A Response to Critics of Darwin's Black Box

by

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Abstract

In 1996 I published *Darwin's Black Box: The Biochemical Challenge to Evolution*. The main thesis of the book was that science has discovered in the cell biochemical systems that are what I term "irreducibly complex", where the removal of one of the components of the system causes it to lose its function, and that such systems are very difficult to explain in Darwinian terms. I argued that irreducibly complex biochemical systems are better explained as the product of deliberate intelligent design. The book has been quite controversial and has been vehemently criticized by Darwinists. In this paper I discuss several of what I consider to be the most serious of their objections. They include contentions that either the biochemical systems I discussed are not irreducibly complex, or that systems of similar complexity have already been shown to be approachable by Darwinian means. I will demonstrate that these arguments are both incorrect. Further arguments I will consider include one attacking my paradigm of irreducible complexity—a mechanical mousetrap—as well as contentions that the evolutionary literature already has seriously addressed the problems I raised.

I. "A True Acid Test"

A. Summary

Here I reply to what I consider to be the most important claim made by any critic of intelligent design: that direct experimental evidence has shown that evolution can indeed generate irreducibly complex biochemical systems. As I will show below, the claim is false.

Briefly, in his book *Finding Darwin's God* (Miller 1999) Kenneth Miller quite rightly says that a "true acid test" of Darwinism is to see if it could regenerate an irreducibly complex system that was knocked out using the tools of molecular biology. He then discusses work from the laboratory of Barry Hall of the University of Rochester on the lac operon of the bacterium *E. coli*. Miller strongly implies that natural selection pieced together the whole pathway in Hall's experiments, but in fact it only replaced one component (and even then it could only replace the component with a spare near-copy of the original component). When two or more components were deleted, or when the bacterium was cultured in the absence of an artificial chemical (called IPTG), no viable bacteria could be recovered. Just as irreducible complexity would predict, when several steps must be taken at once, natural selection is a poor way to proceed.

Since Miller calls this work the "acid test", that of course means that other examples he discusses in his book are not "acid tests"; they are at best indirect arguments. The more indirect the argument, the easier for Darwinists to overlook or conceal difficulties.

B. "A True Acid Test"

Brown University cell biologist Kenneth Miller has written a book recently defending Darwinism from a variety of critics, including myself. In a chapter devoted to rebutting *Darwin's Black Box*, he marshals an array of examples which, he asserts, tell against claims of irreducible complexity. However, for all of his counterexamples I either disagree that he is dealing with irreducibly complex systems, disagree that he is focusing on the irreducibly complex aspects of a system, or disagree that his brief scenarios successfully answer the challenge of irreducible complexity (for an example, see my discussion below of his blood clotting scenario). In this section I focus on his most serious claim—that an experiment has shown natural selection can construct an irreducibly complex system.

Professor Miller correctly states that "a true acid test" of the ability of Darwinism to deal with irreducible complexity would be to "[use] the tools of molecular genetics to wipe out an existing multipart system and then see if evolution can come to the rescue with a system to replace it." (Miller 1999, 145) Therefore the most important and novel part of Miller's rebuttal is his claim that experimental work in a bacterial system has actually succeeded in producing an irreducibly complex system by natural selection. In a section entitled "Parts is Parts," in which he discusses the careful work over the past quarter-century of Barry Hall of the University of Rochester on the experimental evolution of a lactose-utilizing system in *E. coli*, Miller excitedly remarks:

> Think for a moment—if we were to happen upon the interlocking biochemical complexity of the reevolved lactose system, wouldn't we be impressed by the intelligence of its design? Lactose triggers a regulatory sequence that switches on the synthesis of an enzyme that then metabolizes lactose itself. The products of that successful lactose metabolism then activate the gene for the lac permease, which ensures a steady supply of lactose entering the cell. Irreducible complexity. What good would the permease be without the galactosidase? ... No good, of course. By the very same logic applied by Michael Behe to other systems, therefore, we could conclude that the system had been designed. Except we *know* that it was *not* designed. We know it evolved because we watched it happen right in the laboratory! (Miller 1999, 146)

I will show this picture is grossly exaggerated.

Here is a brief description of how the *lac* operon functions. The *lac* operon of *E. coli* contains genes coding for several proteins which are involved in metabolism of the disaccharide lactose. One protein of the *lac* operon, called a permease, imports lactose through the otherwise-impermeable cell membrane. Another protein is an enzyme called β-galactosidase, which can hydrolyze the disaccharide to its two constituent monosaccharides, galactose and glucose, which the cell can then process further. Because lactose is rarely available in the environment, the

bacterial cell switches off synthesis of the permease and β-galactosidase to conserve energy until lactose is available. The switch is controlled by another protein called a repressor, whose gene is located next to the operon. Ordinarily the repressor binds to the *lac* operon, shutting it off by physically interfering with expression of the operon. In the presence of the natural "inducer" allolactose (a by-product of *lac* β-galactosidase activity) or the artificial chemical inducer isopropylthiogalactoside (IPTG), however, the repressor binds to the inducer and releases the operon, allowing the *lac* operon enzymes to be synthesized by the cell.

When I first read this section of Miller's book I was quite impressed by the prospect that actual experiments—not theoretical, "just-so" stories—had produced a genuine, non-trivial counterexample to irreducible complexity. After going back to read Professor Hall's publications, however, I found that the situation was considerably different. Not only were Hall's results not what I expected based on Miller's description, in fact they fit most naturally within a framework of irreducible complexity and intelligent design. The same work that Miller points to as an example of Darwinian prowess I would cite as showing the limits of Darwinism and the need for design.

C. Adaptive Mutation

So what did Barry Hall actually do? To study bacterial evolution in the laboratory, in the mid 1970's Hall produced a strain of *E. coli* in which the gene for just the β-galactosidase of the *lac* operon was deleted. He later wrote:

> All of the other functions for lactose metabolism, including lactose permease and the pathways for metabolism of glucose and galactose, the products of lactose hydrolysis, remain intact, thus re-acquisition of lactose utilization requires only the evolution of a new β-galactosidase function. (Hall 1999)

Thus, contrary to Miller's own criterion for "a true acid test," a multipart system was not "wiped out" — only one component of a multipart system was deleted.

Without β-galactosidase, Hall's cells could not grow when cultured on a medium containing only lactose as a carbon source. However, when grown on a plate that also included alternative, useable nutrients, bacterial colonies could be established. When the other nutrients were exhausted the colonies stopped growing. However, Hall noticed that after several days to several weeks, hyphae grew on some of the colonies. Upon isolating cells from the hyphae, Hall saw that they frequently had two mutations, one of which was in a gene for a protein he called "evolved β-galactosidase," ("*ebg*") which allowed it to metabolize lactose efficiently. (Despite considerable efforts by Hall to determine it, the natural function of *ebg* remains unknown) (Hall 1999). The *ebg* gene is located in another operon, distant from the *lac* operon, and is under the control of its own repressor protein. The second mutation Hall found was always in the gene for the *ebg* repressor protein, which caused the repressor to bind lactose with sufficient strength to de-repress the *ebg* operon.
The fact that there were two separate mutations in different genes—neither of which by itself allowed cell growth (Hall 1982a)—startled Hall, who knew that the odds against the mutations

appearing randomly and independently were prohibitive (Hall 1982b). Hall's results and similar results from other laboratories led to research in the area dubbed "adaptive mutations." (Cairns 1998; Foster 1999; Hall 1998; McFadden and Al Khalili 1999; Shapiro 1997) As Hall later wrote,

> Adaptive mutations are mutations that occur in nondividing or slowly dividing cells during prolonged nonlethal selection, and that appear to be specific to the challenge of the selection in the sense that the only mutations that arise are those that provide a growth advantage to the cell. The issue of the specificity has been controversial because it violates our most basic assumptions about the randomness of mutations with respect to their effect on the cell. (Hall 1997)

The mechanism(s) of adaptive mutation are currently unknown. While they are being sorted out, it is misleading to cite results of processes which "violate our most basic assumptions about the randomness of mutations" to argue for Darwinian evolution, as Miller does.

D. A Nearly-Identical Active Site

The nature of adaptive mutation aside, a strong reason to consider the *lac*/*ebg* results quite modest is that the *ebg* proteins—both the repressor and β-galactosidase—are homologous to the *E. coli lac* proteins and overlap the proteins in activity. Both of the unmutated *ebg* proteins already bind lactose. Binding of lactose even to the unmutated *ebg* repressor induces a 100-fold increase in synthesis of the *ebg* operon. (Hall 1982a) Even the unmutated *ebg* β-galactosidase can hydrolyze lactose at a level of about 10% that of a "Class II" mutant β-galactosidase that supports cell growth. (Hall 1999) These activities are not sufficient to permit growth of *E. coli* on lactose, but they already are present. The mutations reported by Hall simply enhance pre-existing activities of the proteins. In a recent paper (Hall 1999) Professor Hall pointed out that both the *lac* and *ebg* β-galactosidase enzymes are part of a family of highly-conserved β-galactosidases, identical at 13 of 15 active site amino acid residues, which apparently diverged by gene duplication more than two billion years ago. The two mutations in ebg β-galactosidase that increase its ability to hydrolyze lactose change two nonidentical residues back to those of other β-galactosidases in ebg's phylogenetic class, so that their active sites are identical. Thus—before any experiments were done—the ebg active site was already a near-duplicate of other β-galactosidases, and only became more active by becoming a complete duplicate. Significantly, by phylogenetic analysis Hall concluded that those two mutations are the *only* ones in *E. coli* that confer the ability to hydrolyze lactose.

> The phylogenetic evidence indicates that either Asp-92 and Cys/Trp-977 are the only acceptable amino acids at those positions, or that all of the single base substitutions that might be on the pathway to other amino acid replacements at those sites are so deleterious that they constitute a deep selective valley that has not been traversed in the 2 billion years since those proteins diverged from a common ancestor. (Hall 1999)

Such results hardly support extravagant claims for the creativeness of Darwinian processes.

E. Caveats Unmentioned

A critical caveat not mentioned by Kenneth Miller is that the mutants that were initially isolated would be unable to use lactose in the wild—they required the artificial inducer IPTG to be present in the growth medium. The reason is that a permease is required to bring lactose into the cell. However, ebg only has a β-galactosidase activity, not a permease activity, so the experimental system had to rely on the pre-existing *lac* permease. Since the *lac* operon is repressed in the absence of either allolactose or IPTG, Hall decided to include the artificial inducer in all media up to this point so that the cells could grow. Thus the system was being artificially supported by intelligent intervention. Hall clearly wrote:

> At this point it is important to discuss the use of IPTG in these studies. Unless otherwise indicated, IPTG is *always* included in media containing lactose or other β-galactoside sugars. The sole function of the IPTG is to induce synthesis of the lactose permease, and thus to deliver lactose to the inside of the cell. Neither the constitutive nor the inducible evolved strains grew on lactose in the absence of IPTG. (Hall 1982b)

With further growth and selection, Hall isolated secondary mutants with improved β-galactosidase activity. These mutants all had the same two changes (mentioned above) at positions 92 and 977 of *ebg* β-galactosidase. Hall discovered that, in addition to hydrolyzing lactose, the double mutants could also synthesize some allolactose, just as the homologous *lac* β-galactosidase can do, allowing them to induce expression of the *lac* operon without further need of IPTG. Critically again, however, the *lac* permease induced by the action of the double mutant ebg is a pre-existing protein, part of the original *lac* operon, and was not produced in the experiment by the selection procedures. In the absence of that required component, the bacteria cannot use lactose.

Miller's prose ("Irreducible complexity. What good would the permease be without the galactosidase?") (Miller 1999, 146) obscures the facts that most of the system was already in place when the experiments began, that the system was carried through nonviable states by inclusion of IPTG, and that the system will not function without pre-existing components. In contrast to Miller, Hall himself is cautious and clear about the implications of his results.

> The mutations described above have been deliberately selected in the laboratory as a model for the way biochemical pathways might evolve so that they are appropriately organized with respect to both the cell and its environment. It is reasonable to ask whether this model might have any relationship to the real world outside the laboratory. If it is assumed that the selection is strictly for lactose utilization, then a growth advantage exists only when all three mutations are present simultaneously. (Hall 1982a)

Hall is nonetheless optimistic.

> Any one of the mutations alone could well be neutral (it is unlikely that any would be disadvantageous); but neutral mutations do enter populations by random chance events, and are fixed by a chance process termed genetic drift. (Hall 1982a)

However, if a mutation is not selected, the probability of its being fixed in a population is independent of the probability of the next mutation. Such a system is irreducibly complex, requiring several steps to be taken independently of each other before having selective value. If three mutations are required before there is any selective value, then the cumulative probability starts to become very small indeed, even considering the size of bacterial populations. In the present case Hall argued that a small selective value might accrue after the second mutation (in the *ebg* repressor). (Hall 1982a) However, I find his rationale unconvincing and having little experimental support. Furthermore, Professor Hall does not discuss the implications of the requirement for the preexisting *lac* permease gene.

F. Conclusion

Miller ends the section in his typical emphatic style:

> "No doubt about it—the evolution of biochemical systems, even complex multipart ones, is explicable in terms of evolution. Behe is wrong." (Miller 1999, 147)

I disagree. Leaving aside the still-murky area of adaptive mutation, the admirably-careful work of Hall involved a series of micromutations stitched together by intelligent intervention. He showed that the activity of a deleted enzyme could be replaced only by mutations to a second, homologous protein with a nearly-identical active site; and only if the second repressor already bound lactose; and only if the system were also artificially supported by inclusion of IPTG; and only if the system were also allowed to use a preexisting permease. Such results are exactly what one expects of irreducible complexity requiring intelligent intervention, and of limited capabilities for Darwinian processes.

