

graphs of the posterior pituitary but in those of the supraoptic and paraventricular nuclei as well (Fig. 1D). Intravenous administration of other α -adrenergic blocking agents, such as phentolamine and yohimbine, produced similar results, whereas β -adrenergic blocking agents had no such effects (11).

A more likely explanation for the apparent discrepancy in the metabolic responses of the hypothalamic nuclei and their projection areas in the posterior pituitary to stimulation by dehydration may be in their anatomical properties. The surface-to-volume ratios of the nerve terminals in the posterior pituitary are considerably greater than those of the cell bodies in the supraoptic and paraventricular nuclei, and equivalent impulse activity would therefore be expected to lead to greater increases in energy metabolism in the nerve terminals than in the cell bodies (12, 13). Indeed, the energy metabolism of any region may represent primarily the metabolic activities of the nerve terminals and synaptic elements within it. For example, the glucose utilization in the hypothalamic nuclei may reflect mainly the synaptic input and interneuronal activity of these nuclei and not its output (that is, the magnocellular neurons' firing rates). Indeed, the metabolic activation produced by high doses of phenoxybenzamine in the supraoptic and paraventricular nuclei may be a reflection of increased synaptic activity rather than a direct activation of the perikarya. There is already evidence from studies of the visual system of the monkey that it is the neuropil of layer 4 that has the highest rate of glucose utilization in the striate cortex and is the portion most metabolically responsive to alterations in visual input (4). The excellent correlation between functional activity and glucose utilization in the posterior pituitary, which is also composed primarily of small unmyelinated axons and nerve terminals (13), in contrast to the poor correlation in the cell bodies of the pathway in the hypothalamic nuclei may represent another example of the same phenomenon.

On the basis of this reasoning, the [^{14}C]deoxyglucose method may provide a unique approach for the study of afferent pathways in the mammalian brain. In any neural pathway where the site of input (nucleus containing the cell bodies and dendrites) and the site of output (region containing the nerve terminals) are known, it should be possible to electrically stimulate specific, putative afferent pathways and evaluate whether [^{14}C]deoxyglucose uptake increases at the in-

put site. Increased [^{14}C]deoxyglucose uptake at the input site would then provide evidence for the presence of the afferent pathway, and evaluation of [^{14}C]deoxyglucose uptake changes at the output site would provide information on whether the specific afferent pathway is inhibitory or excitatory.

WILLIAM J. SCHWARTZ
CAROLYN B. SMITH, LESLIE DAVIDSEN
HELEN SAVAKI, LOUIS SOKOLOFF
*Laboratory of Cerebral Metabolism,
National Institute of Mental Health,
Bethesda, Maryland 20014*

MARINA MATA
DAVID J. FINK, HAROLD GAINER
*Section on Functional Neurochemistry,
Behavioral Biology Branch, National
Institute of Child Health and Human
Development, Bethesda*

