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HEALTH
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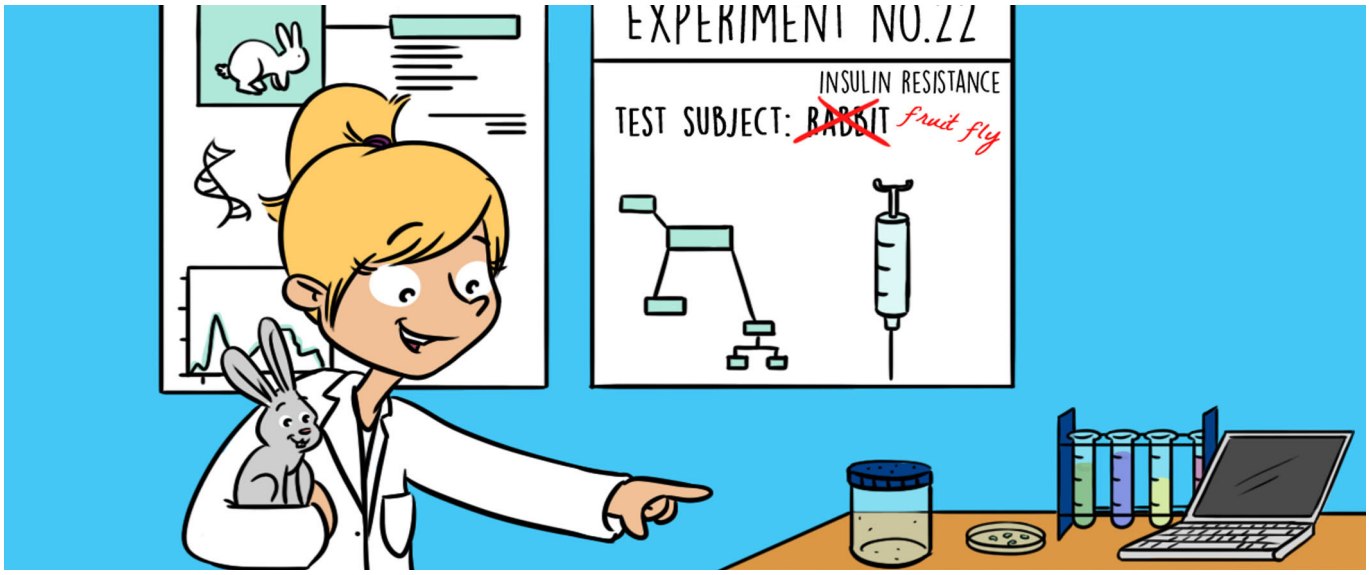

THE 3Rs: WHAT ARE MEDICAL SCIENTISTS DOING ABOUT ANIMAL TESTING?

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The similarities between certain animals and humans mean that animal research can be very useful in understanding how the human body works and in developing and testing new medicines. Many major medical breakthroughs have been made with the help of animal experiments, including the invention of antibiotics, vaccines, and cancer treatments. However, some research can result in pain and suffering for the animals, and although there are laws in place now to protect animals, it would be better if we had alternative ways to move medical science forward. Scientists are working on new approaches that replace, reduce, and refine (improve) animal experiments. This is known as the 3Rs of scientific research. Some of this work focuses on improving the housing for the animals, while other work involves using cells in a test tube or computer models as animal substitutes. The three Rs are a step in the right direction for medical science.

INTRODUCTION

It would be risky to try a new medicine out on humans before checking that it is safe and that it works—people could get very sick or even die in the process. Because there are many similarities between animals and humans, and they

often get the same illnesses, animal experiments can help us to understand different diseases and to design and test new treatments for diseases. Mammals like mice, rats, and rabbits have the same set of organs including a brain, heart, and lungs that work in the same way they do in humans. That means the animal experiments can give us a reasonable idea of what might happen in a person. Even simple animals like fruit flies and worms can be used to understand how our **genes** and **immune systems** work.

Many major medical breakthroughs have been made due to animal experiments. For example, in the 1920s, a surgeon discovered he could relieve the symptoms of **diabetes** in dogs by injecting them with insulin. Before that, people with diabetes got very sick and did not live for long, but now with the help of insulin, diabetics are able to control the level of sugar in their blood and live normal lives. Animals have been used to develop **vaccines** to prevent diseases that previously killed billions of people, including polio and meningitis. Animal experiments also allowed us to develop crucial medical practices we now take for granted, like anesthetics to put people to sleep during surgery, cancer treatments, and antibiotics. While a person born 100 years ago would be expected to live for 30 years, people born these days live around 70 years. Discoveries resulting from animal experiments have a lot to do with that increase in lifespan.