II. In Defense of the Irreducibility of the Blood Clotting Cascade

> *A system of this kind cannot just be allowed to free-wheel. The success of the coagulation process is due to the finely tuned modulation and regulation of all of the partial proteolytic digestions that occur. Too little or too much activity would be equally damaging for the organism. Regulation is a central issue in blood coagulation*.
>
> Torben Halkier (1992, 104)

A. Summary

In *Darwin's Black Box: The Biochemical Challenge to Evolution* I devoted a chapter to the mechanism of blood clotting, arguing that it is irreducibly complex and therefore a big problem for Darwinian evolution. Since my book came out, as far as I am aware there have been no papers published in the scientific literature giving a detailed scenario or experiments to show how natural selection could have built the system. However three scientists publishing outside science journals have attempted to respond. The first is Russell Doolittle, a professor of biochemistry at the University of California at San Diego, member of the National Academy of Sciences, and expert on blood clotting. Second is Kenneth Miller, a professor of cell biology at Brown University and author of *Finding Darwin's God* (Miller 1999). The third scientist is Keith Robison, who at the time of his writing was a graduate student at Harvard University.

I will give their arguments below and my response. Here is a brief summary.

1) Professor Doolittle argued that new laboratory work showed two components of the blood clotting cascade could be eliminated ("knocked-out") from mice and the mice got along fine without them. However, Doolittle misread the laboratory work: the double knock-out mice have severe problems and have no functioning blood clotting system. They are not models of evolutionary intermediates.

   Although anyone can misread a paper, in my opinion the fact that an expert cited a recent and contradictory journal article, instead of a publication directly addressing the evolution of blood clotting, shows that there are indeed no detailed explanations for the evolution of blood clotting in the literature and that, despite Darwinian protestations, the irreducible complexity of the system is a significant problem for Darwinism.

2) Although embedded in a lengthy description of how blood clotting and other systems work, Professor Miller's actual explanation for how the vertebrate clotting cascade evolved consists of one paragraph. It is a just-so story that doesn't deal with any of the difficulties the evolution of such an intricate system would face. Even so, in the one paragraph Miller proposes what looks like a detrimental or fatal situation, akin to the knock-out mice (above) that lack critical components.

3) Keith Robison proposed that a cascade might begin with a single enzyme with three different properties. Upon duplication of the gene for the enzyme, the duplicate loses several of the properties, resulting in a two-component cascade. Repetition of the scenario builds cascades with more components. Although intriguing, the scenario starts with a complex, unjustified

situation (the enzyme with multiple abilities), that already has all necessary activities. What's more, the proposed gene duplication and several steps needed to lose function are "neutral," unselected mutations. Stringing together several very specific neutral mutations to build a complex system is vastly improbable and amounts to intelligent design.

B. Russell Doolittle's Criticism
1. Mice lacking clotting factors have severe health problems

In its issue of Feb/March 1997 *Boston Review* featured a symposium discussing *Darwin's Black Box* and Richard Dawkins' *Climbing Mount Improbable*. Among the dozen essays contributed by academics was one by University of California-San Diego biochemist Russell Doolittle (Doolittle 1997); (Prof. Doolittle's essay can be found at http://www_polisci.mit.edu/bostonreview/BR22.1/doolittle.html). I had devoted a chapter of *Darwin's Black Box* to the blood clotting cascade, asserting that it is irreducibly complex and so does not fit well within a Darwinian framework. Doolittle, an expert on blood clotting, disagreed. Prefacing a discussion of globin homology, he remarked that "the genes for new proteins come from the genes for old ones by gene duplication," later adding "This same kind of scenario can be reconstructed for a host of other physiological processes, including blood clotting." Then, citing a paper by Bugge et al. (Bugge *et al.* 1996) entitled "Loss of fibrinogen rescues mice from the pleiotropic effects of plasminogen deficiency," he commented:

> Recently the gene for plaminogen [*sic*] was knocked out of mice, and, predictably, those mice had thrombotic complications because fibrin clots could not be cleared away. Not long after that, the same workers knocked out the gene for fibrinogen in another line of mice. Again, predictably, these mice were ailing, although in this case hemorrhage was the problem. And what do you think happened when these two lines of mice were crossed? For all practical purposes, the mice lacking both genes were normal! Contrary to claims about irreducible complexity, the entire ensemble of proteins is not needed. Music and harmony can arise from a smaller orchestra. (Doolittle 1997)

The implied argument appears to be that the cited work shows the clotting system is not irreducibly complex, so a simpler clotting cascade might be something like the one that lacked plasminogen and fibrinogen, which could be expanded into the modern clotting system by gene duplication. Perhaps there are other stable systems of lesser complexity, and the entire cascade could then be built up by small steps in what is thought to be the typical Darwinian pattern. However, that interpretation depends on a mistaken reading of Bugge et al (1996).

Bugge et al. (1996) note that the lack of plasminogen in mice "results in high mortality, wasting, spontaneous gastrointestinal ulceration, rectal prolapse, and severe thrombosis. Furthermore, plasminogen-deficient mice display delayed wound healing following skin injury." On the other hand, if the gene for fibrinogen is knocked out, the result is failure to clot, frequent hemorrhage, and that "pregnancy uniformly results in fatal uterine bleeding around the tenth day of gestation." (Suh *et al.* 1995) The point of Bugge et al. (1996) was that if one crosses the two knockout strains, producing plasminogen-plus-fibrinogen deficiency in individual mice, the mice do not suffer the many problems that afflict mice lacking plasminogen alone. Since the title of the paper emphasized that mice are "rescued" from some ill-effects, one might be misled into

thinking that the double-knockout mice were normal. They are not. As Bugge et al. (1996) state in their abstract, "Mice deficient in plasminogen and fibrinogen are phenotypically indistinguishable from fibrinogen-deficient mice." In other words, the double-knockouts have all the problems that mice lacking only fibrinogen have: they do not form clots, they hemorrhage, and the females die if they become pregnant. They are definitely not "[f]or all practical purposes … normal." (Doolittle 1997) (Table 1)

Table 1. Symptoms of mice lacking clotting factors.

lacking plasminogen	lacking fibrinogen	lacking both
thrombosis	no clotting	no clotting
ulcers	hemorrhage	hemorrhage
high mortality	death in pregnancy	death in pregnancy

The probable explanation is straightforward. The pathological symptoms of only-plasminogen-deficient mice apparently are caused by uncleared clots. But fibrinogen-deficient mice cannot form clots in the first place. So problems due to uncleared clots don't arise either in fibrinogen-deficient mice or in mice that lack both plasminogen and fibrinogen. Nonetheless, the severe problems that attend lack of clotting in fibrinogen-deficient mice continue in the double knockouts. Pregnant females still perish.

An important lesson exemplified by Bugge et al. (1996) is that it can be worse for the health of an organism to have an active-but-unregulated pathway (the one lacking just plasminogen) than no pathway at all (the one lacking fibrinogen, which exhibited fewer overt problems). This emphasizes that model scenarios for the evolution of novel biochemical systems have to deal with the issue of regulation from the inception of the system. Most important for the issue of irreducible complexity, however, is that the double-knockout mice do not merely have a less sophisticated but still functional clotting system. They have no functional clotting system at all. They are not evidence for the Darwinian evolution of blood clotting. Therefore my argument, that the system is irreducibly complex, is unaffected by that example.

2. Gene Duplication is not a Darwinian Explanation

I believe that the point about the knockout mice is quite important because it helps illustrate the serious shortcomings of simple invocations of gene duplication as evolutionary explanations. Appeal to gene duplication has been quite common among scientists reviewing my book. Besides Russell Doolittle, it has been invoked by Allen Orr (Orr 1996), Douglas Futuyma (Futuyma 1997), Neil Blackstone (Blackstone 1997), Robert Dorit (Dorit 1997), a committee of

the National Academy of Sciences (National Academy 1999), and others. The typical argument goes something like this: Modern biology has recognized that the sequences and structures of some proteins are quite similar to others (an example is hemoglobin vs. myoglobin), and this similarity is normally interpreted in terms of duplication and divergence of an ancestral gene. Many proteins in complicated pathways, such as the blood clotting cascade, are also similar to other proteins, consistent with the idea that they descended from a relatively few ancestor proteins. We can assume, then, (the argument continues) that although we don't know the details, most complicated pathways were built by natural selection using gene duplication.

A recent publication of the National Academy of Sciences nicely illustrates the argument in action:

> Modern_day intelligent design proponents argue that ... molecular processes such as the many steps that blood goes through when it clots, are so irreducibly complex that they can function only if all the components are operative at once....
>
> Complex biochemical systems can be built up from simpler systems through natural selection.... Jawless fish have a simpler hemoglobin than do jawed fish, which in turn have a simpler hemoglobin than mammals.…
>
> Genes can be duplicated, altered, and then amplified through natural selection. The complex biochemical cascade resulting in blood clotting has been explained in this fashion.
>
> (National Academy of Sciences 1999, 21-22)

But the reaction to Bugge et al. (1996) is a paradox for the typical argument. On the one hand, structural and sequence evidence for gene duplication and domain swapping in the clotting cascade is very clear. So clear, in fact, that cascade proteins are used as textbook examples of those processes (Li 1997). On the other hand, if there were indeed a robust Darwinian explanation for the origin of blood clotting by natural selection, or if sequence analyses had demonstrated how gene duplication might have produced the cascade, it would be difficult to understand why one would point to the knockout mice as exemplifying Darwinian possibilities, when in reality they only underscore the serious problems facing the evolution of irreducibly complex systems. Detailed knowledge of the sequence, structure, and function of the proteins of the clotting cascade did not prevent a wholly unviable model from being proposed as a potential evolutionary intermediate. Why not?

The predicament is easily resolved when a critical point is recalled: **EVIDENCE OF COMMON DESCENT IS NOT EVIDENCE OF NATURAL SELECTION**. Homologies among proteins (or organisms) are the evidence for descent with modification—that is, for evolution. Natural selection, however, is a proposed explanation for how evolution might take place—its mechanism—and so must be supported by other evidence if the question is not to be begged. This, of course, is a well-known distinction (Mayr 1991). Yet, from reviewers' responses to my book, the distinction is often overlooked. Knowledge of homology is certainly very useful, can give us a good idea of the path of descent, and can constrain our hypotheses. Nonetheless, knowledge of the sequence, structure, and function of relevant proteins is by itself insufficient to justify a claim that evolution of a particular complex system occurred by natural selection. Gene

duplication is not a Darwinian explanation because duplication points only to common descent, not to the mechanism of evolution.

3. What Would an Explanation Look Like?

If homology is not sufficient to justify a Darwinian conclusion, what is? The required amount of justification depends on the complexity of the system under consideration. For example, the task of getting from a simple oxygen-binding protein such as myoglobin, with one chain, to hemoglobin, with four chains that bind oxygen, does not appear to present substantial problems, as I discussed in *Darwin's Black Box*. In both cases the proteins simply bind oxygen, with more or less affinity, and neither globin has to interact critically with other proteins in a complex system. There seems to be a straightforward pathway of association leading from a simple myoglobin-like protein to a more complex hemoglobin-like one. In fact, its relative simplicity is probably the reason it is a favorite example in discussions of evolution by gene duplication.

Like hemoglobin/myoglobin, many proteins of the clotting cascade are similar to each other, and also similar to non-cascade proteins. So they too appear to have arisen by some process of gene duplication. I agree this is a good hypothesis. But does gene duplication lead straightforwardly to the blood clotting cascade? No. The important point to keep in mind is that a duplicated gene is simply a copy of the old one, with the same properties as the old one—it does not acquire sophisticated new properties simply by being duplicated. In order to understand how the present-day system got here, an investigator would have to explain how the duplicated genes acquired their new, sophisticated properties.

With clotting, however, the task of initiating and adding proteins to the cascade appears to be quite problematic. With one protein acting on the next, which acts on the next, and so forth, duplicating a given protein doesn't yield a new step in the cascade. Both copies of the duplicated protein would have the same target protein which they activate, and would themselves be activated by the same protein as before. In order to explain how the cascade arose, therefore, an investigator would have to propose a detailed route whereby a duplicated protein turns into a step in the cascade, with a new target, and a new activator. Furthermore, because clotting can easily go awry and cause severe problems when it is uncontrolled, a serious model for the evolution of blood clotting would have to include such things as: a quantitative description of the starting state, including tangentially interacting systems; a description of the initial regulatory mechanisms; a quantitatively-justified proposal for a step-by-step route to the new state; a detailed plan for how regulatory mechanisms accommodated the changes; and more.

An alternative to presenting an exhaustively detailed model would be an experimental demonstration of the capability of natural selection to build a system whose complexity rivals that of the clotting cascade. In fact, experimental evidence is much preferred to mere model building, since it would be extremely difficult for models to predict whether proposed changes in complex systems might have unforeseen detrimental effects.

I pointed out in *Darwin's Black Box* that scenarios for the origin of biochemical systems lack essential detail. But since I am a proponent of an alternative explanation, some Darwinists have accused me of setting the evidentiary standard so high that it is impossible for them to meet it.

The evidentiary standard, however, is set not by me, but by the complexity of the biochemical systems themselves. If malfunctioning of the blood clotting cascade or other complex system can cause a severe loss of fitness, then a Darwinian scheme for its evolution must show how this could be avoided. And if the system can malfunction when small details go awry, then the scheme has to be justified at least to the level of those details. Unless that is done, we remain at the level of speculation.

In noting that not much research has been done on the Darwinian evolution of irreducibly complex biochemical systems, I should emphasize that I do not prefer it that way. I would sincerely welcome more investigation of their supposed Darwinian origins. I fully expect that, as in the field of origin of life studies, the more we know, the more difficult the problem will be recognized to be.

C. Kenneth Miller's Criticism

1. "From that point on ..."

If an eminent scientist and expert on blood clotting such as Russell Doolittle does not know how blood clotting arose, nobody knows. Nonetheless, it is instructive to look at how several other scientists have addressed the issue. In this section I examine Kenneth Miller's writing.

In the chapter of *Finding Darwin's God* (Miller 1999) which defends Darwinism from my criticisms, Professor Miller devotes the largest part—fully nine pages—to blood clotting. During the first five pages he gives an overview of how the blood clotting cascade works, as well as noticing that bleeding can be slowed by platelet aggregation, which is not a part of the clotting cascade. In the next two pages he writes of the sequence similarity of clotting factors and the phenomenon of gene duplication—facts well known to Russell Doolittle. In the final several pages he writes of a totally unrelated clotting system, that of lobsters. In other words, *Miller spends almost all of the space writing about things other than how the vertebrate blood clotting cascade may have arisen step-by-Darwinian-step*.

