Of Mice and Humans

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Abstract:

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De ratones y humanos - Of Mice and Humans

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Experimental data is what we do with it. It is the analysis that makes them relevant (or not). We have to be especially careful to look at it as fairly as possible. Otherwise, we will see whatever each of us wants to see, always. In February 2013, Junhee Seok showed that mouse models poorly mimic human diseases. In June 2014, Keizo Takao and Tsuyoshi Miyakawa used the same data to conclude the opposite. This is the story of how they shocked the scientific community.

It is impressive how much we know from animal studies about how the human body works. The first thing we learned about digestion was from studies on birds and dogs. What we (still little) know about neural connections is thanks to experiments on fish, crabs, mice, cats, monkeys and a lot of other animals. Even advances in diseases like cancer are supported by years of work with little mice.

From Antique Greece to the present day, animal experiments has led us to build a monstrously huge body of biomedical knowledge. Without going any further, a search with the words *mouse model* (i.e., mouse model for the study of human

pathologies) in the world database of scientific publications in medicine provides the incredible number of 284,129 results.

The fact that there are so many publications about experiments done on mice implies a great assumption: the idea that the animal under study and the human being behave in the same way when facing a certain disease. Needless to say, it does not take a genius to realize that a mouse is not a human being, a dog is not a human being, even a monkey (a model widely used in HIV research) is not a human being. At first sight, it seems a huge leap of logic to believe that we can extrapolate the results obtained in a mouse to a human being. And it is: extrapolations must be made very carefully. **A mouse is not a human being just as the map is not the territory.**

Of course there are other grounds for using mice in experimentation: many experiments on animals have developed scientific knowledge, especially in the area of health, while studies on humans are much more limited in scope, or directly forbidden. But also, mice are small, easy to breed, cheap and we can manipulate their genes in a simple way. Of course, there are also grounds for NOT using mice: who are we humans to decide about the life of another living being?

Animal research is not only more convenient, easier and more legal than research on the human body: well done, it is also more complete and gives us a broad picture of the functioning of certain organs and systems, the behaviour of certain diseases or the mechanism of action of drugs in a whole organism. If we go back to the question of who we are to do this, it is relevant to mention that this type of strategy is also strongly regulated by committees for the ethical use of laboratory animals, which follow researchers closely, making sure that they only use animals when strictly necessary and that they use as little as possible, obtaining an interdisciplinary approach to a complex ethical challenge.

But there is an even worse problem anyway: apparently, no matter much we try to rationalise the use of animals in laboratories, something is not working well, not ethically speaking, but practically. Several clinical trials, which is the point where testing on animals is left to humans (who are also animals), are failing. **Of every 10 drugs that entered the first phase of clinical trials between 2003 and 2011, only one ended up being approved. And the proportion is even lower when we focus on cancer therapies.**

Given this concern, the solution was to perform large data mining, remake calculations and answer the question with hard data. And something beautiful happened.

In 2013, researcher Junhee Seok and his collaborators discovered something incredible: not even close the animal models resemble what was seen in human patients. They recreated in the animals different types of wounds and compared the recovery time between humans and mice, including differences at the genetic level, that is, which genes were most expressed in response to those wounds (remember that living beings have many genes but not all are active at the same time, the expression is a measure of that activation). Both in terms of recovery time and gene expression, they recorded the same thing: laboratory animals and humans are not at all alike. We are talking about levels of similarity just above what could be due to chance. In other words, if there was any similarity between mice and people, it was purely by chance. Complex statistical calculations showed that the genetic responses of mice had nothing to do with the responses of humans.

The article, entitled *Genomic responses in mice poorly mimic human inflammatory responses*, shocked the scientific community, the press and the general public. The New York Times published an article in which it simply stated: "(...) as a result, years and billions of dollars were wasted on following false leads (...)". Because, of course, the picture was complex. There were many studies and biomedical advances that

had been made on the basis of a total lie. From the beginning we used animal models because of its resemblance to humans, but even if they 'might look the same', genetically it seemed that we had nothing to do with it.

And so it was that we lived for a year and a half in sorrow. Crisis. What are we doing?. What is the purpose of going through with this?. What is the meaning of life?. But the authors of the 284,129 papers made with mouse models were clearly not happy with this conclusion, so they brought more evidence into the debate.

