During the past few decades, model organisms have helped scientists make several epoch making discoveries. The role of model organisms in medicine was evident when dog was used to decipher the cause and consequence of Type I diabetes mellitus and its recovery using the pancreatic extract insulin.

Way back in 1921, the discovery of insulin was initiated by the University of Toronto based young surgeon, Frederick Banting who along with his assistant Charles Best first tried to reverse the symptoms of diabetes in a dog upon removal of its pancreas. In a follow-up experiment they tied off the pancreas in another dog, then removed it and obtained an extract, which they injected into the first dog. It recovered, albeit only for a day (because it required daily insulin injections, the active component of pancreatic juice to combat diabetes). Later, insulin was purified by James Collip. Banting shared the 1922 Nobel Prize with John Macleod.

There are several such instances in which animals have been used as models in biological research such as advances in medical technology, including open heart surgery, cardiac pacemakers, heart transplants, coronary bypass surgery and so on. Model organisms have also been used in the classroom to help students learn important concepts in various disciplines of biology. For example, *Escherichia coli*, *Saccharomyces cerevisiae*, Drosophila and many other lower eukaryotes have been widely used as model organisms in introductory biology courses to teach microbiology and genetics.

The idea of using model organisms for biological studies was first initiated by Gregor Mendel in the mid 19th century who used cross pollinating pea plants to understand the genetic inheritance pattern. Today scientists rely on a number of model organisms from single cell bacteria and yeast to fruit fly and nematodes, all the way up to mammals such as mice and rats.

What is a Biological Model?
Model organisms are the workhorses of biological science and play a role in deciphering the real mystery of life. These organisms are usually fast-growing non-human species with simple genome and are inexpensive, easy to maintain and breed in a laboratory setting. The main criteria to be satisfied by an ideal model organism includes: 1) short life cycles, 2) small adult size, 3) ready availability, and 4) tractability.

Now, what is the rationale for using model organisms? Humans share with the animals many vital functions such as breathing, digestion, movement, sight, hearing and reproduction. As a biological entity any human being is thus comparable to other organisms because all the living beings on earth are made up of cells having similar genetic information. Therefore, in most cases the structure and function of different body proteins are evolutionarily conserved across a wide variety of species and so are the metabolic and developmental pathways.

Human beings cannot be used as experimental objects because of health-associated risks and other ethical issues. However, different aspects of human biology could be unravelled using different experimental model organisms which best fit the specific question to be answered.

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Since long the prokaryotes and lower eukaryotes have been used to understand different basic biological processes. Animals are mostly used as natural candidates for biomedical research because they share many of the illnesses with humans. For example, rabbits suffer from atherosclerosis (hardening of the arteries); dogs suffer from cancer, diabetes, cataracts, ulcers and bleeding disorders such as haemophilia; cats suffer from some of the visual impairments similar to humans.

Animals are also used extensively as models in different preclinical toxicity studies for testing the efficacy of drugs. Let’s take a look at some of the real heroes of biology: the model organisms.

*Escherichia coli:* Some of the *E. coli* strains constitute the normal bacterial flora in our guts while other strains are capable of causing diarrhoea in humans. In the late 1800s, *E. coli* was discovered by the German paediatrician and bacteriologist, Theodor Escherich and since then it undergoes a transition from single-celled amoebae to a multicellular organism as a natural part of its life cycle. Several *D. discoideum* genes are homologous to human genes and the simplicity of its life cycle makes *D. discoideum* a valuable model organism to study genetic, cellular, and biochemical processes in other organisms.

*Dictyostelium discoideum* (Slime Mold): *Dictyostelium discoideum* is a soil-borne amoeba and is commonly referred to as slime mold. The cellular slime mold is being used to understand many of life’s essential processes because of its rapid growth rate (30 min/generation), simple nutritional requirements and well established genetics. It is easy to manipulate *E. coli* using recombinant DNA technology and is currently the most widely used organism in studying molecular genetics.

