Available online at www.sciencedirect.com
SCIENCE DIRECT®
Structural Change and Economic Dynamics
16 (2005) 557–575
STRUCTURAL CHANGE AND ECONOMIC DYNAMICS
www.elsevier.com/locate/econbase

Technological lock-in, positive institutional feedback, and research on laboratory animals

Joshua Frank*

Department of Economics, Rensselaer Polytechnic Institute, FIREPAW, 228 Main Street, #436, Williamstown, MA 01267-2641, USA

Received September 2003; received in revised form August 2004; accepted November 2004
Available online 28 December 2004

Abstract

There has been considerable debate over the efficacy of animal research. The focus here is on bridging the gap between the current animal research debate and ongoing work in economics regarding lock-in and path dependency. Animal research is analyzed for its fit with the circumstances that cause path dependence. The discussion provides a real world "case study" of possible path dependency with particular focus on the psychological dimensions of path dependency as well as the role of academic research institutions in the process. The general conclusion is that animal research is a good candidate for the path dependency concept.
© 2004 Elsevier B.V. All rights reserved.

JEL classification: O33; B52

Keywords: Path dependence; Lock-in; Animal research

1. Introduction

Animal rights and animal welfare advocates have been at battle with biomedical interests for many years over the use of animals in research. In addition to the moral question of whether sentient animal use is acceptable regardless of the benefits, there is the more technical debate over whether animal research really has scientific value.

* Tel.: +1 518 462 5939; fax: +1 518 658 0979.
E-mail address: firepaw@earthlink.net.

0954-349X/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.strueco.2004.11.001

Although sound arguments have been made that there are superior alternatives to animal research in many situations, these arguments are brought into question by one pervasive yet often unspoken counterargument: if animal research is so lacking in value compared to other modern scientific techniques, how can so many individuals, organizations, and institutions be so strongly behind it? In other words, how can technology this pervasive be wrong?

2. The concept of lock-in

2.1. Technological lock-in

David (1985) and Arthur (1989) pioneered the concept of technological lock-in. Most of traditional economic theory is built on an assumption of diminishing returns, but when industries are instead characterized by positive feedback or increasing returns there can be multiple equilibrium points or possible growth paths leading to distinct outcomes. Minor or "random" events can cause a certain technological growth path to "lock-in" determining which technology will prevail. This can occur even if the technology selected is inferior in the long-run.

Since the concept of path dependency presents a serious challenge too much of traditional neoclassical theory, it is not without critics. The primary criticism is that path dependency leading to suboptimal outcomes creates unexploited profit opportunities for entrepreneurs to take advantage of (Liebowitz and Margolis, 1994). Altman (2000) calls unexploited opportunities "the Achilles Heel of path dependency theory from the perspective of conventional wisdom". But this counterargument has serious shortcomings. First, it relies on extremely strong and unrealistic market efficiency assumptions, and second, it appears to misunderstand part of the technological lock-in argument in the first place. Transaction costs, imperfect information, uncertain outcomes, capital constraints, and imperfect contracting between firms all create frictions reducing the ability of entrepreneurs to take advantage of "unexploited opportunities". In addition, as will be discussed later, institutional and behavioral aspects of lock-in can also make reversing paths difficult. There is also some evidence from the actual data on paths of technological change that adaptation is incremental and subject to path dependence (Anderson, 1998)

But more important than these constraints is the opaque nature of technological change itself. The unexploited profit opportunities argument assumes that clearly visible opportunities exist, but this is a misreading of the path dependency theory as it was originally presented. Technological lock-in proponents do not argue that a technology can never be replaced by clearly superior technology (for example, the CD player for the record player), even if there are some significant barriers to its introduction. Rather they argue that when two technologies are *currently similar in their usefulness* but lead to quite different but *largely unknown* growth paths, the superior long-term path is not necessary the path chosen. Commonly cited examples of lock-in include the QWERTY typewriter keyboard, the choice of VHS over beta video recording technology, nuclear power plant cooling technology, and the gas combustion engine for motor vehicles versus steam technology (Arthur, 1994).

Technology is an incremental building process, and though one can speculate post hoc that a certain path might have been inferior in the long-run it typically cannot be known for certain, since the true outcome of the path not taken can never be known. What can be stated with confidence is that with positive feedback or increasing returns the path taken might well become locked into place, regardless of which long-run path is superior.

Furthermore, David (2001) has pointed out that there has been great focus placed on the issue of "lock-in" which is just one part of the larger concept of "path dependence" and the idea that history matters in economics. David suggest that this is because the idea that inferior paths might become locked-in due to historical events has been interpreted as a direct challenge to much of traditional economic theory. In reality, the broader concept of path dependence applies to many situations where paths cannot be stated to be economically inferior or superior but are simply different. This larger concept of path dependence is also relevant here, since even if two different technological paths are roughly equal in terms of economic benefit, they may be quite different in terms of ethical implications.

2.2. Institutional lock-in

Researchers in political science and economics have made a strong case that institutions can also be subject to lock-in and path dependence. On the political science side, arguments for institutional inertia have been made by March and Olsen (1989) and later by Pierson (2000) among others. The argument is based both on the inherent resistance of both norms and formal rules to change, and the growth of practices by both state and societal actors who have a stake in preserving the status quo and therefore resist change (Banchoff, 2002).

Nobel Laureate economist Douglass North (1990, 1991) also argues that institutions exhibit a large degree of path dependence. His arguments explicitly utilize the prior work by Arthur (1989) and David (1985) and the concept of positive returns. Institutions can be self-reinforcing due to network externalities, economies of scope, and complementarities within the institutional matrix. Or, "in everyday language, the individual organizations with bargaining power as a result of the institutional framework have a crucial stake in perpetuating the system" (North, 1993a, p. 3).

An important insight by North is his acknowledgement of the importance of the psychological and sociological dimensions of lock-in. North places importance not just on the explicit rules and social structure, but also on the less easily observed and measured cultural norms and attitudes that are an important component of path dependence. North also acknowledges the key role played by perceptions and belief systems. Institutions are not just perpetuated by powerful stakeholders advancing their own self-interest. "Belief systems are the underlying determinant of path dependence... The way the institutions evolve reflects the ongoing belief systems of the players" (North, 1994, p. 5).

