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Observations, from 1950 to 1953, of an unusually high incidence of amyotrophic lateral sclerosis and other neurological disorders endemic to Guam were subsequently (1963) correlated with the ingestion of cycad nut meal. This discovery was accomplished by epidemiological investigations, especially those of Leonard T. Kurland and Majore G. Whiting. The cycad (Cycas circinalis) is a plant indigenous to the Mariana Islands, and cycad varieties occur widely from the Japanese Archipelago to the subcontinent of India. The plant is of localized economic importance as a source of foodstuffs, fiber, and medicinal products. The studies of Kurland and Whiting suggested the possibility of the existence of a neurotoxic agent in the nut meal and edible starch extracted from cycad roots, stems, and leaves.

In 1963 Gert L. Laqueur (b. 1912, Strasbourg, France), Chief, Laboratory of Experimental Pathology at the National Institute of Arthritis and Metabolic Diseases, and his associates uncovered a carcinogenic property in the cycad. Crude nut meal from C. circinalis fed to rats failed to elicit neurological symptoms but induced cancers of the liver, kidney, and intestinal tract (G. L. Laqueur, O. Mickelsen, M. Whiting, and L. T. Kurland, Carcinogenic Properties of Nuts from Cycas circinalis L. Indigenous to Guam. J. Natl. Cancer Inst., 31: 919—951, 1963). This work indicated that a glycoside isolated from cycads, and known as cycasin, might yield in its metabolic breakdown a compound with a carcinogenic potential similar to that of dimethylnitrosamine (DMN). This inference was supported by comparable pathological alterations in rats fed toxic cycad nut meal and those reported for rats treated with DMN. Collateral investigations revealed that cycasin was ineffective as a hepatotoxin and a hepatocarcinogen when administered to germfree rats.

A later report by Laqueur and his coworkers showed that a metabolic degradation via β-glucosidase of bacterial origin in the intestinal tracts of rats released the aglycone, a potent carcinogen (G. L. Laqueur, E. G. McDaniel, and H. Matsumoto, Tumor Induction in Germfree Rats With Methylazoxymethanol (MAM) and Synthetic MAM Acetate. J. Natl. Cancer Inst., 39: 355—371, 1967). The aglycone of cycasin (MAM) and the synthetic aglycone acetate ester produced tumors in germfree animals, thus establishing MAM as the proximate carcinogen.

These studies were greatly assisted by the collaboration of Hiromu Matsumoto, whose group prepared synthetic derivatives of MAM (H. Matsumoto, T. Nagahama, and H. O. Larson, Studies on Methylazoxymethanol, the Aglycone of Cycasin: A Synthesis of Methylazoxymethanol. Biochem. J., 95: 13C, 1965; also, A. Kobayashi and H. Matsumoto, Studies on Methylazoxymethanol, the Aglycone of Cycasin: Isolation, Biological and Chemical Properties. Arch. Biochem. Biophys., 110: 373—380, 1965). The cover illustrates a mature cycad plant; upper right, recent photograph of Dr. Laqueur (courtesy of the Information Office of the National Institute of Arthritis and Metabolic Diseases, NIH, and Mrs. Frances W. Davis, Editor, NIH Record). Professor Matsumoto is shown at lower right in a photograph supplied by Dr. Laqueur.