*Saccharomyces cerevisiae:* *Saccharomyces cerevisiae* (budding yeast or baker’s yeast) is the most widely used eukaryotic model system. It grows quickly and is relatively cheap to maintain. Almost 30% of the genes implicated in human diseases have orthologs (genes in different species that evolved from a common ancestral gene by speciation) in yeast. Therefore, it is being used as a model to study different biological processes such as aging, regulation of gene expression, signal transduction, cell cycle, metabolism, apoptosis (programmed cell death), neurodegenerative disorders and so on. *Neurospora crassa* (Bread Mold): Since the landmark discovery (one gene-one enzyme model) of Beadle and Tatum using the model system Neurospora, in 1941, this orange bread mold is being used as a simple model organism for genetic and biochemical studies and has been instrumental in our understanding of several basic and fundamental aspects of biology.

*Drosophila melanogaster:* *Drosophila*, the fruit fly, is a small invertebrate which was first successfully used by Thomas Hunt Morgan at Columbia University and he was awarded the Nobel Prize in 1933 for the discovery of white eyed mutation in 1910. Since then *Drosophila* has been used as a model organism for the study of several diseases, including Parkinson’s disease, Alzheimer’s and various types of cancer. Surprisingly, *Drosophila* shares highly homologous gene sequences with humans, making it one of the most preferred organisms for genetic studies. It is easy to maintain, grows quickly from embryo to adult within 12 days thus generating a number of offspring. It is

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relatively straightforward to disrupt fruit fly genes and introduce foreign ones. The usage of fruit fly as a model organism dates back almost a century and has been widely used in genetic, developmental and behavioural studies, and more recently as a tool to study human diseases and to screen compounds for therapeutic use.

Caenorhabditis elegans: Sydney Brenner was the first to introduce Caenorhabditis elegans as a model organism in 1974 for pursuing research in developmental biology and neurology. It is a very small soil nematode (1 mm length), transparent for ease of manipulation and observation; it grows very easily in large numbers (10,000 worms/petri plate) and is very cheap to breed. C. elegans reproduces with a short life cycle of about 3 days under optimum condition, about the same time needed for genetic crosses in yeast. Its life span is around 2 to 3 weeks under suitable culture condition. Compared to the use of other model organisms, such as mice, the shorter life cycle of C. elegans reduces the experimental time and facilitates biological study.

Studies with this model organism have unveiled different scientific mysteries such as programmed cell death (Nobel Prize in 2002, awarded to Sydney Brenner and associates) and RNA interference process (Nobel Prize in 2006, awarded to Andrew Fire and Craig C. Mello).

Arabidopsis thaliana: Friedrich Laibach is the founder of experimental Arabidopsis research. Arabidopsis thaliana is the most common eukaryotic model organism for studying plants. It possesses a relatively small, genetically tractable genome that can be manipulated through genetic engineering more easily and rapidly than any other plant genome. Some of its notable advantages are that it reproduces relatively quickly, produces numerous progeny through self pollination, requires limited space, and is easily grown in a greenhouse or indoor growth chamber with simple growth requirements like light, air, water and a few minerals to complete its life cycle. Therefore, it is being used as a model system for several decades to understand the genetics and molecular biology of flowering plants.

Xenopus laevis: Xenopus is a genus of highly aquatic frogs native to Sub-Saharan Africa. Xenopus is a bizarre looking frog that was introduced as a model system in the 1950s. The eggs and embryos of X. laevis can be produced in large numbers by means of a simple hormone injection and, like other amphibian embryos, can be easily manipulated. Much of the early uses of X. laevis in the 1930s and 1940s were confined to physiological research. More recently it has gained the primary focus of model system in molecular biology.

Puffer fish (Fugu rubripes): Pufferfish is a great delicacy in Japan that has occupied an important niche in biological science as a genetic model system. Its genome sequence was published in 2002. It has the shortest genome so far identified – just 400 million base pairs. Even though men and fish diverged from their common ancestor over 450 million years ago, the Fugu genome contains roughly the same number of genes as its human counterpart, which is eight times larger. The compactness of the pufferfish genome simplifies the detection and analysis of genes and their regulatory elements. The Fugu project was initiated in 1989 in Cambridge, UK, by a small research group led by molecular biologist Sydney Brenner.

