Heavy Metal Toxicity and Energy Metabolism in the Developing Brain
Lead as the Model

JOHN J. O’NEILL and DAVID HOLTZMAN

LEAD ENCEPHALOPATHY

1. Introduction

1.1. The Clinical Problems and Animal Models

It has long been recognized that lead poisoning produces devastating neurologic damage to the CNS in children (encephalopathy) that is characterized by cerebral edema, convulsion, and coma (Aub et al., 1925; Byers and Lord, 1943). Poisoning in adults results largely from occupational exposure and produces clinical or subclinical signs of peripheral neuropathy usually without CNS involvement. The reasons(s) for this maturational change in brain sensitivity to lead toxicity are uncertain, but perhaps can be related to the development of the mammalian nervous system (Reiter, 1982). In the protracted period of CNS development, there are specific time-related processes termed “growth spurts” by Davison and Dobbing (1968), who related brain growth to differing time scales depending on the species, i.e., days in rats and mice, months for human development. Since such estimates fail to take into account individual growth rates for neurons and glia, Rodier (1979) described the prenatal and postnatal time course of neuron proliferation. His studies showed that although different neuronal systems develop at different rates within a single species, and the exact timing may vary, the sequence of development is similar for all
species studied. In addition to such neuroanatomic correlates of growth, periods of neurochemical transition termed “critical periods” have been described by Himwich (1951). Toxic damage following exposure to noxious chemicals has been related in specific cases (e.g., methyl mercury) to these stages of nervous system development (Suzuki, 1980).

In recent years, there has been a growing awareness of the toxic dangers to the developing nervous system from prolonged exposure to low lead levels (e.g., Lin-Fu, 1980). The encephalopathic effects of low-level lead exposure may be expressed as deficits in IQ, learning problems, and poor classroom behavior (de la Burde and Choate, 1975; Beattie et al., 1975; Landrigan et al., 1975). The difficulty encountered in establishing a causal relationship between exposure and toxicity may be due to the lack of analytical data relating extent of exposure to specific periods of CNS development. Some attempts have been made by measuring lead content in hair samples (Pihl and Parkes, 1977) and in deciduous teeth (Needleman et al., 1979). Needleman’s group described a comprehensive study of Boston elementary school children and reported deficits in psychologic testing and poor classroom behavior that correlated with cumulative lead content in dentine of the child’s first teeth. The data are persuasive that an association exists between lead exposure and psychosocial behavior, but such studies may suffer from the inherent weakness of not being able to relate the age and duration of lead exposure to these deficits.

In rat, as in man, acute lead encephalopathy occurs predominantly at young ages and rarely in adults (Goldstein et al., 1974; Clasen et al., 1974). Based on the pioneering work of Pentschew and Garro (1966), many studies using the rat as a model have reported toxic effects of high-dose lead feedings on the developing nervous system. The pathologic changes are similar in the rat pup and young children including hemorrhage, edema, neuronal necrosis, and capillary hypertrophy most marked in the cerebellum, but present also in basal ganglia, neocortex, and hippocampus at younger ages (Clasen et al., 1974; Press, 1977a,b). Largely through the efforts of Michaelson (1973), Patel et al. (1974), Krigman and Hogan (1974), Maker et al. (1975), and Holtzman and Hsu (1976), much has been established concerning the neurochemical effects of lead on brain growth and metabolism.

Neuropathologic changes also have been reported to occur following exposure to low lead doses in drinking water. The brains of rat pups, exposed to lead through their dam’s consumption of lead in drinking water (10 mg/ml

<table>
<thead>
<tr>
<th>Age of animals (days)</th>
<th>Control</th>
<th>Pb treated</th>
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<tbody>
<tr>
<td></td>
<td>Number of cells counted</td>
<td>Spine density</td>
</tr>
<tr>
<td>20</td>
<td>71</td>
<td>29.31 ± 0.88</td>
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<tr>
<td>56</td>
<td>73</td>
<td>32.32 ± 1.45</td>
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</tbody>
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*From Kiraly and Jones (1982).*

*a Mean ± SE number of spines per 100 μm of dendrite.

38.74