Table 2. Comparison of M_4 mutant and normal plants derived from S636-1. Data on leaves and spikes are means as in Table 1. Coleoptile length was obtained at 20°C from 15 M_5 seedlings from each of the measured plants.

Characteristic	Mutant	Normal
Flag leaf sheath (cm)	24.4	25.6
Spike length (cm)	11.5*	13.5
Spikelets per spike (No.)	21.5*	22.8
Coleoptile length (cm)	7.2*	7.9
Seed weight (mg)	29.5*	35.3

* Significant difference from normal ($P < .05$).

30-cm spacing in field plantings at Davis, California, in 1968 and 1969.

From 16 M_3 plants produced by S636-1, five were classified as normal and 11 as mutant type on the basis of appearance and culm measurements. The M_4 families from these plants were classified in the following year. All normal M_3 plants produced normal, nonsegregating families; 9 of 11 mutant plants produced both normal and mutant plants in the M_4 families. The remaining two mutant M_3 plants produced all mutant M_4 progeny. Complete dominance is indicated for this character because, based on measurements of the culm, mutant M_3 plants were phenotypically similar and progeny-testing proved that some of the M_3 plants were heterozygous. The data for M_4 families fit a ratio of one mutant to two segregating to one normal; in the segregating families, a ratio of three mutant to one normal was closely approximated. These results suggest that a single dominant gene conditions the mutant phenotype. Mutant plant S636-4 produced all mutant M_4 progenies, and S785-5 segregated similarly to S636-1 in the M_4. Stability of expression of the mutant phenotype has been obtained through three generations.

This mutation mainly affects the length of the first internode below the spike (peduncle) (Table 1), and the reduction in length of lower internodes lessened until there was no reduction at internodes 5 and 6. In this regard it is similar to mutants found by Konzak *et al.* (*6*). The total height of the mutant, including the spike, is 18 percent less than that of the normal phenotype. The length of the flag leaf sheath is not reduced in the mutant type (Table 2), although elongation of the peduncle may be modified somewhat by population density. This characteristic apparently has not been observed previously with wheat mutants. It is the unmodified length of the flag leaf sheath that results in altered canopy structure of the population. At present it is not suggested that this is a desirable feature for improvement of photosynthetic efficiency, but it is believed that this mutant provides a means by which certain relationships of light interception in the canopy may be evaluated. Translocation of carbohydrates from the flag leaf lamina and sheath or peduncle and lower internodes to the spike may be altered in this mutant and must be considered along with its effect on canopy structure. With respect to the subtended spike, mutant plants appear somewhat similar to the high-yielding 'IR-8' rice in which the panicle is displayed somewhat below the flag leaf lamina (*7*).

Table 2 shows other effects apparently associated with the mutant character: reduction in seed size, spike length, number of spikelets per spike, and coleoptile length. Coleoptile length has selective value for seedling emergence, and the reduction in length with this mutant is less than with many short-statured wheats (*8*). Nilan (*9*) has pointed out that pleiotropism is a common feature of induced mutations in higher plants; he suggested that this is an indication of the "gross and extragenic nature of detectable mutations in plants." Detailed genetic and developmental analyses are required to judge the appropriateness of this remark for the present mutant.

The induction of dominant mutations by chemical or physical means is quite rare (*9*); however, dominant short-stature mutations were found recently in common wheat (*10*) and in durum wheat (*11*). With both of these mutants the normal relationship of flag leaf sheath and peduncle was maintained so that the presently described mutant is morphologically distinct.

C. O. QUALSET
G. N. FICK
Department of Agronomy and Range Science, University of California, Davis 95616
M. J. CONSTANTIN
University of Tennessee–Atomic Energy Commission, Agricultural Research Laboratory, Oak Ridge 37830
T. S. OSBORNE
Department of Biological Sciences, Smith College, Northampton, Massachusetts 01060

