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# Causal Disanalogy I

## Strong Models and Theoretical Expectations

In the previous two chapters we examined the theory of evolution. We focussed specifically on those elements of the theory that have significant implications for our understanding of the practice of biomedicine. Here we further clarify the standard view of the use of the role of animals in biomedical research, namely, their use as *Causal Analog Models* (CAMs) of human biomedical phenomena. Then, using insights gleaned from the theory of evolution, we will spell out its theoretical implications for the use of animals as CAMs. In this chapter we specifically focus on CAMs as *strong* models, models that are supposed to be causally isomorphic to the human systems they model. While strong models are generally recognized to be *ideal* models, some researchers have asserted the actual existence of causal isomorphisms, and this is part of a tradition extending back to the writings of Claude Bernard.

In connection with strong models, we explain how a proper understanding of the theory of evolution leads us to expect evolved causal disanalogies (failure of causal isomorphism) between members of different species. Then, in the following chapter, we summarize some relevant empirical findings, findings that are consistent with these theoretical expectations. The existence of causal disanalogies between members of different species does not establish that animal research is worthless. However, it does suggest that apologists' grand claims about the direct and substantial benefits of such research are exaggerated. In chapter 9 we consider *weak models* -- CAMs in which there is a partial breakdown of causal isomorphism. While such models represent many instances of the real-world experimental situation, they turn out nevertheless to be problematic.

The presence of causal disanalogies undermines the claim that

animal research is of immediate and direct relevance to human biomedical phenomena. More specifically, these disanalogies will undercut claims about the direct benefits of applied research -- like predictive toxicology and teratology -- which aims to make *predictions* about human biomedical phenomena. These arguments will *not* show that findings in animals invariably differ from findings in humans. Rather, they show that we do not know, before tests on humans, if there are causally relevant disanalogies between humans and animal test subjects with respect to the phenomenon under study. Thus, the predictive value of these tests is, at best, uncertain. That is, any benefits of applied research to humans will be much more indirect.

As we explain in chapter 12, the existence of causal disanalogies does not undermine the scientific legitimacy of basic research in the same way or to the same extent that it undermines applied research. Some types of basic research may be relatively insensitive to causal disanalogies between the species; indeed, they may even exploit these differences. However, the *reason* these forms of research may be less adversely affected by the existence of causal disanalogies is that any benefits of this research are itself indirect. Understanding that any benefits of animal experimentation are relatively indirect is important when we evaluate public policy documents. For, as you may recall from chapter 1, such documents proclaim that animal experimentation is immediately and directly beneficial to humans.

A word of caution: we do not think that a hard and sharp distinction can be drawn between basic and applied research. In reality there will be a spectrum of cases. However, this does not mean that no distinction can be drawn. Moreover, some research programs have both applied and basic aspects. For such programs, the existence of causal disanalogies will be of variable importance: likely they will have less of an impact on the basic research, but will be more directly relevant to evaluation of the applied aspects of that research.

### THE RESEARCHER'S EXPECTATIONS

As we explained in chapter 4, biomedical researchers claim there is significant biomedical information about humans that can be discovered only by experiments on intact animals (AMA 1988: 2). Although epidemiological studies, computer simulations, clinical

investigation, and cell and tissue cultures have become important weapons in biomedical scientists' arsenal, these are primarily adjuncts to the use of animals in research (Sigma Xi 1992: 76). The researchers claim controlled laboratory experiments on animals are the core of scientific medicine. After observing the effects of various stimuli in non-human subjects, we can legitimately infer the likely effects of these stimuli in humans. Perhaps what is more important, we can understand the biomedical condition's causal mechanisms.

That is, tests on animal subjects are supposed to uncover the causal mechanisms that produce and direct the course of a disease or condition in animals. These results can then be extended by analogy to humans, enabling physicians to prevent or treat the disease or condition under investigation. There are other uses of experiments on animals, most especially, their use as *Hypothetical Analog Models* (HAMs). We shall discuss HAMs in chapter 12. Here we shall focus on the primary use of animal models as CAMs.

## THE LOGIC OF CAMS

When conducting a laboratory experiment, a chemist or physicist manipulates some substance X and records the results. Then, using the principles of causal determinism ((a) all events have causes, and (b) for qualitatively identical systems, same cause, same effect), the investigator infers that, other things being equal, similar manipulations of X outside the laboratory will have similar effects. It is a sound inductive inference.

