Observations About Amyotrophic Lateral Sclerosis and the Parkinsonism-Dementia Complex of Guam with Regard to Epidemiology and Etiology

John C. Steele and Tomasa Guzman

ABSTRACT: For more than 150 years, Chamorro natives of the Mariana Islands in the Western Pacific Ocean, have developed fatal paralysis in middle and later life, which we term amyotrophic lateral sclerosis/parkinsonism-dementia (ALS/PD). The cause of the disease might be exposure to seeds of the indigenous cycad. Motor system disease is induced in cynomolgus monkeys by feeding them beta-N-methylamino-L-alanine (BMAA), an amino acid present in cycad seeds. We believe that the cycad seeds which usually cause no immediate adverse symptoms when prepared and eaten as flour, or applied topically as medicine, can give rise to widespread and severe nerve cell degeneration after a latency of many decades. Furthermore, it may be that only a single exposure to this potent but silent toxin(s) can result in fatal neurological disease years later.

RÉSUMÉ: Observations sur l'épidémiologie et l'étiologie de la sclérose latérale amyotrophique et du complexe Parkinson-Démence de Guam. Pendant plus de 150 ans, des Chamorros natifs des îles Mariana situées dans le Pacifique ouest ont développé, vers l'âge moyen ou plus tardivement, une paralysie évoluant vers la mort, que nous connaissons sous le terme sclérose latérale amyotrophique/Parkinsonisme-Démence (SLA/PD). La cause de cette maladie pourrait être une exposition aux graines d'une plante indigène le cycas. Une maladie du système moteur peut être provoquée chez les singes cynomolgus en leur faisant ingérer de la bêta-N-méthylamino-L-alanine (BMAA), un acide aminé présent dans les graines du cycas. Nous croyons que les graines du cycas, qui ne causent pas d'effets nocifs immédiats quand elles sont préparées et consommées en farine ou en application topique comme médicament, peuvent provoquer une dégénérescence étendue et sévère des cellules nerveuses après une période de latence de plusieurs décennies. De plus, il se peut qu'une seule exposition à cette toxine puissante, mais silencieuse, puisse provoquer une maladie neurologique fatale à un âge plus avancé.

Can. J. Neurol. Sci. 1987; 14:358-362

We are reporting our recent observations about Amyotrophic Lateral Sclerosis (ALS) and the Parkinsonism-Dementia complex (PD); neurological syndromes which are particularly common among the indigenous Chamorro people of the Mariana Islands.

These observations are in keeping with Kurland and Spencer's hypothesis that exposure to seeds of Cycas circinalis is the cause of these illnesses, and that the neurotoxin(s) they contain occasion progressive neurological dissolution, but only after an interval of many decades.

History

Spread across the vastness of the Pacific Ocean, there are thousands of islands, high and low, lush and dry, volcanic and coral. They are all the peaks of submerged mountain ranges and the clusters they form are called archipelagos. The Mariana Islands is such an archipelago, a chain of fifteen small islands in the Western Pacific which spread northward from Guam towards Japan (Figure 1).

Four thousand years ago, the Pacific islands were settled by migrants from the IndoMalay peninsula. Those who settled the Mariana Islands called themselves Chamorros and, as did other indigenous Pacific people, they evolved a society adapted to the smallness of these islands and in harmony with their fragile ecology.

The Mariana Islands were discovered by the Western world in 1521 when Ferdinand Magellan landed at Umatac in southern Guam. His historic arrival marked the entry of the white man

From the Veterans Administration Office, U.S. Naval Hospital, Guam
Reprint requests to: Dr. John C. Steele, Veterans Administrations Office, U.S. Naval Hospital, P.O. Box 7613, F.P.O., San Francisco, CA., U.S.A. 96630

