many compounds which prolong hypnotic activity can lower body temperature[8], melatonin (25 mg/kg) had no hypothermic action in the rabbit. Melatonin at doses of 10 mg/kg produced no change in post-synaptic spike potentials in the cat superior cervical ganglion, and no change in the response of the nictitating membrane. In mice, 30 mg/kg of melatonin given intraperitoneally every 3 h for 18 h caused no change in gross behaviour or in the amount of noradrenaline in the brain or heart.

These findings are intriguing because of some of the known activities of the compound. Melatonin lightens the frog skin melanocyte at a concentration of 10^{-13} g/ml., a dose one ten-thousandth that of the next most active agents—noradrenaline, adrenaline, serotonin, and acetylcholine. Because of the possible derivation of the melanocyte from neural crest tissue and the nature of the other compounds which affect the melanocyte there is ample reason to believe that melatonin may affect processes in the central nervous system. Indeed, our results on the acute pharmacology of the compound are further evidence for that view.

Melatonin is found in human peripheral nerves, where it is not synthesized, and in human urine[9]. The human pineal gland can synthesize melatonin throughout life[10]. Melatonin formed in the pineal gland may possibly be elaborated and exert an effect on other sites of the brain in addition to any peripheral effects of a hormonal nature[2] that it may have. It is not yet possible to say whether this pharmacological evidence of a central effect of melatonin is due to the compound or one of its metabolites. Further experiments are necessary to determine the possible relation of melatonin, or a related compound, to the systems regulating sleep and to processes in the central nervous system.

JACK BARCHAS*
FRANCES DACOSTA†
SYDNEY SPECTOR

Laboratory of Clinical Biochemistry and
Experimental Therapeutics Branch,
National Heart Institute,
Bethesda, Maryland.

* Present address: Department of Psychiatry, Stanford Medical Center Palo Alto, California.

† Present address: Division of Pharmacology, Food and Drug Administration, Washington.

[1] Lerner, A. B., Case, J. D., and Takahashi, Y., *J. Biol. Chem.*, **235**, 1992 (1960).

[2] Lerner, A. B., and Case, J. D., *Fed. Proc.*, **19**, 590 (1960). Lerner, A. B., Case, J. D., Takahashi, Y., Lee, T., and Mori, W., *J. Amer. Chem. Soc.*, **80**, 2587 (1958).

[3] Baschieri, L., De Luca, F., Cramrossa, L., De Martino, L., Oliverio, A., and Negri, M., *Experientia*, **193**, 15 (1963). Wurtman, R. J., Axelrod, J., and Chu, E., *Science*, **141**, 277 (1963). Kappers, J. A., *Gen. Comp. Endocrinol.*, **2**, 610 (1962). Ebels, I., and Prop, N., *Acta Endocrinol.*, **49**, 567 (1965).

[4] Freedman, D. X., and Giarman, N. J., *E.E.G. and Behavior* (edit. by Glasser, G. H.) (Basic Books, New York, 1963.) McIssac, W. M., Khairallah, P. A., and Page, I. H., *Science*, **134**, 675 (1961). Wooley, D. W., and van der Hoeven, T., *Fed. Proc.*, **23**, 146 (1964).

[5] Gessner, P. K., McIssac, W. M., and Page, I. H., *Nature*, **190**, 179 (1961). Vaughan, M., and Barchas, J., *J. Pharmacol. Exp. Therap.*, **152**, 298 (1966). Hertz-Eshel, M., and Rahamimoff, R., *Life Sci.*, **4**, 1367 (1965). Rahamimoff, R., and Bruderman, I., *Life Sci.*, **4**, 1383 (1965).

[6] Kramer, S. Z., and Seifter, J., *Life Sci.*, **5**, 527 (1966).

[7] Marczynski, T. I., Yamaguchi, N., Ling, G. M., and Grodzinska, L., *Experientia*, **20**, 435 (1964).

[8] Fastier, F. N., *Experientia*, **12**, 351 (1956). Fastier, F. N., Speden, R. N., and Waal, H., *Brit. J. Pharmacol.*, **12**, 251 (1957).

[9] Barchas, J. D., and Lerner, A. B., *J. Neurochem.*, **11**, 489 (1964).