His proposed model for the evolution of the vertebrate cascade is confined to just one paragraph. After postulating that, when a blood vessel breaks and they enter the new environment of a tissue, some blood proteins might be non-specifically cut by serine proteases and non-specifically aggregate, Miller writes:

> What happened next? ... A series of ordinary gene duplications, many millions of years ago, copied some of these serine proteases. One of these duplicate genes was then mistargeted to the bloodstream, where its protein product would have remained inactive until exposed to an activating tissue protease—which would happen only when a blood vessel was broken. From that point on, each and every refinement of this mechanism would be favored by natural selection. Where does the many-layered complexity of the system come from? Again, the answer is gene duplication. Once an extra copy of one of the clotting protease genes becomes available, natural selection will favor slight changes

> that might make it more likely to activate the existing protease. An extra level of control is thereby added, increasing the sensitivity of the cascade.
>
> (Miller 1999, 156-157)

Let's start with the last half of the paragraph ("From that point on..." and forward). The first thing to notice is that it's terminally fuzzy—too sketchy for much criticism. As I explained above, simply chanting "gene duplication" does not show how a complex system can be built, since duplication does not explain how new enzyme properties and targets arise. Russell Doolittle knew all about gene duplication, and yet postulated as a model for an evolutionary intermediate mice that turned out to be severely disabled. Professor Miller simply tries to use the term "gene duplication" as a magic wand to make the problem go away, but the problem does not go away. Miller's assertion that natural selection would favor each additional step is made quite problematic by the fact that each step in clotting has to be strictly regulated or else it is positively dangerous, as noted by Torben Halkier in the opening quotation of this document. In other words, what Halkier calls the "central issue" of regulation is ignored by Miller. Miller's statement does not even say what the newly duplicated proteases are envisioned to be acting on—whether the tissue protease, the original mistargeted circulating protease, plasma proteins, or everything at once.

Such a brief story is of no use at all in understanding how the irreducible complexity of the clotting cascade could be dealt with by natural selection. It strikes me that the main purpose of the paragraph is not to actually contribute to our understanding of how clotting actually may have arisen, but to persuade those who aren't familiar with biochemical complexity to believe Darwinism has the problem under control. It doesn't.

2. Problems from the get-go

Now lets's look at the beginning of Miller's scenario. It turns out that as soon as he tries to get past the simple postulated beginning (that is, the nonspecific aggregation of proteins that have been nonspecifically degraded when a blood vessel is broken) his scenario runs into severe problems.

Miller's first step postulates a potentially deadly situation: a *non-regulated* zymogen circulating in the bloodstream with clottable proteins. Although we don't have access to Miller's imaginary organism to test the effects of this situation, to understand what it might mean we can look to several cases situations where regulatory proteins are missing from modern organisms: 1) Because the condition is very likely lethal in utero, no cases have been reported in the medical literature (Scriver 1989, 2213) of human patients missing antithrombin, a prominent regulator of the clotting cascade; 2) As described earlier, knockout mice missing the gene for plasminogen to remove blood clots suffer severe thrombosis and increased mortality, as well as other debilitating symptoms. (Bugge *et al.* 1995) It seems quite likely that Miller's hypothetical organism would experience the unregulated zymogen not as an improvement, but as a severe genetic defect.

Regulation is the *key issue* in clotting, but Miller does not address it at all. Miller's brief scenario does not even address potentially fatal difficulties— it ignores them. However, while Darwinists telling just-so stories can ignore difficulties, real organisms can't.

Here are several more problems with the brief scenario. First, it should be noted that the problem the scenario is trying to solve—hemostasis—can't initially be severe, because the starting point is a living organism, which must already be quite well adjusted to its environment. Second, the protein that Miller postulates to be mistargeted to the bloodstream would then no longer be doing its initial job; that would be expected to be detrimental to the organism. Third, Miller begins by postulating the mistargeting of a *non-specific* protease-precursor (a zymogen) to the bloodstream of some unfortunate organism. (Miller writes that if his scenario is correct, then "the clotting enzymes would have to be near-duplicates of a pancreatic enzyme..." (Miller 1999, 157) Pancreatic enzymes, which have to digest a wide variety of protein foodstuffs, are among the most nonspecific of enzymes). Now, that would pose a severe health threat to the mutant organism even greater than just an unregulated clotting cascade. For example, if the digestive enzyme precursor trypsinogen were mistargeted to the bloodstream, the potential for disaster would be very large. In the pancreas, misactivation of trypsinogen is prevented by the presence of trypsin inhibitor. In Miller's scenario one cannot plausibly suppose there to be a trypsin inhibitor fortuitously circulating in the plasma. If the mistargeted enzyme were accidentally activated, it would most likely cause generalized damage in the absence of a regulatory mechanism. It would not be a viable evolutionary intermediate.

Problems of regulation aside, it is difficult to see the advantage of the protease mistargeted to the bloodstream in the first place. While Miller's initial cellular or tissue protease would by necessity be localized to the site of a cut, a circulating zymogen would not. In modern organisms thrombinogen has a vitamin K-dependent gla-domain which allows it to localize to cell surfaces. In order to be effective before membrane-binding features had been acquired, it would seem that the postulated circulating protease would have to be present at rather high concentrations, exacerbating the regulatory difficulties discussed above.

As I wrote in *Darwin's Black Box* (Behe 1996, 86), the problem of blood clotting is not in just forming a clot—any precipitated protein might plug a hole. Rather the problem is *regulation*. The regulatory problems of the clotting cascade are particularly severe since, as pointed out by Halkier (1992, 104), error on either side—clotting too much or too little—is detrimental. As irreducible complexity would predict, Kenneth Miller's scenario has no problem postulating a simple clot (the initial nonspecific aggregation) but avoids the problem of regulation.

The take-home lesson is that Miller doesn't deal with the problem of irreducible complexity and other obstacles that I pointed out in *Darwin's Black Box*—he just ignores them.

D. Keith Robison's Proposal

Soon after *Darwin's Black Box* was published Keith Robison posted some criticisms on talk.origin (www.talkorigins.org/faqs/behe/review.html), one of which concerned the blood clotting cascade. I think his proposed scheme for adding steps to cascades, while it doesn't work, is the most serious and interesting one I have come across (grad students often come up with the best ideas). It spurred me to think more about the situation and has led me to formulate the concept of irreducible complexity in more explicitly evolutionary terms.

Robison's proposal was not focused on blood clotting per se, so he doesn't worry about forming a clot. Rather he concentrates on how new steps might be added to a cascade such as occurs in blood clotting, as well as other systems such as complement. His starting point is a rather complex one, which I will grant for purposes of argument. He postulates a protein X which already has three pertinent properties: 1) it is activated by some external factor (perhaps by tissue trauma); 2) the activated protein X* then can activate more X by hydrolysis; and 3) activated X* cleaves some additional target. It's pretty much a cascade all by itself.

Fine, let's start there. Now begins the interesting scenario that I'll contest. To build a new step in the cascade, Robison then postulates several further steps. First is an initial gene duplication. Both genes make X, and the X from either gene when activated can activate the other. The second postulated event is a mutation in just one of the X genes that causes it to lose the ability to interact with the target. Nonetheless, it retains the ability to activate itself and the X coded by the original gene. The third step is loss of the yet-unmutated protein's ability to either respond to the external factor or activate itself and the other protein. At the end we have one of the proteins responsive to the external factor and able to activate both itself and the second protein, and just the second protein is able to cleave the target. Replication of the scenario yields more steps in the cascade, building irreducible complexity.

I argue that, while Robison's scenario does indeed build a new step in the cascade, it doesn't do it by Darwinian means. Rather, it does so by Robison's intelligent direction. Here are a couple pertinent quotes from the several steps of his scenario (Robison 1996): "This arrangement is neutral; the species has gained no advantage."; "Again, this genotype is neutral; it is neither beneficial nor detrimental."; "The initial steps are neutral, neither advantageous nor disadvantageous." "The final step locks in the cascade. It is *potentially* advantageous ...." (my emphasis—the "potentially" advantageous final step would require a further mutation to make it actually advantageous, so before that happens it is neutral.).

Thus his scenario postulates four successive, very specific steps: 1) gene duplication of the particular multi-talented enzyme; 2) the first loss of function step; 3) the second loss of function step; 4) a step to take advantage of the situation. As Robison emphasized, the first three steps are neutral; that is, they do the organism neither harm nor good. Only when the fourth step is completed is there a selective advantage. Now, it must be remembered that the Darwinian magic depends on natural selection. If a trait is advantageous, it will take over a population, thus providing a large base from which the next advantageous mutation might arise. However, if a trait is neutral, providing no advantage, it is far, far less likely to spread, so the odds of a second mutation appearing that depends on the first are not improved at all—they're pretty much the same as luckily getting the two specific mutations simultaneously. In the final analysis Robison's scenario is completely non-Darwinian. It postulates an already-functioning system that wasn't justified in Darwinian terms, and it then goes through three neutral, non-selected steps. Only at the very end is there a selectable property that wasn't postulated at the beginning.

To get a flavor of the difficulties Robison's scenario faces, note that standard population genetics says that the rate at which neutral mutations become fixed in the population is equal to the mutation rate. Although the neutral mutation rate is usually stated as about 10^{-6} per gene per

generation, that is for any random mutation in the gene. When one is looking at particular mutations such as the duplication of a certain gene or the mutation of one certain amino acid residue in the duplicated gene, the mutation rate is likely about 10^{-10}. Thus the fixation of just one step in the population for the scenario would be expected to occur only once every ten billion generations. Yet Robison' scenario postulates multiple such events.

E. A Modest Conclusion

I would like to pause here for a moment to point out that all three scientists who tried to meet the challenge to Darwinian evolution of blood clotting—Russell Doolittle, Kenneth Miller, and Keith Robison—foundered on exactly the same point, the point of irreducible complexity. Yet they foundered in three different ways. Doolittle mistakenly thought that even the current cascade might not be irreducibly complex, but experimental results showed him to be wrong. Miller either proposed unregulated steps or just waved his hands and shouted "gene duplication", avoiding the problem by obfuscation. Robison directly attacked a piece of the problem, but failed to see he was intelligently guiding events in a distinctly non-Darwinian scenario. Perhaps we may be allowed to conclude that when three scientists, highly intelligent and strongly motivated to discredit it, all come up empty, that irreducible complexity is indeed a big hurdle for Darwinism.

F. An Evolutionary Perspective on Irreducible Complexity

In *Darwin's Black Box* I defined the concept of irreducible complexity (IC) in the following way.

> By irreducibly complex I mean a single system which is composed of several well-matched, interacting parts that contribute to the basic function, and where the removal of any one of the parts causes the system to effectively cease functioning.
>
> (Behe 1996, 39)

While I think that's a reasonable definition of IC, and it gets across the idea to a general audience, it has some drawbacks. It focuses on already-completed systems, rather than on the process of trying to build a system, as natural selection would have to do. It emphasizes "parts", but says nothing about the properties of the parts, how complex they are, or how the parts get to be where they are. It speaks of "parts that contribute to the basic function", but that phrase can, and has, been interpreted in ways other than what I had in mind (for example, talking about whole organs that contribute to complex functions such as "living"), muddying the waters in my view. What's more, the definition doesn't allow for "degree" of irreducible complexity; a system either has it or it doesn't. Yet certainly some IC systems are more complex than others; some seem more forbidding than others.

While thinking of Keith Robison's scenario, I was struck that irreducible complexity could be better formulated in evolutionary terms by focusing on a proposed *pathway*, and on whether each step that would be necessary to build a certain system using that pathway was selected or unselected. If a system has to pass through one unselected step on the way to a particular

improvement, then in a real evolutionary sense it is encountering irreducibility: two things have to happen (the mutation passing through the unselected step and the mutation that gives a selectable system) before natural selection can kick in again. If it has to pass through three or four unselected steps (like Robison's scenario), then in an evolutionary sense it is even more irreducibly complex. The focus is off of the "parts" (whose number may stay the same even while the nature of the parts is changing) and re-directed toward "steps".

Envisioning IC in terms of selected or unselected steps thus puts the focus on the process of trying to build the system. A big advantage, I think, is that it encourages people to pay attention to details; hopefully it would encourage really detailed scenarios by proponents of Darwinism (ones that might be checked experimentally) and discourage just-so stories that leap over many steps without comment. So with those thoughts in mind, I offer the following tentative "evolutionary" definition of irreducible complexity:

> An irreducibly complex evolutionary pathway is one that contains one or more unselected steps (that is, one or more necessary-but-unselected mutations). The degree of irreducible complexity is the number of unselected steps in the pathway.

That definition has the advantage of promoting research: to state clear, detailed evolutionary pathways; to measure probabilistic resources; to estimate mutation rates; to determine if a given step is selected or not. It allows for the proposal of any evolutionary scenario a Darwinist (or others) may wish to submit, asking only that it be detailed enough so that relevant parameters might be estimated. If the improbability of the pathway exceeds the available probabilistic resources (roughly the number of organisms over the relevant time in the relevant phylogenetic branch) then Darwinism is deemed an unlikely explanation and intelligent design a likely one.

III. Irreducible Complexity and the Evolutionary Literature

A. Summary

Although several persons have cited numerous references from the scientific literature purporting to show that the problem of irreducible complexity I pointed out in *Darwin's Black Box* is being seriously addressed, the references show no such thing. Invariably the cited papers or books either deal with non-irreducibly complex biochemical systems, or do not deal with them in enough detail for critical evaluation. I strongly emphasize, however, that I do not prefer it that way. I would sincerely welcome much more serious, sustained research in the area of irreducible complexity. I fully expect such research would heighten awareness of the difficulties of Darwinian evolution.

