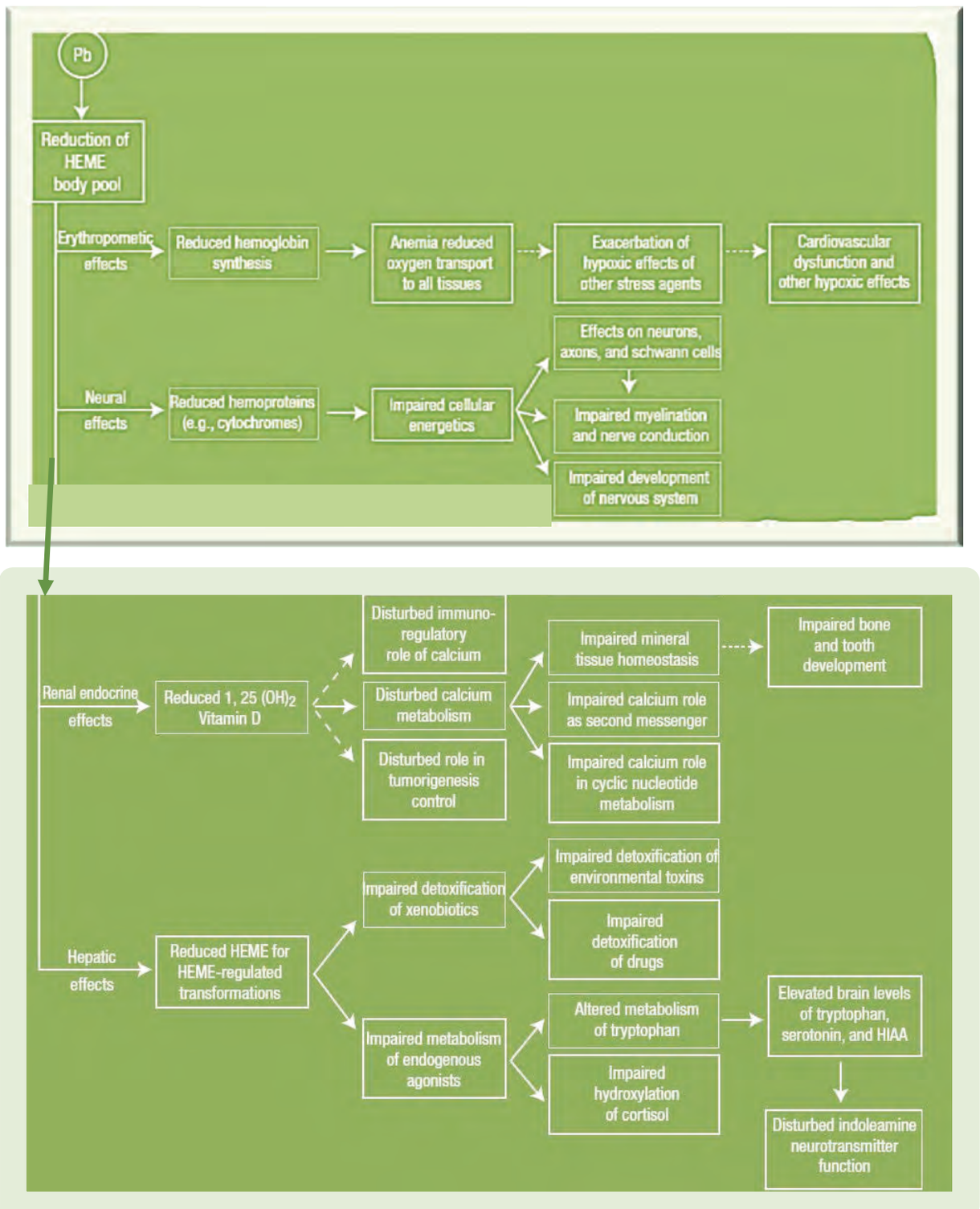
Immunohistochemical characterisation of Alkaline phosphatase and Placental alkaline phosphatase in lead induced testicular damage was reported in the germinal epithelium of rats [.Falana 2013]. The study concluded that Alkaline phosphatase is involved in intrinsic regulation of DNA cleavage in apoptosis by functioning similar to endonucleases and also regulates membrane transport in perioxidated biomembranes.

