MICHAEL J. BEHE

ANSWERING SCIENTIFIC CRITICISMS OF INTELLIGENT DESIGN

Introduction

In 1859 Charles Darwin published his great work *On the Origin of Species*, in which he proposed to explain how the great variety and complexity of the natural world might have been produced solely by the action of blind physical processes. His proposed mechanism was, of course, natural selection working on random variation. In a nutshell, Darwin reasoned that the members of a species whose chance variation gave them an edge in the struggle to survive would tend to survive and reproduce. If the variation could be inherited, then over time the characteristics of the species would change. And over great periods of time, perhaps great changes would occur.

It was a very elegant idea. Nonetheless, Darwin knew his proposed mechanism could not explain everything, and in the *Origin* he gave us a criterion by which to judge his theory. He wrote: "If it could be demonstrated that any complex organ existed which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down."[1] Adding, however, that he could "find out no such case", Darwin of course was justifiably interested in protecting his fledgling theory from easy dismissal, and so he threw the burden of proof on opponents to "demonstrate" that something "could not possibly" have happened—which is essentially impossible to do in science. Nonetheless let us ask, what might at least *potentially* meet Darwin's criterion? What sort of organ or system seems unlikely to be formed by "nu-

merous, successive, slight modifications"? A good place to start is with one that is *irreducibly complex*. In *Darwin's Black Box: The Biochemical Challenge to Evolution*, I defined an irreducibly complex system as: "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."[2]

A good illustration of an irreducibly complex system from our everyday world is a simple mechanical mousetrap. A common mousetrap has several parts, including a wooden platform, a spring with extended ends, a hammer, holding bar, and catch. Now, if the mousetrap is missing the spring, or hammer, or platform, it does not catch mice half as well as it used to, or a quarter as well. It simply does not catch mice at all. Therefore it is irreducibly complex. It turns out that irreducibly complex systems are headaches for Darwinian theory, because they are resistant to being produced in the gradual, step-by-step manner that Darwin envisioned.

As biology has progressed with dazzling speed in the past half century, we have discovered many systems in the cell, at the very foundation of life, that, like a mousetrap, are irreducibly complex. I will mention only one example here—the bacterial flagellum. The flagellum is quite literally an outboard motor that some bacteria use to swim. It is a rotary device that, like a motorboat, turns a propeller to push against liquid, moving the bacterium forward in the process. It consists of a number of parts, including a long tail that acts as a propeller, the hook region, which attaches the propeller to the drive shaft, the motor, which uses a flow of acid from the outside of the bacterium to the inside to power the turning, a stator, which keeps the structure stationary in the plane of the membrane while the propeller turns, and bushing material to allow the drive shaft to poke up through the bacterial membrane. In the absence of the hook, or the motor, or the propeller, or the drive shaft, or most of the forty different types of proteins that genetic studies have shown to be necessary for the activity or construction of

the flagellum, one does not get a flagellum that spins half as fast as it used to, or a quarter as fast. Either the flagellum does not work, or it does not even get constructed in the cell. Like a mousetrap, the flagellum is irreducibly complex. And again like the mousetrap, its evolutionary development by "numerous, successive, slight modifications" is quite difficult to envision. In fact, if one examines the scientific literature, one quickly sees that no one has ever proposed a serious, detailed model for how the flagellum might have arisen in a Darwinian manner, let alone conducted experiments to test such a model. Thus in a flagellum we seem to have a serious candidate to meet Darwin's criterion. We have a system that seems very unlikely to have been produced by "numerous, successive, slight modifications".

Is there an alternative explanation for the origin of the flagellum? I think there is, and it is really not difficult to see. But in order to see it, we have to do something a bit unusual: we have to break a rule. The rule is rarely stated explicitly. But it was set forth candidly by Christian de Duve in his important 1995 book, *Vital Dust*. He wrote: "A warning: All through this book, I have tried to conform to the overriding rule that life be treated as a natural process, its origin, evolution, and manifestations, up to and including the human species, as governed by the same laws as nonliving processes."[3]

In science journals the rule is always obeyed, at least in letter, yet sometimes it is violated in spirit. For example, several years ago David DeRosier, professor of biology at Brandeis University, published a review article on the bacterial flagellum in which he remarked: "More so than other motors, the flagellum resembles a machine designed by a human."[4] That same year the journal *Cell* published a special issue on the topic of "Macromolecular Machines" (issue of February 6, 1998). On the cover of the journal was a painting of a stylized protein apparently in the shape of an animal, with a watch (perhaps William Paley's) in the foreground. Articles in the journal had titles such as "The Cell as a Collection of Protein Machines";

"Polymerases and the Replisome: Machines within Machines"; and "Mechanical Devices of the Spliceosome: Motors, Clocks, Springs and Things". By way of introduction, on the contents page was written: "Like the machines invented by humans to deal efficiently with the macroscopic world, protein assemblies contain highly coordinated moving parts."