3. Is animal research a candidate for lock-in?

3.1. The animal research debate

For decades or even centuries, there has been an ongoing debate regarding the morality of animal research. Although many researchers actively involved in animal research claim there are important human benefits, some philosophers such as Singer (1975) and Regan (1983) argue that the exploitation of sentient beings for human benefit is simply wrong regardless of the benefits it might bring. The opponents of animal research make a strong case that it is ethically unjustifiable. However, the focus here is not on the philosophical debate, but on the more technical issue of the efficacy of animal research. The two issues are clearly linked, since the justification typically given by those making an ethical argument for animal research is that the benefits to humans (who are given more value) outweigh the costs to animals (who are given little weight). If animal research cannot be shown to have substantial benefits, then the argument in favor of such research fails regardless of the weights given to humans and animals.

There have been voices raising concerns about animal research's efficacy even before Singer's book sparked renewed debate on the ethical issues of animal exploitation. For example, in 1930s one physician writing in a medical publication called drug experiments on animals "useless" and "misleading" in terms of their applicability to man (Medical World, 1933) while another physician in the 1960s called animal experimentation "doubtful and misleading" and advocated the use of clinical observation as a superior alternative (Bayly, 1961). It should be noted that though these and other arguments against animal research were credible, they were a minority opinion, and the majority of the medical community remained in support of animal research.

The debate on the benefits of animal research has grown much stronger recently, with growing criticism both from vocal animal advocacy organizations such as People for the Ethical Treatment of Animals and in Defense of Animals and a growing number of publications for the public on the topic such as Sacred Cows and Golden Geese, Greek and Greek (2000), Vivisection or Science? Croce (1999), and 1000 Doctors against Vivisection, Ruesch (1989). The institutional structure has often positioned these viewpoints as outside of the mainstream, with the researchers or publications against animal research being somehow affiliated with animal rights/animal welfare organizations. Nevertheless, when looked at objectively, the arguments against animal research have often been thoughtful, well documented, and logically compelling.

3.2. Is animal research a candidate for technological lock-in?

To determine whether animal research is a candidate for lock-in we must look to what properties are associated with a technology or institution likely to be path dependent. According to Arthur (1994), resource-based sectors of the economy are likely to face diminishing returns and be subject to conventional economic theory. However, knowledge-based sectors are largely subject to increasing returns and are therefore likely to experience technological lock-in. These are areas which require large initial investments in research and development but for which incremental production is relatively cheap. Arthur specifically includes pharmaceuticals as an industry subject to increasing returns.

What about the basic scientific research on animals that is not directly tied to product development? According to Arthur, technologies typically improve as more people adopt them and firms gain experience that guides further development. This creates a positive feedback loop that gives such technologies a "selectional advantage" once they gain a foothold. This certainly seems applicable to most scientific disciplines involving animal research. For example, scientists choose mice and rats as experimental subjects because so much is known about them from prior experiments. This knowledge has made these subjects a logical next choice after humans for mapping their genome. The mapping of the mouse genome would again create positive feedback, enabling further research on these "subjects". Likewise, experience in animal toxicity tests builds a knowledge-base that makes animal research an easier method for future toxicity tests even if other methods could be developed.

Knowledge in animal research disciplines is an incremental building process, with the existing knowledge facilitating future knowledge development. The same is true for alternatives to animal research. The relatively scant knowledge on alternatives to animal testing makes these alternatives less likely to be selected as a research option, perpetuating the lag in knowledge-base for these alternatives. There is a strong case for animal research to be a candidate for technological lock-in.

3.3. Is animal research a candidate for institutional lock-in?

North often emphasizes the importance of historical factors in determining institutional paths. Early medical research by Hippocrates in the fourth century B.C.E. was based on clinical observation of humans. However, a few centuries later the Church's policy of not allowing human autopsies drove a shift to animal research by Galen in second century Rome (Greek and Greek, 2000). Although Galen's conclusions contained many serious errors, the Church's ongoing prohibition on human dissection would make dissection of animals the dominant method of medical discovery for over a thousand years. Although human study began to grow in the rennaissance, in 1865 the work of Claude Bernard reversed any trend away from the study of animals. Bernard (1865) declared that "true medical science" only occurs in the setting of the animal experimentation laboratory. Bernard further urged scientists to not "hear the cries of the animals", nor "see their flowing blood", when studying a problem they seek to solve. Greek and Greek blame much of the willingness of the scientific community to embrace Bernard's animal research ideal on the climate of the times, which included the growth of the Industrial Revolution as well as strong anthropocentric sentiments. The animal research ideal clearly quickly took hold; only 10 years later dissenters already feared that speaking out would cause them to be expelled from their profession (Hoggan, 1875). Since that time, animal research has dominated methodology in medicine and related areas for over a century.

In the current environment, it is not difficult to establish that animal research is a candidate for institutional lock-in due to the actions of self-interested stakeholders. Animal research currently is an industry of enormous proportions with large stakeholders in government, industry, and academia. Key beneficiaries include faculty members, academic departments and entire universities, private testing companies, animal breeders and equipment suppliers, government agencies and elected officials, pharmaceutical companies, non-profit organizations that exist primarily as funding conduits for animal research, and other major corporations that utilize products tested on animals (chemical companies, cosmetics producers, etc.). It is not merely a logical conclusion that these groups would try to protect their interests. As proof, one merely needs to point to the numerous influential groups that exist explicitly fully or in part to promote animal research such as the National Association for Biomedical Research, the Foundation for Biomedical Research, Americans for Medical

Progress Educational Foundation, the American Association for Laboratory Animal Science, among many others. Other major organizations whose memberships includes those with an interest in animal research such as the American Medical Association and governmental agencies that rely on this research such as the National Institute for Health and the National Institute for Mental Health have also become vigorous advocates for animal research. In assessing the self-interest of entities such as regulatory and funding agencies, it is important to recognize that not only do the institutions themselves exist in large part to fund animal research, but that there is a strong flow of personnel between regulatory/funding agencies, private corporations doing animal research, and academic institutions involved in such research.