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5. The mammalian hypothalamo-neurohypophysial system is composed of magnocellular neurosecretory cells with perikarya located in the supraoptic and paraventricular nuclei and nerve terminals located in the posterior pituitary [see H. Heller, *Handb. Physiol.* **4**, 103 (1974)]. Two distinct cell types, vasopressin- and oxytocin-secreting cells, are present in this system and have been identified physiologically (6, 7) and immunocytochemically [E. A. Zimmerman, A. G. Frantz, W. H. Sawyer, *Endocrinology* **95**, 931 (1974); F. Vandesande and K. Dierckx, *Cell Tissue Res.* **164**, 153 (1975)].
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8. The oxytocin cells in the supraoptic and paraventricular nuclei selectively respond (by increased spike activity and oxytocin release) to suckling during the milk ejection reflex [J. B. Wakerley and D. W. Lincoln, *J. Endocrinol.* **57**, 477 (1973); D. W. Lincoln and J. B. Wakerley, *J. Physiol. (London)* **242**, 533 (1974)]. Vasopressin cells respond most selectively to hemorrhage as a stimulus [(6); J. B. Wakerley, D. A. Poulain, R. E. J. Dyball, B. A. Cross, *Nature (London)* **258**, 82 (1975)]. Both cell types respond vigorously to hyperosmotic stimuli (6, 7).
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11. H. Savaki, unpublished data. It should be pointed out that the injection of phenoxybenzamine into rats (1.5 mg/kg) itself causes considerable vasopressin release [T. E. Bridges and N. A. Thorn, *J. Endocrinol.* **48**, 265 (1970)]. However, α -adrenergic antagonists, such as phenoxybenzamine and phentolamine, also inhibit specific stimulation-induced release of oxytocin and vasopressin [Bridges and Thorn, *ibid.*; E. Tribollet, G. Clarke, J. J. Dreifuss, D. W. Lincoln, *Brain Res.* **142**, 69 (1978)].
12. The posterior pituitary represents a uniquely high concentration of axon terminals. Morphometric studies of rat neurohypophysis indicated that more than 42 percent of the total volume of this tissue is composed of axon terminals [J. J. Nordmann, *J. Anat.* **123**, 213 (1977)].
13. Previous studies have shown that the increase in energy metabolism (oxygen consumption) in nervous tissue in response to electrical activity is due principally to the activity of the sodium pump in restoring the ionic gradients [J. M. Ritchie, *J. Physiol. (London)* **188**, 309 (1967); P. De Weer, in *Physiology*, Ser. 1, vol. 3, *Neurophysiology*, C. C. Hunt, Ed. (Butterworth, London, 1975)]. In any nerve process, the increase in concentration of intracellular sodium (or decrease in potassium) per impulse is an inverse function of the diameter of that process [for quantitative relations see P. Greengard and J. M. Ritchie, in *Handbook of Neurochemistry*, A. Lajtha, Ed. (Plenum, New York, 1971), vol. 5A, pp. 317-335]. Hence, neural tissues containing fibers of smaller diameter (or fibers with greater surface-to-volume ratios) will need to pump more sodium ions per impulse and consequently will utilize more oxygen and glucose per impulse than tissues of equal mass (or volume) containing fibers of larger diameter. We examined the relationship of [^{14}C]deoxyglucose uptake to impulse activity in a preparation of rat posterior pituitary. Under conditions of depolarizing stimulation, glucose utilization was increased and this increase could be blocked by ouabain. The incremental increase in glucose utilization accompanying membrane depolarization was primarily a function of the increased activity of the sodium pump (M. Mata, D. J. Fink, H. Gainer, C. B. Smith, L. Davidsen, H. Savaki, W. J. Schwartz, L. Sokoloff, *J. Neurochem.*, in press).

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Lead Enhancement of Lithium-Induced Polydipsia

Mailman *et al.* (1) concluded in the abstract of their report that their data were "evidence that there may be permanent neural changes induced by postnatal exposure to lead that are manifested by pharmacological challenge with lithium." The report documents that massive oral doses of lead administered postnatally lead to subsequent enhancement of lithium-induced polydipsia. Urine osmolality was not given so that we have no idea of the role of antidiuretic hormone in this syndrome. Sodium excretion and free water clearance are similarly unre-

corded. Moreover, no information is given about renal histology or lead content. The report documents only that the polydipsia was not due to changes in the renin-angiotensin system.

Acute lead intoxication in the young is well known to produce a proximal tubular transport defect (2). This could lead to proximal renal sodium wasting which might show up in the final urine as an increased sodium supply to the diluting segment of the distal nephron or as natriuresis. In either case the polydipsia would be the result of lead nephropathy

which could be discerned histologically or physiologically, or both (3). Lithium is known to inhibit antidiuretic responsiveness of the collecting duct resulting in nephrogenic diabetes insipidus (4). Before the hypothesized neural mechanism of polydipsia is accepted the direct renal effects of lead should be ruled out.

RICHARD P. WEDEEN
*Veterans Administration Hospital,
East Orange, New Jersey 07019*

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There are important implications inherent in Wedeen's comments (1) that we attempted to address in our report (2). First, to say that we administered "massive oral doses of lead" (1) does not allow for the fact that only a portion of this dose was absorbed by the rats, as manifested by the fact that blood lead levels 24 hours after the last dose were usually between 90 and 150 $\mu\text{g}/\text{dl}$. The dose of 200 mg per day used in our model of administration to the neonate was chosen because it was the highest one at which we found no difference in body weight between treated and control rats when the animals were 60 days old (2). At the cessation of lead treatment (30 days of age), there was ample evidence of lead exposure in treated animals. Free erythrocyte protoporphyrin (FEP) values were more than doubled, and there appeared to be a small, but significant, increase in urine production and water consumption. As expected, there were large increases in blood and renal lead concentrations. Morphologically, there were increases in both numbers and size of vacuoles in the proximal convoluted tubules in the lead-treated animals, but there were no observable lead inclusion bodies.