However, this model cannot quite capture most biological phenomena which are best described probabilistically. That is, an experimenter observes some phenomenon in a certain percentage of the laboratory subjects of species X and infers that a similar percentage of creatures of that species will react similarly outside the laboratory (all other things being equal). Although some people think probabilistic reasoning cannot be genuine causal reasoning, since it fails to satisfy the requirement of Humean "constant conjunction" (according to which events of type A are to be invariably followed by events of type B, if the A-type events are to stand as causes of B-type events). But, we see no reason to embrace this restricted view of causality. Probabilistic causal reasoning in the biological sciences is ubiquitous, even if there are debates about how the phenomenon is to be explained. Most reasonable

people accept that smoking causes lung cancer, even though not all smokers develop lung cancer -- a case of A-type events not invariably being followed by B-type events. Some claim that the element of probability arises from researchers' ignorance of initial conditions; others claim it reflects the fundamentally probabilistic nature of the universe.

Those who claim it arises from ignorance note that small, often imperceptible, differences in initial conditions can, even in deterministic systems, lead to probabilistic outcomes, especially if the differences are unknown to the investigator. That, they say, is why researchers are so concerned to control experimental variables: they want to limit the effects of any differences in initial conditions. However, we can never completely control all relevant variables. In complex biological systems, there will generally be some causally relevant differences between experimental subjects (and their environments) -- differences that lead subjects to respond differently to similar experimental stimuli.

Other philosophers of science claim that probabilities describe significant strands the fabric of the universe. *Probabilistic causality*, according to Wesley Salmon, is a "coherent and important scientific concept," (1984: 190). In fact, according to Salmon, there is ". . . compelling (though not absolutely incontrovertible) evidence that cause-effect relations of an ineluctably statistical sort are present in our universe" (1984: 188). Whether Salmon is right, we need not decide here. All we need note is that most biomedically significant data are statistical in nature.

Researchers do not see this as a bar to extrapolating results from animals to humans. They assume their research methods rely on either deterministic or straightforwardly probabilistic reasoning, that is, they think inferences from non-human CAMs to humans exhibit normal causal reasoning. However, animal experimentation is neither deterministic nor probabilistic in either of the senses discussed above. In both standard methodologies, experimenters make inferences from what happens to Xs in the lab to what will happen to Xs outside the lab. Not so with animal experiments. Here researchers make predictions from what happers to Xs (some non-human CAM) in the lab to what will happen to Ys (humans) outside the lab based. This cannot be straightforward casual reasoning, not even probabilistic causal reasoning.

Biomedical experiments on animals are doubly probabilistic: experimenters discover that some percentage of laboratory animal

subjects react in some particular way and conclude that it is probable or likely that a similar percentage of humans will react similarly outside the lab. There is probabilistic behavior within the (non-human) lab population, probabilistic behavior within the human population outside the lab, and also a *probabilistic (epistemological) uncertainty* about whether the results observed in the non-human animal population will be (statistically) relevant to humans.

That is why, contrary to many researchers' expectations, they are not engaged in normal causal reasoning, but in some form of analogical reasoning. The basic of idea of analogical reasoning, according to David Hull is that:

> . . .the behavior of a poorly understood system is assimilated to the behavior of a well-understood paradigm system. Hopefully the principles that govern the behavior of the paradigm system can be extrapolated to the poorly known system (1974: 105).

To the extent that either of these systems is poorly understood, we can never be confident that these systems are relevantly similar. If they are different, they may be different in ways that undermine our ability to extrapolate from one species to the other.

At first glance it appears the theory of evolution would guarantee that there would be no relevant differences that would undermine our ability to extrapolate from one species to another, especially phylogenetically close species. After all, the theory of evolution suggests that there exist important biological similarities between members of distinct species.

Certainly such causal analogical inferences would be legitimate if experimenters were merely concerned with gross toxicological effects. For example, if injecting a rat with concentrated sulfuric acid destroys its tissues, it is reasonable to expect a similar result in humans. Unfortunately, that expectation is grounded more in the antecedently known effects of such an acid on organic compounds rather than in any detailed knowledge about the organization and evolution of biological organisms. However, it is these latter details that are especially relevant to the practice of biomedicine. For instance, if we are interested in the long term effects of exposure to low levels of sulfuric acid (perhaps from acid rain), we cannot know that the results of such exposure in rats can be extrapolated

to humans. At least that is something scientists cannot assume without argument and evidence.