References and Notes

1. C. M. Donald, *Euphytica* **17**, 385 (1968); ———, in *Proceedings of the Third International Wheat Genetics Symposium*, K. W. Finlay and K. J. Sheppard, Eds. (Australian Academcy of Sciences, Canberra, 1968), p. 377; P. R. Jennings, *Crop Sci.* **4**, 13 (1964).
2. F. J. Grundbacher, *Bot. Rev.* **29**, 366 (1953).
3. C. O. Qualset, C. W. Schaller, J. C. Williams, *Crop Sci.* **5**, 489 (1965).
4. N. E. Borlaug, in *Proceedings of the Third International Wheat Genetics Symposium*, K. W. Finlay and K. J. Sheppard, Eds. (Australian Academy of Sciences, Canberra, 1968), p. 1.
5. E. A. Jackson, *Agr. Sci. Rev.* **4**, 21 (1966).
6. C. F. Konzak, R. A. Nilan E. E. Froese-Gertzen, I. A. Ramirez, *Hereditas Suppl.* **2**, 66 (1966).
7. *International Rice Research Institute, Annual Report 1966*, Manila, Philippines.
8. R. E. Allan, O. A. Vogel, C. J. Peterson, Jr., *Agron. J.* **54**, 347 (1962); J. T. Feather, C. O. Qualset, H. E. Vogt, *Calif. Agr.* **22**(9), 12 (1968).
9. R. A. Nilan, *Abh. Deut. Akad. Wiss. Berlin No. 2* (1967), p. 5.
10. S. C. Woo and C. F. Konzak, in *The Nature, Induction and Utilization of Mutations in Plants* (International Atomic Energy Agency, Vienna, in press).
11. A. Bozzini and G. T. Scarascia-Mugnozza, *Wheat Inf. Serv. No. 23/24* (1967), p. 5.
12. Supported by AEC contract AT-40-1-GEN-242.

25 February 1970; revised 12 June 1970

Demyelinating Encephalomyelopathy Associated with Lead Poisoning in Nonhuman Primates

Abstract. *Lead poisoning was diagnosed in four primates by the finding of toxic amounts of lead in tissues. Abnormalities in the brain and spinal cord were characterized by vascular lesions and demyelination. These findings suggest a new animal model for the study of demyelination and strengthen the supposition that lead may be a factor in some idiopathic demyelinating diseases.*

Reports of lead poisoning in nonhuman primates are sparse. We are aware of only a few accidental poisonings (*1*), none of which was necropsied, and several experimental poisonings (*2*). This report summarizes the findings in four primates in which accidental lead intoxication existed for various lengths of time before death. A spectrum of central nervous system changes was found. The lesions closely resembled one or the other of two previously described conditions of unknown cause in primates. A detailed study of a larger number of similar cases is being prepared for publication elsewhere.

Case 1. A female Barbary ape (*Macaca sylvanus*) was born in an outdoor all-season cage where she resided for 22½ months until found dead. Intermittent convulsions had occurred over a period of 18 months. Gross necropsy findings were not remarkable and attempts to isolate viruses from brain, cerebral spinal fluid, throat, and intestine were unsuccessful. Histologic examination revealed focal, symmetrical demyelination of subcortical white matter (Fig. 1) associated with degenerative and proliferative vascular lesions (Fig. 2). Acid-fast intranuclear inclusion bodies, typical of heavy metal poisoning, were found in hepatocytes and renal proximal tubular epithelial cells (Fig. 3). Wet liver and kidney tissue contained lead in concentrations of 110 and 120 parts per million, respectively.

Case 2. An adult red-faced macaque (*Macaca speciosa*) lived in an indoor cage for 11½ months prior to death. During the last 2 days of life he had a series of convulsions. Gross necropsy findings were not remarkable, but histologic examination of the brain revealed marked cortical edema, degenerative vasculitis, and subcortical demyelination. Acid-fast intranuclear inclusions were found in renal convoluted tubular epithelia and hepatocytes. Wet liver and kidney tissue contained 65 and 90 parts of lead per million, respectively.

Case 3. A juvenile male red-faced macaque (*Macaca speciosa*) was acquired and quarantined in a galvanized cage for 6 weeks before being placed in an indoor display cage. Eight weeks later he had a convulsion and was taken to the hospital where he appeared to be blind and had frequent intermittent convulsions for 6 days. The animal was comatose for most of the last 2 days of hospitalization and euthanasia was performed. At necropsy the cerebral cortices were swollen, especially in the left occipital region, where the sulci were shallow and the gyri considerably flattened. Histologically there was marked diffuse cortical macrogliosis, edema, laminar necrosis (Fig. 4), proliferative vasculitis, and focal demyelination of the optic tracts. Acid-fast intranuclear inclusion bodies were prominent in both renal tubular epithelial cells and hepatocytes. Analysis of dehydrated, paraffin-embedded liver tissue indicated 360 parts of lead per million.