In June 2014, another article was published with the title *Genomic responses in mice excellently mimic human inflammatory responses*. And not only that: the authors (Keizo Takao and Tsuyoshi Miyakawa) used THE SAME DATA as in the previous work to draw a diametrically opposed conclusion. The good thing about having raw data available is that anyone can verify the veracity of a result.

Takao and Miyakawa destroyed Seok. Initially, because he had not made a 'selection' of genes to study, so any method of finding differences between mice and humans loses sight of a real difference by being 'diluted' between genes that do not matter. For example, perhaps the genes involved in wound healing behaved the same, but genes related to the ability to smell cheese did not, and the result of the latter covered up the others. According to Takao, it turns out that the intricate statistical accounts showing that the organisms have nothing to do with it were poorly done: Seok had used a statistical calculation (Pearson's correlation coefficient) which assumes that the data meet certain assumptions (a normal distribution and a linear type of correlation). Takao used the same data, but first checked, rather than assumed, whether they met those rules. When he saw that they did not, and using the appropriate method (the Spearman coefficient) for such a data set, he fully demonstrated that mice and humans are quite similar in their inflammatory responses. At least enough to get thousands of researchers around the

world breathing easy again (and asking for more money for projects based on animal models).

"Since Takao and Miyakawa published their PNAS, I'm 74% happier!"

But then, are mice similar to humans or not? Beyond all the money, which may or may not have been wasted on clinical trials for drugs that seemed to work in animals, what about all the discoveries based on animal models? What about the drugs developed and approved as treatments for diseases? What about vaccines? Is it all a big lie? Clearly, something is working because we were able to eradicate several diseases that used to kill us and develop effective therapies for many others, based on experiments with animal models. It is also clear that we need to improve our aim when designing experiments, because not all questions are answered with a mouse, but the usefulness of working with models throughout the history of biomedicine and health advances is undeniable. Moreover, the important thing is that these studies are never completely finished, the drugs are always under constant review and surveillance, and no new drug is approved unless it has at least the same effectiveness as the one used in therapy up to the time of its approval.

Certainly, the data does not lie. But neither do 'tell the truth'. The data are there, they are numbers, they do not say, *a priori*, anything. This worldwide warning is the clear evidence. It is the processing of the data that makes them relevant. It is putting them at the service of a hypothesis. But that is also what is dangerous. As this case illustrates, the same data can support a certain hypothesis or the opposite. All evidence can be manipulated. Data can be twisted in favor of the beliefs of the beholder, and it is not even necessary to lie with the data to do so. There are plenty of examples of this. There is no scientific consensus that Seok is right or that Takao is right. It is also not clear who has the last word, because there is no such thing as been right in science. The last word is only the last one until a better explanation comes along and displaces the one that until then was considered the best. Is not that beautiful?

Takao was not the only one who responded to Seok's work. Dozens of letters were shot between people in favor or against the use of animal models. Among the criticisms and defenses, one of those letters describes a kind of 'steps to follow' when choosing how to do an experiment, based on the question we want to answer: is it necessary to use an animal or can we do this experiment by taking blood from a person and analyzing it? If we are going to use an animal, is it going to be a mouse, a rat, a primate, a cat? Everything will depend on the question and how good (or bad) what happens in a human is reproduced in the chosen animal: symptoms of a disease, characteristics of a tissue, infective capacity of a parasite. **Animals in research are important, and not less important is to know how to choose them, why we use them and when it is not necessary to do so.**

Scientists who work with animals, of course, would do well to believe that mice are a reliable model for treating human diseases. But it would be foolish to throw Takao's article at anyone who criticizes the extrapolation of knowledge gained from models. Especially since there are so many drugs that are never approved because, no matter good they heal a mouse, they are not effective in humans, which clearly

means that we are doing something wrong by changing species. On the other hand, we must continue to gather evidence to support the research, but at the same time pay attention to those that do not support it, in order to be as careful as possible in the conclusions that are drawn. Science is enriched by this type of exchange with arguments, with foundations, with knowledge. Two people build their case and defend it, with so many foundations, data and evidence, that choosing who to believe in is up to each of us, as long as we choose on the basis of the data, and not on the basis of our preconception.

After all, data is what we do with it, and we have to be especially careful to look at it as fairly as possible. Otherwise, we will see what each of us wants to see, always. Or worse: we are going to see what others want us to see.

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