*Reformulating the logic of CAMs*

In chapter 4 we stated the following schema for causal analogical arguments: *X (the model) is similar to Y (the subject being modeled) with respect to properties {a, ..., e}. X has additional property f. While f has not yet been observed directly in Y, it is likely that Y also has the property f.* However, we can now see why that first statement of the logic of CAMs is inadequate. Since CAMs are a sub-species of analogical arguments in which (some of) the premises and conclusions involve *causal analogical* claims, the CAMs must satisfy two further conditions: *(1) the common properties {a, …, e} must be causal properties which (2) are causally connected with the property {f} we wish to project -- specifically, {f} should stand as the cause(s) or effect(s) of the features {a,…, e} in the model.*

These are rigorous requirements. But not yet rigorous enough. Animal researchers insist that only properly controlled experiments are scientically acceptable; that is why they think epidemiological studies are poor cousins of properly controlled animal experiments. These researchers want to ensure that there are no differences in conditions that might skew test results. Differences between the causal mechanisms of the model and the object modeled could skew experimental results.

Hence, we can be confident that extrapolations from animal test-subjects to humans are highly probable only if we are confident that the relevant causal mechanisms in the non-human animal are relevantly similar to those in the human animal. For the investigators who followed Bernard, that assumption was innocent enough. Bernard thought " . . . all animals may be used for physiological investigations, because with the same properties and lesions in life and disease, the same result everywhere recurs . . . " (1949: 115). However, evolutionary theory tells us that assumption is anything but innocent. Hence, it should not be an unstated assumption: it should be an explicit condition of causal analogical reasoning.

That is, if animal subjects are to be good CAMs of human biomedical phenomenon, then, in addition to conditions (1) and (2), we must also require that *(3) there must be no causally relevant disanalogies between the model and the thing modeled.* Some researchers are aware that CAMs should ideally satisfy condition (3). As Nomura, *et al*., explain it: ". . .the most useful animal models are those with an etiology mechanistically identical to that of human diseases" (1987: 352). Models that satisfy condition (3) will be called *strong models*.

To the extent that there are no (or insignificant) causal disanalogies between the test subjects and humans, then the additional layer of probability or uncertainty mentioned earlier will be minimal. To the extent that there are important disanalogies, then this additional layer of probability will attenuate our confidence in animal test subjects as CAMs of human biomedical phenomena of interest. To the extent that we do not *know* the extent and significance of disanalogies, we should be less confident that the results found in the model are relevant to humans.

There is scope for at least two kinds of evolved disanalogy in biological systems. First, we may find *intrinsic disanalogy* at any level in the biological hierarchy. As a result of evolution, causal properties (and structures and mechanisms) found in the systems of members of one species may be absent in members of another species; for example, rats lack gall bladders. Furthermore, because many biological systems are intact systems, systems composed of mutually interacting subsystems, we may find *systemic disanalogy*, that is, evolved differences in the relations between an organism's systems. Phylogenetic compromise is an especially likely source of systemic disanalogy.

Besides evolved disanalogies, researchers must also be concerned with what we call *intervention disanalogies*. These disanalogies may arise from any causally relevant differences in the environments of animals subject and human populations, especially differences caused by experimental intervention. For example, experimental rats will almost certainly be exposed to suspect toxins in a different way than humans will be. These different routes of administration might be relevant to the way animals and humans react to the substance. If so, this will be a source of *intervention disanalogy*. These disanalogies can arise in at least two ways: (a) in experiments to uncover the causes of biomedical phenomena of interest, the means of inducting the condition in the animal subjects may not

correspond to the way(s) in which these phenomena are caused in humans; and (b) in experiment to treat a condition (however caused), the investigator may be aware that the mechanisms of induction are different in model and humans, but may assume (erroneously) that similarities in observable symptoms and deficits imply that what is causally efficacious in ameliorating symptoms and deficits in the model, will thereby be causally efficacious in humans. Examples of both types of intervention disanalogy will be discussed in the next chapter.

We now have a precise way to formulate the epistemological problem of relevance first mentioned in chapter 2: even if researchers could be confident that both conditions (1) and (2) were satisfied for any particular animal model, condition (3) would remain a substantial stumbling block. That is, researchers cannot assume, without presentation of evidence, that there are no causal disanalogies. They can be confident there are no causal disanalogies only if they know the model and subject modeled are *causally isomorphic*, i.e., only if they know the model is a *strong* model.

