Rodents in Scientific Research - Hindrance or Help?

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It is a well-known fact that rodents are the most widely used of any species of animal in scientific and medical research. This research ranges from drug testing to vaccine production, from surgical procedures to cosmetic product testing and from genetic investigations to the study of pathological conditions. Many of these animals are genetically modified in order to produce the desired result, for example, genetically engineered diabetic rats. In fact, the 2003 statistics issued by the Home Office in the United Kingdom revealed that 87% of animals used in research are rodents. Of this, 67% are mice, 18% are rats, and the remaining 2% are represented by hamsters, guinea pigs, gerbils and others. This translates into a staggering 2.5 million rodents alone. And this is just in the United Kingdom. What about the rest of the world? It was reported that in 2002, 76% of the total animals used in Europe were rodents; over 8,000,000.[1]

If we consider that the law states that pharmaceutical drugs and chemical substances must be tested on a rodent and a non-rodent species, we must also consider that these drugs or chemicals are later to be issued for use in human beings. And yet, in the western world we find that the fourth leading cause of death in humans after heart disease, cancer and stroke is adverse drug reactions. Clearly, there is something wrong. We need to consider species differences within the rodents themselves and species differences between them and humans. Let us focus on drugs and chemical substances.

Most of the common antibiotics are lethal in guinea pigs and hamsters, whilst they may be tolerated by rats, mice and gerbils. Two antibiotics of note are penicillin and erythromycin, used to treat common bacterial infections.[2] Had Flemming used guinea pigs or hamsters in his research into penicillin, the drug would never have been marketed. He used rats. And although the drug was passed for human use, nothing could have predicted that even humans would show variability manifested by allergic reactions to this new wonder drug. If within the rodents themselves, there are differences, how many more differences can there be between them and humans? And this does not apply to antibiotics only - other drugs such as aspirin, cortisone and thalidomide may be considered. Aspirin causes birth defects in most rodents, but not in humans. Cortisone causes birth defects in mice, but not in rats and in humans it caused an increased risk of cleft palate if taken in the first trimester of pregnancy. And the classic example, thalidomide, was tested in the 1960's on rats, mice and hamsters without any ill effect, and yet when given to humans caused gross limb malformations known as phocomelia.[3] Drugs that cause cancer may differ between the rodents themselves and between these animals and humans. Animal screening may reveal tumour development in certain species that would not occur in humans. Conversely, certain tumours may occur in humans which would not be detected in rodents. Aspartame, an artificial sweetener, has been shown to cause lymphoid cancers in rats, whereas there is no clear evidence that it is unsafe in humans and has been used for many years in over 6,000 marketed foodstuffs. With regards to general carcinogenesis, the animals are fed with huge amounts of the chemical during their short life spans. This represents amounts far in excess of that which a human would ever consume even if they lived to be over 100 years of age.

The way in which a drug or substance is dealt with by the body is important. And even here there are species differences. This is the branch of pharmacology called pharmacokinetics. The rates at which drugs are absorbed, distributed, metabolically detoxified and then eliminated from the body, are the major factors determining the extent and activity of a drug.[4] The liver is the major detoxifying organ of the body. A human liver is not the same as a mouse liver which is not the same as a guinea pig liver. It was not until recent years that rodents, most notably rats and mice, have been shown to exhibit major differences from humans in the function of a major detoxifying substance called glutathione contained in the liver. This glutathione, a protein, protects against drug and chemical toxicity. Rodents use their glutathione for a wide variety of purposes, whilst humans conserve this vital commodity for the most

critical, life saving processes such as detoxifying overdoses of paracetamol in suicide attempts.[5] Under normal circumstances, humans use another enzyme system, the cytochrome P-450 microsomal enzyme series, also present in rodents. This system is water based.[5] And, even in rodents, there are differences in the metabolism of paracetamol. In mice and hamsters, it is much more readily activated and thus more toxic than in guinea pigs and rats. The amounts of enzymes active in the liver differ from species to species. It has been shown that in mouse liver, the major cytochrome is P-448, while in the rat, like man, the major cytochrome is P-450.[4]

These stark differences between the rodents themselves, and between them and humans begs a question: Are rodents the ideal models for research into the human condition? Research should be species-specific and directed at the species for which it is designed. One cannot safely apply data from one species to another, and especially not from rodents to humans. It would be advisable to use human cell lines, progressing onto human organ slices, then human whole organs, and finally onto humans themselves. Here, one would use humans who had limited life expectancies, offering them the option of taking a trial drug which may or may not prolong their life and enhance its quality. Another powerful technique in use these days is toxicogenomics. This is a new approach to understanding the genetic mechanisms and biochemical pathways to disease by environmental toxins via the simultaneous analysis of gene and protein expression, using human genes.[6] It is highly specific, sensitive, reproducible and reliable. More importantly, it is applicable for the species in question - humans!

There is no question, then, that alternatives to animal testing do exist. It is not only unethical to use rodents in research, it is not safe, cannot give the appropriate data and represents bad science. In this 21st Century, we should be using only that technology available such that research can make this a better world for all concerned.

References:

1. Hepple, Professor Sir Bob (Chairman); 2005; *The ethics of research involving animals*; Nuffield Council on Bioethics; London.
2. Harkness, J.E., and Wagner, J.E.; 1992; *The Biology and Medicine of Rabbits and Rodents - fourth edition*; Lea and Febiger; United States of America.
3. Cohen, M.S.; Special Aspects of Perinatal and Pediatric Pharmacology; In: Katzung, B.G. (Ed); 1989; *Basic and Clinical Pharmacology - Fourth Edition*; Appleton and Lange; London.
4. Parke, D.V.; 1983; Species differences in pharmacokinetics; *Veterinary Research Communications*; **7**:285-300; Elsevier Science Publishers B.V.; Amsterdam.
5. Parke, D.V.; 1995; Ethical aspects of the safety of medicines and other social chemicals; *Science and Engineering Ethics*; **1**:283-298; Opragen, Surrey.
6. Selkirk, J.K. and Tennant, R.W.; 2003; Workshop 2.1 Toxicogenomics: Impact on human health; *Pure Applied Chemistry*; **75**, Nos 11-12: 2413-2414; IUPAC.