Figure 1. Effects of Lead on Heme Biosynthesis



Adapted from: Needleman H. Lead poisoning. *Annu Rev Med* 2004;55:208-222.
EPA Air Quality Criteria for Lead. Research Triangle Park, NC: U.S. EPA, Office of Reseach and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA600883028F. 1986.

Figure 2. Multiorgan Impact of Reduced Heme Body Pool



From: EPA Air Quality Criteria for Lead. Research Triangle Park, NC: U.S. EPA, Office of Reseach and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA600883028F. 1986. Used with permission.

Earliest symptoms

- Irritability
- Headache
- Myalgia
- Diffuse muscle weakness
- Diminished libido
- General fatigue/lethargy
- Weight loss of 10 lbs or more without known cause

Symptoms of chronic exposure

- Inability to concentrate
- Nausea/vomiting
- Depression
- Abdominal pain
- Impotence
- Incoordination
- Short-term memory loss
- Numbness and tingling in extremities

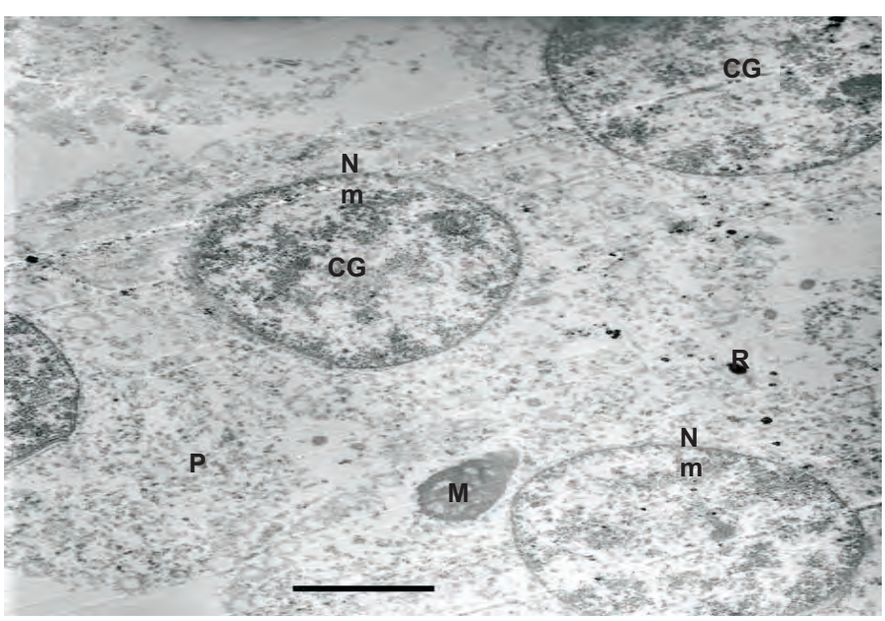
Lead toxicity in general

- Increased intracranial pressure
- Tremors
- Forearm extensor weakness (wrist drop)
- Blood lead over 10 µg/dl
- Hypertension
- Decrease nerve conduction velocity
- Hyper-reflexia
- Upper extremity weakness
- papilledema

