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Are Animal Models Relevant in Modern Psychiatry?

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The use of animals in medical research became firmly established in 1865, with the publication of *An Introduction to the Study of Experimental Medicine* by Claude Bernard.[1] This scientific discourse laid the groundwork for the study of comparative physiology between animals and humans. Half a century later, the animal model was introduced into the behavioral sciences by early theorists Pavlov (classical conditioning), Watson (behaviorism), and Skinner (operant conditioning). Later, the animal model was used to investigate conditions ranging from maternal deprivation to depression and learned helplessness.

Most early psychiatric drugs were discovered through serendipity rather than through the use of animal models. Isoniazid(Drug information on isoniazid), originally used to treat tuberculosis, was found to possess mood-altering properties and was marketed as the first antidepressant in 1957.[2,3] MAO inhibitors originated from an effort to develop antituberculosis medications; they were superseded by tricyclic antidepressants (TCAs), which were discovered by clinical observation.

The potential psychotropic effect of chlorpromazine(Drug information on chlorpromazine), originally used as an anesthetic adjunct in a Paris hospital in 1952, was discovered by a military surgeon later in the same year.[4,5] Thus, the phenothiazines came from a search for better pre-anesthetic agents.

The Australian physician John Cade[6] reported the calming effect of lithium(Drug information on lithium) in humans in 1949. The first benzodiazepine, chlordiazepoxide(Drug information on chlordiazepoxide) (Librium), was discovered accidentally in 1955.[7] The first studies of benzodiazepines were unsuccessful attempts to treat patients with schizophrenia.[8]

In contrast to discoveries made through chance observation, newer psychotropic drugs, such as SSRIs, were discovered through the process of rational drug design. Five SSRIs (citalopram, fluvoxamine(Drug information on fluvoxamine), fluoxetine(Drug information on fluoxetine), paroxetine(Drug information on paroxetine), sertraline(Drug information on sertraline)) were produced independently by 5 different companies.[9] Rational drug design remains the main driving force behind the development of modern psychiatric drugs.

Animals as model systems in psychiatry

Since the mid-20th century, researchers have designed animal models of stress, anxiety, depression, and obsessive-compulsive conditions in the laboratory to develop, test, and validate drugs to treat human disorders.[10-13] Rats and mice are most commonly used in specific behavioral tests, such as the despair test, tail suspension test, and open field test.

Current animal models of human psychiatric conditions face the same methodological limitations as they did 30 years ago. According to Beach[14]:

> The validity of interspecific generalization can never exceed the reliability of intraspecific analysis; and the latter is an indispensable antecedent of the former. . . . Significant comparison of a particular type of behavior in two different species is impossible unless and until the behavior has been adequately analyzed in each species by itself.

This hypothesis is conditional on the existence (or availability) of animal models to accurately mimic human psychiatric conditions. In reality, the overwhelming majority of mental disorders recognized by DSM, the International Statistical Classification of Diseases and Related Health Problems (published by the World Health Organization), and the American Psychiatric Association do not have a counterpart in laboratory animals. For those human conditions that are considered to have animal homologues, there often exist critical causal mechanisms that differ between humans and animals, which raise methodological questions about the soundness and relevance of these animal models.[15]

Because of the multifactorial nature of conditions such as depression and anxiety and the ambiguities inherent in psychiatric diagnosis and treatment, the use of animal models in psychiatry presents unique challenges—unlike those found in other medical disciplines. In most cases, animal models represent a compromise because the cause and mechanism of the human condition under investigation may not be fully understood. In addition, researchers are using a relatively simple system (receptor activation or inactivation) to represent a more complex and less readily studied system (human mental disorders). While examples can be found to demonstrate common and conserved modes of action of neurotransmitter chemicals throughout phylogenetically remote organisms, this approach has its limits when studying complex systems, such as the human CNS.[16] According to molecular biologist Marc van Regenmortel[17]:

> The reductionist method of dissecting biological systems into their constituent parts has been effective in explaining the chemical basis of numerous living processes. However, many biologists now realize that this approach has reached its limit. Biological systems are extremely complex and have emergent properties that cannot be explained, or even predicted, by studying their individual parts. The reductionist approach—although successful in the early days of molecular biology—underestimates this complexity and therefore has an increasingly detrimental influence on many areas of biomedical research, including drug discovery and vaccine development.