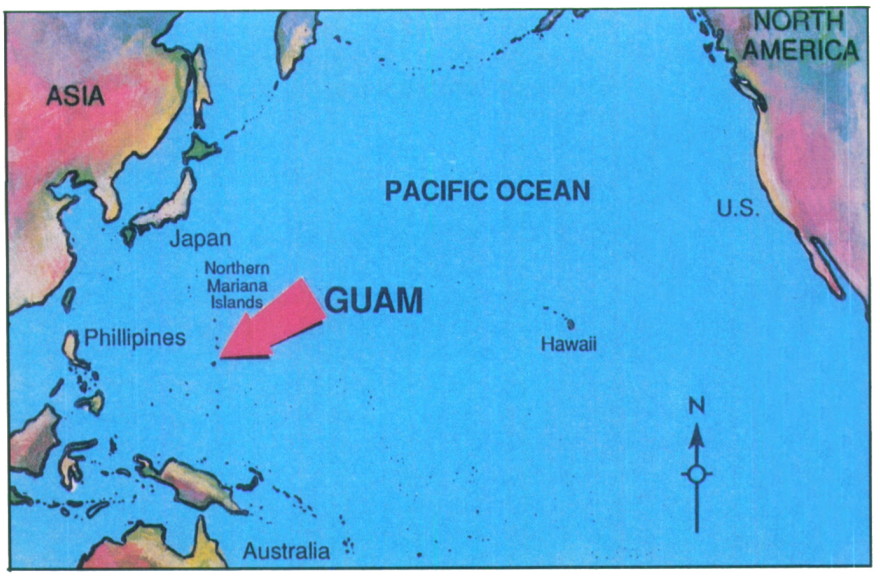

Figure 1 — Map of the Pacific indicating Guam and the Mariana Islands.

into the Pacific and provided for the first contact between Europeans and Pacific Islanders.

At the time of Magellan's arrival in Guam, the native population was a large one. The people that comprised it were robust and healthy and had developed an advanced society and subsistence economy that took full advantage of the island environment. They were skilled in the art of fishing, agriculture and navigation and they had an abundance of food for trade.

With colonization, by 1710, the Chamorro population was reduced from 73,000 to only 1,600. Those who survived were settled in villages in southern Guam, and a few hid out on the adjacent island of Rota. The few remaining Chamorros, most of them women, married Mexican, Filipino and Spanish soldiers sent to tend the islands. Slowly the native population began to increase.

During the 18th century, the Jesuits oversaw the economic and social welfare of the surviving Chamorros, they taught them European ways and encouraged them in agriculture. Despite this, the native lot was a miserable one. They suffered leprosy and tuberculosis brought by outsiders and many died in frequent epidemics of smallpox and measles.

In 1769, Augustinian Monks took the place of the Jesuits and the native condition deteriorated further. By the early 19th century, poverty was widespread, food resources had declined and the Chamorros were often forced to scavenge in the forests for food.[1]

It was about this same time that Guam's governors began to report the native custom of preparing flour from the seeds of the indigenous cycad, Cycas circinalis (Figure 2).

The seeds of the plant they called "fadang" were abundant in Guam's dense forests and always available to gather. After typhoons, the trees survived when all other food sources were destroyed. The seeds were known to be poisonous, but Spanish speaking immigrants had taught the natives to soak them first to remove this poison. They were then sun-dried and could be stored for many months before they were ground into a fine flour which was used in the preparation of tortillas (Figure 3). The flour was also used to prepare petit pain, dumplings in soup, and as a drink when mixed with coconut milk.[2] Fresh grated seeds were also found to help heal open sores.

Figure 2 — Cycas circinalis.

Though the use of cycad as a food source began of necessity during a time of privation, it subsequently became a dietary staple for many families in Guam, particularly in the south of the island where there is very little land for growing crops and where poverty and distance prevent the importation of foods from the main center of Agana. Things changed in Guam with the end of World War II. The United States then administered Guam and the other Micronesian islands and encouraged their rapid westernization. American military and public health service physicians began to describe diseases of the region and to develop health services to address them.

https://doi.org/10.1017/S0317167100037744 Published online by Cambridge University Press

ALS/Parkinsonism-Dementia — Description of the Disease

In 1945, Zimmerman, who was then a Navy pathologist on Guam, reported that seven Chamorro natives died of ALS in the space of only one month and in two of those patients he verified that diagnosis by autopsy.[3]

Zimmerman was not alone in his observation. Subsequent clinical studies done in the 1950's by Navy physicians assigned to Guam also reported an unusually high rate of ALS among Chamorros.[4-6]

These several reports came to the attention of Kurland who was then with the Neurological Institute of NIH, and he came to Guam in 1953 to investigate this remarkable phenomena. He was joined by Mulder and together they made a number of important observations.[7,8] They confirmed that the illness which Chamorros suffered was indistinguishable from classical ALS. Moreover, they found that, overall, ALS was one hundred times more common than elsewhere in the world and that in certain villages of southern Guam and on the adjacent island of Rota, its incidence was even higher. It was, however, uncommon among the Chamorros of Saipan and did not seem to affect long term residents of the other Mariana, or Caroline Islands. Kurland and Mulder also noted a striking familial aggregation of ALS patients; more than one third of the affected individuals had other family members who suffered from the disease.

