These experiments represent the necessary initial observations. Whether the observed effects are permanent, whether intermittent exposure to hydrogen gas is equally effective, whether the observed results are quantitatively proportional to the hydrogen exposure time, and whether any deleterious effects are caused by the hydrogen are questions that remain to be answered. In any future work involving hyperbaric hydrogen, explosion hazards of hydrogen and oxygen mixtures should be scrupulously avoided.

The exact mechanism of the hydrogen effect should be elucidated if possible. For example, in the radiation chemistry studies mentioned above, no hydrogen catalytic effect could be observed on the decay of the allyl-type free radicals in irradiated PE, such as $-CH_2CHCH{=}CHCH_2-$, or on the decay of the $-CH_2OCHOCH_2-$ free radical in irradiated polyoxymethylene. The possibility exists that the hydrogen effect observed here is the result of a completely different mechanism. For example, the hydrogen might act to scavenge the $\cdot OH$ radical by means of the exothermic reaction

$$H_2 + \cdot OH \rightarrow H_2O + H\cdot$$
$$(\Delta E \sim -12 \text{ kcal/mole})$$

followed by the $H\cdot$ radical scavenging the O_2^- radical ion by the reaction

$$H\cdot + O_2^- \rightarrow HO_2^-$$

This sequence of reactions might prevent the reaction of O_2^- with H_2O_2, which Fridovich (*9*) has described as "the most damaging reaction that O_2^- can undergo" because this reaction results in the formation of the $\cdot OH$ radical, "the most potent oxidant known to mankind" (*9*).

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Implication of *Phlebotomus* Sand Flies as Vectors of Bartonellosis and Leishmaniasis as Early as 1764

Abstract. *A written account implicating* Phlebotomus *sand flies as vectors of Carrion's disease and cutaneous leishmaniasis in Peru was published by Cosme Bueno in 1764. Bueno's report precedes other publications implicating sand flies in the transmission of human pathogens by nearly a century and a half.*

Evidence that *Phlebotomus* sand flies transmit *Bartonella bacilliformis* (Carrion's disease) and *Leishmania* spp. remained circumstantial for many years. During the present century these minute flies were initially incriminated as vectors of Carrion's disease in 1913 (*1*). *Bartonella bacilliformis* was transmitted experimentally in 1928 to *Macaca mulata* by exposing the monkey to wild-caught sand flies collected in an area where the disease was endemic (*2*). The first published reports suggesting *Phlebotomus* sand flies as potential vectors of human pathogens (*Leishmania tropica* and sand fly fever virus) appeared in 1905 (*3–5*).

A recent note by Gooneratne (*6*) quoted an 1884 report by Mitford (*7*) on cutaneous leishmaniasis (Aleppo boil) in the Middle East; the disease was thought to be caused by "some mineralogical impregnation of the water, or some minute insect that inhabits it." Although in this case the possible participation of some insect was considered, its exact role in the transmission of the Aleppo boil was not clearly indicated. The first solid evidence that sand flies were involved in the epidemiolo-