Animal models, in general, have not been subjected to the rigors of evidence-based medicine. Few systematic reviews or meta-analyses have been conducted to compare treatment outcomes in laboratory animals with outcomes in clinical trials. Overall, the animal model has performed poorly as a predictive modality of human outcome in these reviews.[18-22]

Examples of animal models in psychiatry

Behavioral despair. The behavioral despair model is commonly used to screen candidate antidepressants. Like other TCAs, imipramine(Drug information on imipramine) was screened using the Porsolt forced swim test. In this test, the animal (a rat or a mouse) is placed in a container with cold water and is forced to swim until exhausted; it is then briefly taken out of the water. This is repeated until the animal reaches a state of helplessness and stops swimming. Although immobility time is reduced by antidepressant agents such as imipramine, significant strain differences have been reported.[23]

The Porsolt forced swim test has been criticized on the grounds that the state of helplessness is more a strategy of survival than a sense of "despair." The increased immobility simply demonstrates a positive behavioral adaptation, in which the animal has learned that it cannot escape and is conserving energy until it is removed from the water. In addition, while the test is reported to distinguish antidepressants and neuroleptics from anxiolytics, false positives have been reported for a number of other compounds, including stimulants, convulsants, anticholinergics, pentobarbital, and opiates.[24,25]

Canine acral lick dermatitis. This is considered by some researchers to be a suitable animal model for the study of obsessive-compulsive disorder (OCD) in humans.[26] However, most cases of acral lick dermatitis in animals have an underlying allergic cause; if the allergen is eliminated, the condition resolves. In humans, OCD is an anxiety disorder characterized by intrusive thoughts, unrelated to allergies. Although SSRI treatment may be effective for both acral lick dermatitis in animals and OCD in humans because of a shared neurotransmitter response, this does not confer homology on the animal model. According to Nonneman and Woodruff,[27] "If every aspect is fully isomorphic between the animal model and the human condition, including cause and mechanism, the model is homologous." Clearly, the OCD dog model does not fulfill these criteria. In addition, the dog model ignores the existence of a genetic component and the presence of comorbidities, which are thought to play an important role in human OCD.[28,29]

Transgenic mice and the study of anxiety-like endophenotypes. Humans and mice share approximately 97% of their working DNA and approximately 24,000 genes per body cell.[30] In light of these facts, scientists have turned their attention to the study of differential gene expression patterns in genetically altered mice to investigate anxiety through the corticotropin-releasing hormone system, the serotonin system, and the GABA system.[31] However, because genes work in networks and animals are examples of complex systems, small changes at the gene level can have major consequences for the individual. Thus, it is irrelevant to point to observed similarities in genetic makeup (including transgenes) between species, since the details of the differences are in the interactions between conserved genes, not in the genes themselves.[32]

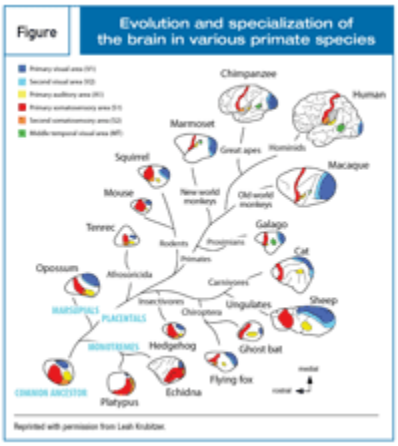
As Hirst and colleagues[33] have shown in the example of the serotonin system, it is unlikely that serotonin type 6 knockout mice will be useful for validating the serotonin type 6 receptor as a therapeutic target because of unexpected species differences in both receptor regional distribution and pharmacological profiles. It is now evident that slight variations in rodent and human amino acid sequences can lead to unexpectedly large differences in the pharmacology of the receptors, with potentially disastrous effects for drug development. What has not been clearly documented until the study by Hirst and colleagues is that mouse receptors could be significantly different from rat receptors.