In addition to the power of self-interest, there are other forces that cause institutional inertia that helps perpetuate animal research. There is a massive existing animal research infrastructure that helps to perpetuate such research. Physical infrastructure includes facilities designed to house and experiment on animals, breeding facilities, specialized equipment, and a large "inventory" of animals at any given time. Conferences, journals, associations, granting organizations, and academic programs exist devoted to animal research. Ongoing contractual relationships also help to perpetuate inertia. Aside from self-interest, all of these infrastructure elements make animal research an easier option to execute than building new alternative research programs. The existence of numerous publication and speaking venues devoted to animal research results begs the question of whether this research is valid and truly useful; the fact that publication is likely makes the research viable from an academician's perspective, and the existence of ongoing research with new findings by "leaders in the field" makes the continuation of such venues viable.

The legal environment, including explicit laws, regulations, and case history also helps to create inertia. Animal testing is required by law or regulatory agency in many situations (e.g. in toxicity testing). Even when animal testing is not required, the legal environment still often favors animal testing as a method for companies to show they have done due diligence to prove a product is safe or effective when they are sued.

Walker (2000), using an example of a nuclear reprocessing plant in the UK concludes that large technology systems can have embedded legal, social, and political commitments that can create institutional inertia perpetuating the technology long after it is viable. Walker finds that this inertia is especially likely where there are complex products and infrastructures and state involvement. It is difficult to find a better case for inertia than the animal research infrastructure.

The behavioral component of lock-in is probably the most subtle yet the most powerful. Even if agents ignored self-interest, they are likely to make decisions biased by their previous experience, psychology, and the nature of the institutions. North (1993b) argues that part of the explanation for path dependence comes from the way that perceptions limit choice sets. These perceptions come from the mental constructs of agents that are "partly a result of their cultural heritage, partly the result of the 'local' everyday problems they confront and must solve, and partly a result of non-local learning" (p. 2). What does this mean for agents involved in animal research? Although each researcher has an individual cultural heritage, the many years of schooling and job training they must complete creates a second cultural heritage for them which has implicit in its belief system that "animal research is ethically justifiable" and "animal research is useful". As a researcher doing their own work and with exposure mainly to the results of other animal research, the local and non-local learning they experience will probably serve to further reinforce their belief in this research.

Heiner (1983) argues that when facing complex decisions, humans with their limited cognitive capacities tend to construct rules to restrict the flexibility of choices. In later works, Heiner (1985, 1988) expands this concept to conclude that agents will choose not to use information sources too distant from their local experience. In terms of animal research, this implies that agents will likely use the results of other similar research and often dismiss the results from alternative sources. This once again creates a self-reinforcing belief system.

The nature of animal research institutions also creates self-reinforcing beliefs. For most of medical history, animal research was an institutionally required step to getting a drug or technique accepted as valid (both in terms of efficacy and in terms of possible risks). Therefore, almost every medical advance has involved animal testing.[1] But this was through institutional requirement rather than necessarily any benefit from that testing. In fact, Greek and Greek (2000) give many examples of where success is mistakenly associated with animal tests that had nothing to do with the true breakthrough. Nevertheless, it is likely that many agents involved in animal research will associate successes with animal testing. This possibility is supported by the psychological evidence that people tend to find patterns in data even when there is none (for example, Feldman, 1959). Of course, finding patterns in data where none exist is a potential problem in any scientific endeavor. However, this is a hazard in particular for medical research because drugs that show promise and sometimes other advances are institutionally required to be tested on animals, creating an artificial and spurious pattern of breakthroughs being associated with animal research.

3.4. Psychological lock-in and animal research

There are a variety of psychological reasons to expect agents in the field of animal research to establish a belief system that supports this research. A recent review of psychological biases as they apply to economics can also be found in Rabin (1998). One of these, “confirmatory bias” is especially applicable here. People’s beliefs tended to persevere in the face of contradictory evidence. In fact, people have been found to even interpret contradictory evidence as confirmation of their original hypothesis. This suggests that even evidence that animal research is flawed or inferior may be interpreted by its supporters as confirmation of its superiority. In fact, Greek and Greek (2000) cite multiple cases where animal research results delayed drug releases or other discoveries yet which are nevertheless presented as confirmation of their view by supporters of animal research. It should be noted that the implications of “confirmatory bias” apply to any case where belief systems may be locked in to a certain track, not just animal research. People are also subject to self-serving bias (Fletcher and Ward, 1988) and motivated reasoning (Kunda, 1990), both of which would suggest that animal research agents may overestimate their field’s contribution even if they were making their best effort to give an objective assessment.

Given the obvious ethical issues and ongoing debate regarding animal research, cognitive dissonance theory (originally theorized by Festinger, 1957 and applied to economics by

[1] This does not mean that animal testing “caused” the advance. In many cases, animal testing actually impeded progress by giving “false positive” or “false negative” results (Greek and Greek, 2000).

Akerlof and Dickens, 1982) probably plays an important role in agent judgment in this arena. When beliefs and actions conflict, it creates dissonance within the individual that must be rectified by changing the actions or the beliefs. Animal researchers often claim simultaneously to be “animal lovers”. Even if they are not animal lovers, people generally desire to believe they are ethical people doing ethical work. Yet the job of the animal researcher often involves obvious pain, suffering and death. Surely the only way to prevent dissonance in this type of work would be to establish a belief system that establishes their work as morally justified. The most likely (and perhaps the only) moral justification for causing pain, suffering, and death would be a strong belief that the work has great value to society. Therefore, dissonance is a strong unconscious motive for researchers to believe their work has great value. It is surely reasonable to think that there will be a psychological tendency for people in any field to believe that their chosen career is valuable. However, the concept of cognitive dissonance suggests that this tendency may be particularly powerful in fields that involve the use of ethically questionable methods.