B. Web Spinners

The necessary starting point of *Darwin's Black Box* was the contention that, despite the common assumption that natural selection accounts for adaptive complexity, the origins of many intricate

cellular systems have not yet been explained in Darwinian terms. After all, if the systems have already been explained, then there's no need to write. While most scientist-reviewers disagreed (often emphatically) with my proposal of intelligent design, most also admitted to a lack of Darwinian explanations. For example, microbiologist James Shapiro of the University of Chicago declared in *National Review* that "There are no detailed Darwinian accounts for the evolution of any fundamental biochemical or cellular system, only a variety of wishful speculations." (Shapiro 1996) In *Nature* University of Chicago evolutionary biologist Jerry Coyne stated, "There is no doubt that the pathways described by Behe are dauntingly complex, and their evolution will be hard to unravel. ... [W]e may forever be unable to envisage the first proto-pathways." (Coyne 1996) In a particularly scathing review in *Trends in Ecology and Evolution* Tom Cavalier-Smith, an evolutionary biologist at the University of British Columbia, nonetheless wrote, "For none of the cases mentioned by Behe is there yet a comprehensive and detailed explanation of the probable steps in the evolution of the observed complexity. The problems have indeed been sorely neglected — though Behe repeatedly exaggerates this neglect with such hyperboles as 'an eerie and complete silence.'" (Cavalier-Smith 1997) Evolutionary biologist Andrew Pomiankowski agreed in *New Scientist*, "Pick up any biochemistry textbook, and you will find perhaps two or three references to evolution. Turn to one of these and you will be lucky to find anything better than 'evolution selects the fittest molecules for their biological function.'" (Pomiankowski 1996) In *American Scientist* Yale molecular biologist Robert Dorit averred, "In a narrow sense, Behe is correct when he argues that we do not yet fully understand the evolution of the flagellar motor or the blood clotting cascade." (Dorit 1997)

A prominent claim I made in *Darwin's Black Box* is that, not only are irreducibly complex biochemical systems unexplained, there have been very few published attempts even to try to explain them. This contention has been vigorously disputed not so much by scientists in the relevant fields as by Darwinian enthusiasts on the Internet. Several web-savvy fans of natural selection have set up extensive, sophisticated sites that appear to receive a significant amount of notice. They influence college students, reporters, and, sometimes, academic reviewers of my book such as Cal State-Fullerton biochemist Bruce Weber, who lists the addresses of the web sites in his review in *Biology and Philosophy* as "summaries of the current research that Behe either missed or misrepresented" (Weber 1999), and Oxford physical chemist Peter Atkins, who writes:

> Dr. Behe claims that science is largely silent on the details of molecular evolution, the emergence of complex biochemical pathways and processes that underlie the more traditional manifestations of evolution at the level of organisms. Tosh! There are hundreds, possibly thousands, of scientific papers that deal with this very subject. For an entry into this important and flourishing field, and an idea of the intense scientific effort that it represents (see the first link above) [*sic*]. (Atkins 1998)

The link Atkins refers to is a web-site called "Behe's Empty Box" (www.world-of-dawkins.com/box/behe.htm) that has been set up by a man named John Catalano, an admirer of Oxford biologist Richard Dawkins (his larger site is devoted to Dawkins' work, schedule, etc.). The Empty Box site is, I think, actually a valuable resource, containing links to many reviews, comments and other material, both critical and favorable, related to my book. One subsection of the site is entitled "Alive and Published," and contains citations to a large number of papers and

books which Catalano believes belie my claim that "There has never been a meeting, or a book, or a paper on details of the evolution of complex biochemical systems." (Behe 1996) (p. 179) The citations were solicited on the web from anyone who had a suggestion, and then compiled by Catalano.

Something, however, seems to be amiss. The assertion here that very many papers have been published clashes with statements of the reviews I quoted earlier which say, for example, that "The problems have indeed been sorely neglected." (Cavalier-Smith 1997) Would reviewers such as Jerry Coyne and Tom Cavalier-Smith—both antagonistic to my proposal of intelligent design—be unaware of the "hundreds, possibly thousands, of scientific papers that deal with this very subject"? Both claims—that the problems have been neglected and that the problems are being actively investigated—cannot be correct. Either one set of reviewers is wrong, or there is some confusion about which publications to count. Which is it?

In the context of my book it is easy to realize that I meant there has been little work on the details of the evolution of irreducibly complex biochemical systems by Darwinian means. I had clearly noted that of course a large amount of work in many books and journals was done under the general topic of "molecular evolution," but that, overwhelmingly, it was either limited to comparing sequences (which, again, does not concern the mechanism of evolution) or did not propose sufficiently detailed routes to justify a Darwinian conclusion. Yet the Catalano site lists virtually any work on evolution, whether it pertains to irreducible complexity or not. For example it lists semi-popular books such as *Patterns in Evolution: The New Molecular View* by Roger Lewin, and general textbooks on molecular evolution such as *Molecular Evolution* by Wen-Hsiung Li.

Such books simply don't address the problems I raise. *Molecular Evolution* by Wen-Hsiung Li (Li 1997) is a fine textbook which does an admirable job of explicating current knowledge of how genes change with time. That knowledge, however, does not include how specific, irreducibly-complex biochemical systems were built. The text contains chapters on the molecular clock, molecular phylogenetics, and other topics which essentially are studies in comparing gene sequences. As I explained in *Darwin's Black Box*, comparing sequences is interesting but cannot explain how molecular machines arose. Li's book also contains chapters on the mechanisms (such as gene duplication, domain shuffling, and concerted evolution of multigene families) that are thought to be involved in evolution at the molecular level. Again, however, no specific system is justified in Darwinian terms.

Here is an illustration of the problem. Li spends several pages discussing domain shuffling in the proteins of the blood clotting cascade (Li 1997). However, Li himself has not done work on understanding how the obstacles to the evolution of the clotting cascade may have been circumvented. Since those investigators who do work in that area have not yet published a detailed Darwinian pathway in the primary literature, we can conclude that the answer will not be found in a more general text. We can further assume that the processes that text describes (gene duplication, etc.), although very significant, are not by themselves sufficient to understand how clotting, or by extension any complex biochemical system, may have arisen by Darwinian means.

Catalano's site lists other books that I specifically discussed in *Darwin's Black Box*, where I noted that, while they present mathematical models or brief general descriptions, they do not present detailed biochemical studies of specific irreducibly complex systems. (Gillespie 1991; Selander *et al.* 1991) There is no explanation on Catalano's web site of why he thinks they address the questions I raised. The site also points to papers with intriguing titles, but which are studies in sequence analysis, such as "Molecular evolution of the vertebrate immune system" (Hughes and Yeager 1997) and "Evolution of chordate actin genes: evidence from genomic organization and amino acid sequences." (Kusakabe *et al.* 1997) As I explained in *Darwin's Black Box*, sequence studies by themselves can't answer the question of what the mechanism of evolution is. Catalano's compendium also contains citations to papers concerning the evolution of non-irreducibly complex systems, such as hemoglobin and metabolic pathways, which I specifically said may have evolved by natural selection. (Behe 1996) (pp. 150-151; 206-207)

C. Equivocal Terms

Another website that has drawn attention (as evidenced from the inquiries I receive soliciting my reaction to it) is authored by David Ussery (Ussery 1999), associate research professor of biotechnology at The Technical University of Denmark. One of his main goals is to refute my claim concerning the dearth of literature investigating the evolution of irreducibly complex systems. For example, in a section on intracellular vesicular transport he notes that I stated in *Darwin's Black Box* that a search of a computer database "to see what titles have both *evolution* and *vesicle* in them comes up completely empty." (Behe 1996) (p. 114) My search criterion, of having both words in the title, was meant to be a rough way to show that nothing much has been published on the subject. Ussery, however, writes that, on the contrary, a search of the PubMed database using the words evolution and vesicle identifies well over a hundred papers. Confident of his position, he urges his audience, "But, please, don't just take my word for it — have a look for yourself!" (Ussery 1999)

The problem is that, as I stated in the book, I had restricted my search to the *titles* of papers, where occurrence of both words would probably mean they concerned the same subject. Ussery's search used the default PubMed setting, which also looks in abstracts. [In a later version of his review (the Web site has been updated several times, making it a moving target that is hard to pin down precisely), Ussery did note explicitly that one needed to search abstracts as well as titles to come up with the total of 130 papers. He then noted that a total of just four papers have both words in the title. These papers were not picked up in my search because they either were published after my search was completed in 1995, or because the papers were published before the mid 1980s (which is outside the scope of a CARL search). None of the papers affects the questions discussed in this manuscript.] By doing so he picked up papers such as "Outbreak of nosocomial diarrhea by *Clostridium difficile* in a department of internal medicine." (Ramos *et al.* 1998) This paper discusses the "clinical evolution" (i.e., course of development) of diarrhea in hospitalized patients, who also had "vesicle catherization." Not only do the words evolution and vesicle in this paper not refer to each other, the paper does not even use the words evolution and vesicle in the same sense as I did. Since the word evolution has

many meanings, and since the word vesicle can mean just a container (like the word "box"), Ussery picked up equivocal meanings.

The paper cited above shows Ussery's misstep in an obvious way. However, there are other papers resulting from an Ussery-style search where, although they do not address the question I raised, the unrelatedness is not so obvious to someone outside the field. An example of a paper that is harder for someone outside the field to evaluate is "Evolution of the trappin multigene family in the *Suidae*." (Furutani *et al.* 1998) The authors examine the protein and gene sequences for a group of secretory proteins (the trappin family) which "have undergone rapid evolution" and are similar to "seminal vesicle clotting proteins." The results may be interesting, but the seminal vesicle is a pouch in the male reproductive tract for storing semen—not at all the same thing as the vesicle in which intracellular transport occurs. And trappins are not involved in intracellular transport.

A second example is "Syntaxin-16, a putative Golgi t-SNARE." (Simonsen *et al.* 1998) This paper actually does concern a protein involved in intracellular vesicular transport. However, as the abstract states, "Database searches identified putative yeast, plant and nematode homologues of syntaxin-16, indicating that this protein is conserved through evolution." The database searches are sequence comparisons. Once again I reiterate, sequence comparisons by themselves cannot tell us how a complex system might have arisen by Darwinian means.

Instead of listing further examples let me just say that I have not seen a paper using Ussery's search criteria that addresses the Darwinian evolution of intracellular vesicular transport in a detailed manner, as I had originally asserted in my book.

It is impossible for me to individually address the "hundreds, possibly thousands" of papers listed in these web sites. But perhaps I don't have to. If competent scientists who are not friendly to the idea of intelligent design nonetheless say that "There are no detailed Darwinian accounts for the evolution of any fundamental biochemical or cellular system, only a variety of wishful speculations," (Shapiro 1996) and that "We may forever be unable to envisage the first proto-pathways" (Coyne 1996), then it is unlikely that much literature exists on these problems. So after considering the contents of the web sites, we can reconcile the review of Peter Atkins with those of other reviewers. Yes, there are a lot of papers published on "molecular evolution," as I had clearly acknowledged in *Darwin's Black Box*. But very few of them concern Darwinian details of irreducibly complex systems, which is exactly the point I was making.

D. Kenneth Miller

In *Finding Darwin's God* (Miller 1999) Kenneth Miller is also anxious to show my claims about the literature are not true (or at least are not true now, since the handful of papers he cites in his section "The Sound of Silence" were published after my book appeared). Yet none of the papers he cites deals with irreducibly complex systems.

The first paper Miller discusses concerns two structurally-similar enzymes, both called isocitrate dehydrogenase. The main difference between the two is simply that one uses the organic cofactor

NAD while the other uses NADP. The two cofactors are very similar, differing only in the presence or absence of a phosphate group. The authors of the study show that by mutating several residues in either enzyme, they can change the specificity for NAD or NADP. (Dean and Golding 1997) Although the study is very interesting, at the very best it is microevolution of a single protein, not an irreducibly complex system.

The next paper Miller cites concerns "antifreeze" proteins. (Logsdon and Doolittle 1997) Again, these are single proteins that do not interact with other components; they are not irreducibly complex. In fact, they are great examples of what I agree evolution can indeed do—start with a protein that accidentally binds something (ice nuclei in this case, maybe antibiotics in another case) and select for mutations that improve that property. But they don't shed light on irreducibly complex systems.

Another paper Miller cites concerns the cytochrome *c* oxidase proton pump (Musser and Chan 1998), which is involved in electron transfer. In humans six proteins take part in the function; in some bacteria fewer proteins are involved. While quite interesting, the mechanism of the system is not known in enough detail to understand what's going on; it remains in large part a black box. Further, the function of electron transfer does not necessarily require multiple protein components, so it is not necessarily irreducibly complex. Finally, the study is not detailed enough to criticize, saying things such as "It makes evolutionary sense that the cytochrome bc_1 and cytochrome *c* oxidase complexes arose from a primitive quinol terminal oxidase complex via a series of beneficial mutations." In order to judge whether natural selection could do the job, we have to know what the "series of beneficial mutations" is.

Finally Miller discusses a paper which works out a scheme for how the organic-chemical components of the tricarboxylic acid (TCA) cycle, a central metabolic pathway, may have arisen gradually. (Melendez-Hevia *et al.* 1996) There are several points to make about it. First, the paper deals with the chemical interconversion of organic molecules, not the enzymes of the pathway or their regulation. As an analogy, suppose someone described how petroleum is refined step by step, beginning with crude oil, passing through intermediate grades, and ending with, say, gasoline. He shows that the chemistry of the processes is smooth and continuous, yet says nothing about the actual machinery of the refinery or its regulation, nothing about valves or switches. Clearly that is inadequate to show refining of petroleum developed step by step. Analogously, someone who is seriously interested in showing that a metabolic pathway could evolve by Darwinian means has to deal with the enzymic machinery and its regulation.

