troversy: the efficacy of animal testing. Huntingdon Life Sciences Group (formerly of Huntingdon, UK, now Life Sciences Research, US) and others use mice, dogs, and other animals to test drugs (as mandated by law) and explore mechanisms of disease. But are the results generated from these tests really useful to humans?

Studies of animals have revealed similarities between animals and humans on the gross or macroscopic level. We all have hearts that pump blood, lungs that breathe, and immune systems that fight disease. But animals do not suffer from coronary artery disease or the human version of AIDS, and most do not contract lung cancer from smoking. Disease occurs at the cellular and molecular level, and it is the very small differences at the cellular level, developed in the course of speciation, that prevent us from getting reliable data about humans from animal models.

The dietary drug Fen–Phen (fenfluramine–dexfenfluramine) tested safe in dogs and other animals but damaged the human heart[1]. Phenacetin, an analgesic, was shown to cause cancer and renal toxicity and was withdrawn from the market. Many other drugs, recently including clioquinol, benoxaprofen, phenphormin, zimeldine, indoprofen, methazone, fenclofenac, domperidone, suprofen, rapacuronium, phenylpropanolamine, grepafloxacin, and bromfenac, have caused serious adverse events, ranging from liver or gastrointestinal toxicity to hemorrhagic stroke and blood abnormalities[2–4]. Hoffmann–La Roche's (Nutley, NJ) heart drug Posicor (mibefradil) caused 143 deaths alone[5]. All these and others were withdrawn from the market.

Clearly, testing these drugs on animals did not protect the public. There is an equally long list of drugs that were kept off the market because of adverse side effects in animals that did not occur in humans. The US National Cancer Institute (Bethesda, MD) believes it may have lost cancer drugs that would have been effective in humans because they were ineffective or toxic in animals.

Saccharin was labeled carcinogenic and is still avoided by many because it caused cancer in male rats. We now know that the male rat has an enzyme in the bladder that humans do not have, which causes saccharin to be converted into a carcinogen[6]. The publicity over phenolphthalein, the active ingredient in Ex-lax that caused adverse effects in rats when it was in fact safe in humans, is another example of animal testing yielding costly and inconsequential results that harmed industry.

The use of animals as models of human disease has also resulted, indirectly, in many human deaths. Smoking was thought not to cause cancer, based on the results of experiments on animals[7,8]. Asbestos was thought noncarcinogenic, so many continued to be exposed[9]. Animal models of heart disease failed to show that a diet high in cholesterol increased the risk of coronary artery disease[10,11]. Animal models of stroke and sepsis resulted in patients receiving medications that were dangerous, harmful, and not efficacious[12,13]. There are countless other examples[14].

Modern-day biomedical research should not be looking for answers from animals. It should be exploring alternatives that exploit burgeoning information from pharmacogenetics, protein profiling, *in vitro* molecular toxicology, and *in silico* evaluation. In turn, knowledge of receptor physiology, physicochemical information, structure–activity relationship, and computer-aided drug design should enable the creation of more efficacious and safe lead candidates.

Though such alternatives may still be some way off, the inefficiency of animal models means that there is a financial as well as an ethical imperative to direct more funding to research focused on models with real predictive power.

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Cloning similarities

To the editor:

According to reports early this year[1], the cloned sheep "Dolly," born five years ago at the Roslin Institute (Edinburgh, UK), has begun to show untimely symptoms of osteoarthritis. This has prompted suggestions that inoculation of somatic nuclei into enucleated oocytes and subsequent *in vitro* and *in vivo* manipulation of the embryos might predispose cloned animals to precocious senescence.

Cloning is a very old, well-tested process in propagation of arboreal plants. Apomixis (vegetative propagation and asexual seed formation) is very common in certain plants (such as angiosperms and pteridophytes). For example, some trees can grow both from cross-fertilized and from naturally occurring apomictic seeds (such as nucellar embryogenesis in some citrus), the latter of which carry only the complete maternal genotype. For centuries, a great many cultivated trees have been vegetatively propagated by cuttings, grafting, and in the past 20 years also by *in vitro* culture of somatic organs, such as shoots, apical meristems, and protoplasts (micropropagation).

Asexually propagated trees show ontogenetic patterns that differ from those of the corresponding sexually propagated seedlings. For example, compared with cross-fertilized pears, grafted pears (*Pirus communis* L.) have a shorter lifespan (20–30 years versus 100 years) and become sexually mature sooner (3–4 years instead of 20–30 years). In addition, grafted seedlings can still exhibit morphological characters typical of juvenility (such as thorny shoots and smaller leaves), which usually disappear from the canopy top at the same time as onset of flowering and fruiting.

Modern horticulturists take the earlier sexual maturity of vegetatively propagated trees as one of the most important economic benefits of this procedure, whereas they consider the shorter lifespan of these plants to be less important as trees are reared intensively in orchards and are normally renewed long before their physiological end.

Animals and plants follow similar ontogenetic models: after birth, they grow, reach sexual maturity, become old, and die. Despite the obviously different physiological and biochemical backgrounds of these patterns, in both animals and plants apoptosis depends on the coordinate expression of genes regulating divisional cycles and apoptotic pathways. Therefore, it seems reasonable that the behavior of asexually propagated trees could mirror the precocious senescence now being witnessed in cloned animals.

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