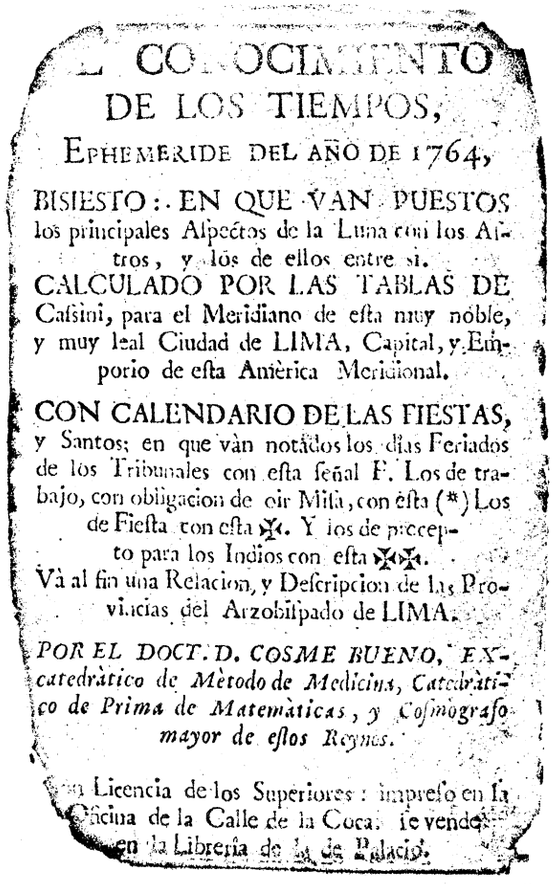
EL CONOCIMIENTO
DE LOS TIEMPOS,
EPHEMERIDE DEL AÑO DE 1764,
BISIESTO: EN QUE VAN PUESTOS
los principales Aſpectos de la Luna con los Aſtros, y los de ellos entre si.
CALCULADO POR LAS TABLAS DE
Caſsini, para el Meridiano de eſta muy noble, y muy leal Ciudad de LIMA, Capital, y Emporio de eſta Amèrica Meridional.
CON CALENDARIO DE LAS FIESTAS,
y Santos; en que vàn notados los dias Feriados de los Tribunales con eſta ſeñal F. Los de trabajo, con obligacion de oir Miſſa, con eſta (*) Los de Fieſta con eſta ✠. Y los de precepto para los Indios con eſta ✠✠.
Và al fin una Relacion, y Deſcripcion de las Provincias del Arzobiſpado de LIMA.
POR EL DOCT. D. COSME BUENO, Excatedràtico de Mètodo de Medicina, Catedràtico de Prima de Matemàticas, y Coſmografo mayor de eſtos Reynos.
Con Licencia de los Superiores: impreſo en la Oficina de la Calle de la Coca: ſe vende en la Libreria de la de Palacio.

Fig. 1. Front cover of *El Conocimiento de los Tiempos*, a kind of almanac published in Lima, Peru, under the direction of Cosme Bueno during the 18th century. A single copy of this publication is available in the Biblioteca Nacional, Lima. This copy was partially burned during a fire on 10 May 1943.

gy of the disease came in 1921 when a volunteer developed cutaneous leishmaniasis after being inoculated with a triturate of wild-caught *Phlebotomus* (*8*). In 1941 *Leishmania tropica* was transmitted to volunteers through the bite of experimentally infected *Phlebotomus papatasi* (*9*). Subsequent investigations have supported the hypothesis that *Phlebotomus* sand flies are the principal if not the sole vectors of human bartonellosis and leishmaniasis.

The first written account describing human bartonellosis appeared in 1630 (*10*) in Peru, only a century after the arrival of the first Spaniards. Carrion's disease, and a peculiar epidemiological form of cutaneous leishmaniasis called uta, are endemic in certain areas of the Peruvian highlands. Their antiquity has been substantiated mainly on the basis of linguistic considerations (*11*) and certain pathological representations in Peruvian anthropomorphic potteries from the Inca and pre-Inca times (*12*). The endemism of both diseases in small and isolated areas of the Peruvian Andes has also been pointed out as an indication of their great antiquity (*13*). In 1764 Cosme Bueno discussed in *El Conocimiento de los Tiempos* the folklore about the natural transmission of both diseases as follows (translated from the Spanish):

> The narrow valleys are very unhealthy where two kinds of maladies are noted; these diseases are also present in other cool provinces. One is verruga [Carrion's disease] which happens to be very troublesome and dangerous if not accompanied by cutaneous eruptions. The other results in corrosive ulcers, located on the face, is very difficult to cure, and causes the death of some people. It is said that both diseases originate from the bite of a small insect called uta [sand fly].

The term uta is still used synonymously for the vector and the disease of cutaneous leishmaniasis in certain areas of the Peruvian highlands.