Both in academic training and later at the professional level there is a tendency to reinforce established beliefs. More specifically, agents with views conforming to discipline norms are more likely to gain prominent and frequent publication, funding for their research, and advancement in their field. Completing the circle, the agents who gain strong reputations are the ones who are most likely to gain positions of power allowing them to determine publication, funding and advancement of future researchers. Thus, selection processes at both the student and professional help to perpetuate existing norms and belief systems. In animal research disciplines and sub-disciplines, these norms and belief systems are likely to include the efficacy of prevailing methods.

As described in Frank (2003), there may be other reasons to expect a bias in favor of certain beliefs. The adoption of an idea is related to its internal psychological appeal. Animal research may have initially been appealing because it had on its surface a scientific nature that was difficult to find in other methodologies of the time. Animal research allowed quantified numerical analysis and the use of emerging statistical methods at a time when other methods did not. The method also allowed manipulation of subjects to create cleanly defined experimental groups free of complicating factors. These factors are appealing since they create an appearance of scientific rigor. And in fact, these factors are associated with real scientific rigor in many situations. However, if the animal models are not valid for their intended purpose—i.e. as a proxy for human biology, then all the scientific rigor in the world is merely at a superficial level and does not address the underlying failure of the model.

3.5. Is animal research more locked-in than other forms of research?

Many of the lock-in issues discussed here apply to any type of research that dominates its discipline. There will often be a tendency for established paradigms and techniques to remain in place even after they are optimal due to inertia. However, animal research in the biomedical field may be more firmly locked into place than would be the case for a specific perspective or method in other disciplines.

First, the very fact that animal research is under attack leads to entrenchment. This tendency at the individual level was discussed within the context of “cognitive dissonance”.

However, it also probably occurs at a larger institutional level. Few other scientific methodologies face the ethical criticism that animal research does. This has caused a conscious and explicit effort by interested parties within the animal research community to set up institutions to resist criticism. It is likely that this resistance makes change on any grounds more difficult.

Second, other research disciplines do not have the same degree of financial incentives nor industry contact that animal research does. For example, the New England Journal of Medicine was forced to relax its rules on conflict of interest with industry because there were too few experts that did not have financial ties with drug companies. In fact, one recent article contained a disclaimer because every single member of the review board had a financial relationship with the company that produced the drug under study. Sixty-two percent of the investment in biomedical research comes from the pharmaceutical industry. The pharmaceutical industry is also the largest contributor of any sector to lobbying (Greek and Greek, 2004).

Third, related to the influence of the pharmaceutical industry, there are legal influences that help to perpetuate animal research. Although this is changing in some areas, legal requirements may perpetuate the use of animal research in both drug and toxicity testing. In addition, even when not explicitly required, the traditional use of animal testing combined with its appeal to juries who are not aware of its low reliability give firms a strong incentive to use animal testing as protection against liability.

Finally, there are reasons to believe that animal research may have particular appeal relative to other dominant disciplines both due to psychology and self-interest. As already discussed, the cleanness, ease of quantification, and ability to manipulate experiment designs in animal research make it attractive to researchers. This is not common to all research disciplines, but it is also not completely unique. For example, economic models with sweeping assumptions that lead to mathematical tractability, deterministic conclusions, and clean results sometimes may have strong appeal despite having low applicability. Animal research similarly has a certain mathematical tractability and cleanliness of results[2] that enhances its appeal. Begley (2003) argues that top biology journals prefer the “simple elegant studies doable on simple lab organisms” to “the messy, often ambiguous ones on humans”. It has also been argued that animal research is preferred by some researchers and by industry because it is so prone to interspecies variability that researchers can achieve any result they desire. Companies and researchers can prove a drug or treatment is safe or effective by simply by publicizing the results for the right animal model (Bross, 1989; Greek and Greek, 2004)

In the end, it may not matter whether animal research is more locked-in than the dominant form of research in other disciplines. Even if animal research is no more locked-in than other areas of study, there are important ethical issues regarding this field that warrant special attention.

[2] This cleanliness and lack of complicating factors is not true for example of epidemiological or clinical data which has arguably much greater validity and applicability.

4. Comparing animal research to its alternatives

Although Arthur and David typically have talked about lock-in of equally viable technologies by chance events, their theories equally apply to a situation where rates of change in complementary technologies determine the dominant technology. In the case of animal research, alternatives which are viable today depend a great deal on complementary technologies. Technologies that drive these alternatives include computer simulation, sophisticated databases and information systems with large sets of epidemiological data, advanced technologies in the use of cellular tissue, and advances in chemistry. These complementary technologies were not viable at the time when animal research gained strength, quite likely leading to lock-in of one technology due in part to historical circumstance. However, as complementary technologies have developed, these alternatives now seem to be at least as viable as animal research, with inertia for animal research impeding their development.

Although alternatives to animal research are arguably underfunded, there is no shortage of viable alternatives available for consideration. The National Institutes of Health publishes at intervals a bibliography of research on alternatives with abstracts (Hudson and Nguyen, 2002). The directory for 2000–2001 alone describes thousands of research studies on alternatives. The volume and range of research is indicative of the potential of alternatives. However, although the volume is of great value to researchers and practitioners looking for alternatives on a specific topic, there is little research that compares the viability of alternatives broadly to the viability of animal research techniques. One difficulty in doing a fair comparison is defining the fruitfulness of animal research compared to alternatives in a fair and consistent manner. According to LaFollette and Shanks (1995), determining the success rate of animal research is not as straightforward as it seems because failures are often not reported or underreported. Historical literature similarly focuses on breakthroughs without reporting failures at a comparable rate to successes.

A study by Dagg (2000) uses citation analysis to come up with an unbiased comparison of success. The study compares the success (as measured by citations) of animal models in cancer research to alternative models, specifically, human studies and tissue studies. The study found that the alternatives received significantly more citations per publication than the animal research publications. It is quite possible to challenge the validity of using citations as a metric for the value of various forms of research or the use of publications as the base. For example, disciplines with a larger body of research will tend to have a lower citation rate within the discipline simply because the amount of research available dilutes the chances of any particular work being cited. Although animal models and their alternatives are both in the same broadly defined discipline, they probably are somewhat segmented in terms of their citations. Therefore, alternatives might get more citations simply because they are currently a smaller field. However, citation analysis still is in some ways an improvement over prior efforts in that it at least utilizes a metric other than subjective opinion.