Mouse (Mus musculus): Mouse, most familiar as an agricultural and household pest, has immense potential as the foremost genetically tractable model organism for understanding human biology and disease. It bears a lot of similarity with humankind in terms of physiology, tissue structure and organization. In effect, this creature has to combat many of the common diseases we suffer. This kinship is also reflected in the 99% resemblance of the mouse and the human genome. Probably no two mammals have shared such a closer relationship, even though their

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Evolutionary lineages diverged more than 96 million years ago. The added feature of this model system is its low maintenance cost and its reproduction time as low as nine weeks. Different disease models in mice can be created by manipulating the mouse genome, and these models can be used to test the efficacy of new drugs in different preclinical trials.

**Nude mouse:** A nude mouse is a laboratory mouse with a genetic mutation that causes a deteriorated or absent thymus, resulting in a non-functional immune system due to a greatly reduced number of T cells. This defect is manifested in its outward appearance such as lack of body hair, hence is name “nude mouse”. It is also known as NIH-III as it was developed at the NIH (National Institutes of Health, Bethesda). The nude mouse is valuable to research because it can receive different types of tissue and organ grafts, as it mounts no rejection response. These xenografts (tissue or organs from one species transplanted into or grafted onto an organism of another species) are commonly used in cancer research to test different drugs.

**Zebrafish (Danio rerio):** The zebrafish (Danio rerio) is a small tropical fresh-water fish found in northern India, northern Pakistan, Nepal, and Bhutan. This aquarium showpiece has occupied an aquarium showpiece has occupied an important place in the catalogue of model organisms due to its small size and ease of culture. It is widely used for the study of embryonic development and gene function because their embryos develop outside the mother’s body and remain transparent until most of the organs have fully developed.

‘Casper’ is a mutant form of Zebrafish developed in 2008 at the Boston Children’s Hospital that is ghostly transparent. This transparency allows any abnormality in the cells to be visualised and tracked through the developing body. Thus, zebrafish permit scientists to follow the formation of tissues and organs in microscopic detail as the organism grows.

This small fish may be the key to understanding how vertebrates, including human beings, develop. The zebrafish genome is 1700 million base pairs in length, about half the size of the human genome. Many human developmental and disease genes have counterparts in the zebrafish. A number of zebrafish mutants so far generated are good models of human diseases and can therefore be used to test candidate drugs.

**HeLa cells:** HeLa cell is an immortal cultured cell line used in many scientific researches. This mammalian cell culture model is often used to study the ageing process due to the difficulty associated with high throughput lifespan analysis on different mammals. It is the oldest of all the cell lines and was derived from cervical cancer cells from a cancer patient Henrietta Lacks who died of cancer on 4 October 1951. This cell line is remarkably durable and prolific and the ease of use makes HeLa a genetically tractable, high-throughput platform.

**Ethical Issues**

The experimental use of lower animals such as microorganisms, plants, reptiles, and amphibians does not raise any ethical issues. However, the use of higher animals in scientific and medical research has been a subject of heated debate for many years.

In 1964, CPCSEA (the Committee for the Purpose of Control and Supervision of Experiments on Animals), a statutory body was formed by the Indian Parliament under the Prevention of Cruelty to Animals Act 1960. It was again revived in 1998, under the chairpersonship of Ms Maneka Gandhi. This committee is composed of members of the scientific community, regulatory authorities and animal activists and proactively trains and guides scientific and non-scientific personnel on different issues of laboratory animal welfare.

Animal welfare activists throughout the world are vociferous against the use of animal experimentation and have questioned the unethical and inhumane experiments conducted on animals. It must be emphasised that use of animals in research cannot be abandoned in the interest of both human and animal welfare.

So a balance should be struck so as to minimise the use of animals using different non-animal models and lower animals. In case of any dire necessity of animal experimentation, the research should be conducted only within the ethical framework ensuring the use of animal in a humane manner as far as possible thus minimising pain, distress and discomfort to the animals.

The use of model organisms in biological science has come a long way. A huge wealth of biological data has been amassed using these model systems. Consequently, the model organisms that were once developed for a specific domain of basic biological studies are now being used with greater success for a wider spectrum of studies involving preclinical studies, health, disease related studies and so on.

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