In 1961, Hirano characterized a second neurological syndrome in Chamorros which he and Kurland termed the "Parkinsonism-Dementia complex" (PD), because of characteristic clinical features. Some considered PD and ALS to be separate diseases, though closely related. Others suggested they were parts of a continuum of neurological involvement in a single disease process.[9]

In a companion report about the pathological features of PD, Malamud and Hirano also described widespread nerve cell loss and neurofibrillary and granulovacuolar degeneration of nerve cells in cortical, subcortical and brain stem regions which correlated with the clinical features of dementia and parkinsonism. They noted that those same changes were also present in patients with ALS.[10]

Subsequent studies by Anderson in 1979,[11] Chen in 1981,[12] and Perl in 1982[13] have confirmed that neurofibrillary degeneration is very common among Chamorros and is similar to that which occurs in Alzheimer's Disease and with aging of the nervous system. It becomes more severe and widespread with increasing age but unlike neurofibrillary degeneration, senile plaques rarely occur.

Since the 1950's, investigators have been aware that in some Chamorros, ALS/PD does not occur until many years after they have left Guam. In 1957, Kurland noted that Chamorros who had left Guam suffered the same high incidence of ALS as residents of the island, even though they had lived away from Guam for many years.[14] This suggests a long latency, if indeed the cause relates to environmental exposure on Guam.

Garruto and Eldridge confirmed that ALS and PD may not occur until many decades after emmigration from the island.[15,16]

A few Filipinos who immigrated to Guam as young adults in the 1940's have been identified to have histologically verified ALS/PD. None have developed symptoms until at least 17 years after arriving here.[17]

For 40 years investigators have sought for the cause of ALS/PD. Because it was so common among Chamorros and because aggregations of patients in some families did not seem to follow established patterns of Mendelian inheritance, in the 1950's, Kurland began to seek an environmental factor which was unique to the Chamorros to explain its occurrence among them.

Fosberg, a botanist and authority about plants of the Pacific, noted that the Chamorros used cycad seeds and they were an important source of food in spite of their recognized toxicity. Although the local method of preparation usually removed toxins causing an acute effect, Fosberg and Whiting, a nutritionist, thought there was the possibility of a cumulative effect from small residual quantities of toxin.[18]

Cycad seeds contain a potent hepatotoxic and carcinogenic agent called cycasin, but this was shown not to be particularly neurotoxic in experimental animals. Vega and Bell did identify a second toxin, beta-N-methylamino-L-alanine, BMAA with neurotoxic properties[19] but because its concentrations were low, it was felt unlikely to be a major factor in the occurrence of neurological disease in man.[20]

In April 1986, Spencer and his associates reported their results of tests on the second identified toxin of the cycad seed. Each day they fed large amounts of BMAA to a pair of cynomolgus monkeys and within eight weeks, the monkeys developed a motor system disorder with pyramidal and extrapyramidal components. Pathological studies showed degeneration of Betz cells and lower motor neurons, those same cell types affected in human ALS.[21]

Recent Observations in Keeping With Cycad Seeds as the Possible Cause of ALS/PD

Our first observation is that the ALS/PD complex of Guam occurs only where cycad trees grow and where people use its seeds for food and medicine. On Guam and Rota, there are dense cycad forests growing in limestone areas of both islands. ALS/PD is most common among residents of villages in the south of Guam which depend heavily on cycad, be it because of traditional practice, isolation or poverty.

Historical accounts indicate that ALS/PD has occurred amongst the natives of Guam for at least 150 years. First accounts of it coincide with the Chamorros use of cycad seeds as food and medicine. For many families, cycad flour became a staple of their diet. It was eaten most frequently in the southern villages of Guam and Rota, those same regions where ALS/PD is most common.