However, animal research comes at a cost to the animals, and it is sometimes unavoidable that they will experience pain and suffering. For example, the animals might be given injections, surgery, or an illness like cancer, in order to test new medicines. The procedures carried out on animals are classified as "mild," "moderate," or "severe" depending on the level of suffering. About two-thirds of animal experiments are carried out on mice, and 8% of these are considered severe.

THE LAW

In the past, there were no laws in place to control how animal experiments were carried out and some of those experiments caused unacceptable suffering to the animals. Thankfully, in 1876, the UK Parliament passed the "Cruelty to Animals Act," which meant researchers had to follow a list of rules and would be regularly inspected and would face consequences for cruelty. This act also meant that animal experiments could only be performed if they were absolutely necessary and would help to save human lives, not just because the scientists were curious.

In the 1980s, the law was updated, and there are now very precise instructions on how to care for the animals as well as which experiments can and cannot be done. Scientists have studied animals to work out the best living conditions for them, and this information is used when writing the rules that

GENES

The biological "instructions" passed down from our parents, which determine our characteristics.

IMMUNE SYSTEM

Our natural protection against disease-causing organisms like bacteria and viruses.

DIABETES

A lifelong condition that causes the level of sugar in a person's blood to become too high. This is because the pancreas does not produce enough of the hormone insulin, or the cells in the body are not responding properly to the insulin that is produced.

VACCINE

Small amounts of weak or dead bacteria or viruses that help prepare the immune system to fight the disease faster and more effectively, to prevent sickness.

scientists must follow. All research plans get judged beforehand to make sure the pros outweigh the cons, and these plans must be approved by specialist vets. There are also laws banning the use of great apes like chimpanzees and gorillas in UK research; almost all experiments are done on mice, rats, fish, and birds. Testing of cosmetics (like shower gel and shampoo) and household products (like detergents) is now illegal in many countries, including Europe and India.

In the United States, the Animal Welfare Act was introduced in 1966 and is a federal law that protects mammals used in scientific research.

THE 3Rs

Although important discoveries have been made and there is much improvement in how laboratory animals are treated, we would all prefer it if we did not have to use animals in experiments at all. So, are scientists doing anything to find alternatives? The answer is a resounding yes! 50 years ago, Bill Russell and Rex Burch wrote a book that introduced the "3Rs" for scientific research [1]. Rather than reading, writing, and arithmetic (as you may have come across in school), Bill and Rex were referring to replacement, reduction, and refinement. Replacement is about finding different options for experiments, other than animals, and reduction is about developing methods so that fewer animals are needed in each experiment. Refinement is concerned with improving current animal research so that the animals suffer as little as possible.

The 3Rs are now used in deciding the laws around animal research, and these days no experiment can be performed if there is an alternative available that does not use animals. Each experiment has to use the minimum possible number of animals, and the method has to result in the least pain and suffering for the animal. Research using animals in the United States is regulated by the US Department of Agriculture. In the UK, there is a specialized organization called the National Centre for the 3Rs (NC3Rs),[1] which supports work to develop new research methods that replace, reduce, or refine the use of animals.

[1] https://nc3rs.org.uk/ (Accessed: May 22, 2018).

REPLACEMENT

The ultimate replacement for animal experiments would be to use humans or human blood or tissue samples, as the results of human experiments would be the most accurate and relevant to humans. This is not possible in many cases because of the risks involved, but a method called "micro-dosing" is being developed, in which people are given tiny amounts of new medicines to look at how their immune systems respond. Animals like mice and rats can

also sometimes be replaced with other living things that are not thought to be able to experience suffering, like fruit flies. Worms have recently been used to discover new antibiotics.

One option for replacing animals is to use *in vitro* models. "*In vitro*" literally means "in the glass" and refers to studies performed in a test tube in the laboratory, rather than inside a person or animal (which would be called *in vivo*). Using *in vitro* models, complicated systems in the body are simplified so that scientists can concentrate on the one part they are interested in and they can run lots of experiments in a short amount of time. *In vitro* work has resulted in many important discoveries, including the identification of antibodies, which are a key part of the immune system that recognizes microbes and helps to destroy them.

