Behavior and Performance

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1. Overt and acute behavioral changes (human).

Lead poisoning is characterized by a range of overt symptoms. Among these are severe headaches, depression, insomnia, and hallucinations.

The sensory effects commonly described are abnormal sensations and excessive sensitivity, but especially visual disturbances ranging from mild, transitory changes to partial or complete blindness. Motor effects include paralysis, which usually develops slowly and varies in severity, muscular twitching, and tremors. Acute lead psychosis is described as similar to other psychoses, with hallucinations, emotional lability, disorientation, delusions of persecution, etc. However, epileptiform seizures are present.

TEL SECTION

Gasoline-sniffing by adolescents has been reported, as well as one extreme case in an adult in which lead encephalopathy developed (Law and Nelson, 1968). Hallucinations, excitability, impairment of recent memory and a slightly ataxic gait were associated with an elevated blood lead level.

2. Insidious changes in behavior?

Lane (1964) has pointed out that only the lead worker exhibiting some toxic episode comes to medical attention. The worker who has become slowly and insidiously poisoned, who is "below par," but without acute manifestations, is

apparently well only because he presents no overt health problems. However he is later subject to chronic nephritis and cerebral hemorrhage (Lane, 1964). As Hardy (1966b) points out: "Nonspecificity of sign and symptom, delayed diagnosable damage because of the body's incredible margin of safety, and more than one insult acting like lead or with lead require sophisticated attention to the potential effect of low doses of lead--in much the same manner as low levels of ionizing radiation have been studied since the use of atomic energy for military purposes in 1945." If the notion of "insidious poisoning" is valid, one might expect that workers exposed to lead levels below those producing overt symptoms of toxicity would also show behavioral changes, similar to the sensory, motor and other alternations characteristic of frank lead poisoning, but to a lesser degree. However, no such investigations have been reported. In the experimental administration of lead to human subjects for long time periods, blood levels rose and remained fairly constant (Kehoe, 1960). However, while the blood remained in a steady state, the body lead burden slowly increased as a small difference between lead intake and output persisted. It would seem that the binding of lead in certain tissues and bone continues after the blood has arrived at a steady state. This picture of positive lead balance should be viewed against the clinical background of lead poisoning in making a decision about the possible effects of low levels of exposure to lead:

"The symptoms of lead poisoning are, initially at least, rather vague; irritability and other mood changes predominate in the early stages, frank psychosis and encephalopathy later. The long biologic half-life results in so slow a buildup of toxic levels in the body that no connection may seem evident between the beginning of exposure to a chronically noxious environment and the development and progression of the symptoms of lead poisoning" (Goldstein et al, 1968).

3. Behavioral effects (animal).

While the nascent sub-discipline of behavioral pharmacology has developed rapidly over the last 10-15 years (Thompson and Schuster, 1968; Dews, 1970; Kelleher and Morse, 1968), behavioral toxicology is much younger in this country (Weiss and Laties, 1969). Consequently, only a few studies are available which deal with the behaviorally toxic properties of lead.

Using a water T-maze, in which an animal must swim into the correct arm of the T to escape from the situation, Bullock et al (1966) found that tetraethyllead administration had little effect on the performance measured. Rats were given TEL intraperitoneally for 8 days to a total dose of 15 mg / kg. Four days after the last dose, maze training was begun. Escape times differed only slightly between control and experimental groups, and swimming times not at all. Other animals were given TEL injections after training had started. There were no performance differences

between experimental and control groups. All TEL-injected rats showed tremor, ataxia, fighting, and after a few days, convulsions and death. The water T-maze is apparently a rather insensitive instrument for evaluating TEL toxicity, nor has it proven suitable for evaluating other pharmacological agents.

