performance with plastic words (*1, 3*), but also, in a sense, with human performance. Although accuracy in humans does not often vary (*4*)—and certainly would not on material of this simplicity—latency on same judgments is typically shorter than that on different judgments (*5*). We have been unable to find comparative data on similar judgments, however.

In tests 1 to 3, accuracy on "same" and "different" varied with the contrasted alternative. In questions in which "same" was the correct answer, Sarah was correct on 93 percent of trials when "different" was the alternative but only 82 percent when "similar" was the alternative. Similarly, in questions in which "different" was correct, she was correct on 80 percent when "same" was the other choice but only 60 percent when "similar" was the other choice. Thus, for both same and different judgments, clear-cut choices (same-different) met with greater accuracy than the finer distinctions (same-similar and similar-different). Also, in line with this conclusion were the results for similarity judgments, which did not vary with the contrasted alternative. In questions in which "similar" was correct, she was correct on 74 percent when the alternative was "same" and 78 percent when the alternative was "different."

The chimpanzee's success on the present tests demonstrated not only rudimentary cognitive and linguistic capacities but a sophisticated perceptual-motor capacity as well. The perceptually most notable feature of the tests, easily missed by the extraordinarily perceptive human observer, is that the question and its potential answers occurred on separate lines. The subject responded not by completing a gap in a string of objects (plastic words), but "read" the question depicted on the page, found the appropriate answer in a list of alternatives, and marked the answer, even though it was physically removed from the question. The results show that chimpanzee, like human, can do readily what many other species can do only with great difficulty, if at all: respond correctly to one location on the basis of stimuli presented elsewhere (*6*).

The present results cannot be interpreted in terms of the subject's sensitivity to inadvertent social cues. However, Sarah's performance may have relied critically on quite different features of her social relationship with the trainer. He was quick to respond to her summons at the end of every trial, and praise or food was soon to follow. Left to herself for longer periods of time with a test booklet, would she continue to respond? Would she answer only those questions on which she was proficient (for instance, only same judgments)? Indeed, does she know that some questions pose difficulties for her? Would she answer all questions rapidly, but review her answers later and make corrections? The potential of the present test format for providing answers to such questions can now be explored.

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Memory Impairment in Korsakoff's Psychosis: A Correlation with Brain Noradrenergic Activity

Abstract. *The concentration of the primary brain metabolite of norepinephrine is diminished in the lumbar spinal fluid of patients with Korsakoff's syndrome. The extent of its reduction is significantly correlated with measures of memory impairment for individual patients. These data suggest that the memory disorder of Korsakoff's syndrome may result from damage to ascending noradrenergic pathways by the diencephalic and brainstem lesions associated with this disease.*

Korsakoff's psychosis, the chronic phase of the Wernicke-Korsakoff syndrome, is an organic brain disease characterized by varying degrees of retrograde and anterograde amnesia with relative sparing of other intellectual functions (*1, 2*). The acute phase of the disease, Wernicke's syndrome, has long been attributed to a specific thiamine deficiency, typically occurring in nutritionally depleted chronic alcoholic individuals and generally improving after treatment with thiamine. Blass and Gibson (*3*) recently reported a defect in transketolase (E.C. 2.2.1.1), a thiamine-dependent enzyme, in cells cultured from patients with the Korsakoff syndrome; however, the relation between thiamine deficiency and the symptoms characteristic of Korsakoff's psychosis is not clear.

The neurologic basis of the memory deficit seen in Korsakoff's psychosis is not understood. Pathologic studies (*2, 4*) have demonstrated consistent diencephalic and brainstem lesions symmetrically located in the region of the third and fourth ventricles and aqueduct. It is of particular interest that these lesions are located along the pathways of monoamine-containing neurons that have been traced by histofluorescence methods (*5*).