The second and more important point is that, while the paper is very interesting, it doesn't address irreducible complexity. Either Miller hasn't read what I said in my book about metabolic pathways, or he is deliberately ignoring it. I clearly stated in *Darwin's Black Box* metabolic pathways are *not* irreducibly complex (Behe 1996) (pp. 141-142; 150-151), because components can be gradually added to a previous pathway. Thus metabolic pathways simply aren't in the same category as the blood clotting cascade or the bacterial flagellum. Although Miller somehow misses the distinction, other scientists do not. In a recent paper Thornhill and Ussery write that something they call serial-direct-Darwinian-evolution "cannot generate irreducibly complex structures." But they think it may be able to generate a reducible structure, "such as the TCA cycle (Behe, 1996 a, b)." (Thornhill and Ussery 2000) In other words Thornhill and Ussery

acknowledge the TCA cycle is not irreducibly complex, as I wrote in my book. Miller seems unable or unwilling to grasp that point.

IV. A Mousetrap Defended

A. Introduction

In *Darwin's Black Box: The Biochemical Challenge to Evolution* I coined the term "irreducible complexity" in order to point out an apparent problem for the Darwinian evolution of some biochemical and cellular systems. In brief, an irreducibly complex system is one that needs several well-matched parts, all working together, to perform its function. The reason that such systems are headaches for Darwinism is that it is a gradualistic theory, wherein improvements can only be made step by tiny step, with no thought for their future utility. I argued that a number of biochemical systems, such as the blood clotting cascade, intracellular transport system, and bacterial flagellum are irreducibly complex and therefore recalcitrant to gradual construction, and so they fit poorly within a Darwinian framework. Instead I argued they are best explained as the products of deliberate intelligent design.

In order to communicate the concept to a general audience, I used a mousetrap as an example of an irreducibly complex system in everyday life. The mousetrap I pictured in my book had a number of parts that all had to work together to catch mice. The usefulness of the mousetrap example was that it captured the essence of the problem I saw for gradualistic evolution at a level that could be understood by people who were unfamiliar with the fine points of protein structure and function—that is, nearly everyone. For that same reason, defenders of Darwinism have assailed it. Although it may seem silly to argue over a mousetrap, it is actually critical to allowing people who are not professional scientists to understand the issues involved. In this article I defend the mousetrap as an example of irreducible complexity that can't be put together by a series of small undirected steps.

Mousetrap rebuttals have popped up in a variety of situations including national television, but most recently (June 2000) was at a conference I attended at Concordia University in Wisconsin where Kenneth Miller, professor of biology at Brown University, spent several minutes during his presentation attacking the mousetrap. In doing so he used images of mousetraps that were drawn by Professor John McDonald of the University of Delaware and can be seen on his web site (http://udel.edu/~mcdonald/mousetrap.html; reproduced below with permission). In defense of the mousetrap I will make a number of points, including: 1) McDonald's reduced-component traps are not single-step intermediates in the building of the mousetrap I showed; 2) intelligence was intimately involved in constructing the series of traps; 3) if intelligence is necessary to make something as simple as a mousetrap, we have strong reason to think it is necessary to make the much more complicated machinery of the cell.

B. Conceptual precursors vs. physical precursors

On his web site Professor McDonald was careful to make a critical distinction. He clearly stated **"the reduced_complexity mousetraps ... are intended to point out the logical flaw in the intelligent design argument; they're not intended as an analogy of how evolution works."** Nonetheless Kenneth Miller discussed McDonald's examples in a way that would lead an audience to think that they were indeed relevant to Darwinian evolution. Only at the end of the presentation did he briefly mention the disanalogy. I believe such tactics are disingenuous at best, like tagging a brief warning onto the end of a cigarette commercial containing attractive images. The purpose of the images is to get you to buy the cigarettes, despite the warning. The purpose of citing McDonald's drawings is to get people to buy Darwinian evolution, despite the brief disclaimer.

The logical point Professor McDonald wished to make was that there are mousetraps that can work with fewer parts than the trap I pictured in my book. Let me say that *I agree completely*; in fact, I said so in my book (see below). For example, one can dig a steep hole in the ground for mice to fall into and starve to death. Arguably that has zero parts. One can catch mice with a glue trap, which has only one part. One can prop up a box with a stick, hoping a mouse will bump the stick and the box will fall on top of it. That has two parts. And so forth. There is no end to possible variation in mousetrap design. But, as I tried to emphasize in my book, the point that is relevant to Darwinian evolution is not whether one can make variant structures, but whether those structures lead, step-by-excruciatingly-tedious-Darwinian-step, to the structure I showed. I wrote:

> To feel the full force of the conclusion that a system is irreducibly complex and therefore has no functional precursors we need to distinguish between a *physical* precursor and a *conceptual* precursor. The trap described above is not the only system that can immobilize a mouse. On other occasions my family has used a glue trap. In theory at least, one can use a box propped open with a stick that could be tripped. Or one can simply shoot the mouse with a BB gun. However, these are not physical precursors to the standard mousetrap since they cannot be transformed, step-by-Darwinian-step, into a trap with a base, hammer, spring, catch, and holding bar. (Behe, 1996)

Since I agree with Professor McDonald that there could be mousetraps with fewer parts, the only relevant question is whether the mousetraps he drew are physical precursors, or merely conceptual precursors. Can they "be transformed, step-by-Darwinian-step" into the trap I pictured (essentially the same structure as the fifth trap shown below), as some people have been led to believe? No, they can't.

C. From the first trap to the second

Professor McDonald started with a complete mousetrap and then showed ones with fewer parts. I will reverse that order, start with his simplest trap, and show the steps that would be necessary to convert it into the next more complex trap in his series. That, after all, is the way Darwinian evolution would have to work. If we are to picture this as a Darwinian process, then

each separate adjustment must count as a "mutation." If several separate mutations have to occur before we go from one functional trap to the next, then a Darwinian process is effectively ruled out, because the probability of getting multiple unselected mutations that eventually lead to a specific complex structure is prohibitive. Shown below are the simplest and next-to-simplest traps.

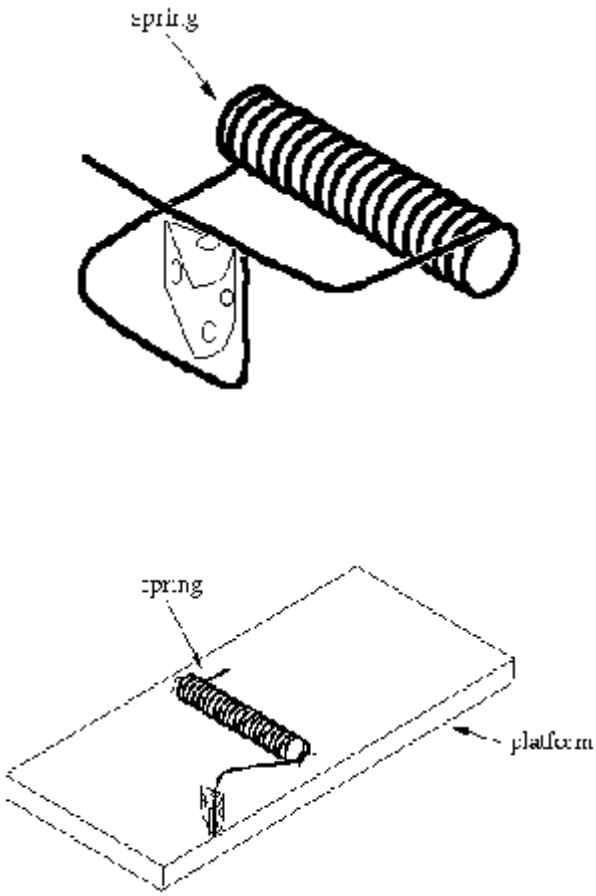

Figure 1. The first trap (top) and second trap (bottom).

The single-piece trap, consisting of just a spring with extended arms, is supposed to have one arm, under tension, propped up on the other arm. When a mouse jiggles it, the arm is released and comes down, pinning the mouse's paw against the other arm. Now, the first thing to notice is that the single piece trap isn't a simple spring—it's got a very specific structure. If the lengths of the extended ends varied by much before their first bend, or if the angle of the bends differed somewhat, the trap wouldn't work. What's more, the strength of the material out of which the spring is made has to be consonant with the purpose of catching a mouse (for example, if it were made from an old Slinky it likely wouldn't work). It is not a simple starting point; it was

intelligently selected. Nonetheless, I realize that in coming up with an analogy we have to start somewhere. So I will not complain about an intelligently-selected starting point. However, *the involvement of intelligence at any other point along the way invalidates the entire exercise* as an analogy to a Darwinian process. Because Darwinism wholly rejects intelligent direction, Darwinists must agree that the involvement of intelligence at any point in a scenario (after the agreed-on starting point) is fatal. That point occurs immediately for our mousetrap.

The second mousetrap (above) has a spring and a platform. One of the extended arms stands under tension at the very edge of the platform. The idea is that if a mouse in the vicinity jiggles the trap, the end of the arm slips over the edge and comes rushing down, and may pin the mouse's paw or tail against the platform. Now, the first thing to notice is that the arms of the spring are in a different relationship to each other than in the first trap. To get to the configuration of the spring in the second trap from the configuration in the first, it seems to me one would have to proceed through the following steps: 1) twist the arm that has one bend through about 90☜ so that the end segment is perpendicular to the axis of the spring and points toward the platform; 2) twist the other arm through about 180☜ so the first segment is pointing opposite to where it originally pointed (the exact value of the rotations depend on the lengths of the arms); 3) shorten one arm so that its length is less than the distance from the top of the platform to the floor (so that the end doesn't first hit the floor before pinning the mouse). While the arms were being rotated and adjusted, the original one-piece trap would have lost function, and the second trap would not yet be working.

At this point we bring in a new piece, the platform, which is a simple piece of wood. One now has a spring resting on top of a platform. However, the spring cannot be under tension in this configuration unless it is fixed in place. Notice that in the second mousetrap, not only has a platform been added, but two (barely visible) staples have been added as well. Thus we have gone not from a one piece to a two-piece trap, but from a one to a four piece trap. Two staples are needed; if there were only one staple positioned as drawn, the tensed spring would be able to rotate out of position. The staples have to be positioned carefully with respect to the platform. They have to be arranged within a very narrow tolerance so that one arm of the spring teeters perilously on the edge of the platform or the trap doesn't work. If either of the staples is moved significantly from where they are drawn, the trap won't function. I should add that I did not emphasize the staples in my book because I was trying to make a simple point and didn't want to exhaust the readers with tedium. However, someone who wishes to seriously propose that the mousetrap I pictured is approachable in the tiny steps required by Darwinian processes would indeed have to deal with all the details, including the staples.

It is important to remember that the placement, size, shape, or any important feature (not just "piece") of a system can't just be chosen to fit the purposes of a person who wishes to simulate a Darwinian process. Rather, each significant feature has to be justified as being a small improvement. In the real world the occasional unselected feature might occur which serendipitously will be useful in the future, but invoking more than one unselected (neutral, nonadaptive) event in a Darwinian scenario seems to me impermissible because the improbability of the joint events starts to soar. In our current case the unselected event we are allowed was used up when we began with a special starting point.

I think the problems of rearranging the already-functioning first mousetrap shows the general difficulties one expects in trying to re-arrange an already-functioning system into something else. The requirements ("selection pressures") that make a component suitable for one specialized system will generally make it unsuitable for another system without significant modification. Another problem we can note is that the second mousetrap is not an obvious improvement over the first; it is difficult to see how it would function any better than the one-piece trap. It's just that it's on the road to where we want to see the system end up—on the road to a distant target. That, of course, is intelligent direction.

The transition from the first to the second mousetrap is not analogous to a Darwinian process because: 1) a number of separate steps are required to make the transition; 2) each step has to fall within a narrow range of tolerance to get to the target trap; and 3) function is lost until the transition is completed. In fact, the situation of going from the first trap to the second trap is best viewed not as a transition, but as building a different kind of trap using some old materials from the first trap (with major modifications) and some new materials. Far from being an analogy to a Darwinian process, **the construction of the second trap is an example of intelligent design**.

D. From the second trap to the third

The way the traps are drawn (below), the transition from the second to the third trap doesn't seem to be a big step. Both drawings are superficially similar. But when one thinks about the transition in detail problems crop up. The first problem is that a new piece is added—the hammer. Unlike the platform that was added in the last transition (which I did not object to), the hammer is not a simple object. Rather it contains several bends. The angles of the bends have to be within relatively narrow tolerances for the end of the hammer to be positioned precisely at the edge of the platform, otherwise the system doesn't work. For the same reason, the length of the second segment of the hammer has to be within a narrow range of values. How does the hammer get into the third trap? It would seem that the extended arm of the second trap has to be held up while the newly-fashioned hammer is inserted through the tunnel of the spring. Thus an intelligent agent has to actively push parts around to get to the configuration of the third trap. Again, there is no obvious improvement in function of the third trap compared to the second or first. Both the second and third traps appear to do the same thing as the first, but require more parts. Such an event is not expected in a Darwinian scenario. It seems the only reason they attract our attention is because they appear to be along the path we wish the process would go. That is intelligent design.

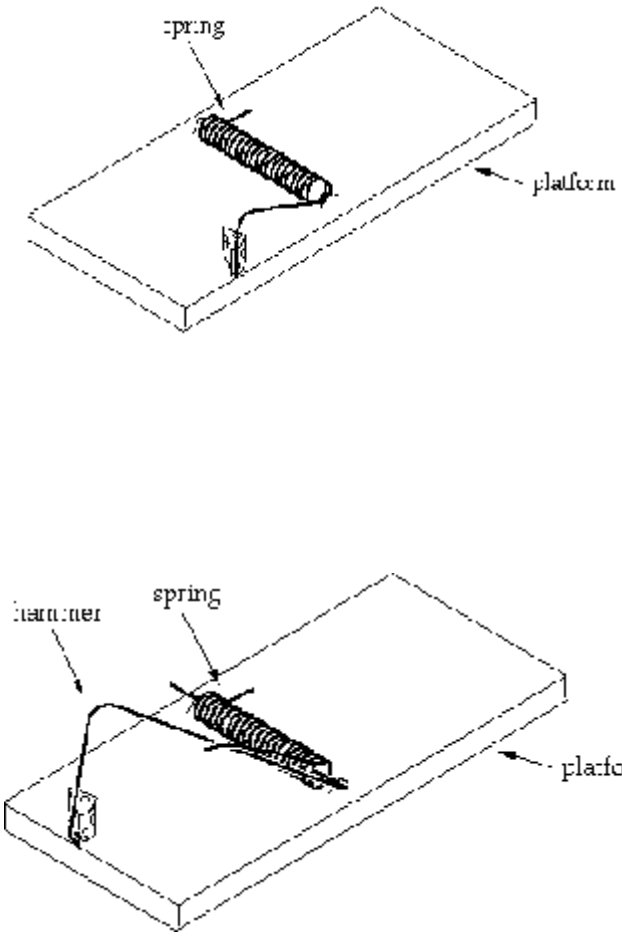

Figure 2. The second trap (top) and third trap (bottom).