After World War II, considerable quantities of food were brought to the islands. Wheat flour was a main import and by the late 1940's, most Chamorros were using this rather than cycad flour, because of its greater convenience and availability. This change in food habit occurred 40 years ago. However, because of the presumed long latency between exposure to cycad and the onset of neurological symptoms, a change in the annual incidence of ALS/PD would not be expected to begin until 20 years later, in the mid-1960's. As Garruto et al[22] and Reed and associates[23] have shown, the decline which began then has continued in steady fashion (Figure 4). The ALS form of the disease which is thought to have a shorter latency than PD by about 10 years, has now almost completely disappeared. PD, because of its presumed longer latency, continues to occur at a higher rate than ALS, but it too is less common and its onset now occurs later and in people in their seventh and eighth decades.

The rarity of ALS/PD among the people of Saipan has been a constant puzzle but recent interviews with elderly Chamorros

seem to provide an explanation. During the Spanish and German administrations, cycad trees were abundant and Saipanese Chamorros used cycad flour as a dietary staple in the same way that the people of Guam and Rota did. In 1914, the Japanese occupied Saipan and began clearing it for sugar planting. By the mid-1920's most of the indigenous vegetation, including the cycad forests, had been cut down; local people were no longer able to prepare the flour. When neurological surveillance teams began to visit Saipan in the mid-1950's, cycad flour had not been used on the island for 30 years. At that time, ALS was much less common there than on Guam or Rota, and all those Saipanese Chamorros who suffered it then were either born before 1917 and could have had exposure to cycad in childhood, or had the probability of being exposed to cycad on Guam or Rota, where it was still being prepared.[24] Cycad trees grow on other Micronesian islands but the seeds have apparently never been used by any other Micronesian people. Even on Saipan, Carolinians who immigrated there in the early 19th century regarded the cycad flour as a "Chamorro" food and did not prepare or eat it.

Cycad flour is not regularly eaten by most of the migrant ethnic groups on Guam and the other Mariana islands, and ALS/PD has not been observed to occur among them. However, there are a few Filipinos who came to Guam in the 1940's, married Chamorro women, and adopted the native lifestyle and food habit. Several developed pathologically verified ALS/PD from 17 to 26 years after their arrival on Guam, but the disease has not been seen in any Filipino who arrived on Guam after 1950, when the flour ceased to be a food staple.[16]

A notable feature of ALS/PD is familial occurrence: this is so prominent that at first it suggested ALS/PD was inherited. Our recent interviews suggest that the familial aggregation of patients may relate to differences between families in the method of preparing the cycad seeds. Chamorros know that the seeds contain a poison and to remove it, they must soak the seeds in water before drying them in the sun. We have recently learned that there are considerable differences between families in regard to the duration of the soaking process and the number of water changes. Some families only soak the seeds overnight while others wash them for three weeks. Some families change the water every three days while others change it three times a day. Some families soak the seeds in sea water, some wash them in streams and others in vats and odd containers. Some admit to shortening the wash process so that the flour has a sharper and stronger taste.

At the present time, we are working with Spencer to determine if cycad flour samples are neurotoxic in tissue culture, and if there are quantitative differences in neurotoxicity between samples which relate to different methods of preparation. At this time, we are not certain about the extent of exposure to cycad that cause ALS/PD.

I wish to conclude by citing the remarkable history of a Saipanese woman and her son, both of whom began to have neurological illness in 1978, 19 years after a single feast of foods made from only four pounds of the flour which was shared among 6 family members. The mother developed parkinsonism and her son developed ALS. This was their only exposure to cycad and occurred in 1959 on the northern island of Pagan. In recent months, we have obtained accurate histories of cycad exposure from 21 other patients with ALS/PD. Two of these also indicate they have had only a single exposure many years before the onset of their illness. Both are residents of Guam and perhaps could have had other unrecalled exposures. In the situation of the Saipanese family, however, we are pretty certain there was no other exposure, since cycad has been unavailable on Saipan for many years.

These observations are in keeping with Spencer's experimental work and they support his suggestion that BMAA and chemically-related neurotoxic compounds deserve serious consideration as the causative agents of motor neurone disease in both Guam and elsewhere.

Thus, on Guam, a common food which causes no apparent symptoms when eaten or used medicinally may give rise to widespread and severe nerve cell degeneration after a latency of many decades. Furthermore, it may be that only a single, apparently innocuous exposure to this toxin may occasion fatal neurological disease years later.