Using a classically conditioned motor response in rats, Gusev (1960) demonstrated behavioral impairment when animals were exposed to atmospheric concentrations of lead oxide at between 10 and 11 ug/m^3 for 6 hours daily for 6 months. The actual number of exposure days, excepting the off days, was 148-150 days. Using force and latency of response measures, no impairment was seen at about 1.13 ug/m^3 of lead. At the higher dose level (11 ug/m^3), disturbed reflexes began to occur about 1.5-2 months after the start of exposure and increased in severity over the exposure period. Baseline conditioned reflex activity was re-established 10-23 days after lead exposure was discontinued. As exposure time increased, differential reactions to strong (bell) and weak (light) conditioned stimuli were often disrupted and positive reactions to a negative conditioned stimulus (buzzer) also occured. No changes in the formed elements of the blood were seen in any of the experimental animals. Pathohistological changes in the CNS were noted in rats and rabbits exposed to about 11 ug/m^3 of lead oxide, and the rat bone lead content was 10 times as high as either control animals or those exposed to the lower dose level.

In an experiment using the same methods and parameters as Gusev (1960), Shalamberidze (1961) found that a lead sulfide concentration of 48.3 ug/m^3, calculated as metallic lead, produced disturbed conditioned reflexes in rats exposed to ore dust inhalation 6 hours daily for 6 months.

Novakova (1969), using similar classical conditioning techniques, found that combined chronic doses of arsenic (0.0025 mg/kg) and lead (0.005 mg/kg) were additive in their effects and disrupted the acquisition of conditioned reflexes. These behavioral tests were administered between the fourth and eighth months of chronic dosing.

Only one study in this country of the behavioral effects of low level exposure to lead was found. Goldfish were given shock avoidance training and then exposed to specific concentrations of lead nitrate for 48 hours (Weir and Hine, 1970). Tests after 24 and 48 hours of exposure, with different groups being exposed to different lead concentrations, yielded significant behavioral impairment as low as 0.07 ppm. This is only 1/857 of the concentration which is lethal to one per cent of the animals and approximates potable water. Mercury was more, and arsenic and selenium less toxic than lead. Impairments were found at 0.003, 0.1, and 0.25 ppm, respectively. In the light of the controversial reception given the Russian experiments [redacted] on the behavioral toxicity of atmospheric lead, it is interesting to note that these results show impairment at a similar order of magnitude.

All of the drugs commonly associated with the production of physical dependence (amphetamines, barbiturates, morphine, alcohol) also suppress the paradoxical, or rapid eye movement (REM), phase of sleep. They also produce a long rebound of this REM phase upon withdrawal of the drug (Oswald, 1969). In the light of this sensitivity of the REM phase to drugs, it is interesting to note that the chronic absorption of lead also effects REM sleep (Xintaras et al, 1967). Rats given lead acetate (1.5 mg/ml) in their drinking water showed altered REM phase patterning. This could be related to the fact that an early sign of plumbism is insomnia (Cantarow and Trumper, 1944).

4. Effects of early exposure to lead.

If the developmental processes of the foetus or immature organism are subject to pathologic alteration by exposure to lead, such pathological changes will necessarily have behavioral implications. If rats nursing their young are fed diets containing either 1 or 4 per cent lead carbonate, lead appears in the milk and effects the neonates (Pentschew and Garro, 1966; Rosenblum and Johnson, 1968). The young show evidence of lead intoxication, faulty growth, and various neurological changes. The latter include paraplegia, changes in the cerebellum and striatum, and blood-brain barrier dysfunction.

While various lead salts (50 mg/kg) administered to hamsters on days 7, 8 or 9 of gestation produced skeletal malformations in sacral and tail vertebrae (Ferm and

Carpenter, 1967), recent evidence reveals a low degree of teratogenic effects in rats and mice (McClain and Becker, 1970). Little radioactive lead was found to cross the placenta. On the other hand, Barltrop (1969) cites evidence of placental penetration by lead in rats, and presents human material suggesting maternal-foetal blood lead equilibrium. The apparent contradiction of these results may be a function of the amount of trace metals present. For example, mother rats injected with mercury or cadmium had higher blood levels of these when also injected with selenium, but the selenium decreased the amounts transfered to foetuses or to sucklings via milk (Parizek et al, 1969).