If the memory disorder of Korsakoff's psychosis is related to impaired central monoamine systems, one might expect to find a change in the cerebrospinal fluid (CSF) concentrations of one or more of the brain metabolites of these putative neurotransmitters: namely, 3-methoxy 4-hydroxyphenyl glycol (MHPG) and vanillylmandelic acid (VMA), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA), central metabolic products of norepinephrine, dopamine, and serotonin, respectively. We have examined the CSF of nine patients with the Korsakoff syndrome and have found an abnormally low concentration of MHPG. We have also noted a correlation between the extent of decrease of MHPG in the CSF and the severity of memory impairment in individual patients.

A number of investigators have implicated ascending catecholamine pathways in learning and memory consolidation (*6, 7*). Anlezark *et al.* (*8*) found that mid-pontine lesions including locus coeruleus are associated with impaired subsequent learning and decreased cortical levels of norepinephrine in rats. Intracranial self-stimulation is supported by electrodes implanted in the locus coe-

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ruleus and along ascending noradrenergic pathways and is selectively affected by drugs influencing brain catecholamine activity (*7*). Puromycin-induced amnesia in mice can be reversed by the administration of drugs increasing noradrenergic activity (*9*), whereas drugs decreasing the concentration of brain monoamines lead to a temporary failure to perform a well-learned conditioned avoidance response (*10*).

Our patients ranged in age from 40 to 57 years, all had a history of chronic alcoholism, and all fulfilled the criteria for Korsakoff's amnesia as described by Victor *et al.* (*2*). All patients moved freely about the hospital and had received no drugs for at least 2 weeks prior to the lumbar puncture except for one patient who was on long-term Dilantin therapy for a seizure disorder. Lumbar punctures were performed and CSF samples processed according to the method described by Gordon and Oliver (*11*). Specimens were delivered frozen to E. K. Gordon at the National Institute of Mental Health, who performed the monoamine metabolite analyses. Samples were analyzed for MHPG, VMA, and HVA by the gas chromatographic-mass fragmentography method of Gordon *et al.* (*12*). The concentration of 5-HIAA was determined by the fluorimetric method of Ashcroft and Sharman (*13*).

Table 1 lists the concentrations of spinal fluid monoamine metabolites obtained for our patients and mean values for a control population of psychiatric patients, determined by the same laboratory (*14, 15*). The significance of the results was determined by Student's *t*-test with a correction for unequal group sizes and population variances (*16*). The concentration of spinal fluid MHPG was significantly lower among the Korsakoff's syndrome population ($t = 2.74$. $P < .01$), whereas the concentrations for VMA ($t = 1.12$), HVA ($t = 0.98$), and 5-HIAA ($t = 0.114$) were not significantly different from those of the psychiatric patients. These results indicated that the major brain metabolite of norepinephrine, in contrast to metabolites of dopamine and serotonin, was significantly reduced in the spinal fluid of the patients with Korsakoff's syndrome. Vanillylmandelic acid, a secondary brain metabolite of norepinephrine, was generally lower among our patients although not significantly so. The lack of significant differences for VMA may be due to the inherent uncertainty in measuring its relatively low concentrations or, as Jimmerson *et al.* (*14*) suggest, to its originating from a different component of central nervous system (CNS) norepinephrine metabolism than does MHPG.

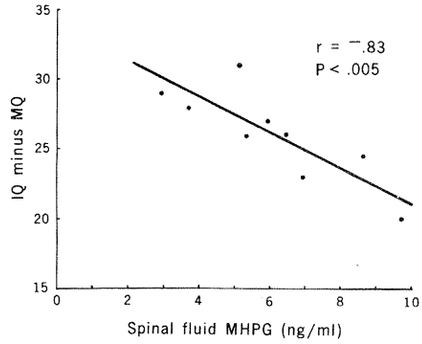

Fig. 1. The IQ-MQ difference as a function of MHPG concentration in lumbar CSF for individual patients with Korsakoff's syndrome. The line depicts the least-squares fit for the data.