For many years, ALS/PD has been a major cause of death and morbidity among the people of Guam and Rota. Today, it is no longer a major health problem but it remains most important as a paradigm for the study of neurodegenerative diseases. We anticipate that these new observations about this disappearing disease on these distant Pacific islands will profoundly change our views about neurotoxins and their effects on the human nervous system.

References

1. Safford WE. The Mariana Islands, from documents in the archives at Agana, the capital of Guam and from early voyages found in the libraries of San Francisco, California. 1901. To be found in the Nieves M. Flores Memorial Library, Agana, Guam.
2. Freycinet L de. Voyage autour du monde. Published in 1824 by the Paris Imprimerie Royale, Paris. To be found at the Micronesia Area Research Center, University of Guam.
3. Zimmerman HM. Monthly report to Medical Officer in Command, U.S. Navy Medical Research Unit, No. 2, June 1, 1945.
4. Arnold A, Edgren DC, Palladino VS. Amyotrophic lateral sclerosis: Fifty cases observed on Guam. J. Nerv & Ment Dis, 1953; 117: 135-139.
5. Koerner D. Amyotrophic lateral sclerosis on Guam: A clinical study and review of the literature. Ann Int Med, 1952; 37: 1204-1220.
6. Tillema S, Wijnberg CJ. "Endemic" amyotrophic lateral sclerosis on Guam; Epidemiological Data; A preliminary report. Docum med geog et trop, 1953; 5: 366-370.
7. Mulder DW, Kurland LT, Iriarte LLG. Neurological diseases on the Island of Guam. U.S. Armed Forces Medical Journal, 1954; 5,10: 1724-1739.
8. Kurland LT, Mulder DW. Epidemiological investigations of amyotrophic lateral sclerosis: 1. Preliminary report on geographic distribution, with special reference to the Mariana Islands, including clinical and pathological observations. Neurology (Minneap), 1954; 4: 355-378, 5: 438-448.
9. Hirano A, Kurland LT, Krooth RS, et al. Parkinsonism-dementia, an endemic disease on the island of Guam: 1. Clinical Features. Brain, 1961; 84: 642-661.
10. Hirano A, Malamud N, Kurland LT. Parkinsonism-Dementia Complex, an endemic disease on the island of Guam: II. Pathological Features. Brain, 1961; 84: 662-679.
11. Anderson FH, Richardson EP Jr, Okazaki H, et al. Neurofibrillary degeneration on Guam, frequency in Chamorros and non-Chamorros with no known neurological disease. Brain, 1979; 102: 65-77.
12. Chen L. Neurofibrillary change on Guam. Arch Neurol, 1981; 38: 16-18.
13. Perl DP, Gadjusek DC, Garruto RM, et al. Intraneuronal aluminum accumulation in amyotrophic lateral sclerosis and parkinsonism-dementia of Guam. Sciences, 1982; 217, 10: 1053-1055.