Some animal investigators have asserted the existence of just such isomorphisms. This claim, which seldom receives any justification, forms part of a tradition going at least as far back as Claude Bernard. Many researchers see causal isomorphism as an ideal to be approximated. As Nonneman and Woodruff state it, "If every aspect is fully isomorphic between the animal model and human condition, including cause and mechanism, the model is *homologous*. Most would agree that such a model represents the ideal" (1994: 9). (Notice this is a different use of the word "homologous" than that occurring in evolutionary biology. In the present context, homologous models are models where there is complete isomorphism. Thus, Nonneman and Woodruff contrast homologous models with analogous models (models where there is only partial isomorphism). These in turn are contrasted with correlational models, models where issues of isomorphism are irrelevant.)

However, causal isomorphism is an incredibly strong condition, even *within* a species. Genetic, developmental, and environmental factors may undermine the hope of causal isomorphism even within the human species. Similar factors often lead to intraspecific variation within laboratory animals: that is why researchers seek genetically homogeneous test animals. More importantly for our current discussion, however, are failures of inter-specific causal isomorphism.

## WHY CONDITION (3) IS NOT SATISFIED: THE IMPLICATIONS OF EVOLUTION

There are powerful theoretical reasons to expect that condition (3) will not be satisfied. Humans and non-human animals have been subject to divergent evolutionary pressures. Their responses to these pressures differ, not merely at the level of gross morphology, but also terms of in their underlying biomedically significant causal mechanisms. Members of a species may change over time through the gradual accumulation of changes resulting from natural selection. And, through the process "adaptive radiation" organisms insinuate themselves into a myriad of environmental niches. This leads to specialization of organic function.

While no organ is an island, the collection of organs in a viable organism interacts so as to constitute an entity capable of surviving in some finite (often quite restricted) range of environmental conditions. As the zoologist Richard Dawkins has pointed out, not only is there a niche to be filled by being a multi-cellular organism, there are also advantages from specialization of organic function:

> The advantage of being in a club of cells doesn't stop with size. The cells in the club can specialize, each thereby becoming more efficient at performing its particular task. Specialist cells serve other cells in the club and they also benefit from the efficiency of other specialists (1989: 258).

And the evolution of specialization, with the associated advantages arising from mutual cooperation between the "specialist" organs, will also be accompanied by many and various phylogenetic compromises elsewhere in the organism -- further differences and potential sources of disanalogy.

In organisms like mammals, adaptive specialization has had consequences especially relevant to animal researchers. As we explained in the previous chapter, biological systems exhibit enormous complexity. Moreover, the organism's sub-systems are tightly interlocked. This is true not just at the level of organs, tissues and cells, but also at the biochemical level. As Cairns-Smith points out:

> Subsystems are highly interlocked . . . [P]roteins are needed to make catalysts, yet catalysts are needed to make proteins. Nucleic acids are needed to make proteins, yet proteins are needed to make nucleic acids. Proteins and lipids are needed to make membranes, yet membranes are needed

> to provide protection for all the chemical processes going on in a cell . . . The whole is presupposed by all the parts. The interlocking is tight and critical. At the centre everything depends on everything (Cairns-Smith 1985: 39).

It is this interlocking of subsystems, which makes even small changes potentially so important. Nowhere is this better seen than in the relationship between structure and function discussed in the previous chapter.

Differently organized complex systems can achieve many of the same functional ends. Biological organisms are usually "built" from similar parts -- they share many of the same biochemicals, many of the same metabolic pathways, etc. However, these organisms are faced with different evolutionary pressures. Over evolutionary time ways were “found” to organize their parts so that they can achieve similar functional ends by different causal means. In short, the fact that two species have similar biological functional properties will give us no reason to think they have relevantly similar underlying causal mechanisms.

Yet researchers think animals are good models of human biomedical conditions precisely because human and their non-human CAMs achieve similar biological functions. However, since the same biological function may be achieved in a variety of causal ways, mere functional similarity does not give us a reason to think condition (3) is satisfied. The process of convergent evolution – which undergirds the evolution of analogous structures (e.g., the wings of bats and butterflies, the dorsal fins of sharks and dolphins) -- unquestionably illustrates that functional similarity does not show that condition (3) is satisfied.