[10] Wurtman, R. J., Axelrod, J., and Barchas, J. D., *J. Clin. Endocrinol. and Metab.*, **24**, 299 (1964).

Excretion of Thiocyanate in Osteolathyrism

THE metabolism and mode of action of nitriles, such as β-aminopropionitrile (BAPN), that cause osteolathyrism in rats and other animals are far from being understood. Lalich[1] has shown that after injection into rats of BAPN labelled in the cyano position with carbon-14, 80–90 per cent of the radioactive material was eliminated in the urine within 20 h. About 40 per cent of the activity was in the form of unchanged BAPN and 20–30 per cent could be recovered as cyanoacetic acid. Lalich also found that cyanoacetic acid had no lathyrogenic effect when fed to young rats and suggested that it was probably a detoxication product of BAPN.

It is known that, when aliphatic cyanides are metabolized in the animal body, hydrogen cyanide is split off, leading to an increase in the excretion of thiocyanates[2]. It was therefore thought desirable to investigate the excretion of thiocyanate in the urine of rats rendered lathyritic by the administration of BAPN. Two groups each of six rats were used. One group served as control and the rats in the other group were each given 70 mg β-aminopropionitrile fumarate daily by gavage for 3 weeks. All rats were fed *ad lib.* on an adequate diet of standard rat cakes and fresh water. Metabolic cages were used for the collection of urine.

Thiocyanate (CNS) in the urine of lathyritic and control animals was estimated by its colour reaction with ferric nitrate and by comparison with a standard solution[3]. The results are shown in Table 1.

Table 1. THIOCYANATE (CNS) EXCRETION IN URINE OF LATHYRITIC RATS

Group	No. of animals	Mean concentration of CNS in urine (mg per cent)	Total CNS excretion per day (mg)
Control	6	4·10	2·05
Lathyritic	6	12·94	6·47

The urine of lathyritic rats contained three times as much thiocyanate as the urine of control animals. The total amount of thiocyanate excreted, however, accounted for only 3 per cent of the dose of β-aminopropionitrile administered. What happens to the rest of the lathyrogen after absorption is not known.

ALI KHOGALI

Department of Physiology,
Medical School,
Khartoum, Sudan.

[1] Lalich, J. J., *Science*, **128**, 206 (1958).

[2] Williams, R. T., *Detoxication Mechanisms* (second ed.), 125 (Chapman and Hall, London, 1949).

[3] King, E. J., and Wootton, I. D. P., *Microanalysis in Medical Biochemistry* (third ed.), 100 (Churchill, London, 1956).

Absence of Renal Fructose-1-phosphate Aldolase Activity in Hereditary Fructose Intolerance

HEREDITARY fructose intolerance (HFI) is a genetically transmitted metabolic disorder known to be characterized biochemically by the virtual inactivity of hepatic fructose-1-phosphate aldolase[1–3]. Fructose-1-phosphate (F-1-P), the initial reaction product of administered fructose, accumulates intracellularly behind this enzymatic defect[4], much as galactose-1-phosphate (Gal-1-P) accumulates intracellularly behind the block of Gal-1-P uridyl transferase in galactosaemia[5,6]. The kinds and similarities of the metabolic and clinical abnormalities of patients with HFI and galactosaemia suggest that the cellular accumulation of hexose-1-phosphate is central in the pathogenesis of the multiple cellular disturbances of both disorders. Increased amounts of Gal-1-P were demonstrated in the kidneys, as well as in the liver, of two infants with galactosaemia diagnosed before death[7]. In both galactosaemia and HFI, a reversible hexose induced proteinuria and amino-aciduria have been reported[8,9]. Komrower *et al.*[10] reported that in two infants with galactosaemia dietary restriction of galactose was followed by disappearance of the biochemical characteristics of renal tubular acidosis (RTA) (a clinical disorder of renal acidification characterized by minimal to absent azotaemia, hyperchloraemic acidosis and alkaline or minimally acid urine). Subsequent experimental ingestion of galactose (as milk) for 10 days by these children, however, did not result in the recurrence of hyperchloraemic acidosis. Mass *et al.* recently described