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EDITORIAL

Do post-mortem brain studies provide useful information for Psychiatry?☆

¿Qué aportan a la Psiquiatría los estudios en cerebro post mórtem?

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Modern medicine's scientific practice draws from nineteenth-century postulate models developed by Claude Bernard under the scope of ''experimental medicine''. At about the same time that Claude Bernard developed his work (1865), worker Phineas Gage had suffered a traumatic injury in 1848, generating a scientific debate on the cause–effect relationship between brain lesions and the onset of abnormal thinking and behavior. Thus, scientific currents that have investigated human brain tissue looking for traces and the etiology of mental illness stem from the same sources as do other areas of modern medicine. The debates in the early twentieth century among Kraepelin, Alzheimer, Wernicke and other neuroscientists are well known in history, which would be known currently as ''translational'', in terms of the clinicopathologic basis for psychiatric disorders. The truth is that, eventually, a morphological view prevailed in this debate, probably heavily influenced by neuropathological findings in dementia, and it has made a mark in mental illness research, lasting until today. Thus, the first World Congress of Neuropathology held in 1951 established psychiatric diseases as ''functional'' nosological entities, officially abolishing the search for macroscopic and microscopic markers that would contribute to their classification. In practice, this meant steering away from looking for brain changes in patients with mental illness. Fortunately by then, neurochemistry and pharmacology were progressing in parallel with neuropathological currents, though still quite far from them. Very soon, empirical observation of therapeutic action stemming from drugs with successful outcomes in affective and psychotic disorders would lead to analyzing their action mechanisms on the nervous system, and building the first neurobiological hypothesis of modern psychiatry. Therefore, what we know now about mental illness etiology and pathophysiology is mainly a result of an interaction between progressive technology development and direct study of the brain in affected individuals, through these technological means. Although controversial, the description of morphological alterations, functional deficits and even molecular changes is widely accepted today as existing in the central nervous systems of psychiatric patients; this is a result of tremendous progress of in vivo neuroimaging techniques, gene development and the use of postmortem brain tissue as a key substrate of the disease.

However, studies predominantly on post-mortem nervous system, as well as other tissues, are still perceived as an exotic and extravagant activity of some investigators. Probably, poor history records of autopsy studies in psychiatric

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patients, resulting in part from the historical influence outlined above, along with declining autopsy requests in all areas of medicine, are reasons accounting for this apparent exoticism. Paradoxically, this phenomenon coexists with the appearance of biobanks, and in particular their formalization, coupled with heavy media explosion. Today, no translational research is designed without comparing pathological human tissue results with their corresponding controls. Resuming postmortem brain use where neuroimaging in vivo is unable to go does not mean a step back, but an indispensable milestone for the future development of psychiatry.[1,2]

Brain banks and collections are not an invention of our time; however, these terms probably are. They have been around for many years as simple working means to solve a scientific necessity. Some institutions with a long-term research history continue preserving samples dating back even prior to the development of psychoactive drugs. However, aware clinicians and translational investigators, like us, gradually observe with some amazement, what appears to be an undesirable effect of media on the biobank concept. Sometimes, some investigators request samples from tissue banks and collections with the frivolity of a person who is going shopping; therefore, believing they can set the conditions and characteristics of the product ordered. This is where the investigator's legitimate aspirations collide with the reality of what we consider must be a process defined by collaboration of all actors involved in translational research. In Spain, the Biomedical Research Act of 2007, and its development in the Biobank Chapter by Royal Decree 2011, establishes legal and ethical foundations for such activities.[3,4] Donor rights, requirements for collecting and releasing samples, research process requisites and other important aspects are fully regulated. However, biobanks cannot be launched by regulating, displaying and promoting the process, and even creating dubious intermediaries to manage it. The core of the process relies on the day-to-day activities of aware investigators and/or clinicians with sample and data requirements to better understand and treat the disease. Unfortunately, acknowledging the donor recruiter's fundamental role, in particular, that of collecting unique samples, one of which is the brain, and establishing attractive conditions for such a laudable activity, remains lost in a legislative tangle. Moreover, the process for ethical-legal assessment of postmortem sampling appears sometimes contaminated with moral visions affecting such aspects as risk/benefit weighting or consent ownership.[5,6]

Research on post-mortem tissue from psychiatric patients is a victim of descriptive studies' own limitations. This is observational research with a case–control design, where established diagnoses are used to investigate biological risk factors. This process may be more or less based on supported assumptions, but today, large-scale exploration lacking initial hypothesis has also reached post-mortem studies from ''-omics'' technologies. There is no doubt that these techniques with great potential in terms of simultaneous analysis and requiring small amounts of tissue may shed light on psychiatry questions. However, hypothesis generation and comparison from investigators' findings and experience remain irreplaceable.[7] Confounding factors are the Achilles heel in descriptive studies, and post-mortem tissue is no exception. Variables such as the process' length, long-term effects of treatments, perimortem variables, and of course, diagnostic criteria, determine results.[8] However, as with any study of this type, controlling these potential biases through maximum information (clinical and also toxicological or on sample storage conditions) availability, and sample size increases, often circumvents methodological constraints. Again, this demonstrates the key role of the donor recruitment and sample collection administrator throughout all processes subsequently involving that tissue.

The most intense discussions in the field focus on aspects relating to disease diagnosis and progression related to patients whose postmortem samples end up being evaluated. The so-called psychological autopsy based on an interview of subjects close to the deceased as a way to establish diagnosis and patient status at the time of death is a very popular method. This is an alternative method in lieu of pre-mortem clinical history, with a diagnosis updated and endorsed by direct observation of health professionals. The other variant, i.e., availability of an official psychiatric diagnosis, conducted in life by standard procedures, is a more feasible alternative in universal health models, and free of financial access barriers, which provides reduced marginalization of the mentally ill. This second option, apparently more rigorous in the scientific aspect, is not always the choice of reviewers preferring the North American model of psychiatric research with postmortem samples, a model where psychological autopsy prevails as a diagnostic procedure. As expected, the correlation between both approaches is more evident for psychotic processes than for depressive processes.[9]

Today, some of psychiatry's questions can only be decrypted using postmortem brain tissue. For example, epigenetics is the crossroads where biological inheritance, fetal development, life events and social imprint meet. Activity of multiple genes is modulated by epigenetic influences able to affect central nervous system cells differently than other tissues, bundling individual and disease into a unique entity, difficult to undergo biological studies with tissues outside the nervous system. Probably, the role of epigenetic influences in etiopathogenesis of mental illness is currently the best argument that proponents of using postmortem brain tissue in research can wield in the field of biological psychiatry.

Ultimately, investigators and scientific journal editors seem to have commented on the poor utilization of postmortem studies to learn about the most significant psychiatric entities.[1,7] This feedback has boosted the use of postmortem materials, albeit under strict methodological rigor, whose results we are, and will be, seeing progressively appear in the coming years. We are living in times of opportunities and challenges where human brain tissue is an irreplaceable tool as a biological substrate of psychiatric illness.

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