In our laboratory at the University of Oxford, we are developing an *in vitro* model to test new vaccines. Normally, to test if a new vaccine works against a certain disease, for example, **tuberculosis**, scientists would immunize animals with the vaccine and then infect them with tuberculosis to see if they are protected. With our *in vitro* method, we infect cells (often human cells) in a test tube so that no animals need to get sick. We can compare whether cells from vaccinated animals or people are better at killing the tuberculosis bacteria than are cells from non-vaccinated animals or people [2]. Other scientists use similar systems to test new medicines and check if they are safe and if they work.

TUBERCULOSIS

A disease that mainly affects the lungs and is caused by bacteria that can be spread by the coughs and sneezes of an infected person.

One of the problems with *in vitro* models is that they may be *too* simple and therefore might not predict what would happen inside an actual body. For example, a medicine that kills a virus in a test tube might not kill it inside an animal, because the virus can hide away in certain parts of the animal's body. Or the medicine might appear safe *in vitro*, but cause side effects in parts of the body that were not represented in the test tube. Scientists are now trying to overcome these problems by building 3D *in vitro* models. These are more complicated and involve lots of different types of cells that come together to form something similar to a whole organ, like a liver or a heart.

Another way of replacing animal experiments is by using computers or mathematical models. These use calculations based on previous research to predict which medicines might be effective or which side effects might occur if the medicines were given to humans. Recent advances in technology mean that computers can simulate real biological processes in a virtual reality. Such methods have been used to develop vaccines based on information about bacterial genes and have also been used in cancer research to model tumors. One group at the University of Oxford built a computer model to test how drugs might affect the heart [3]. The different ways of replacing animal experiments are summarized in Figure 1.

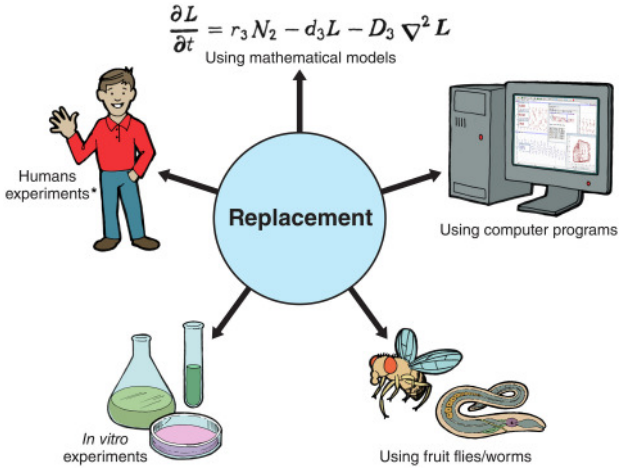

FIGURE 1

Summary of the different ways of replacing animal experiments with other types of experiments.

* The Nuremberg code - a set of research ethics principles for human experimentation - requires that human experiments are based on the results of animal experiments, in order to protect humans from harm. However, there are some situations in which human volunteers may be used in place of animals - for example we can sometimes study the immune response in people who have been naturally infected with a disease rather than infecting animals experimentally.

REDUCTION

To reduce the number of animals used in research, experiments have to be carefully designed and analyzed. If too few animals are used in an experiment, any difference between groups (for example, if an experiment was testing groups of mice receiving different medicines to see which was safest) might be unclear and the experiment would have to be repeated. Repeating the experiment would use even *more* animals in the long run.

Scientists are also trying to maximize the amount of information they can get from each animal. For example, if they are looking at the progression of a tumor, they might need to sacrifice different animals each week to look inside at the size of the tumors. By scanning the tumors instead, the same animals can be assessed each week and fewer are used overall.

Sharing results between different groups of researchers and organizations, by writing articles and giving presentations, makes it less likely that the same experiments get repeated unnecessarily by different people. Publishers of some scientific journals are helping with this by agreeing to share results that might not otherwise be available. The different ways of reducing the number of animals used in experiments are summarized in Figure 2.

REFINEMENT

Refinement is about minimizing pain and suffering and improving the health and happiness of the animals. Refinement includes making sure the animals have comfortable housing conditions that support their natural needs like socializing, hiding, gnawing, and nest building. There are now rules in place about the size of cages needed and the kinds of toys, hiding places, and bedding

FIGURE 2

Summary of the different ways of reducing the number of animals used in experiments.