Case 4. An adult lesser spot-nosed guenon (*Cercopithecus nictitans*) suddenly became paraplegic. Since its arrival in the collection 2 years before, it had been housed in an indoor cage during the winter and an adjoining outdoor cage during the summer. A prolapsed intervertebral disk (T_{12}–L_1) was diagnosed and euthanasia was performed 2 weeks after the first clinical signs had been evidenced. The prolapsed disk was confirmed at necropsy but no obvious compression of the spinal cord was found. The histologic lesions observed in the central nervous system were inconsistent with those associated solely with compression of the spinal cord. Severe, diffuse, nonmalacic demyelination extended throughout the length of the spinal cord (Fig. 5), and symmetrical, multifocal areas of demyelination were present throughout the subcortical white matter of the brain and optic tracts. Vascular lesions were sparse. Acid-fast intranuclear inclusion bodies were present in renal tubular epithelia and hepatocytes. Spectrographic analysis of wet liver indicated 10 parts of lead per million.

Scrapings of paint from bars of both indoor and outdoor cages that housed the affected primates all contained lead (some in excess of 5 percent). Small chips of such paint ingested periodically could provide a toxic, and eventually, lethal dose. Chips of lead-containing paint are the most common source of lead poisoning in children (*3*) and dogs (*4*).

In the first three primates, the clinical signs of lead encephalomyelopathy were primarily amaurosis and epilepsy. The lesions of the central nervous system were characterized by proliferative and degenerative vascular changes, edema, laminar necrosis, and demyelination. These signs and lesions were