Memory function was measured prior to the lumbar puncture for the Korsakoff's syndrome patients by comparing the memory quotient (MQ) derived from the Wechsler Memory Scale with the full-scale intelligence quotient (IQ) derived from the Weschsler Adult Intelligence Scale. This measure was chosen because it is standardized for age differences and provides a direct comparison of memory performance with other intellectual functions (*1, 17*). For a normal population, IQ should be equal to MQ. All of our patients scored at least 20 points lower on the MQ scale than on the IQ scale, indicating memory impairments far more severe than any general deficits in intellectual ability. The extent of the difference between IQ and MQ for individual patients correlated significantly with the concentration of MHPG in the spinal fluid ($r = -.83$, $P < .005$) but not with the concentrations of the other monoamine metabolites. Figure 1 shows the least-squares fit for the IQ-MQ disparity as a function of spinal fluid MHPG.

Our results indicate that spinal fluid MHPG is significantly decreased among Korsakoff's psychosis patients compared to psychiatric controls and that the extent of the decrease is closely related to the degree of memory loss. No comparable correlations were noted in measurements of spinal fluid VMA, 5-HIAA, and HVA. Patients' age, IQ, or duration of amnesic symptoms did not correlate with MHPG level or the IQ-MQ difference. The control group represented a broad range of psychiatric patients including ten depressed patients, nine manic patients, three schizoaffective patients and 12 acute schizophrenic patients. It has previously been reported that the concentrations of MHPG in the CSF are low in depressed patients and normal in manic and schizophrenic patients (*11, 14, 18*). Thus it would be expected that in the patients with the Korsakoff syndrome, spinal fluid MHPG would likewise be low in comparison to a normal population. Furthermore, the concentration of MHPG in the spinal fluid of our patients is substantially lower than in any reported normal control group.

The correlation between the IQ-MQ difference and the concentration of MHPG in the spinal fluid indicates that 69 percent of the variance reflected in the measure of the memory deficit may be directly related to the concentration of MHPG. Although spinal fluid MHPG levels have previously been reported to be decreased in groups of patients with other diseases (*11, 14, 18*), this is the first instance known to us in which severity of symptoms correlated significantly with decrease in spinal fluid MHPG for individual patients. Moreover, to our knowledge, this is the first direct evi-

Table 1. Full-scale intelligence quotients (IQ), memory quotients (MQ) and monoamine metabolite concentrations (nanograms per milliliter) for individual Korsakoff's syndrome patients, and mean metabolite concentrations for the psychiatric control group. Only MHPG was significantly diminished, although VMA also tended to be reduced among the patients with the Korsakoff syndrome.

Patient	Metabolite (ng/ml)					
	IQ	MQ	MHPG	VMA	HVA	5-HIAA
			Korsakoff's syndrome patients			
1	89	61	3.71	0.76	26	17.1
2	104	80	8.66	0.47	40	17.0
3	106	80	6.47	1.19	48	20.9
4	127	88	5.36	0.56	75	65.2
5	122	102	9.75	0.84	25	32.7
6	106	79	5.93	0.22	31	10.6
7	87	64	6.95	0.71	25	17.0
8	89	60	2.96	0.43	21	17.0
9	90	59	5.16	0.43	23	14.9
Mean ± standard error			6.11 ± 0.72	0.62 ± 0.10	34.9 ± 5.8	23.6 ± 5.6
			Psychiatric control group			
Mean ± standard error			12.1 ± 1.1	1.02 ± 0.18	28.1 ± 3.2	24.1 ± 1.7

dence in humans of a relation between CNS noradrenergic activity and memory function.