Pound et al. (2004) similarly found little evidence that animal research benefited humans. The authors examined prior systematic reviews comparing animal research to clinical results. One finding of the authors is that very little work has been done to test the benefits of animal research. In addition, the systematic reviews the authors examined found that animal research gave little or no guidance to human clinical work in the same area.

Stephens (1987) examined Nobel Prize awards in medicine and physiology and found that alternatives to animal research made a major contribution in two-thirds of the prize awards. In addition, this percentage has grown over time and has been closer to 90% when examining Nobel Prize awards since 1960.

4.1. Negative consequences of using animal-based research over alternatives

There are numerous cases where false positive and false negative results due to differences between animal results and human results have led either to potentially beneficial treatments being overlooked or to harmful effects not being acknowledged. Greek and Greek (2000) give numerous examples which are credible and well documented. Other authors have also provided many cases of errors with serious consequences. For example, despite testing before release that indicated the products were safe, the antibiotics Omniflox and Floxin were withdrawn from the market after one caused seizures and psychosis and the other caused deaths (Fried, 1998), a "vaccine" for tuberculosis that worked in mice, not only did not work, it also cause the disease to flare up in humans (Westacott, 1949), and penicillin's release was delayed when tests on rabbits suggested it was ineffective (Ruesch, 1989).

LaFollette and Shanks (1994) document how treating polio was led astray through animal research. Despite substantial clinical evidence to the contrary, experiments on Rhesus monkeys led researchers to stubbornly hold onto a mistaken belief regarding the disease's pathogenesis. This in turn led to fruitless therapeutic strategies such as a nasal spray that proved useless during a 1937 epidemic in Toronto. The breakthrough that finally identified polio as an enterovirus occurred a decade later through clinical studies.

In the case of testing whether a substance is carcinogenic, false positive results are a serious problem. In one test, rats developed cancer when exposed to 19 out of 20 human non-carcinogens (Lave et al., 1988). An error rate this high clearly has serious negative consequences.

Using animal models to test health risks also requires extrapolating different dose levels and animal sizes using possibly erroneous assumptions. When testing mutagenic risks, a technique developed by Waldren et al. (1986) found that the current estimates of risk based on linear extrapolation of animal models may underestimate mutagenic risk by a factor of 200 or more. According to Bross (1989), this level of underestimation of risk has caused extensive human suffering and death. Bross gives further examples of misleading information from animal models leading to harm to humans including the overuse of an ineffective chemotherapy treatment for breast cancer and the initial rejection of effective chemotherapy agents.

4.2. Human-based research

Human-based research methods include clinical observation, epidemiological studies, and autopsies. Arguably the most useful technique throughout the history of medicine has been clinical observation. Steinman and Szalavits (2002) also argue that more emphasis should be placed on clinical study of humans. The authors argue other methods, such as "basic research" performed on animals, lead to uncertainty and error rather than an increase in knowledge.

If we put aside ethical, legal, and cost issues, there is clearly a superior alternative to research on animals, and that would be performing the identical research on people. For human physiology, disease, and treatment, clearly human beings are a closer model than any other animal. The vast majority of research done on animals could theoretically be done on humans with greater reliability and accuracy. However, much of what we subject animals to we would be ethically unwilling to do with humans. In addition, animal research is often less costly.

But even if research on animals can be performed more easily, Greek and Greek (2000) argue that the differences in the biology of humans and animals are sizable enough to make animal research useless (except for understanding animal biology rather than human biology). Although there will certainly be cases where the results in humans and animals are similar, the authors argue animal experiments suffer from an unacceptably high rate of both false positives and false negatives. However, all scientific methodologies are subject to error and no comparison is made between the error rate of animal research relative to other methodologies. Such a comparison is probably impossible given current data limitations. However, since most of the animal research errors are due to basic differences between animal and human physiology, the implicit assumption is that clinical study on humans would have a much lower error rate. This assumption is well founded. Supporters of animal research would probably not disagree, but would argue that there are other time, cost, and ethical reasons for using animals as a preliminary research methodology before performing comparable studies on humans. However, Greek and Greek argue that the error rate for animal research is so high due to differences from humans that animal studies lend no useful guidance.

Of course, from an economic perspective, even very high error rates are not enough to prove that it is useless as a prescreening tool. If animal research were costless (ethically as well as monetarily), as long as it had a correlation significantly different from zero with clinical results, it would have some value. Or, to create an example in terms of Bayesian probability, if we call a successful animal drug test event X and a successful human clinical drug result event Y, then if $P(Y) = p$, as long as $P(Y|X) \neq p$, then test X gives some useful information about Y. By arguing that animal studies are useless, Greek and Greek are implicitly arguing that $P(Y|X) = P(Y)$. This cannot be adequately proven by the error rates they provide. However, in reality, animal tests are far from costless. Evidence of high error rates does suggest that the likely value of the information provided by animal test Y (for example) is less than the cost of that test. This is particularly true when the opportunity cost of alternative research programs not undertaken with those same resources are included in the calculation.

Although Bernard (1865) and others since then have argued that quantifiable animal research is more “scientific”, nobody denies that qualitative clinical observations have historically been responsible for a large number of medical discoveries and continue to be featured in a large number of research papers at top medical journals. Barnes (1987) and Greek and Greek (2004) also point out that human autopsies are an overlooked tool that have yielded much valuable medical information including information on hepatitis, appendicitis, congenital heart disease, and sudden infant death syndrome.

There is one area where human observation has benefited from complementary technology, and now has the ability to contribute to medical advances like never before. This is in epidemiological studies. In epidemiological studies, large sets of data on human disease and medical outcomes are compiled and statistically analyzed. This is not a new concept, but the growth of technology to store, manage, and transfer large amounts of data has exponentially expanded the opportunities to utilize epidemiological techniques. Concurrently, institutional developments have made the storing and sharing of such data more common. In addition, improvements in statistical techniques and computational power have increased the opportunities for epidemiological research. Many opportunities for fruitful epidemiological research still exist. The potential for future breakthroughs through epidemiological research is limited mainly by resources, coordination in data use, and the imagination of the researchers involved.