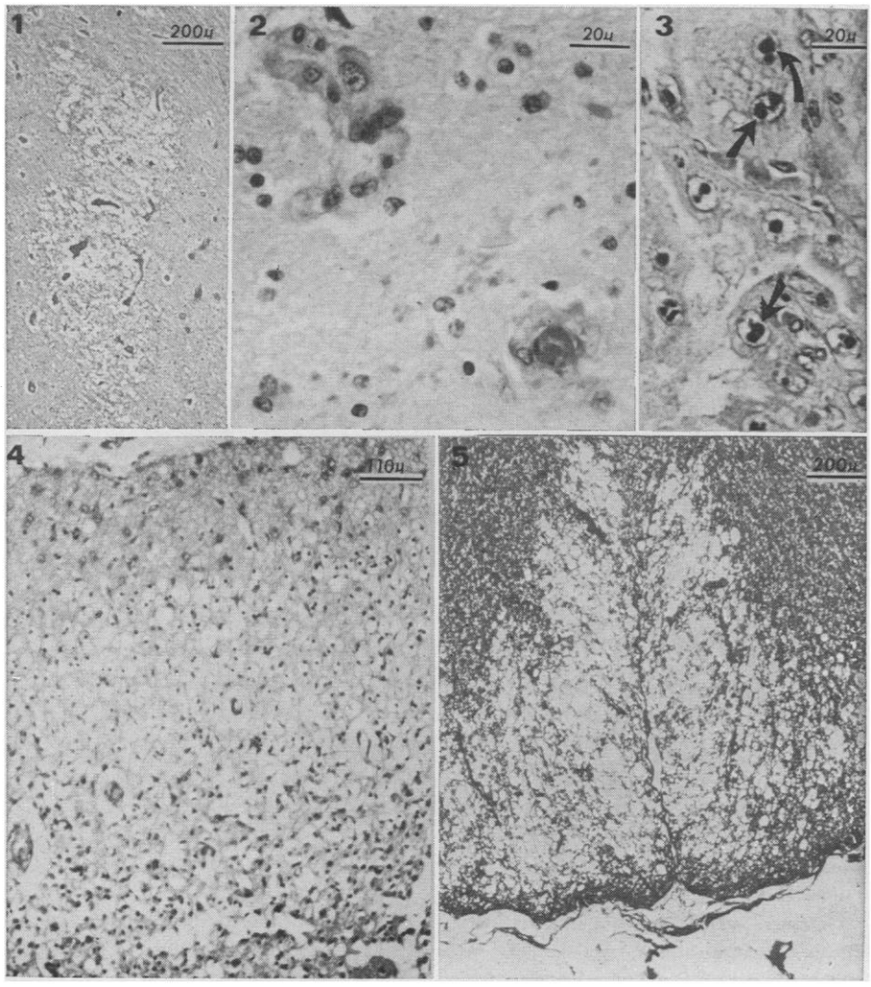

Fig. 1. Focus of demyelination in subcortical white matter. Luxol blue stain. Fig. 2. Proliferative (upper left) and degenerative (lower right) vascular lesions in white matter. Hematoxylin and eosin stain. Fig. 3. Acid-fast inclusion bodies (arrows) next to nucleoli of renal tubular epithelia. Ziehl-Neelsen acid-fast stain. Fig. 4. Marked edema and necrosis in cerebral cortex. Hematoxylin and eosin stain. Fig. 5. Severe demyelination in spinal cord. Luxol blue stain.

strikingly similar to those that have been described for lead encephalopathy in children (*5*) and idiopathic amaurotic epilepsy of nonhuman primates (*6–8*). It is interesting to note that other workers have suspected that a relationship may exist between lead poisoning and amaurotic epilepsy (*8*, *9*) of monkeys.

The last case described differs from the others in that sudden paraplegia was present rather than epilepsy; vascular lesions were minimum, and bilateral symmetrical demyelination was much more extensive. These signs and lesions were essentially the same as those described for idiopathic leukoencephalomyelosis of nonhuman primates, a disease that has occurred concurrently with amaurotic epilepsy (*7*).

The lesions associated with lead poisoning in these four primates suggest a new animal model for the study of demyelination and tend to support the contention of others that lead may in some way be a factor in certain idiopathic demyelinating diseases of animals (*9*, *10*) and man (*11*).

R. M. SAUER
National Zoological Park
Washington, D.C. 20009

B. C. ZOOK
Department of Pathology, School of Medicine, George Washington University, Washington, D.C. 20037

F. M. GARNER
Armed Forces Institute of Pathology, Washington, D.C. 20305

References and Notes

1. L. E. Fisher, *J. Amer. Vet. Med. Ass.* **125**, 478 (1954); D. de Bisschop (Royal Society of Zoologists, d'Anvers), unpublished communication to Directors, International Union of Zoological Societies, Chicago (1956); W. D. Houser, *J. Amer. Vet. Med. Ass.*, in press.
2. A. Ferraro and R. Hernandez, *Psychiat. Quart.* **6**, 121 and 319 (1932); C. Lampert and J. E. Desmedt, *C. R. Seances Soc. Biol.* **160**, 2504 (1966); Anonymous, *Environ. Sci. Tech.* **2**, 731 (1968).
3. H. Jacobziner, *Clin. Pediat.* **5**, 277 (1966).
4. B. C. Zook, J. L. Carpenter, E. B. Leeds, *J. Amer. Vet. Med. Ass.* **155**, 1329 (1969).
5. A. Pentschew, *Acta Neuropathol.* **5**, 133 (1965).
6. H. M. Langdon and W. B. Cadwallader, *J. Comp. Pathol.* **28**, 334 (1915); H. Fox, in *Diseases of Laboratory Primates*, T. C. Ruch, Ed. (Saunders, Philadelphia, 1959), p. 437; L. van Bogaert, *Bull. Acad. Roy. Méd. Belg.* **15**, 245 (1935); ———, *J. Belge Neurol. Psychiat.* **36**, 1 (1936); ——— and H. J. Scherer, *Z. Ges. Neurol. Psychiat.* **152**, 757 (1935); ———, *Arch. Neurol. Psychiat.* **40**, 521 (1938).
7. J. R. M. Innes and L. Z. Saunders, *Comparative Neuropathology* (Academic Press, New York, 1962), pp. 67–76, 94–103, and 132.
8. J. F. Wright, *Report on the National Zoological Park, Smithsonian Report* (U.S. Government Printing Office, Washington, D.C., 1960), p. 164; *ibid.* (1961), p. 166; *ibid.* (1962), p. 169.
9. J. Minckler, *Pathology of the Nervous System* (McGraw-Hill, New York, 1968), pp. 65–67.
10. J. R. M. Innes and G. D. Shearer, *J. Comp. Pathol. Therap.* **53**, 1 (1940).
11. A. M. G. Campbell, G. Herdan, W. F. T. Tatlow, E. G. Whittle, *Brain* **73**, 52 (1950); H. V. Warren, *Nature* **184**, 56 (1959); ———, R. E. Delavault, C. H. Cross, *Ann. N.Y. Acad. Sci.* **136**, 657 (1967); W. Cone, C. Russel, R. Harwood, *Arch. Neurol. Psychiat.* **31**, 236 (1934); W. J. C. Verhaart, *Amer. J. Dis. Child.* **61**, 1246 (1941); H. Eichhorst, *Med. Klin.* **9**, 201 (1913); G. de Morsier and Y. Chesni, *Schweiz. Med. Wochschr.* **82**, 443 (1952); G. Hermann, *Wien. Med. Wochschr.* **101**, 657 (1951); A. Berger, *Psychiat. Neurol.* **25**, 168 (1905).