Role of non-human primates in psychiatric and neurological research. The use of non-human primates by Harlow and associates[34] to demonstrate the effects of maternal deprivation has been well documented. In experiments conducted between 1957 and 1963, they removed baby rhesus monkeys

from their mothers and observed the effects of partial and total social isolation. Some of the monkeys were kept in solitary confinement for up to15 years. These studies have been criticized on both ethical and methodological grounds.[15]

Diagnosing "depression" in a monkey is at odds with the successful ongoing process of clarifying psychiatric diagnoses by using DSM criteria. It is not possible to ascertain feelings of worthlessness and excessive guilt, indecisiveness, and thoughts of death from observations of monkeys.[35] Harlow's student Stephen Suomi became more circumspect in 1995, when he carefully referred to the condition in monkeys as "something equivalent to depression" rather than "depression."

The non-human primate is considered by some researchers to be the most appropriate model for the study of brain function. Among non-human primates, the rhesus macaque is the animal of choice for cognitive studies. While there may be similarities between the brains of humans and non-human primates, the monkey brain is not a scaled down version of the human brain.[36] Rather, each primate brain is the unique result of evolutionary biology, molded over millions of years in response to environmental, social, and genetic influences (***Figure***). With the human brain, the effects of cultural evolution are also considered.



There are numerous differences in the anatomy and physiology of the CNS in monkeys and humans, including differences in locations of specialized areas in the brain. The visual 1 area accounts for 10% of the total cortex in the monkey but only 3% in humans, and anatomically corresponding visual areas in monkeys and humans can perform very different functions.[37] The human brain's architecture and physiology is far more complex than that of the monkey brain. One indication of this is the length of time it takes for the brain to develop in its major phase: 136 days for monkeys and 470 days for humans.[38] Other significant differences include the number of synapses a human neuron makes (between 7000 and 10,000) compared with the number a rhesus monkey neuron makes (between 2000 and 6000) and the expression of at least 91 genes involved in a variety of neural mechanisms that differ between monkeys and humans.[37,39] According to Kreiman and associates[37]:

> Even though the hippocampus appears to be one of the most conserved areas of the brain (most similar among mammals), there are still considerable differences. Neurotransmitter receptor distribution varies widely between species. For example, there is an additional small layer of high-density kainate receptors in the deepest part of the hippocampal molecular layer in the monkey, but not in humans. The inhibitory $GABA_A$ receptors are located with high density in the human CA 1 hippocampal region, but not in the same region in monkeys. These results demonstrate considerable changes of the regional and laminar distribution of important signaling molecules in an otherwise evolutionary conservative brain region.

The validity of the animal model in regulatory toxicology

From a regulatory perspective, psychiatric drugs are required to undergo animal testing to demonstrate safety and efficacy.[40] Safety relates to toxicity testing, which requires a rodent species (usually a rat) and a non-rodent species (usually a dog) to undergo single-dose (acute), repeated-dose, and long-term exposure to a candidate compound. The acute toxic dose (LD50) is the median lethal dose of a compound required to kill 50% of a group of test animals. Repeated-dose exposures usually require 14-

to 28-day studies, while long-term exposure requires up to 90 days in the rat and up to 12 months in the dog. Significant variations in the toxicity profile of a test compound may occur because of species differences in absorption, distribution, metabolism, and excretion (ADME).

Human lethal overdose figures are compiled by national poisons information centers. These are empirical data obtained from human accidental or deliberate poisoning and overdose (A. Vale, personal communication, 2009). Human lethal overdose cannot be *predicted* from animal LD50 values (**Table**). Animal studies are in fact poor predictors of human outcome with respect to drug toxicity.[41-44] The use of retrospective correlation is often inadvertently confused with *prediction*.

