The Ethical-Industrial-Academic Nexus: How Our Understanding of Brain Physiology May Be Hindered by the Dominance of a Single Animal Model: The Mouse

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A troubling issue in contemporary medicine is the thirty-year lack of new drugs in the field of neurology and psychiatry. The causes considered are varied, but here I would like to attempt to analyze the problem through the broader lens of research history.

Many will recall the witch-like methods by which psychiatry sought to treat mental and neurological illness for much of its existence. Essentially, therapy was singular: containment and isolation from society. The situation changed radically in 1953 with the discovery of chlorpromazine: the first antipsychotic. The drug's effect triggered an epochal change, well-described by the reaction of Parisians near the psychiatric hospital, where for the first time the molecule was administered to patients: people were indeed greatly concerned about the silence emanating from the building. What had long been a noise of illness had suddenly disappeared. Psychopharmacology and neuropharmacology proceeded over the next 3-4 decades to produce new molecules with broad-scale effects: benzodiazepines became the treatment for anxiety and insomnia, SSRIs for depression, L-Dopa for Parkinson's, and new antiepileptics improved the lives of many patients.

How were these molecules discovered? Often by chance. Searching for one thing and finding something else. The serendipity with which pharmacology harvested successes in the brain sector on the one hand worried the sector – which did not actually have a working method, but on the other hand could offer some optimism: if monumental discoveries were made without knowing almost anything about the CNS, who knows what horizons could open up with a more solid neuroscience foundation.

Here, then, arises an extremely broad field: neuroscience.

Therefore, the neuroscientific horizon implied a practical destination of great value: understanding the basic mechanisms of CNS functioning would allow us to comprehend and treat new diseases. However, this promised land is proving to be more difficult to reach than we had thought. There have certainly been significant advances in our understanding of neuroscience, but without the applied pharmacological implications we might have expected. Perhaps this is nothing more than further evidence of the difficulty of the task that neuroscience sets out to accomplish. After all, the brain is perhaps the most complicated object in the universe. But here I would like to propose an alternative interpretation. Beyond the undeniable difficulty of the research task, the way in which modern research is approached may not be the most effective.

In particular, I'd like to focus on the role of animal models in current neuroscience research.

The use of an animal model, allowing a certain degree of reductionism, presents undeniable investigative advantages. But which animal model to use? In the last century, before the birth of modern neuroscience, most physiologists relied on animals that had two key characteristics: 1) they had rich behavioral modalities; 2) they had sizes compatible with the use of physiological investigation technologies. Depending on the type of investigation, different animal models were therefore used: dogs, cats, monkeys, but also frogs and lizards. Since the 1980s, however, rodents have rapidly supplanted other models. Mice, in particular, are now the dominant animal model.
Why has the use of this small rodent become almost exclusive? Could this be one of the problems behind the thirty-year psycho-pharmacological sterility?

The identification of DNA as the molecule of heredity of bodily characteristics, the decoding of its language, and the birth of DNA manipulation technologies have pushed basic research from physiological-behavioral study models to genetic-behavioral models. With the realization of the first KO mouse and the first transgenic mouse, a vast area of investigation was opened that promised to observe the behavioral correlates of genes: in other words, behavior (in the very broad sense of phenotype) is, for the geneticist, the study model of the genome itself.

The contemporary rise of the animal rights movement has also increased public sensitivity to the use of animals in research and pushed the legislature to act.

I'll be arguing that the combined pressure from the field of molecular biology and the field of bioethics created a set of reciprocally supportive relations among the academic institution, the biotech industry, the legislative and regulatory bodies that sank life science research into a single animal model, the mouse, reducing the predictive power that comes from comparative research.

Moreover, from the mouse, ethical pressure today pushes towards even simpler models (zebrafish), and researchers, in an attempt to avoid the additional administrative burden required by ethics committees, are moving towards extra-vertebrate models (zebrafish larvae). On the other hand, the biotech industry today no longer has a particular interest in the use of the mouse, except for regulatory reasons, and would like to push for the adoption of in vitro study models (organoids), which are much cheaper in terms of large-scale applications.

The new frontier is emerging with the use AI and the production of in silico data as an investigative tool: in other words, after feeding constructed data to AI, the behavior of AI is observed to make inferences about the natural system (which has never been seen).

In conclusion, I will argue that the Ethical-Industrial-Academic Nexus (EIA Nexus) may be directed towards a stable configuration in terms of research models that may actually obstacle our comprehension of the neural physiology, delaying the birth of a complete theory of brain and, in the end, delaying the discovery of new therapeutic interventions.