22 June 1970

Indole Metabolism in the Pineal Gland: A Circadian Rhythm in N-Acetyltransferase

Abstract. *The activity of* N*-acetyltransferase in the rat pineal gland is more than 15 times higher at night than during the day. This circadian rhythm persists in complete darkness, or in blinded animals, and is suppressed in constant lighting. The* N*-acetyltransferase rhythm is 180° out of phase with the serotonin rhythm and is similar to the norepinephrine and melatonin rhythms. Experiments in vitro indicate that norepinephrine, not serotonin, regulates the activity of* N*-acetyltransferase through a highly specific receptor.*

N-Acetyltransferase converts serotonin to *N*-acetylserotonin (*1*). In the pineal gland, *N*-acetylserotonin is *O*-methylated by hydroxyindole-*O*-methyl transferase to form the pineal specific compound melatonin (*2*). Our studies with cultured rat pineal glands have indicated that *N*-acetyltransferase activity is stimulated manyfold by the neurotransmitter norepinephrine by way of an adenyl cyclase mechanism which is dependent on protein synthesis (*3*). *N*-Acetyltransferase seems to regulate the synthesis of melatonin by limiting the availablity of *N*-acetylserotonin for *O*-methylation (*3*).

We now report that the activity of *N*-acetyltransferase in the rat pineal gland increases rapidly at night to values which are more than 15 times greater than the day values. This circadian rhythm (*4*) is 180° out of phase with the rhythm in pineal serotonin (*5*, *6*) and is similar to the rhythm in the concentration of melatonin (*7*) and norepinephrine (*8*, *9*) in the pineal.

Male Osborne-Mendel rats (NIH strain) weighing 180 to 220 g were used. The intensity of light in cages was 108 to 340 lumen/m^2. Animals were killed by a blow to the head, and within a minute the pineals were removed. Glands were stored for less than 5 minutes at room temperature in Ringer injection solution while the extraneous tissue was removed. The activity of *N*-acetyltransferase was determined by a modification of a previous method (*3*). A single pineal gland was homogenized in 20 μl of 0.1*M* sodium phosphate buffer (*p*H 6.8) containing [^{14}C]serotonin (0.5 m*M*) and acetyl coenzyme A (0.5 m*M*). The reaction mixture was incubated for 10 minutes at 37°C. The [^{14}C]*N*-acetylserotonin and [^{14}C]melatonin that were formed during incubation were isolated by thin-layer chromatography and eluted, and the radioactivity was then determined.

A circadian rhythm in the activity of *N*-acetyltransferase is present in the rat pineal gland (Fig. 1). A 15-fold increase in enzyme activity occurs during the first 3 hours of the dark period, suggesting that darkness may cue the rhythm.

To determine whether this circadian rhythm could be endogenously generated in the absence of lighting shifts, we maintained some animals in continual darkness for 6 days. A comparison of the enzyme activity at 11:00 a.m. and 11:00 p.m. indicates that a rhythm does persist (Table 1). In the group tested at 11:00 a.m., the average of six of the seven enzyme activities was 45 units (a unit of activity is the number of picomoles of [^{14}C]serotonin *N*-acetylated per gland homogenate per hour). The remaining pineal had an activity of 720 units. A similar variation in the distribution of enzyme activities was observed in the group tested at 11:00 p.m., with the majority of the values greater than 800 units. The greatly increased variability in the data indicates that the pineal *N*-acetyltransferase rhythm becomes asynchronous among a group of rats maintained in darkness.

The exposure of rats to continual lighting suppresses the *N*-acetyltransferase rhythm (Table 1). The measurement of *N*-acetyltransferase at six evenly spaced times during a 24-hour period provided no evidence that a rhythm was present (*10*). The sup-