Cosme Bueno was born in Spain and arrived in Peru in 1730 at the age of 19. He studied in Lima, where he became recognized as a distinguished physician, mathematician, and geographer. He traveled extensively throughout the Peruvian territory and other South American countries. Much of the information published in *El Conocimiento de los Tiempos* was gathered by Bueno himself. His report precedes other early records implicating sand flies as the vectors of leishmaniasis and Carrion's disease by about a century and a half.

An epidemiological peculiarity of uta and Carrion's disease is their persistence in the same areas for centuries. The diseases remain endemic today in the regions where Carrion's disease was reported by Vadillo in 1630 (*10*) and both diseases were reported by Bueno in 1764 (*14*). The antiquity of both diseases in Peru may explain the existence of the rich folklore about them.

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Delivery of a Quaternary Pyridinium Salt Across the Blood-Brain Barrier by Its Dihydropyridine Derivative

Abstract. *A dihydropyridine-pyridine type redox system was successfully applied for delivering a quaternary pyridinium salt,* N*-methylpyridinium-2-aldoxime chloride (2-PAM), through the blood-brain barrier. The dihydropyridine derivative of 2-PAM was quickly oxidized to 2-PAM after crossing the blood-brain barrier. As a result of this approach, the brain cholinesterase blocked by organophosphates could be reactivated. The new method should be useful in delivering numerous drugs which are otherwise inaccessible to the brain because of their polar ionic character.*

An appropriately designed transient derivative of a drug enables the drug to be transported efficiently, without any unwanted metabolism prior to and during its delivery to the site or sites of action where the drug is released from its derivative by chemical or enzymatic (or both) cleavage. We now report successful application of the transient derivative (hereafter called pro-drug) concept for delivering a drug of the quaternary ammonium salt type across the blood-brain barrier (BBB).

Serious poisoning with anticholinesterase agents such as organophosphates is still a big and possibly increasing problem (*1*). It is known that pyridine aldoxime type quaternary ammonium salts are the best cholinesterase reactivating agents and among them, *N*-methylpyridinium-2-aldoxime chloride (2-PAM chloride) is the preferred drug, although as an ionic compound, 2-PAM would not be expected to cross the BBB. Consequently, it could not reactivate the blocked cholinesterase in the brain. It is generally accepted that one of the crucial points in overcoming organophosphate poisoning is the extent of reactivation of the blocked cholinesterase in the brain, since it was concluded (*2*) that a certain minimum cholinesterase activity level is necessary for the survival of an organism poisoned by an organophosphate compound. Although this minimum level appears to be different for different parts of the brain as well as different for various species, it appears that access by relatively small quantities of 2-PAM to some parts of the central nervous system (CNS) might be enough to elicit pharmacologic effects and reactivate a small percentage of the blocked cholinesterase, and thus save the life of the intoxicated patient. However, no experiments have been reported on the influence of unreactivated acetylcholinesterase (AChE) on the brain functions of the

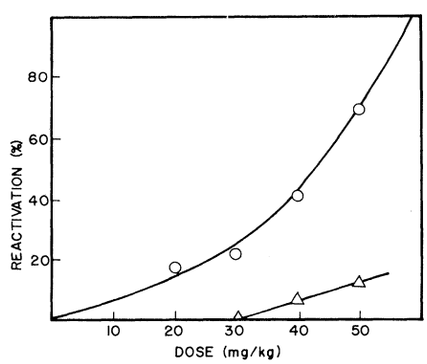

Fig. 1. In vivo reactivation of AChE in mice brains inhibited by subcutaneous administration of DFP (2 mg/kg) as a function of the dose of 2-PAM (△) or Pro-2-PAM (○). The percent of reactivation is equal to $(A_r - A_i)/(A_n - A_i) \times 100$, where A_n is the normal activity of AChE in brain; A_i is the activity after intoxication; and A_r is the activity after intoxication followed by treatment with a reactivator.