E. From the third trap to the fourth

Going from the third trap to the fourth requires major rearrangements. The hammer is bent, lengthened, and an extra segment is added to it. Two new pieces are added: the "hold-down bar" and a staple to hold down the hold-down bar. The end of the hold-down bar is endowed with a closed curl so that the staple has something to hang on to. The staple again has to be positioned in a specific region of the trap. Depending on details, this configuration may be an improvement over the first three traps because it appears that, depending on the tension of the spring, the trap could kill a mouse outright, rather than just pinning it (yet that feature could probably easily be built into the earlier versions). On the other hand the arm of the spring is now being pushed through a much greater displacement in the fourth trap than previous versions. It seems unlikely a spring optimized for use in earlier traps would work well in the fourth trap (unless of course we are "looking ahead"). Rather than a "transition," this process is again better viewed as building a new trap using refashioned parts of the old trap plus new ones. This is intelligent design.

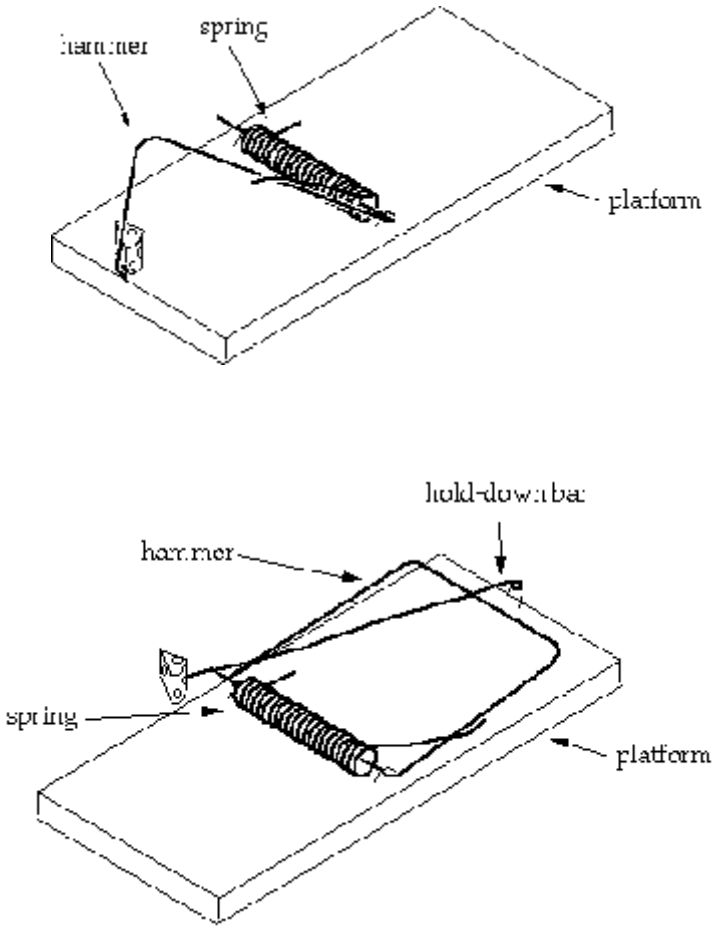

Figure 3. The third trap (top) and fourth trap (bottom).

F. From the fourth trap to the fifth
This is left as an exercise for the reader.

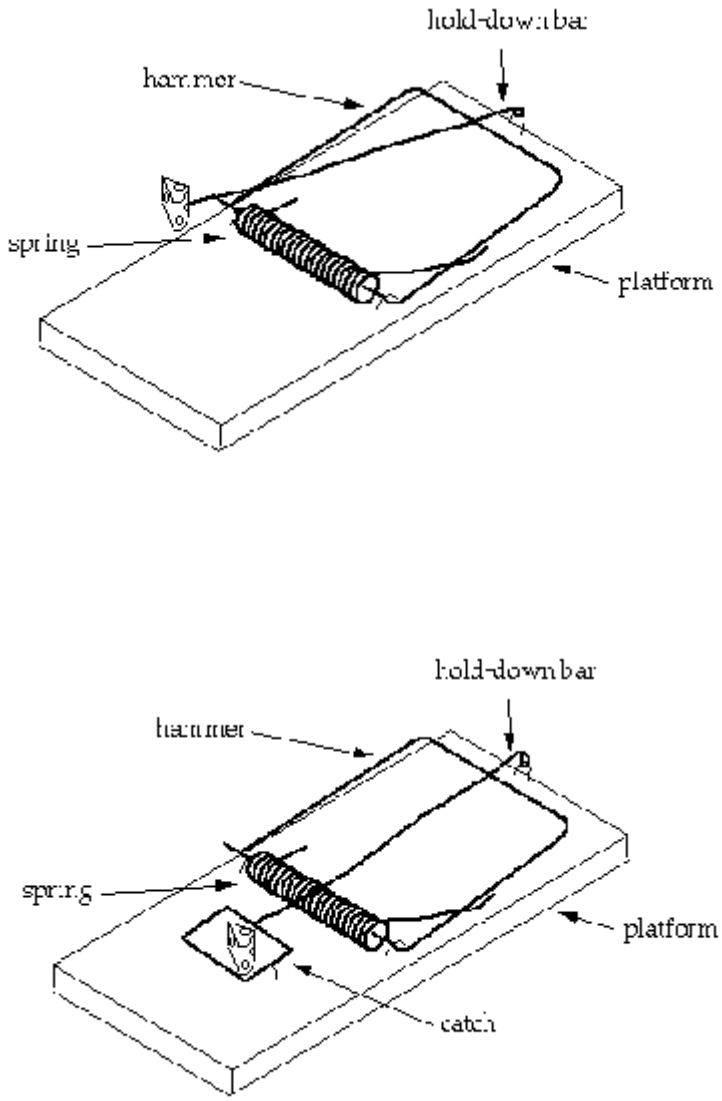

Figure 4. The fourth trap (top) and fifth trap (bottom).

G. Discussion

I have to admit that even I find it tedious to discuss mousetraps in such excruciating detail. But the critical point is that that is exactly the level at which Darwinian evolution would have to work in the cell. Every relevant detail has to fit or the system fails. If an arm is too long or an angle not right or a staple placed incorrectly, the mouse dances free. If you want to get to a certain system, but the road there isn't a series of continual improvements, Darwinism won't take you there. It's important for those interested in these issues to realize that, when evaluating descriptive evolutionary scenarios (as opposed to experiments—see below), one has to attend to the tiniest details (as I did here) to see if intelligence is directing the show. On the other hand, if one doesn't pay the strictest attention, Darwinian scenarios look much more plausible because one sees only the possibilities, not the problems. It's easy for a speaker to persuade an audience that the McDonald mousetraps represent a series of Darwinian intermediates on the way to a standard trap—that they show irreducible complexity is no big deal. All one has to do is gloss over the difficulties. But although our minds can skip over details, nature can't.

In the real world of biology the staples, bends, and so forth would be features of molecules, of proteins in particular. If two proteins don't bind each other in the correct orientation (aren't stapled right), if they aren't placed in the right positions, if their new activity isn't regulated correctly, if many details aren't exactly correct, then the putative Darwinian pathway is blocked. Now, it's hard, almost impossible, for persons without the appropriate science background to tell where such difficulties would occur in Darwinian scenarios for blood clotting or ciliary function or other biological systems. When they read Darwinian stories in a book or hear them in lectures, they generally have no independent information to judge the scenario. In such a situation one should ask oneself, "If a simple mousetrap requires intelligent design, what is the likelihood that the much more complicated molecular machines of the cell could be built step-by-tiny-Darwinian-step?" Keeping that question in mind will foster a healthy skepticism toward optimistic scenarios.

Why do the McDonald mousetraps look persuasive to some people? Certainly one reason is the way they are drawn. Drawings of four of the five traps are dominated by the image of the large rectangular platform and prominent spring in the center. That makes them all look pretty much the same. The staples are barely visible and the various metal bars protruding here and there seem like insignificant details. In fact, they are critical. Another reason is that the scenario starts with the completed mousetrap. Any question about the placement of the parts, their size, stiffness, and so on doesn't easily arise because the parts were already placed where they needed to be for the ultimate goal in the original drawing (that is, the fifth mousetrap here, which is the first drawing in McDonald's series) and their properties could be inferred from the fact we started with a working trap. The universe of possibilities was tightly but implicitly circumscribed by the already-completed starting point. A third reason it seems persuasive is that the series is always presented as parts being removed from the complete mousetrap. Looking at it in such a backward manner—the reverse of what evolution would have to do—obscures the teleology of the building process. Going in a forward direction there is strong reason to think we would not end up at the fifth mousetrap when starting from the first, because the first works as well as the second and third, so greater complexity would be disfavored. In going backwards, however,

lesser complexity is favored so it seems "natural" to move to simpler traps. Yet Darwinian evolution can't work like that.

A final reason for the persuasiveness of the example we can call the "Clever Hans effect." Clever Hans was the name of a horse who seemed to be pretty good at arithmetic. Its owner would give Hans a simple math problem such as 5+5, and the horse would stamp his hoof ten times, then stop. It eventually turned out that Clever Hans could pick up unconscious cues from its owner, who might raise his eyebrows or tilt his head when the horse's stamping reached the right value. The horse could even pick up unintentional cues from other people, not just the owner, who also apparently gave telltale reactions. In the case of Clever Hans, the human intelligence of the owner was inadvertently attributed to the horse. In my experience the same is invariably true of Darwinian scenarios—human intelligence is critical to guiding the scenario through difficulties toward the "proper" goal, but the intelligence is then attributed to natural selection. As with Clever Hans, the guidance is usually unconscious, but is intelligent nonetheless.

Clever Hans was exposed as mathematically clueless by carefully controlled experiments. To see whether natural selection can work wonders on its own—without the aid of human intelligence— we also have to do carefully controlled experiments. One way to do this is to ask bacteria in the laboratory if they can evolve irreducibly complex biochemical systems. (Kenneth Miller has called this the "acid test.") Bacteria are a good choice because they can be grown in huge numbers with short generation times—just what Darwinian evolution needs. However, when this was repeatedly tried over the course of 25 years for bacteria missing a comparatively simple biochemical system (called the "lac operon") natural selection came up empty (see the section on "The Acid Test" above). It could make the small changes typically termed "microevolution," but whenever it had to do a couple things at once, such as would have to be done to make irreducibly complex systems, it got stuck. Like Clever Hans on his own, natural selection seems to have much less intelligence than we had given it credit for. There is currently no experimental evidence to show that natural selection can get around irreducible complexity.

Darwinian scenarios, either for building mousetraps or biochemical systems, are very easy to believe if we aren't willing or able to scrutinize the smallest details, or to ask for experimental evidence. They invite us to admire the intelligence of natural selection. But the intelligence we are admiring is our own.

V. Philosophical Objections to Intelligent Design

A. Is Intelligent Design Falsifiable?

Some reviewers of *Darwin's Black Box* (Behe 1996) have raised philosophical objections to intelligent design. I will discuss several of these over the next few sections, beginning with the question of falsifiability. To decide whether, or by what evidence, it is falsifiable, one first has to be sure what is meant by "intelligent design." By that phrase someone might mean that the laws of nature themselves are designed to produce life and the complex systems that undergird it. In

fact, something like that position has been taken by the physicist Paul Davies and the geneticist Michael Denton in their recent books, respectively, *The Fifth Miracle: The Search for the Origin and Meaning of Life* (Davies 1999) and *Nature's Destiny: How the Laws of Biology Reveal Purpose in the Universe*. (Denton 1998) That stance also seems to pass muster with the National Academy of Sciences:

> Many religious persons, including many scientists, hold that God created the universe and the various processes driving physical and biological evolution and that these processes then resulted in the creation of galaxies, our solar system, and life on Earth. This belief, which sometimes is termed "theistic evolution," is not in disagreement with scientific explanations of evolution. Indeed, it reflects the remarkable and inspiring character of the physical universe revealed by [science]. (National Academy of Sciences 1999, 7)

In such a view even if we observe new complex systems being produced by selection pressure in the wild or in the laboratory, design would not be falsified because it is considered to be built into natural laws. Without commenting on the merits of the position, let me just say that that is not the meaning I assign to the phrase. By "intelligent design" I mean to imply design beyond the laws of nature. That is, taking the laws of nature as given, are their other reasons for concluding that life and its component systems have been intentionally arranged? In my book, and in this essay, whenever I refer to intelligent design (ID) I mean this stronger sense of design-beyond-laws. Virtually all academic critics of my book have taken the phrase in the strong sense I meant it.

In the strong sense ID is no longer approved by the National Academy, for a specific reason: "[I]ntelligent design ... [is] not science because [it is] not testable by the methods of science." (National Academy of Sciences 1999, 25) In his review of *Darwin's Black Box* for *Nature*, Jerry Coyne, professor of evolutionary biology at the University of Chicago, explains why he also thinks intelligent design is unfalsifiable.