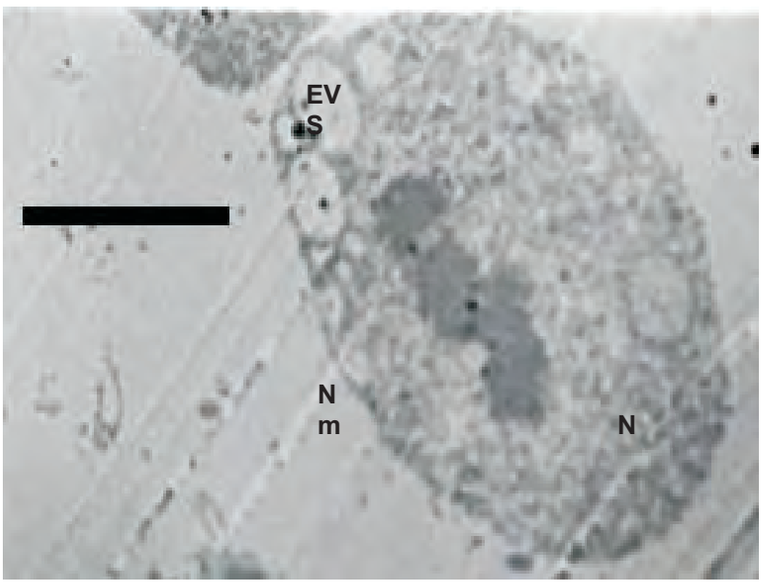
Symptoms in children

- Behavioral change/ hyperactivity
- Aminoaciduria
- Language delay
- Growth failure
- Abdominal pain

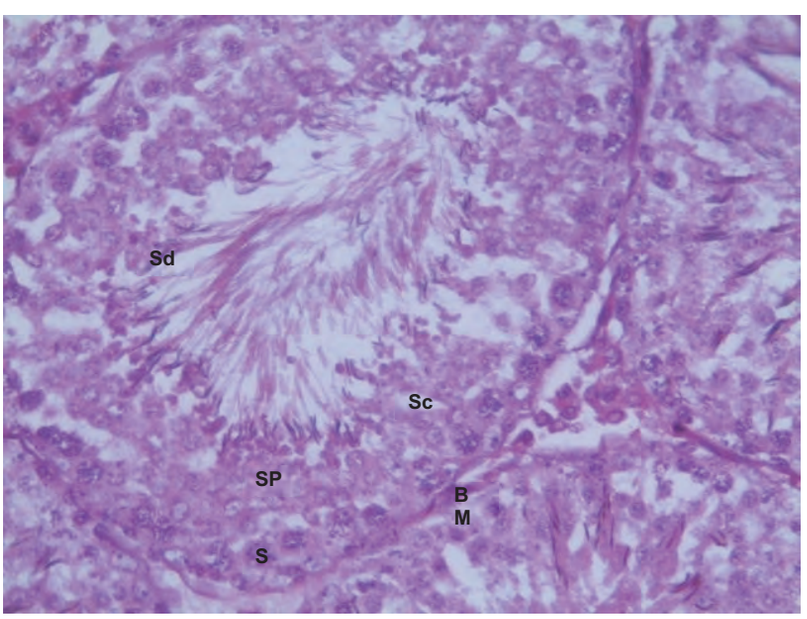
MICROANATOMY OF LEAD INDUCED TESTICULAR DAMAGE IN THE SPRAGUE-DAWLEY RAT.



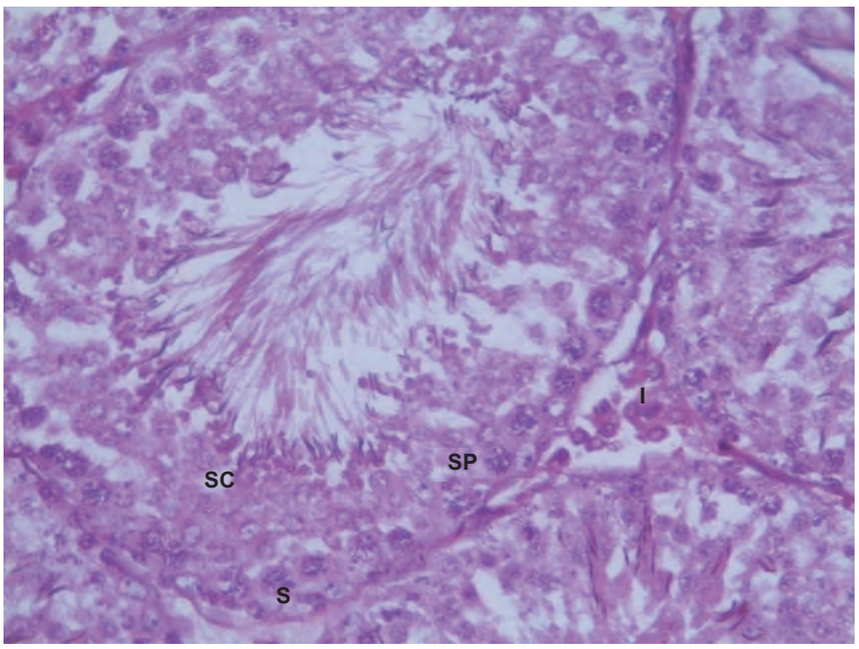
EM1: Ultrastructure of the testis of Control animals showing the Sertoli cell cytoplasm. And the germ cells suspected to be secondary spermatocytes. The nuclear membrane Nm is turgid and a prominent nucleolus Nu. The mitochondrion M lie close to a nuclei. Prosecretory granules P, Chromatin granules CG and free ribosomes R are scattered throughout the cytoplasm. Scale bar = 2.17µm.