Barnes (1987) suggests that the potential for systematic human clinical analysis is greatly underutilized. The vast majority of clinical observations of symptoms, diagnoses, treatments, and outcomes are discarded or remain in paper files, inaccessible for analysis. Spending our limited resources to systematically collect and study untapped data on human cases could easily prove more fruitful than putting those same dollars into animal research.

4.3. *"In vitro" research*

"In vitro" is Latin for "in glass", and refers to research on tissue in test tubes, or otherwise outside of a living organism (although research on bacteria and other whole microscopic organisms typically fall under the category of "in vitro"). Of recent Nobel Prizes in Medicine or Physiology, the "lion's share" have been for in vitro work (Greek and Greek, 2004).

Among other things, in vitro tests have been useful in creating viable or even superior alternatives to animal-based toxicity tests. However, according to Langley (1989), the establishment has been slow in adopting these tests, and the barriers to their adoption have been institutional rather than medical in nature.

Along with refinements in laboratory techniques, in vitro research has also benefited from other recent developments, including the growth of human tissue banks for use in research. The National Cancer Institute's in vitro Cell Line Screening Project is one example of this. Japan's Health Sciences Foundation has also developed a human tissue bank in response to the failure of many drug development projects when tested on humans even though they were successfully used on animals (Greek and Greek, 2004).

According to Bross (1989), animal research has had some success historically in studying infectious disease but little to no success whatsoever in cancer research. However, the cases of historical success with infectious diseases were caused not by the appropriateness of the animal model, but rather because animals served as a place to store the disease, i.e. as a form of "living tissue culture". If this is true, in vitro techniques have the potential to replace animal research models for infectious diseases. While some organisms have proven difficult in the past to grow in vitro, improvements in laboratory technology have the potential to allow in vitro techniques to replace the inefficient use of animals as a tissue culture in all cases.

Like using live human subjects, in vitro techniques have the advantage of being able to use human cells, thereby avoiding any lack of applicability due to large interspecies differences. At the same time, in vitro techniques avoid many of the ethical concerns of using human subjects, are often less costly, and allow for quantification of data from a controlled environment. In vitro techniques will continue to be of great importance in the future of medical research.

4.4. Mathematical and computational models

Bross (1989) directly compares three biomedical mathematical techniques to their animal model alternatives. In all three cases, the animal model was found to be misleading while the mathematical model proved superior in its ability to predict outcomes and the efficacy of potential treatments. Nevertheless, institutional forces created a bias towards the animal models. Bross was involved in the development of some of these mathematical techniques and presents a convincing case for their superiority in these instances. These three cases alone are insufficient to demonstrate the superiority of mathematical models in general. However, they do demonstrate the potential of these relatively new methods.

The rapid growth in computational power has been key to the growth of mathematical and computational models in the biomedical field. As a relatively young technology, this field has very strong potential for yielding powerful benefits with additional investments of resources.

4.5. Other alternatives

A variety of other alternatives rely on new technology and have become important new areas of research and treatment only in recent years. These alternatives must fight an uphill battle to gain funding and acceptability due to the existing inertia for more traditional methods. Yet at the some time, their recent development and the rapid growth in complementary technology suggests that there are many fruitful opportunities for research and that the ratio of gains relative resources devoted to these fields may be high.

Although genetics has been around a long time, genetic research is an area that has blossomed only recently and has been experiencing rapid growth. The Human Genome Project was a key development in this area. Burgeoning fields related to genetic research and the human genome project include proteomics, which is the study of the function, regulation, and expression of proteins. There is also a Human Genome Diversity Project underway which will focus on the variation of the genetic code across the human population.

Our growth in understanding of genetics has been possible only recently due to the development of complementary technology. Technologies that have been key to studying genes and proteins include mass spectrometry, computer algorithms, and the development of DNA microarrays (Greek and Greek, 2004).

Recent developments in physics, chemistry, and computer technology have had important implications for alternatives to animal research in the biomedical field. More and more, researchers are able to move away from pure trial and error in the development of drugs to a technique called “rational drug design”. This involves looking at receptors at the molecular level and designing a drug that will be likely to interact with these receptors in the desired manner. This technology relies heavily on developments in chemistry and typically uses in vitro techniques (Greek and Greek, 2004). Computer-aided medical design (CAMD) is also being used to take advantage of modern computational power in the development of drugs. X-ray crystallography and nuclear magnetic resonance spectroscopy are being used to study protein structures. Magnetic resonance imaging and positron emission tomography are being used to study the brain and have been instrumental in the development of treatment techniques such as the "Gamma Knife" for treating tumors with radiation (Greek and Greek, 2004). Ultrasound technology has also allowed the biomedical field to see inside living bodies in new ways.

Though no single study can be said to demonstrate that alternatives are superior to animal research, the explosion of the possibilities for these alternatives due in large part to the growth of complementary technologies suggests that these alternatives would be at least as fruitful uses of the limited resources available for research. Though the research is limited, the efforts that have been made to directly compare animal research to alternatives also suggest that alternatives are at least as viable. In addition, due to high error rates, virtually all animal research must eventually be confirmed in humans. Therefore, at best it is suggestive, giving information on the probability of success in similar research on humans. A variety of alternatives can achieve this goal, and the possibilities for these alternatives are growing rapidly.

5. De-locking from the animal research path

If it becomes evident in hindsight that society has chosen an inferior technological path, then devoting some societal resources to "de-lock" or change paths may be appropriate. A second possible reason for intervention exists if there are significant externalities or ethical issues with the dominant, locked-in path. In this second case, the alternative technology need not be superior, but only equally viable in the long-term to make it appropriate for society to attempt to de-lock.

In the case of animal research, it may be difficult to prove that the alternatives are superior, but there is ample reason to believe that alternatives are currently at least equally viable.