> If one accepts Behe's idea that both evolution and creation can operate together, and that the Designer's goals are unfathomable, then one confronts an airtight theory that can't be proved wrong. I can imagine evidence that would falsify evolution (a hominid fossil in the Precambrian would do nicely), but none that could falsify Behe's composite theory. Even if, after immense effort, we are able to understand the evolution of a complex biochemical pathway, Behe could simply claim that evidence for design resides in the other unexplained pathways. Because we will never explain everything, there will always be evidence for design. This regressive ad hoc creationism may seem clever, but it is certainly not science. (Coyne 1996)

Coyne's conclusion that design is unfalsifiable, however, seems to be at odds with the arguments of other reviewers of my book. Clearly, Russell Doolittle (Doolittle 1997), Kenneth Miller (Miller 1999), and others have advanced scientific arguments aimed at falsifying ID. (See my articles on blood clotting and the "acid test" on this web site.) If the results with knock-out mice (Bugge *et al.* 1996) had been as Doolittle first thought, or if Barry Hall's work (Hall 1999) had indeed shown what Miller implied, then they correctly believed my claims about irreducible complexity would have suffered quite a blow. And since my claim for intelligent design requires

that no unintelligent process be sufficient to produce such irreducibly complex systems, then the plausibility of ID would suffer enormously. Other scientists, including those on the National Academy of Science's Steering Committee on Science and Creationism, in commenting on my book have also pointed to physical evidence (such as the similar structures of hemoglobin and myoglobin) which they think shows that irreducibly complex biochemical systems can be produced by natural selection: "However, structures and processes that are claimed to be 'irreducibly' complex typically are not on closer inspection." (National Academy of Sciences 1999, p. 22)

Now, one can't have it both ways. One can't say both that ID is unfalsifiable (or untestable) and that there is evidence against it. Either it is unfalsifiable and floats serenely beyond experimental reproach, or it can be criticized on the basis of our observations and is therefore testable. The fact that critical reviewers advance scientific arguments against ID (whether successfully or not) shows that intelligent design is indeed falsifiable.

In fact, *intelligent design is open to direct experimental rebuttal*. Here is a thought experiment that makes the point clear. In *Darwin's Black Box* (Behe 1996) I claimed that the bacterial flagellum was irreducibly complex and so required deliberate intelligent design. The flip side of this claim is that the flagellum can't be produced by natural selection acting on random mutation, or any other unintelligent process. To falsify such a claim, a scientist could go into the laboratory, place a bacterial species lacking a flagellum under some selective pressure (for mobility, say), grow it for ten thousand generations, and see if a flagellum—or *any* equally complex system—was produced. If that happened, my claims would be neatly disproven.

How about Professor Coyne's concern that, if one system were shown to be the result of natural selection, proponents of ID could just claim that some other system was designed? I think the objection has little force. If natural selection were shown to be capable of producing a system of a certain degree of complexity, then the assumption would be that it could produce any other system of an equal or lesser degree of complexity. If Coyne demonstrated that the flagellum (which requires approximately forty gene products) could be produced by selection, I would be rather foolish to then assert that the blood clotting system (which consists of about twenty proteins) required intelligent design.

Let's turn the tables and ask, how could one falsify the claim that, say, the bacterial flagellum was produced by Darwinian processes? (Professor Coyne's remarks about a Precambrian fossil hominid are irrelevant since I dispute the mechanism of natural selection, not common descent. I would no more expect to find a fossil hominid out of sequence than he would.) If a scientist went into the laboratory and grew a flagellum-less bacterial species under selective pressure for many generations and nothing much happened, would Darwinists be convinced that natural selection is incapable of producing a flagellum? I doubt it. It could always be claimed that the selective pressure wasn't the right one, or that we started with the wrong bacterial species, and so on. Even if the experiment were repeated many times under different conditions and always gave a negative result, I suspect many Darwinists would not conclude that the claim of its Darwinian evolution was falsified. Of complex biochemical systems Coyne himself writes "we may forever be unable to envisage the first proto-pathways. It is not valid, however, to assume that, because one man cannot imagine such pathways, they could not have existed." (Coyne 1996) If a person

accepts Darwinian paths which are not only unseen, but which we may be forever unable to envisage, then it is effectively impossible to make him think he is wrong.

Kenneth Miller announced an "acid test" for the ability of natural selection to produce irreducible complexity. He then decided that the test was passed, and unhesitatingly proclaimed intelligent design falsified ("Behe is wrong"; Miller 1999, 147). But if, as it certainly seems to me, *E. coli* actually fails the lactose-system "acid test," would Miller consider Darwinism to be falsified? Almost certainly not. He would surely say that the experiment started with the wrong bacterial species, used the wrong selective pressure, and so on. So it turns out that his "acid test" was not a test of Darwinism; it tested only intelligent design. The same one-way testing was employed by Russell Doolittle. He pointed to the results of Bugge et al (1996) to argue against intelligent design. But when the results turned out to be the opposite of what he had originally thought, Professor Doolittle did not abandon Darwinism.

It seems then, perhaps counterintuitively to some, that intelligent design is quite susceptible to falsification, at least on the points under discussion. Darwinism, on the other hand, seems quite impervious to falsification. The reason for that can be seen when we examine the basic claims of the two ideas with regard to a particular biochemical system like, say, the bacterial flagellum. The claim of intelligent design is that "*No* unintelligent process could produce this system." The claim of Darwinism is that "*Some* unintelligent process could produce this system." To falsify the first claim, one need only show that at least one unintelligent process could produce the system. To falsify the second claim, one would have to show the system could not have been formed by any of a potentially infinite number of possible unintelligent processes, which is effectively impossible to do.

I think Professor Coyne and the National Academy of Sciences have it exactly backwards. A strong point of intelligent design is its vulnerability to falsification. (Indeed, some of my religious critics dislike intelligent design theory precisely because they worry that it will be falsified, and thus theology will appear to suffer another blow from science. See, for example, (Flietstra 1998).) A weak point of Darwinian theory is its resistance to falsification. What experimental evidence could possibly be found that would falsify the contention that complex molecular machines evolved by a Darwinian mechanism?

B. What Is "Irreducible Complexity" and What Does It Signify?

Some reviewers have criticized the concept of irreducible complexity. In *Boston Review* University of Rochester evolutionary biologist H. Allen Orr agrees that many biological systems are "irreducibly complex," but argues that Darwinian evolution can, at least in theory, directly account for them. However, as I will show, his argument depends on changing the definition of irreducible complexity, which obscures the difficulty.

In his review Orr initially seems to clearly understand what I meant by "irreducible complexity" (quoted earlier). Of the example I used in *Darwin's Black Box* he writes: "A mousetrap has a clear function (crushing mice) and is made of several parts (a platform, a spring, a bar that does the crushing). If any of these parts is removed, the trap doesn't work. Hence it's irreducibly

complex." (Orr 1996) So far, so good. Nonetheless, later in the review he seems to lose hold of the concept:

> An irreducibly complex system can be built gradually by adding parts that, while initially just advantageous, become—because of later changes—essential. The logic is very simple. Some part (A) initially does some job (and not very well, perhaps). Another part (B) later gets added because it helps A. This new part isn't essential, it merely improves things. But later on, A (or something else) may change in such a way that B now becomes indispensable. This process continues as further parts get folded into the system. And at the end of the day, many parts may all be required. (Orr 1996)

Now, how can we square this paragraph with his initial agreement that if any part of a mousetrap is removed, it doesn't work? Thinking of the mousetrap example, what would correspond to "Some part (A)" that "initially does some job"? In fact, the whole point of the mousetrap example was to show that there is no "part (A)" that will initially do the job. There is no "part (B)" that helps gradually improve "part (A)." A gradual addition of parts is not possible for the mousetrap example (or at least it is very far from obvious that it is possible). Orr later gives a biological example of what he has in mind.

> The transformation of air bladders into lungs that allowed animals to breathe atmospheric oxygen was initially just advantageous: such beasts could explore open niches—like dry land—that were unavailable to their lung-less peers. But as evolution built on this adaptation (modifying limbs for walking, for instance), we grew thoroughly terrestrial and lungs, consequently, are no longer luxuries—they are essential. The punch-line is, I think, obvious: although this process is thoroughly Darwinian, we are often left with a system that is irreducibly complex. (Orr 1996)

In Orr's example, however, what is the irreducibly complex system? Is it the swim bladder? The lung? The whole organism? What is the function of the system? Is it "swimming," "breathing," "living," or something else? If we assume he meant that the irreducibly system is, say, the lung, can the lung be considered "a single system," as my definition requires (Behe 1996, p. 39)? What are the parts of the lung without which it will stop working, like a mousetrap without a spring? What is "part (A)" and what is "part (B)"? None of these things is clear at all—certainly not as clear as the parts and function of a mousetrap.

Let me preface my remaining remarks on this subject by acknowledging that it is often notoriously difficult to rigorously define a concept, as exemplified by the problems encountered in trying to define "science," "life," or "species." Furthermore, I am no philosopher; my end purpose is not to come up with a string of words that completely defines the phrase "irreducible complexity." Rather, my purpose is to focus attention on a class of biochemical systems that pose a particular challenge to Darwinian evolution. The examples I gave in my book—a mousetrap, cilium, clotting cascade, and so on—clearly show the necessity for some systems of having a number of discrete parts working together on a single function. The examples, I think, better get across the concept of irreducible complexity than does the definition I offered (Behe 1996, 39), although I think the definition I gave does an adequate job.

With those comments in mind, it can be seen that Orr simply switched concepts in mid-review, as shown by his conflicting remarks quoted above. He jumped from my idea of irreducible complexity to a hazy concept that can perhaps be paraphrased as, "if you remove this part, the organism will eventually die." I'm happy to agree for purposes of discussion that a class of biological phenomena exists which are required for life and which can be changed gradually by natural selection, perhaps even including the swim bladder/lungs Orr mentions (although it is not nearly so obvious as he assumes it to be). It's just that they are not the same types of things as, nor do they somehow obviate the problem of, irreducibly complex systems like mousetraps and cilia. If they were, then Orr could have explained them away as easily as he does swim bladders and lungs. (After all, lung tissue contains cilia plus many, many other components; Orr should thus find it easier to explain cilia alone, rather than cilia-plus-other-components.) Implicitly changing the definition of irreducible complexity, as Orr did, does not tell us how the blood clotting cascade or the bacterial flagellum could have been produced. On the contrary, it distracts our attention from those features of the systems that make them recalcitrant to Darwinian explanation.

Other scientific reviewers have made arguments similar to Orr's which depend on implied definitions of irreducible complexity different from what I used. Writing in the *Wall Street Journal* Paul Gross compares biochemical systems to cities, where features can be added over time. (Gross 1996) But the analogy is poorly chosen because no city completely stops working when a part is removed, as does a mousetrap or cilium. In *Boston Review* Douglas Futuyma writes:

> In mammals, successive duplications of the beta gene gave rise to the gamma and epsilon chains, which characterize the hemoglobin of the fetus and early embryo respectively, and enhance uptake of oxygen from the mother. Thus a succession of gene duplications, widely spaced through evolutionary time, has led to the "irreducibly complex" system of respiratory proteins in mammals. (Futuyma 1997)

But the several hemoglobins that Futuyma calls the "'irreducibly complex' system of respiratory proteins" in fact do not constitute an irreducibly complex system in my sense of the term. They do not interact with each other, as do the parts of a mousetrap or clotting cascade. They go their separate ways, and for the most part aren't even present at the same time in the organism. Like Allen Orr, Futuyma implicitly switches the meaning of "irreducibly complex." Unfortunately, that does not solve the problem I pointed out, but only obscures it. (As an aside, it is difficult to understand what Futuyma intends by the quotation marks around the phrase irreducibly complex. He can't be quoting me; I never used the term in connection with hemoglobin—quite the opposite. He may intend them to be taken as "scare quotes," to warn the reader to take the phrase with a grain of salt. But since he is the one who decided to use the term in conjunction with hemoglobins and then to argue against it, the effect is that of setting up a straw man.)
A different question about irreducible complexity is asked by David Ussery on his web site. He notes that, whereas a bacterial flagellum in *E. coli* requires about 40 different proteins, in *H. pylori* only 33 are required. Since fewer proteins are required, how can the flagellum be irreducibly complex? Two responses can be made. First, some systems may have parts that are necessary for a function, plus other parts that, while useful, are not absolutely required. Although one can remove the radio from a car and the car will still work, one can't remove the battery or

some other parts and have a working car. Ussery himself seems to recognize this when he writes "I would readily admit that there is STILL the problem of the evolution of the 'minimal flagellum,'" (Ussery 1999) but he hopes gene duplication will explain that. Second, one must be careful not to identify one protein with one "part" of a biochemical machine. For example, genes coding for two proteins in one organism may be joined into a single gene in another. A single protein in one organism may be doing the jobs of several polypeptides in another. Or two proteins may combine to do one job (an example is the ∀- and ∃-subunits of tubulin, which together make microtubules, a "part" of the eukaryotic cilium).

In his review Ussery mistakenly attributes to me the belief that 240 separate proteins are required for the bacterial flagellum. The confusion apparently arose because at the end of a chapter on the eukaryotic cilium and bacterial flagellum, I stated that a typical cilium contains over two hundred different kinds of proteins. In the next paragraph I wrote, "The bacterial flagellum, in addition to the proteins already discussed, requires about forty other proteins for function." (Behe 1996, p. 72) Although I meant in addition to the flagellar proteins I had discussed a few pages earlier in the chapter, Ussery interpreted the statement to include the several hundred ciliary proteins as well. Ordinarily I would simply overlook such a mistaken attribution, since it should be obvious to informed readers that I wouldn't be lumping the proteins of cilia and flagella together—after all, they are completely different structures that occur in separate kinds of organisms. In his review in *Biology and Philosophy*, however, Bruce Weber writes "Behe cannot imagine how anything short of the full 240 components of the flagellum could propel a bacterium. But only 33 proteins are needed to produce a functional flagellum for *Helicobacter pylori*." (Weber 1999) And Weber then cites Ussery's web site as his source. Since Ussery's misreading of my book seems to be spreading, and since naive readers might be more impressed by a drop from 240 to 33 than by a change from 40 to 33, I have to state for the record that I did not mean the bacterial flagellum requires the proteins of the eukaryotic cilium!