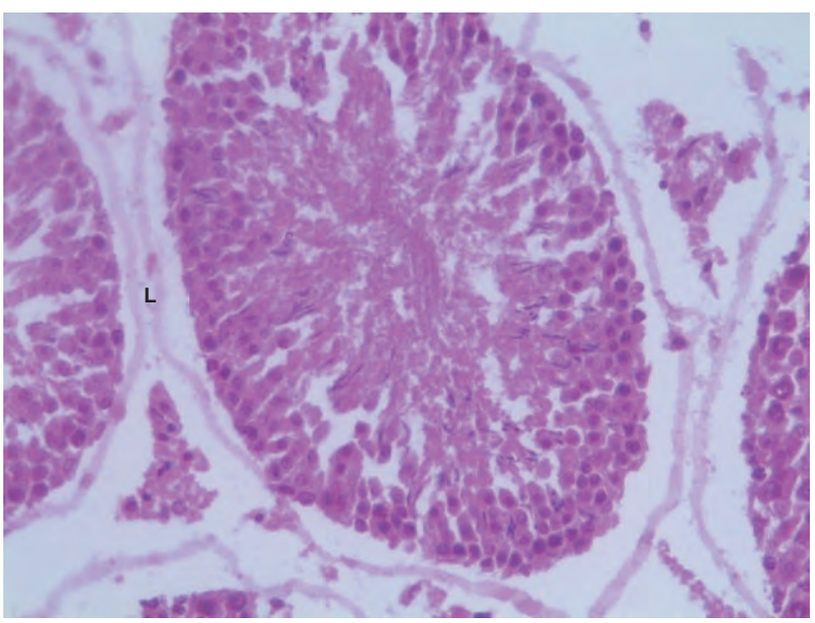
EM002: Ultrastructure of the testis of Pb only treated animals showing a degenerating germ cell (spermatocyte). There are empty extravacuolar space in the cytoplasm and the chromatin granules appear inconspicuous with ill-defined nuclear membrane. Scale bar = 2µm. N, nucleus; EVS, extravacuolar space NM, nuclear membrane.



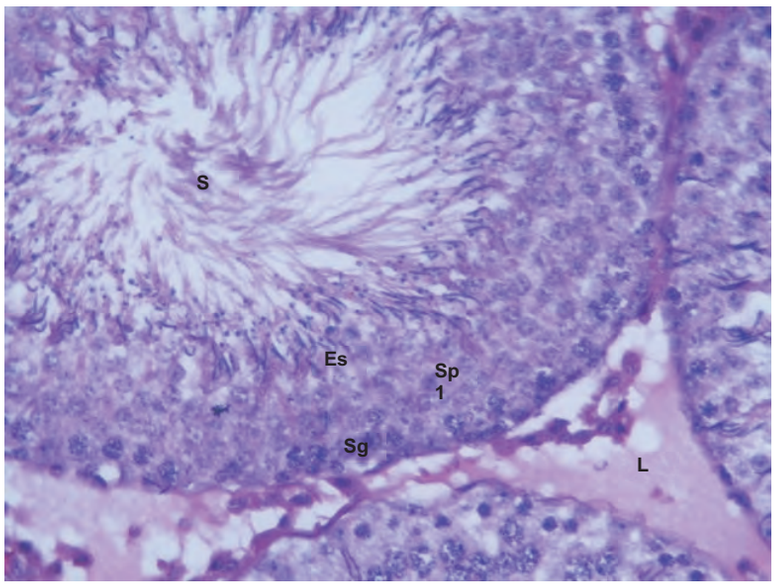
LM 001 basement membrane BM that is well defined and all the germ cells are represented. Spermatogoonia S, primary spermatocyte Sp,Spermatids Sd and Sertoli cell Sc. Magnification: Photomicrograph of control section of the testes of Sprague Dawleyrat.