5. Late effects of early lead exposure (humans).

Byers and Lord (1943) studied 20 school children who had been hospitalized for lead poisoning in early childhood. None of these had shown evidence of encephalopathy and were judged, at that time, to have made complete recoveries. Only one of these children made satisfactory progress in school, the others showing various intellectual and emotional difficulties.

In a recent review of this important area, Wiener (1970) concludes that while most studies report behavioral impairment due to lead poisoning, none satisfies the demands of statistical control. There are also problems with respect to sampling bias and the application of various diagnostic procedures and definitions.

The evidence with respect to the special effects of

early exposure to lead, particularly in its implications for later behavior, remain unclear at this time.

6. Suggested lines of behavioral investigation.

Perhaps the most controversial and also the most pressing aspect of the lead exposure problem is the effect of chronic, low levels of lead in the environment. The extent to which such chronic levels influence behavior needs to be evaluated with reference to well-understood behavior baselines. Long-term studies, similar to those undertaken by the Russian investigators, but utilizing operant conditioning as well as other methods, need to be instituted. There is also no substitute for the chronic exposure of organisms to various dose levels and the consequent delineation of dose-effect functions. Demonstrations that some dose level "has an effect" on behavior provide an insufficient base from which to proceed toward the study of behavioral mechanisms of action. The lessons afforded by behavioral pharmacology in this regard are well worth noting.

Certain areas of investigation could be used to illuminate the particular effects lead may be suspected of having at low levels. Since lead poisoning produces peripheral neuropathy (Fullerton, 1966; 1969) and muscular changes (Cantarow and Trumper, 1944); and lead ions produce preganglionic transmission block (Kostial and Vouk, 1957), the the effects of chronic exposure to lead on motor control tasks (Falk, 1969) might yield early indications of the behavioral toxicity of lead.

Lead poisoning also produces various visual disturbances. These might be evaluated not only by acuity and flicker fusion determinations, but by the use of the evoked response technique. Promising investigations along this line have been instituted by Xintaras et al (1966).

In evaluating the effect of lead on sleep patterns, Xintaras et al (1967) have opened the area of complex, natural behavioral sequences to behavioral toxicology. While the study of complex, learned behavior schedules (Ferster and Skinner, 1957) is likely to prove indispensible, the effects of lead exposure on the patterning of REM phases, thresholds of aggression (Hutchinson et al, 1965), and food-fluid intake patterns should receive attention. Also, ethological studies of courtship and parental sequences should not be neglected as they may provide early indications of wildlife problems not likely to be discovered in laboratory studies.

In studying the toxicology of lead, it is imperative for investigators to utilize more well-known agents in the research program as reference standards to validate their experimental arrangements. Thus, Xintaras et al (1966) used the well-known effects of pentobarbital on the evoked response in order to validate their evoked response preparation before studying the lesser known effects of carbon monoxide and ozone.

Since lead is not the only toxic substance to which an organism might be subjected at a particular time, investigators should also consider the combined effects of lead with

other pollutants (e.g. carbon monoxide) or probable vehicles (e.g. ethanol). The possible synergistic effects of various pollutants are largely unknown (Tomashefski and Mitchell, 1969), however, the not uncommon combination of alcoholism and lead poisoning is known to be a medical problem (Cheatham and Chobot, 1968; Hardy, 1966a).

Finally the relative sensitivity of the fetus, neonate and adult to chronic, low-level exposure to lead needs investigation, as does the question of both the reversibility of any toxic effects upon the termination of undue exposure, and an evaluation of residual effects. The possibility of specific susceptibility at various fetal and juvenile stages in the developing brain should be evaluated most carefully.

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