Society has begun to recognize the ethical issues involved in animal research and put laws in place that at the very least acknowledge that there are animal welfare issues to be considered. The prevailing defense of animal experimentation is that it is a "necessary evil" and that it is the only way to make sufficient progress. However, given the wealth of alternatives now available, this is no longer true (if it ever was). Clearly, animal research is a case with both significant externalities and ethical issues making it a likely candidate for intervention.[3]

Dosi and Metcalfe (1991) discuss multiple causes of irreversibilities in economics as well as discussing some ways of countering these irreversibilities. Regarding changing irreversibilities, the authors state, "one has also the continuous opportunity of, so to speak, 'breaking out', not by re-writing the past which is indeed unalterable, but by turning the irreversibility of the future in one's own favor and creating another (although still irreversible) new world" (pp. 149–150). Since an important cause of irreversibility is the idea that the business environment is endogenous, individual actors, or groups of actors have the power

[3] Even if animals are not given standing as economic agents, there is a negative externality involved because many economic agents suffer sympathetic utility loss from the suffering of animals in laboratories.

to shape the future environment. The authors emphasize the possibility of novel, intentional, or even “deviant” behavior as shaping the future environment.

This in fact is already taking place in biomedical research, where some individual actors are actively seeking out alternatives either for ethical reasons or because they simply believe alternatives are more viable. However, so far this has only created a small drag on the sizeable inertia that animal research already has.

Though Dosi and Metcalfe emphasize the actions of individual actors, policy intervention may be necessary as well. Possible interventions include vigorously promoting and funding alternative technologies as well as providing financial incentives to discourage animal use (i.e. taxes on research based on harm caused). More radical alternatives include prohibiting specific types of animal research. Such a policy may appear extreme, but if we are truly locked in to an inferior technology, or even a technology that is equally likely to be inferior or superior in an uncertain future, there arguably is a moral imperative to select the technology which does not lead to certain death and suffering.

Addressing certain institutional issues can also be of value. For example, it has been claimed that animal tests are often done to protect companies from liability since they play well to a jury even if they are not truly reliable (Greek and Greek, 2000). Explicitly changing liability laws to address this would be of value, as would the speedy incorporation of alternatives when viable for government-mandated testing (e.g. toxicity tests).

But in addition to public policy solutions, Dosi and Metcalfe are correct in suggesting that the creative and innovative actions of individuals within the research community ultimately will play a key role in determining the course of future change. Langley (1989) argues that mental resistance, “lethargy” and a “failure of imagination” have often been responsible for the slow rate at which alternatives have been adopted. The author gives an example of how researchers insisted a certain toxicity test would be impossible to do without animal tests. Yet just 2 years later an alternative in vitro test was found to do the job effectively. Dunayer (2001) also gives an example of a well-known experiment where the researchers insisted animal suffering was necessary, yet another researcher 6 years later achieved the same results using much more benign methods on human volunteers. The growth of alternatives will depend greatly on the creativity and openness of the research community to new possibilities, rather than an attitude of entrenchment against change.

6. Conclusion

Animal research is a very strong candidate for both institutional and technological lock-in. Animal research has positive feedbacks in technology and considerable time to gain technological advantage over competing methods, numerous powerful constituencies with an interest in perpetuating it dominance over other methods (including government, academic, industry interest groups), and other institutional factors leading to inertia. In addition, there are powerful reasons to expect behaviors and perceptions to be path dependent. In fact, it may prove difficult to find a better candidate for path dependency and lock-in than animal research.

It is important to recognize that if research in certain fields has in fact locked-in to an animal use methodology, this alone does not necessarily mean that animal research is an inferior technological path (although others have attempted to make the case that it is). Technological lock-in by its very nature involves decisions made in situations where the course of technological progress is unknowable. What it does demonstrate, however, is that if animal research is an inferior path, there is no reason to expect the path to self-correct. This is an important point since much of the public is likely to assume animal research must be the most effective method simply due to its prevalence. Furthermore, not only do those involved in animal research have an interest in advocating its merits, but the analysis here suggests there are reasons to expect that they will likely be biased in favor of animal research in terms of what they actually believe. It should also be acknowledged that experts arguing against the efficacy of animal research often also have a moral objection to such research, giving them at least one source of bias as well. Conclusions as to which methodology is superior cannot simply be based on the number of experts on either side of the debate due to self-interested advocacy as well as the behavioral aspects of lock-in causing actual beliefs to change. If the animal research path is in fact locked in, then its prevalence is also uninformative as evidence of its efficiency.

In addition to providing insight into animal research, this paper has attempted to provide by analysis of an example insight into possible technological and institutional lock-in. Animal research demonstrates how one set of historical circumstances and one set of institutions can lead to possible lock-in.

This analysis has also placed particular focus on the potential for lock-in in behaviors, beliefs, and perceptions. Although North has acknowledged that this is an important component of institutional lock-in, it arguably still receives too little emphasis and may be the most powerful component of institutional path dependence. Behavioral lock-in is also probably the least understood dimension of institutional path dependence. The animal research case demonstrates how known psychological biases and other considerations can cause perceptions and beliefs to resist change.

References

Akerlof, G.A., Dickens, W.T., 1982. The economic consequences of cognitive dissonance. American Economic Review 72, 307–319.

Altman, M., 2000. A behavioral model of path dependency: the economics of profitable inefficiency and market failure. Journal of Socio-Economics 29, 127–145.

Anderson, B., 1998. The evolution of technological trajectories 1890–1990. Structural Change and Economic Dynamics 9, 5–34.

Arthur, B.W., 1989. Competing technologies, increasing returns, and lock-in by historical events. The Economic Journal 99, 116–131.

Arthur, B.W., 1994. Positive feedbacks in the economy. McKinsey Quarterly 81 (1).

Banchoff, T., 2002. Institutions, Inertia and European Union Research Policy. Journal of Common Market Studies 40 (1), 1–21.

Barnes, D.J., 1987. The case against the use of animals in science. In: Fox, M.W., Mickley, L.D. (Eds.), Advances in Animal Welfare Science. Martinus Nijhoff, Boston.