There is some uncertainty as to whether lumbar spinal fluid MHPG directly reflects brain norepinephrine metabolism in humans. Insignificant amounts of labeled MHPG administered intravenously in three patients were detected in the CSF (*19*), indicating that MHPG found in lumbar CSF is derived from norepinephrine degradation in the CNS; however, the relative contributions of brain and spinal cord norepinephrine metabolism to lumbar MHPG are not known. Humans with spinal cord transection have diminished lumbar MHPG concentrations, suggesting that spinal cord norepinephrine catabolism does contribute to spinal fluid MHPG at this level (*20*). Spinal cord norepinephrine is found principally in descending tracts whose cell bodies are located in the same regions of the brainstem as those giving rise to ascending norepinephrine pathways (*5*). Apart from occasional mild pallor of the dorsal columns related to peripheral neuropathy, spinal cord pathology is not a feature of the Wernicke-Korsakoff syndrome (*2*); it therefore seems reasonable to attribute the decrease in spinal fluid MHPG observed in our patients to supraspinal lesions known to occur in this disease.

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Fractional Factorial Analysis of Growth and Weaning Success in *Peromyscus maniculatus*

Abstract. *Fractional factorial designs were used to explore simultaneously the effects of eight variables on survival and growth of neonatal deer mice,* Peromyscus maniculatus. *Two of the variables had significant effects on weaning success. The magnitudes of their effects are illustrated.*

We have used fractional factorial designs sequentially to identify variables affecting the ability of female mice to raise young to weaning. Two of the variables considered were significant and were used in full factorial designs to establish a response surface. Fractional factorial experimental designs, which require fewer experiments to estimate main effects of the variables, permit the screening of large numbers of variables.

Knowledge of survival, growth, and reproductive potential for any species in different climates may aid our understanding of aspects of animal distributions and the role of climate in population dynamics. Heat and mass transfer equations have been used to predict survival requirements of adults of several species (*1*), but prediction of growth and reproduction potential as influenced by climate has been done only for ectotherms (*2*). Growth and reproductive potential for small endotherms may depend on heat and mass transfer, and on other "black box" variables, whose effects must be empirically determined, such as photoperiod, amount of fresh green sprouts, presence of other animals, and so on. The problem is to sort out those variables that have a significant impact in the context of the environmental variables, such as air temperature and movement, that also affect potential for growth and reproduction.

For our analysis, we chose variables (Table 1) that might affect growth rates of the young and chose initial variable levels arbitrarily for the first experiment. The results of our initial experiment guided our selection of new levels for subsequent experiments. The plus, minus coding is for high, low levels for each variable.

Table 1. Data from experiments 1 to 4 on *Peromyscus maniculatus*. Survival was 55 ± 5 percent for all center replicates; *N*, variable number; *n*, number of litters.

Variable		Level		Main effect (g) in experiments:			
N	Description	−	+	1 and 4	1 only	2 and 3	2 only
1	Sprouts	None	Free access	2.34		1.24	
2	Frequency of weighing	Once per day	Once per 3 days	−1.44	0.96	2.01	0.62
3	Nest box	No	Yes	1.25	−0.46	0.86	1.29
4	Remove young	No	Leave 2	−1.79	−0.95	0.80	0.39
5	Male presence	Yes	No	0.16	−1.39		
5	Photoperiod	LD 10 : 14	LD 14 : 0			−1.19	0.08
6	Exercise wheel	Locked	Free	−0.56		0.73	
7	Available food	80 percent	Free access	4.24	5.73	0.44	0.65
8	Available water	40 percent	80 percent			2.54	2.04
		80 percent	Free access	1.15	.18		

Mean weight/run (g) for:	
Blocked experiments for 1 and 4	5.93 ± 3.25 (n = 23)
Blocked experiments for 2 and 3	4.62 ± 2.08 (n = 40)
Blocked experiments for 1	4.76 ± 3.67 (n = 16)
Blocked experiments for 2 with variables 1 and 6 confounded	3.46 ± 1.74 (n = 32)
Center replicates for experiments 1 and 4	5.21 ± 3.49 (n = 14)
Center replicates for experiments 2 and 3	3.32 ± 2.52 (n = 27)

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