Several reviewers have questioned whether irreducible complexity is necessarily a hallmark of intelligent design. James Shapiro, who has worked on adaptive mutations, writes in the *Boston Review* (Shapiro 1997) of "some developments in contemporary life science that suggest shortcomings in orthodox evolutionary theory" while arguing for "a growing convergence between biology and information science which offers the potential for scientific investigation of possible intelligent cellular action in evolution." Thus Shapiro appears to think that irreducibly complex biochemical structures might be explained in a non-Darwinian fashion without invoking intelligence beyond the cells themselves. In *Biology and Philosophy* Bruce Weber (1999) writes that the work of Stuart Kauffman and others on self-organizing phenomena "disrupts the dichotomy Behe has set up of selection or design." Most explicitly, Shanks and Joplin argue in *Philosophy of Science* that self-organizing phenomena such as the Belousov-Zhabotinsky reaction demonstrate that irreducible complexity is not necessarily a pointer to intelligent design. (Shanks and Joplin 1999) I have responded to Shanks and Joplin's argument in a separate paper. (Behe 2000) Briefly, complexity is a quantitative feature; systems can be more or less complex. Although it produces some complexity, the self-organizing behavior so far observed in the physical world has not produced complexity and specificity comparable to irreducibly complex biochemical systems. There is currently little reason to think that self-organizing behavior can explain biochemical systems such as the bacterial flagellum or blood clotting cascade.

The underlying point of all these criticisms that needs to be addressed, I think, is that it is possible future work might show irreducible complexity to be explainable by some unintelligent process (although not necessarily a Darwinian one). And on that point I agree the critics are entirely correct. I acknowledge that I cannot rule out the possibility future work might explain irreducibly complex biochemical systems without the need to invoke intelligent design, as I stated in *Darwin's Black Box*. (Behe 1996, 203-204) I agree I cannot prove that studies of self-organization will not eventually show it to be capable of much more than we know now. Nor can I definitively say that Professor Shapiro's ideas about self-designing cells might not eventually prove true, or that currently unknown theories might prevail. But the inability to guarantee the future course of science is common to everyone, not just those who are supportive of intelligent design. For example, no one can warrant that the shortcomings of self-organization will not be exacerbated by future research, rather than overcome, or that even more difficulties for natural selection will not become apparent.

I agree with the commonsense point that no one can predict the future of science. I strongly disagree with the contention that, because we can't guarantee the success of intelligent design theory, it can be dismissed, or should not be pursued. If science operated in such a manner, no theory would ever be investigated, because no theory is guaranteed success forever. Indeed, if one ignores a hypothesis because it may one day be demonstrated to be incorrect, then one paradoxically takes unfalsifiability to be a necessary trait of a scientific theory. Although philosophers of science have debated whether falsifiability is a requirement of a scientific theory, no one to my knowledge has argued that unfalsifiability is a necessary mark.

Because no one can see the future, science has to navigate by the data it has in hand. Currently there is only one phenomenon that has demonstrated the ability to produce irreducible complexity, and that is the action of an intelligent agent. It seems to me that that alone justifies pursuing a hypothesis of intelligent design in biochemistry. In his recent book *Tower of Babel: The Evidence against the New Creationism*, however, philosopher of science Robert Pennock argues that science should avoid a theory of intelligent design because it must of necessity embrace "methodological naturalism." (Pennock 1999) I have responded to Pennock elsewhere. (Behe 1999) Briefly, science should follow the data wherever it appears to lead, without preconditions. Further, the question of the identity of the designer remains open (see below) — just as the cause of the Big Bang has been open for decades. Thus, science can pursue theories with extra-scientific implications (such as the Big Bang or intelligent design) as far as it can, using its own proper methods.

C. Can We—May We—Detect Design in the Cell?

Several reviewers have argued against the legitimacy of reasoning to a conclusion of intelligent design based on biochemical evidence. In the same review discussed above Allen Orr raises an intriguing question of how we apprehend design. He writes:

> We know that there are people who make things like mousetraps. (I'm not being facetious here—I'm utterly serious.) When choosing between the design and Darwinian

> hypotheses, we find design plausible for mousetraps only because we have independent knowledge that there are creatures called humans who construct all variety of mechanical contraptions; if we didn't, the existence of mousetraps would pose a legitimate scientific problem. (Orr 1997)

So, Orr says, we know mousetraps are designed because we have seen them being designed by humans, but we have not seen irreducibly complex biochemical systems being designed, so we can't conclude they were.

Although he makes an interesting point, I think his reasoning is incorrect. Consider the SETI project (Search for Extraterrestrial Intelligence), in which scientists scan space for radio waves that might have been sent by aliens. Those scientists believe that they can distinguish a *designed* radio wave (one carrying a message) from the background radio noise of space. However, we have never observed space aliens sending radio messages; we have never observed aliens at all. Nonetheless, SETI workers, funded for years by the federal government, are confident that they can detect intelligently-designed phenomena, even if they don't know who produced them.

The relevance to intelligent design in biochemistry is plain. Design is evident in the designed system itself, rather than in pre-knowledge of who the designer is. Even if the designer is an entity quite unlike ourselves, we can still reach a conclusion of design if the designed system has distinguishing traits (such as irreducible complexity) that we know require intelligent arrangement. (A formal analysis of how we come to a conclusion of design is presented by William Dembski in his recent monograph, *The Design Inference* (Dembski 1998).)

We can probe Orr's reasoning further by asking how we know that something was intelligently designed even if it indeed resulted from human activity. After all, humans engage in all sorts of activities which we would not ascribe to intelligence. For example, in walking through the woods a person might crush plants by his footsteps, accidentally break tree branches and so on. Why do we not ascribe those marks to purposeful activity? On the other hand, when we see a small snare (made of sticks and vines) in the woods, obviously designed to catch a rabbit, why do we unhesitatingly conclude the parts of the snare were purposely arranged by an intelligent agent? Why do we apprehend purpose in the snare but not in the tracks? As Thomas Reid argued in response to the skepticism of David Hume, intelligence is apprehended only by its effects; we cannot directly observe intelligence. (Dembski 1999) We know humans are intelligent by their outward actions. And we discriminate intelligent from non-intelligent human actions by external evidence. Intelligence, human or not, is evident only in its effects.

Michael Ruse in *Boston Review* raises another objection, saying that scientists *qua* scientists simply can't appeal to design.

> Design is not something you add to science as an equal—miracles or molecules, take your pick. Design is an interpretation which makes some kind of overall metaphysical or theological sense of experience. (Ruse 1997)

Contrary to Ruse's argument, however, many scientists already appeal to design. I mentioned the SETI program above; clearly those scientists think they can detect design (and nonhuman design

at that.) Forensic scientists routinely make decisions of whether a death was designed (murder) or an accident. Archaeologists decide whether a stone is a designed artifact or just a chance shape. Cryptologists try to distinguish a coded message from random noise. It seems unlikely that any of those scientists view their work as trying to make "metaphysical or theological sense of experience." They are doing ordinary science.

Ruse probably meant that scientists can't specifically appeal to God or the supernatural. Evolutionary biologist Douglas Futuyma echoes Ruse's sentiment with rousing rhetoric:

> When scientists invoke miracles, they cease to practice science.... Behe, claiming a miracle in every molecule, would urge us to admit the defeat of reason, to despair of understanding, to rest content in ignorance. Even as biology daily grows in knowledge and insight, Behe counsels us to just give up. (Futuyma 1997)

In speaking of "miracles"—relying for rhetorical effect on that word's pejorative connotations when used in a scientific context—Ruse and Futuyma are ascribing to me a position I was scrupulous in my book to avoid. Although I acknowledged that most people (including myself) will attribute the design to God—based in part on other, non-scientific judgments they have made—I did not claim that the biochemical evidence leads ineluctably to a conclusion about who the designer is. In fact, I directly said that, from a scientific point of view, the question remains open. (Behe 1996, 245-250) In doing so I was not being coy, but only limiting my claims to what I think the evidence will support. To illustrate, Francis Crick has famously suggested that life on earth may have been deliberately seeded by space aliens (Crick and Orgel 1973). If Crick said he thought that the clotting cascade was designed by aliens, I could not point to a biochemical feature of that system to show he was wrong. The biochemical evidence strongly indicates design, but does not show who the designer was.

I should add that, even if one does think the designer is God, subscribing to a theory of intelligent design does not necessarily commit one to "miracles." At least no more than thinking that the laws of nature were designed by God—a view, as we've seen, condoned by the National Academy of Sciences (National Academy of Sciences 1999). In either case one could hold that the information for the subsequent unfolding of life was present at the very start of the universe, with no subsequent "intervention" required from outside of nature. In one case, the information is present just in general laws. In the other case, in addition to general laws, information is present in other factors too. The difference might boil down simply to the question of whether there was more or less explicit design information present at the beginning—hardly a point of principle.

While we're on the subject of God, another point should be made: A number of prominent scientists, some of whom fault me for suggesting design, have themselves argued for atheistic conclusions based on biological data. For example, Professor Futuyma has written: "Some shrink from the conclusion that the human species was not designed, has no purpose, and is the product of mere mechanical mechanisms—but this seems to be the message of evolution." (Futuyma 1982) And Russell Doolittle remarks concerning the blood clotting cascade: "…no Creator would have designed such a circuitous and contrived system." (Doolittle 1997) It is rather disingenuous, however, for those who use biological data to argue that life shows no evidence of design, to complain when others use biological evidence to argue the opposing view.

D. "Giving Up" in "Ignorance"

Some scientific reviewers have dismissed the conclusion of design as an "argument from ignorance," or a "God of the gaps" argument. This can take several forms. One form of the objection is presented by University of London evolutionary biologist Andrew Pomiankowski, who writes:

> Most biochemists have only a meagre understanding of, or interest in, evolution. As Behe points out, for the thousand-plus scholarly articles on the biochemistry of cilia, he could find only a handful that seriously addressed evolution. This indifference is universal. (Pomiankowski 1996)

So, Pomiankowski argues, we do not have answers because nobody has looked, and biochemists haven't looked because they have little interest in the subject.

Although initially plausible, this interpretation suffers from the fact that there is demonstrable interest in evolution among molecular bioscientists. (One doesn't have to officially call oneself a "biochemist" to address such problems. Molecular biologists, geneticists, immunologists, embryologists— investigators in all of these disciplines are in a position to work on them.) The authors of the large number of books and papers listed on John Catalano's and David Ussery's web sites are clearly interested in evolution (see my discussion of the evolutionary literature on this web site), as are the authors of numerous other studies that involve sequence comparisons. Since many papers are published in the general area of molecular evolution, we have to ask why there are so few in the particular area of the Darwinian evolution of irreducibly complex systems. Pomiankowski proposes it is because the problem is so difficult (Pomiankowski 1996); I suggest it is difficult because irreducibly complex systems fit poorly within a gradualistic theory such as Darwinism.

A less reasonable form, I think, of the "ignorance" accusation is presented by Neil Blackstone. An evolutionary biologist at Northern Illinois University, Blackstone levels a formal charge at me of an error in logic—the "argumentum ad ignorantium," as his review is titled (Blackstone 1997). He even cites a philosophy textbook by Irving Copi to give the charge authority. Those who chop logic to rule out a hypothesis, however, should make sure they are on very firm logical ground. Blackstone is not.

Copi defines the fallacy as follows: "The argumentum ad ignorantium is committed whenever it is argued that a proposition is true simply on the basis that it has not been proved false, or that it is false because it has not been proved true." (Copi 1953) But I certainly did not argue that the Darwinian evolution of biochemical complexity is false "simply on the basis" that it has not been proved true. Nor did I say that intelligent design is true "simply on the basis" that it has not been proved false. To lay the groundwork for a proposal of intelligent design I did argue extensively that the blood clotting cascade and other systems have not been explained by Darwinism. That, of course, was necessary because many people have the impression that Darwinian theory has already given a satisfactory account for virtually all aspects of life. My first task was to show the readership that that impression is not correct.

But my argument did not stop there. I spent many pages throughout the book showing that there is a *structural reason*—irreducible complexity—for thinking that Darwinian explanations are unlikely to succeed. Furthermore, I argued that irreducible complexity is a hallmark of intelligent design, took several chapters to explicate how we apprehend design, showed why some biochemical systems meet the criteria, and addressed objections to the design argument. Truncating my case for intelligent design and then saying I commit the fallacy of argumentum ad ignorantium is not, in my opinion, fair play.

Let's explore the intricacies of formal logic a little further. Although Blackstone didn't mention it, Copi has more to say on the argument from ignorance.

> A qualification should be made at this point. In some circumstances it can be safely assumed that if a certain event had occurred, evidence of it could be discovered by qualified investigators. In such circumstances it is perfectly reasonable to take the absence of proof of its occurrence as positive proof of its non-occurrence. (Copi 1953)

Although I did not limit my argument to the lack of evidence for the Darwinian evolution of irreducibly complex biochemical systems, when qualified investigators (such as, say, those investigating blood clotting) come up empty, it is "perfectly reasonable" to weigh that against Darwinism. (By itself, of course, it is not positive evidence for design.) Although lack of progress is not "proof" of the failure of Darwinism, it certainly is a significant factor to consider.

In a milder variation of the "argument from ignorance" complaint, other scientific reviewers have objected that an appeal to intelligent design is tantamount to "giving up." For example, in the *Forward* Emory University evolutionary biologist Marc Lipsitch remarks:

> [Behe] correctly suggests that a complete theory of evolution would include an account of how the intricate chemical systems inside our bodies arose (or might have arisen) from inanimate molecules, one step at a time. Mr. Behe's question is a fair one, but instead of suggesting a series of experiments that could address the question, he throws up his hands. (Lipsitch 1996)

Unfortunately, the point is made with circular logic: it depends on the presupposition that life is not designed, which is the point at issue. If life is not designed then, yes, a theory of intelligent design is ultimately a blind alley (if not quite "giving up"). However, if aspects of life are indeed designed, then the search for the putative unintelligent mechanisms that built them is the blind alley. But how do we decide ahead of time which is correct?

We can't decide the correct answer ahead of time. Science can only follow the data where they lead, as they become available.

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