However, within 30 to 60 days after cessation of lead treatment, these alterations disappeared, or were significantly attenuated. Basal water consumption and urine production did not differ between groups [see (2)], nor did urine pro-

tein, pH, specific gravity, or urobilinogen. FEP was still slightly elevated (about 20 percent) at 60 days as were concentrations of lead in the blood (20 $\mu\text{g}/\text{dl}$ for the treated rats as opposed to 6 $\mu\text{g}/\text{dl}$ for controls). Renal lead concentrations, which were 8.8 parts per million (ppm) at 30 days of age, were less than 4 ppm at 60 days of age. This is interesting because it was demonstrated (3) that aminoaciduria and renal edema do not occur until renal lead levels exceed 10 ppm.

As we reported (2), lithium administration caused greater increases in water consumption in the 60-day-old (or older) lead-treated rats, with concomitant increases in urine production. However, there were similar increases in urine protein and pH and decreases in urine specific gravity in both lead-treated and control animals. Prior to lithium administration, there were also no differences between 60-day-old (or older) lead-treated and control rats in water consumption (2), or urine production or composition. Further, light or electron microscopic evaluation of lead-treated and control animals at 60 days of age revealed no difference in renal morphology.

These data demonstrate that no alteration occurred in kidney function that would directly explain the increased lithium-induced polydipsia (LIP). The increased LIP in neonatally lead-treated rats persisted unattenuated for at least 180 days, at which time neither blood nor soft tissue lead content differed between control and treated groups (2). In contrast, in recent experiments when we administered still greater quantities of lead to older rats (lead given from postnatal days 30 to 60) we found no evidence of increased LIP when the animals were tested at 90 days of age (4). These data clearly demonstrate that the change responsible for altered LIP is permanent, and that the "lesion" must occur during early postnatal development. Further, since the 30- to 60-day exposure would also be expected to cause kidney damage, it appears that altered renal function is not the most likely mechanism. Until a precise locus for effects of lead on LIP is found, we cannot rule out the possibility that lithium administrations cause a latent kidney pathology. However, since renin secretion from the kidney is an im-

portant homeostatic step in the maintenance of fluid and electrolyte homeostasis, the fact that we found no differences in plasma renin activity (PRA) or angiotensin I or II concentrations between lead-treated and control animals, either before or after lithium challenge (2), provides further evidence that differences in kidney function were probably not the causal mechanism for our observation. Both the control and the lead-treated rats showed the expected large increases in PRA after lithium treatment (2), but they did not differ from each other.

We therefore think that our statement that "there may be permanent neural changes induced by postnatal exposure to lead" is reasonable and is the most probable explanation for our results. We are aware of the many unanswered questions related to lithium actions in the central nervous system, as well as the peripheral-central interactions involved in fluid-electrolyte homeostasis. Additional research will be necessary to answer definitively the interesting questions raised by this action of lithium in rats treated with lead as neonates.

RICHARD B. MAILMAN
GEORGE R. BREESE

*Departments of Psychiatry
and Pharmacology*

MARTIN R. KRIGMAN
PAUL MUSHAK

Department of Pathology

ROBERT A. MUELLER

*Departments of Anesthesiology and
Pharmacology and Biological Research
Center, University of North Carolina
School of Medicine, Chapel Hill 27514*

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4. In these experiments, rats were intubated with, per kilogram of body weight, 400 mg of lead (as the acetate) from days 30 to 45. From 45 to 60 days, they had sufficient lead acetate placed in their drinking water to approximate an exposure of 400 mg/kg. These rats had blood levels greater than 400 $\mu\text{g}/\text{dl}$ at 45 days and greater than 100 $\mu\text{g}/\text{dl}$ at 60 days of age. In three separate experiments utilizing two litters each, no differences in LIP was found when testing was done at 90 days of age.
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