Aristides Leão’s discovery of cortical spreading depression

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This essay looks at the historical significance of three APS classic papers that are freely available online:


THE DISCOVERY OF SPREADING DEPRESSION (SD) illustrates how an unexpected chance observation, if made by an alert experimenter, can open a new major area of investigation. Aristides Leão (Fig. 1) was working for his PhD thesis at Harvard Medical School when his experiment turned out quite differently from what was expected. He was working under the supervision of Hallowell Davis, and he also had advice from Arturo Rosenblueth and later collaborated with R. S. Morison. In other words, he was the right person at the right moment in the right environment to work on the electrophysiology of the brain, a field at the time as yet in its infancy.

Originally, Leão intended to study “experimental epilepsy,” specifically the propagation of electrically provoked seizure discharges in the cerebral cortex (4). To this end, he opened the skull of rabbits under anesthesia and arranged a row of chlorided silver wire electrodes in contact with the cortical surface. Of these electrodes, one pair served for stimulation and the others, connected in six staggered pairs, for bipolar recording of the electrocorticogram (ECoG) at increasing distance from the stimulated points (Fig. 2F). Unexpectedly, instead of seizure-like discharge, the stimulation was frequently followed by a flattening of the spontaneous ECoG waves traced by the Grass oscillograph. The ECoG activity in the electrodes nearest to the stimulated area was silenced first, and then the extinction spread in orderly sequence from one electrode pair to the next, eventually covering almost all the cortex. Recovery of the ECoG waves occurred in the same sequence as their previous depression (Fig. 2).

Considering the ease with which SD can be provoked in the brains of experimental animals, one must wonder whether others might have seen the phenomenon before Leão did but dismissed it as some kind of artifact or an annoying interruption of the planned experiment. On the contrary, Leão became intrigued and made it his major topic. In his very first paper (4), he described many of the basic features that were subsequently confirmed by countless others. These features were as follows: 1) the depression of the spontaneous ECoG lasted a few minutes; 2) it took 3–6 min for the wave to reach from the frontal to the occipital pole of a rabbit; 3) aside from electrical stimulation, touching the brain with a blunt glass rod could provoke SD; 4) the threshold of SD varied among cortical areas, but, once triggered, it could spread in all directions; 5) by strong stimulation, it was possible to provoke SD in the hemisphere opposite to the one stimulated (callosal propagation); 6) while a cortical area was occupied by SD, neither sensory stimulation nor direct cortical stimulation produced an evoked potential wave; 7) ongoing experimental epilepsy (i.e., seizure discharge) was suppressed by SD, yet sometimes tonic-clonic activity preceded or followed SD (Figs. 18 and 19 of Ref. 4 show spike-wave activity as well); 8) SD does not require the cooperation of subcortical nuclei; 9) SD could be provoked also in the brains of pigeons and cats. In the discussion, Leão (4) suggested that SD and seizures are related. He supported this contention by the similar propagation of the two processes.

In a shorter companion paper, Leão described the vasodilation that accompanies an SD wave (5). Using microscopy and photography of pial vessels to assess cortical circulation rather than the then-customary heated thermocouple method, he was able to see not only that arteries dilated but also that veins “become as scarlet as the arteries” (5). He never saw a darkening of the color of the blood to precede its brightening. This, to my knowledge, was the first realization that increase in cerebral blood flow can exceed the increase in the demand for oxygen—a matter that is occupying the attention of investigators of cerebral circulation to this day.

The third paper in our focus (Leão, Ref. 6) came 3 yr later, after Leão had returned to his native Rio de Janeiro. In it he described the slow voltage shift that accompanies SD as well as sudden total ischemia of the brain. Recorded by direct current (DC)-coupled amplification from the cortical
surface, the main negative wave lasted 1–2 min and it attained an amplitude of 8–15 mV, the largest extracellular voltage variation observed in living brain tissue. The negative wave was sometimes preceded by a small, brief positivity, and it was always followed by a positive overshoot of 3–5 min. Remove the time calibration, and Fig. 1 of this paper could be mistaken for a compound action potential recorded from a nerve or a fiber bundle. Brief, acute ischemia suppressed the ECoG waves and yet caused no DC voltage shift, but it augmented the potential shift of an ongoing SD. More prolonged ischemia did cause a negative DC shift even in the absence of SD, and this outlasted the cessation of the blood flow. Leão suggested that the negative voltage shifts of SD and of cortical ischemia are the result of “some change of the same nature” (6). This last point is controversial, but in my opinion it is essentially correct (8).

Over the years these three seminal publications were followed by many, not only from Leão’s group but from laboratories around the world. SD is recognized as a stereotypical response pattern of gray matter. Whether it is entirely pathological or whether it could perhaps have some physiological or protective function is not clear (2). No doubt it is a feature of certain clinical conditions. The underlying biophysical process is governed by all-or-none feedback in which slowly inactivating inward membrane ion currents and a redistribution of ions between neuronal cytosol and interstitial fluid play equal roles. The early literature has been reviewed in detail by Buresˇ et al. (1) and in recent work by Gorji (3), Martins-Ferreira et al. (7), Somjen (8, 9), and Strong and Dardis (10).

FIG. 1. Aristides Azevedo Pacheco Leão. [Reproduced from Anais de Academia Brasileira de Ciências, 56: (4), 1984, by permission.]

FIG. 2. Leão’s original illustration of spreading depression. The traces show electrocorticograms from the surface of the brain of a rabbit. At the bottom of each panel is the time elapsed since the stimulation. The inset (F) shows the position of the electrodes; s, stimulation; 1–7, recording electrodes paired as indicated in A.
REFERENCES