LM 002 Photomicrograph of testis of rats treated with Pb only for 16 days in the - Sprague Dawley rat. Not all the germ cell are present here and the Sertoli cell cytoplasmic appear to contain vacuoles. Magnification 400



LM 003: Photomicrograph of testis of rats treated with Pb only for 56 days. The spermatids are almost absent, indicating abnormal spermatogenesis or arrest of spermatogenesis ,the interstitial spaces contains little or no leydig cell L cytoplasm, here energy metabolism, and mitochondrial functions have been impaired and compromised.



*LM 004 : Photomicrograph of the testis of rat treated with distilled water only. sections show: Spermatogonia Sg primary spermatocyte Sp1, Elongating spermatids Es undergoing meiosis. Arrow shows the interstitium (leydig cell cytoplasm L). A clear lumen with mature spermatozoa S, there is restoration of spermatogenesis as evidenced by the arrangement of the cellular structure in both the interstitium and the tubules . Magnification *400*

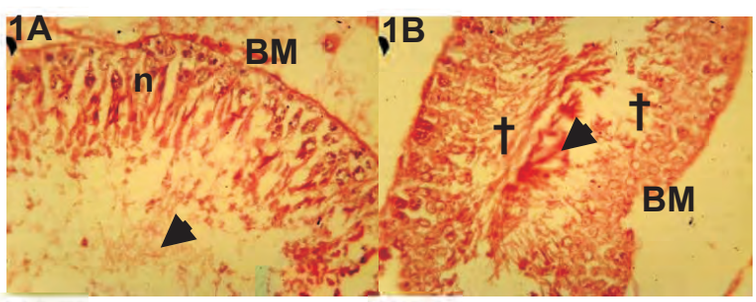


Figure 1: General Morphology of the germinal epithelium of rats (stained with Hematoxylin and Eosin). (A) Control (B) 100mg/Kg Pb- Acetate (BM) basement membrane, arrow head indicates the lumen of the seminiferous tubule (Magnification X400).

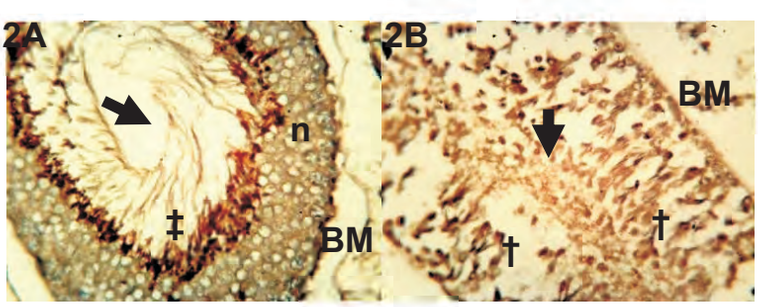


Figure 2: Alkaline phosphatase immunohistochemistry in the germinal epithelium of rats. (A) Control (B) 100mg/Kg Pb - Acetate (‡) represents regions of ALP immunopositivity and (†) represents regions of cellular degeneration, (n) represents normal cells of the epithelium, (BM) basement membrane, arrow head indicates the lumen of the seminiferous tubule (Magnification X400).

CONCLUSION

Risk management strategies should be undertaken by various states and developing countries in general. Means of reducing occupational lead exposure should be adopted and supplementation by trace metals probably helps in reducing the effect of heavy metal poisoning.

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