Even where underlying structures are homologous, we cannot assume condition (3) is satisfied. The phenomenon of phylogenetic compromise makes that evident. Adaptive changes one place in an organism often requires a wide range of changes, ripple effects if you will, elsewhere in that organism. The parts of organisms did not evolve on their own. Any changes in one part of an organism must be accommodated with other changes elsewhere. For instance, if evolutionary pressures "encourage" faster animals, those pressures cannot be accommodated simply by developing larger leg muscles. The animal may also need a more efficient heart to get more blood to those muscles -- or perhaps the animal needs a different skeletal structure.

For another example, if some organisms evolve the capacity for flight, that capacity will not come into being simply through the evolution of wings, there will also have to be metabolic and other changes. In humans ammonia is excreted in the form of urea in urine, via the kidneys. However, this will not suffice for organisms in arid or aerial niches. Lehninger, *et al.,* note:

> Excretion of urea into urine requires simultaneous excretion of a relatively large volume of water; the weight of the required water would impede flight in birds, and reptiles living in arid environments must conserve water. Instead, these animals convert amino nitrogen into uric acid, a relatively insoluble compound that is extracted as a semisolid mass of uric acid crystals with the feces (1993:521-522).

Consequently, humans, birds and reptiles achieve a similar function -- excretion of ammonia --by different causal routes. That is exactly what the discussion of the causal/functional asymmetry would lead us to expect. Generally, then, since the organism's parts did not evolve on their own, any changes one place in an organism must be accommodated by, and reflect, other changes elsewhere. This is what renal physiologist Homer Smith had in mind when he remarked of the kidneys:

> Only because they work the way they do has it become possible for us to have bones, muscles, glands and brains. Superficially, it might be said that the function of the kidneys is to make urine, but in a more considered view, one can say that kidneys make the stuff of philosophy itself (1961: 3).

In addition to phylogenetic compromise, host-parasite co-evolution may also be a source of evolutionary causal disanalogy between members of different species. Consider vegetarian primate species. They have evolved relationships with intestinal flora that are different from those found in humans, and yet are relevant in drug metabolism (Mitruka, *et al.* 1976: 342). As Sipes and Gandolfi note:

> An aspect of *in vivo* extrahepatic biotransformation of xenobiotics frequently overlooked is modification by intestinal microbes. It has been estimated that the gut microbes have the potential for biotransformation of xenobiotics equivalent to or greater than the liver. With over 400 bacterial species

> known to exist in the intestinal tract, differences in gut flora content as a result of species variation, age, diet, and disease states would be expected to influence xenobiotic modification (1993: 109).

Once again, differences with respect to evolutionary history may lead to causal differences which result in violations of condition (3).

Thus, even a seemingly small change in an organism will almost certainly be associated with a variety of other changes -- changes that may be biomedically significant. Perhaps occasionally these accompanying differences are not biomedically significant. However, this is not something we can know in advance. Certainly we cannot merely assume these differences will not be significant.

In summary, species' differences may come in at two levels: there may be evolved differences in sub-systems at any point in the hierarchy and there may be evolved differences in the relationships between these sub-systems. Thus, there will be scope for causal disanalogy, not only from the species-specific manner in which the individual sub-systems have evolved, but also from the mutual interactions that have evolved between these sub-systems.

Hence, evolutionary theory tells us that animal models cannot be *strong* models of human disease: Thus, we are theoretically unjustified in assuming that results in test animals can be extrapolated to humans. We have a theoretical expecation that there is an ontological problem of relevance. Although humans are not "essentially" different from rats, nor are we "higher" lifeforms, we are differently complex. Species' differences, even when small, often result in radically divergent responses to qualitatively identical stimuli. Evolved differences in biological systems between mice and men cascade into marked differences in biomedically important properties between the species.

Minimally, we should not assume, *a priori,* that condition (3) is satisfied. If it is satisfied (and if not, the extent to which it is not) must be established empirically. That is, we could be confident that condition (3) is satisfied only after we have conducted extensive, controlled tests on humans -- tests that show that the systems are not disanalogous. However, as we pointed out in chapter 2, animal tests are deemed desirable primarily because they are thought to eliminate the need for such tests on humans. As we point out in the following chapter, the empirical evidence supports these theoretical expectations.