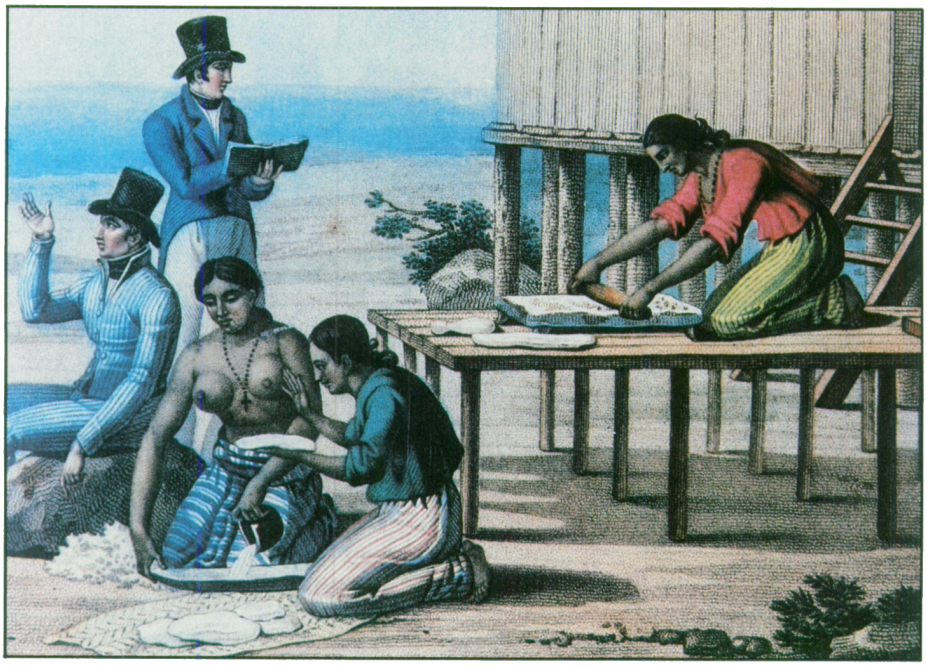

Figure 3 — Preparing cycad flour and tortillas. From "Voyage autour du monde" by L. de Freycinet.

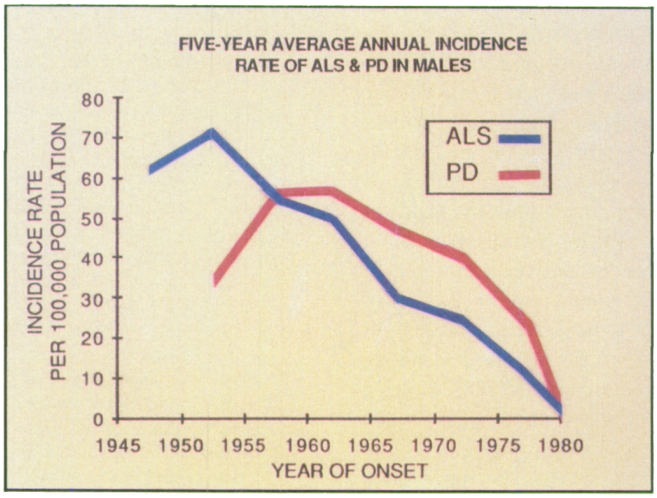

Figure 4 — Decline in incidence of ALS/PD.

14. Torres J, Iriarte LL, Kurland LT. Amyotrophic lateral sclerosis among Guamanians in California. California Medicine, 1957; 86, 4: 385-388.
15. Garruto RM, Gajdusek DC, Chen K-M. Amyotrophic lateral sclerosis among Chamorro migrants from Guam. Annals of Neurology, 1980; 8, 6: 612-618.
16. Eldridge R, Ryan E, Rosario J, et al. Amyotrophic lateral sclerosis and parkinsonism dementia in migrant population from Guam. Neurology (Minneap), 1969; 19: 1029-1037.
17. Garruto RM, Gajdusek DC, Chen K-M. Amyotrophic lateral sclerosis and parkinsonism-dementia among Filipino migrants to Guam. Annals of Neurology, 1981; 10, 4: 341-350.
18. Kurland LT. An appraisal of the neurotoxicity of cycad and the etiology of amyotrophic lateral sclerosis of Guam. Federation Proceedings, 1972; 31, 5: 1540-1542.
19. Vega A, Bell EA. Alpha-amino-beta-methylaminopropionic acid: A new amino acid from seeds of Cycas circinalis. Phytochemistry, 1967; 6: 759-762.
20. Polsky FI, Nunn PB, Bell EA. Distribution and toxicity of alpha-amino-beta-methylaminopropionic acid. Federation Proceedings, 1972; 31, 5: 1473-1475.
21. Spencer PS, Nunn PB, Hugon J, et al. Motor neurone disease on Guam: Possible role of a food neurotoxin. Lancet, 1986; 1: 965.
22. Garruto RM, Yanagihara R, Gajdusek DC. Disappearance of high-incidence amyotrophic lateral sclerosis and parkinsonism-dementia on Guam. Neurology (Minneap), 1985; 35: 193-198.
23. Reed D, Labarthe D, Chen K-M, et al. A cohort study of amyotrophic lateral sclerosis and parkinsonism-dementia on Guam and Rota. Am J Epid, 1986; 125, 1: 92-100.
24. Yanagihara RT, Garruto RM, Gajdusek DC. Epidemiological surveillance of amyotrophic lateral sclerosis and parkinsonism-dementia in the Commonwealth of the Northern Mariana Islands. Annals of Neurology, 1982; 13, 1: 79-86.

https://doi.org/10.1017/S0317167100037744 Published online by Cambridge University Press