Bayly, M.B., 1961. Clinical Medical Discoveries. National Anti Vivisection Society, London.

Begley, S., 2003. Physician–researchers needed to move cures out of the rat's cage. The Wall Street Journal B1.

Bernard, C., 1865. Introduction to the Study of Experimental Medicine. Henry Schuman, Paris, 1949 (reprint).

Bross, I.D., 1989. Mathematical models vs. animal models. In: Perspectives on Animal Research. Medical Research Modernization Committee, New York.

Croce, P., 1999. Vivisection or Science? An Investigation into Testing Drugs and Safeguarding Health. Zed Books, London.
Dagg, A.I., 2000. Animal experimentation in cancer research: a citation analysis. Journal of Applied Animal Welfare Science 3 (3), 239–251.
David, P.A., 1985. Clio and the economics of QWERTY. American Economic Review 75, 332–337.
David, P.A., 2001. Path dependence, its critics and the quest for 'historical economics'. In: Garrouste, P., Ioannides, S. (Eds.), Evolution and Path Dependence in Economic Ideas: Past and Present. Elgar Publishing, Cheltenham, UK.
Dosi, G., Metcalfe, J.S., 1991. On some notions of irreversibility in economics. In: Saviotti, P.P., Metcalfe, J.S. (Eds.), Evolutionary Theories of Economic and Technological Change. Harwood, Manchester, UK.
Dunayer, J., 2001. Animal Equality: Language and Liberation. Ryce Publishing, Derwood, MD.
Feldman, J., 1959. An analysis of predictive behavior in a two-choice situation. PhD Dissertation. Carnegie Institute of Technology.
Festinger, L., 1957. A Theory of Cognitive Dissonance. Stanford University Press, Palo Alto, CA.
Fletcher, G.J.O., Ward, C., 1988. Attribution theory and processes: a cross-cultural perspective. In: The Cross-cultural Challenge to Social Psychology. Sage, Newbury Park, CA.
Frank, J., 2003. Natural selection, rational economic behavior, and alternative outcomes of the evolutionary process. Journal of Socio-Economics 32 (6), 601–622.
Fried, S., 1998. Bitter Pills. Bantam Books, New York.
Greek, C.R., Greek, J.W., 2000. Sacred Cows and Golden Geese. Continuum, New York.
Greek, J.W., Greek, C.R., 2004. What will we do if we don't Experiment on Animals? Trafford, New York.
Heiner, R.A., 1983. The origins of predictable behavior. American Economic Review 83, 560–595.
Heiner, R.A., 1985. Origin of predictable behavior: further modeling and application. American Economic Review 75, 391–396.
Heiner, R.A., 1988. Imperfect decisions in organization: toward a theory of internal structure. Journal of Economic Behavior and Organization 9, 22–44.
Hoggan, G., 1975. Morning Post, February 2.
Hudson, V.W., Nguyen, Q., 2002, 2000–2001. Alternatives to the use of live vertebrates in biomedical research and testing: a bibliography with abstracts. Toxicology and Environmental Health Information Program. Specialized Information Services, National Library of Medicine, National Institutes of Health, Bethesda, MD.
Kunda, Z., 1990. The case for motivated reasoning. Psychological Bulletin 108, 480–498.
LaFollette, H., Shanks, N., 1994. Animal experimentation: the legacy of Claude Bernard. International Studies in the Philosophy of Science, 195–210.
LaFollette, H., Shanks, N., 1995. Two models of models in biomedical research. Philosophical Quarterly, 141–160.
Langley, G., 1989. Establishment reactions to alternatives. In: Paterson, D., Palmer, M. (Eds.), The Status of Animals; Ethics, Education and Welfare. CAB International, Wallingford, UK.
Lave, L.B., et al., 1988. Information value of the rodent bioassay. Nature 336 (3), 631.
Liebowitz, S.J., Margolis, S.E., 1994. Network externalities: an uncommon tragedy. Journal of Economic Perspectives 8, 133–150.
March, J., Olsen, J., 1989. Rediscovering Institutions: The Organizational Basis of Politics. Free Press, New York.
Medical World, 1933. December 1, p. 335.
North, D.C., 1991. Institutions. Journal of Economic Perspectives 5 (1), 97–112.
North, D.C., 1990. Institutions, Institutional Change and Economic Performance. Cambridge University Press, Cambridge.
North, D.C., 1993a. The new institutional economics and development. Washington University Working Papers Series No. 9309002.
North, D.C., 1993b. Five propositions about institutional change. Washington University Working Papers Series No. 9309001.
North, D.C., 1994. The Historical Evolution of Polities. Washington University Working Papers Series No. 9411007.
Pierson, P., 2000. Increasing Returns, Path Dependence, and the Study of Politics. American Political Science Review 94 (2), 251–267.

Pound, P., Ebrahim, S., Sandercock, P., Bracken, M., Roberts, I., 2004. Where is the evidence that animal research benefits humans? British Medical Journal 328, 514–518.

Rabin, M., 1998. Psychology and economics. Journal of Economic Literature 36, 11–46.

Regan, T., 1983. The Case for Animal Rights. University of California Press, Berkeley.

Ruesch, H., 1989. 1000 Doctors against Vivisection. Civis Publications.

Singer, P., 1975. Animal Liberation. The New York Review, New York.

Steinman, R.M., Szalavits, M., 2002. Patients have been too patient with basic research. Cerebrum 4 (4).

Stephens, M., 1987. The significance of alternative techniques in biomedical research: an analysis of Nobel Prize awards. In: Fox, M.W., Mickley, L.D. (Eds.), Advances in Animal Welfare Science. Martinus Nijhoff Publishers, Boston.

Waldren, G., Correll, L., Sognier, J., Puck, T., 1986. Measurementof low levels of X-ray mutagenesis in relation to human disease. Proceedings of the National Academy of Sciences 83, 4839–4843.

Walker, W., 2000. Entrapment in large technology systems: institutional commitment and power relations. Research Policy 29 (7–8), 833–846.

Westacott, E.D., 1949. A Century of Vivisection and Antivivisection. Saffron, Walden.