Table — Comparison of LD50 in animal models with LD in humans for select drugs/agents (mg/kg)

Drug/agent	Rat LD50	Mouse LD50	Dog LD50	Monkey LD50	Human LD
Amitriptyline	240 - 320	140 - 350			25
Amphetamine	55	24			
Caffeine	192	127			192
Chlorpromazine	142	135			
Citalopram	800	1000			
Diazepam	352 - 1200	48 - 700	1000	400	71
Fluoxetine	452	248	> 100	> 50	25
Fluvoxamine	1470 - 2000				20
Isoniazid	160 - 1250	133			125
Lithium	613	1190			
Nicotine	50	3			0.7
Orphenadrine	255	100			
Paroxetine		500			
Phenobarbital	162	137	85		71
Propranolol	466	320			
Sertraline	1480	500	80		
Thioridazine	995	385			

LD50, median lethal dose required to kill 50% of the test group of animals; LD, lethal overdose.
[illegible]

A classic study by Olson and colleagues[45] looked at the concordance between adverse events seen in humans and data obtained from preclinical animal toxicity studies. While this study measured sensitivity, it ignored specificity; therefore, its conclusions are largely irrelevant to the great prediction debate.[32] Although this study has been quoted in support of animal use as a predictive modality, Olson[45] stated that “this study did not attempt to assess the predictability of preclinical experimental data to humans.”

In addition to the challenges presented by differences in ADME between species, other variables can influence the outcome of animal studies. The laboratory environment is inherently stressful for the animals. In addition to caged housing, which provides little or no environmental enrichment, even routine procedures can lead to significant changes in physiological parameters correlated with stress (eg, serum or plasma concentrations of corticosterone or glucose, heart rate, and blood pressure).[46] While these changes may not be considered to be of much significance with respect to routine drug testing, the same cannot be said of drugs specifically designed to treat stress and similar conditions. According to Zinberg and Robertson,[47] the difference between an animal’s natural setting and an artificial laboratory environment cannot be underestimated; it may produce major pharmacological effects. Variables such as group housing versus single housing, type of bedding, light-dark cycle, and handling by humans can affect the outcome of a study.[48-50]

Evidence-based psychiatry

Evidence-based medicine aims to apply the best available evidence gained from the scientific method to clinical decision making. Clinical research is the solid ground of medicine, whereas biological theory is a necessary but changing superstructure.[51] In an era of the human genome and advanced noninvasive screening techniques, it is perhaps timely to examine the relevance of the animal model in modern psychiatry. This becomes all the more interesting when we consider the notion that psychiatry is the only medical discipline that attempts to treat a conceptual abstraction—namely the human mind—in addition to organs and physiological processes.[15] Although molecular psychiatry provides some insight into the mechanism of mental illness, external psychosocial factors that influence human behavior fall well outside of its scope.[52]

Some researchers continue to justify the need for invasive cognitive studies in animals (particularly the non-human primate) on grounds that single neuron studies are not feasible in humans.[53,54] That is no longer the case, since single neuron activity can now be studied in patients with Parkinson disease who undergo deep brain stimulation and in patients with epilepsy in whom electrode probes are used to identify epileptic foci. We need to reconcile ourselves with the fact that the level of detail that has been achieved in the study of the macaque brain will likely never be achieved in studies of the human brain.[55]

Current trends indicate that diagnosis and treatment of psychiatric disorders in the 21st century will rely more on an integrative approach, including the best of genomic advances (eg, human brain transcriptome; pharmacogenomics in drug development geared toward personalized medicine); noninvasive screening techniques combined with ethical pharmacological studies, such as pharmaco-magnetoencephalography[56,57]; and clinical observation and other relevant human-based methodologies.

Empathy in psychiatry

There is an urgent need to acknowledge the role of empathy in science. The inclusion of empathy as a fundamental tenet is especially important in psychiatry and psychology, as an antidote to the mechanistic view of disease and the undervaluing or even ignoring of psychological and spiritual components.[15] Animal researchers have traditionally been circumspect about including any notion of empathy in their work, for fear of being stigmatized as anthropomorphic.

In contrast, some researchers have openly expressed the moral conflict they face when using non-human primates in experiments.[58] These researchers occasionally acknowledge the very negative effects of family separation, isolation, and boredom, in addition to the pain and suffering inflicted on the animals during the experiments.

Several studies have indicated that mammalian species, especially the chimpanzee, have a sense of self and self-awareness.[59,60] This has led some scientists, particularly behaviorists, to suggest that these animals should be afforded special protection from pain, suffering, and incarceration.[61] In addition, studies of other mammalian species, including mice and rats, suggest that they also possess awareness of self and even more subtle "human" qualities associated with empathy and social joy.[62] All of this empirical evidence points to a need to embrace a paradigm of "ultimate concern in science."[63]

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