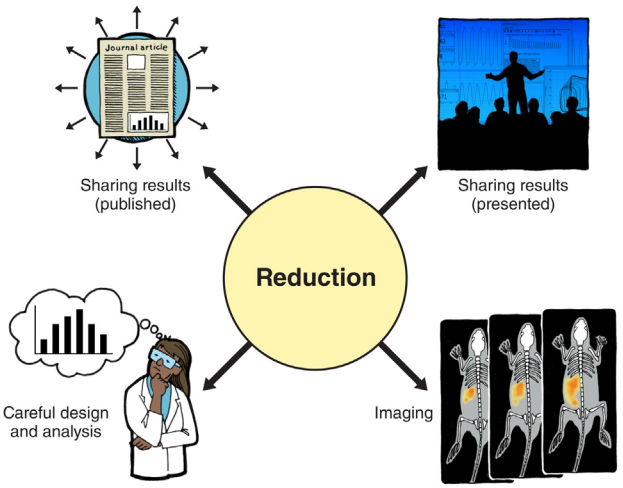

FIGURE 2

FIGURE 3

Summary of the different ways of refining (improving) animal experiments.

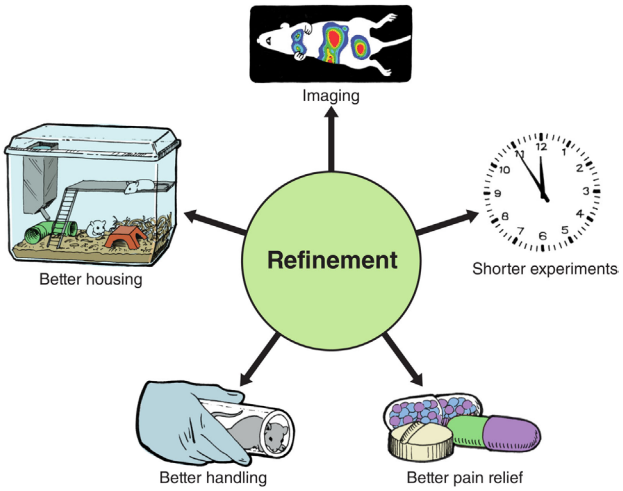

FIGURE 3

material that should be provided. Scientists at the University of Liverpool have been studying the best way to pick up mice to minimize their stress [4]. Others at the University of British Columbia found that rats prefer to have burrowing materials and the opportunity to climb [5].

IMAGING TECHNOLOGIES

Creating pictures of the inside of a body for analysis. These include techniques such as X-rays and ultrasound.

One important refinement in animal experiments is using **imaging technologies** instead of invasive techniques like surgery or taking blood. Rather than ending an animal's life to observe how a disease has spread inside the body, pictures can be taken with minimum disturbance while the animal is alive. Imaging can be done with X-rays or scans, or by making parts of the animal's body "glow in the dark," using chemicals that occur naturally in algae and jellyfish. Many scientists now monitor cancerous tumor growth and infections

with viruses or bacteria in this way. They can even use these methods to look at where medicines travel in the body. Making experiments shorter and using better pain relief are also methods of refinement. The different ways of refining animal experiments are summarized in Figure 3.

CONCLUSION

Many important medical discoveries have resulted from animal research and countless human lives have been improved or saved by experiments using animals. Animal testing has come a long way since the unregulated experiments of the last century and there are now strict laws in place to protect animals and prevent suffering. However, everyone would prefer it if we could stop using animals in medical research altogether.

Scientists around the world have been working hard to find new methods to replace the use of animals, reduce the numbers of animals used, or improve the experiments to minimize animal suffering. This is in line with the 3Rs principles of scientific research. Most research is now carried out using alternative methods and the number of laboratory animals used in the UK has been reduced by half in the last 30 years, but animals still need to be used in many situations. Bodies are so complicated that we cannot always know how they will react to a disease or medicine just by looking at cells in a test tube, or at a computer program or fruit flies. However, as technology advances in the future and scientists continue to work on the 3Rs, there is hope that one day laboratory animals will only be found in history books.

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My favorite subject at school is maths. I speak German and Norwegian and learn English at school. I like training my cat at home and enjoy playing board games. My hobby is gymnastics and I am good at doing backflips and flic-flacs. I have fun going cross-country skiing in winter.

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I am a Post-doctoral Research Fellow and Lecturer in Human Sciences at the University of Oxford. I became a medical scientist because I was shocked by how many people are still getting sick and dying every day from diseases like tuberculosis and HIV. I wanted to do something to help, and as everyone knows, prevention is better than cure—so I started working on vaccines. I now study the immune response to tuberculosis and try to develop new ways of testing vaccines instead of using animals for experiments. During my free time, I enjoy ballroom dancing, playing polo, and occasional archery on horseback! *rachel.tanner@ndm.ox.ac.uk