Well, if the flagellum and other biochemical systems strike scientists as looking like "machines" that were "designed by a human" or "invented by humans", then why do we not actively entertain the idea that perhaps they were indeed designed by an intelligent being? We do not do that, of course, because it would violate the rule. But sometimes, when a fellow is feeling frisky, he throws caution to the wind and breaks a few rules. In fact, that is just what I did in *Darwin's Black Box*: I proposed that, rather than Darwinian evolution, a more compelling explanation for the irreducibly complex molecular machines discovered in the cell is that they were indeed designed, as David DeRosier and the editors of *Cell* apprehended —purposely designed by an intelligent agent. In the interests of time I will not discuss here how we apprehend design; I will just recommend to you William Dembski's book *The Design Inference*.[5]

Although I think that intelligent design is a rather obvious hypothesis, nonetheless my book seems to have caught a number of people by surprise, and so it has been reviewed rather widely. The *New York Times*, the *Washington Post*, the *Allentown Morning Call*—all the major media have taken a look at it. Unexpectedly, not everyone agreed with me. In fact, in response to my argument, several scientists have pointed to experimental results that, they maintain, either cast much doubt over the claim of intelligent design or outright falsify it. In the remainder of this paper I will discuss these counterexamples. I will show not only that they fail to support Darwinism but that they actually fit much better with a theory of intelligent design. After that, I will discuss the issue of falsifiability.

An "Evolved" Operon

Kenneth Miller, a professor of cell biology at Brown University, has recently written a book entitled *Finding Darwin's God*, in which he defends Darwinism from a variety of critics, including myself. In a chapter devoted to rebutting *Darwin's Black Box*, he 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".[6] He then cites the careful work over the past twenty-five years of Barry Hall of the University of Rochester on the experimental evolution of a lactose-utilizing system in *E. coli*.

Here is a brief description of how the system, called the *lac* operon, functions. The *lac* operon of *E. coli* contains genes coding for several proteins that are involved in the metabolism of a type of sugar called lactose. One protein of the *lac* operon, called a permease, imports lactose through the otherwise impermeable cell membrane. Another protein is an enzyme called galactosidase, which can break down lactose 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 the genes 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 the operon. However, in the presence of the natural "inducer" allolactose or the artificial chemical inducer IPTG, the repressor binds to the inducer and releases the operon, allowing the *lac* operon enzymes to be synthesized by the cell.

After giving his interpretation of Barry Hall's experiments, Kenneth 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! No doubt about it—the evolution of biochemical systems, even complex multipart ones, is explicable in terms of evolution. Behe is wrong.[7]

The picture Miller paints is grossly and misleadingly exaggerated. In fact, far from being a difficulty for 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.

So what did Barry Hall actually do? To study bacterial evolution in the laboratory, in the mid 1970s Hall produced a strain of *E. coli* in which the gene for just the 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.[8]

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. The *lac* permease and repressor remained intact. What is more, as we shall see, the artificial inducer IPTG was added to the bacterial culture, and an alternate, cryptic galactosidase was left intact.

Without galactosidase, Hall's cells could not grow when cultured on a medium containing only lactose as a food source. However, when grown on a plate that also included alternative 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. 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[9]—startled Hall, who knew that the odds against the mutations appearing randomly and independently were prohibitive.[10] Hall's results and similar results from other laboratories led to research in the area dubbed "adaptive mutations".[11] 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.[12]

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

The nature of adaptive mutation aside, a strong reason to consider Barry Hall's results to be quite modest is that the *ebg* proteins—both the repressor and 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.[13] Even the unmutated *ebg* galactosidase can hydrolyze lactose at a level of about 10 percent that of a "Class II" mutant galactosidase that supports cell growth.[14] 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 preexisting activities of the proteins. In a recent paper[15] Professor Hall pointed out that both the *lac* and *ebg* galactosidase enzymes are part of a family of highly conserved galactosidases, identical at thirteen of fifteen active site amino acid residues, which apparently diverged by gene duplication more than two billion years ago. The two mutations in *ebg* galactosidase that increase its ability to hydrolyze lactose change two nonidentical residues back to those of other galactosidases, so that their active sites are identical. Thus—before any experiments were done—the *ebg* active site was already a near duplicate of other 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—that is, no other protein, no other mutation in *E. coli* will work. Hall wrote:

> 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.[16]

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

Another 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. As Barry Hall states clearly,[17] in the absence of IPTG, no viable mutants are seen. The reason is that a permease is required to bring lactose into the cell. However, *ebg* only has a galactosidase activity, not a permease activity, so the experimental system had to rely on the preexisting *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.*

The prose in Miller's book obscures the facts that most of the lactose 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 preexisting components. From a sceptical perspective, the admirably careful work of Barry 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 induced by IPTG; and only if the system were also allowed to use a preexisting permease. In my view, such results are entirely in line with the expectations of irreducible complexity requiring intelligent intervention and of limited capabilities for Darwinian processes.

Blood Clotting

A second putative counterexample to intelligent design concerns the blood clotting system. Blood clotting is a very intricate biochemical process, requiring many protein parts. I had

devoted a chapter of *Darwin's Black Box* to the blood clotting cascade, claiming that it is irreducibly complex and so does not fit well within a Darwinian framework. However, Russell Doolittle, a prominent biochemist, member of the National Academy of Sciences, and expert on blood clotting, disagreed. While discussing the similarity of the proteins of the blood clotting cascade to each other in an essay in the *Boston Review* in 1997, he remarked that "the genes for new proteins come from the genes for old ones by gene duplication."[18] Doolittle's invocation of gene duplication has been repeated by many scientists reviewing my book, but it reflects a common confusion. Genes with similar sequences only suggest common descent—they do not speak to the mechanism of evolution. This point is critical to my argument and bears emphasis: *evidence of common descent is not evidence of natural selection*. Similarities among either organisms or proteins 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 it must be supported by other evidence if the question is not to be begged.

Doolittle then cited a paper entitled "Loss of Fibrinogen Rescues Mice from the Pleiotropic Effects of Plasminogen Deficiency".[19] (By way of brief explanation, fibrinogen is the precursor of the clot material; plasminogen is a protein that degrades blood clots.) 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.[20]

The implied argument seems to be that a simpler clotting cascade might be missing factors such as plasminogen and fibrinogen, and perhaps it could be expanded into the modern clotting system by gene duplication. However, that interpretation does not stand up to a careful reading of Bugge et al.[21]

In their paper Bugge et al. note that the lack of plasminogen in mice results in many problems, such as high mortality, ulcers, severe thrombosis, and delayed wound healing. On the other hand, lack of fibrinogen results in failure to clot, frequent hemorrhage, and death of females during pregnancy. The point of Bugge et al. 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. state in their abstract, "Mice deficient in plasminogen and fibrinogen are phenotypically indistinguishable from fibrinogen-deficient mice."[22] 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.[23] They are definitely not promising evolutionary intermediates.

The probable explanation is straightforward. The pathological symptoms of mice missing just plasminogen apparently are caused by uncleared clots. But fibrinogen-deficient mice cannot form clots in the first place. So problems due to uncleared clots do not 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.

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.

Other work from the same laboratory is consistent with the view that the blood-clotting cascade is irreducibly complex. Experiments with "knock-out" mice in which the genes for other clotting components, called tissue factor and prothrombin, have been deleted separately show that those components are required for clotting, and in their absence the organism suffers severely.[24]

Falsifiability

Let us now consider the issue of falsifiability. Let me say up front that I know most philosophers of science do not regard falsifiability as a necessary trait of a successful scientific theory. Nonetheless, falsifiabilty is still an important factor to consider since it is nice to know whether or not one's theory can be shown to be wrong by contact with the real world.

A frequent charge made against intelligent design is that it is unfalsifiable, or untestable. For example, in its recent booklet *Science and Creationism*, the National Academy of Sciences writes: "[I]ntelligent design . . . [is] not science because [it is] not testable by the methods of science."[25] Yet that claim seems to be at odds with the criticisms I have just summarized. Clearly, Russell Doolittle and Kenneth Miller advanced scientific arguments aimed at falsifying intelligent design. If the results of Bugge et al.[26] had been as Doolittle first thought, or if Barry Hall's work had indeed shown what Miller implied, then they correctly believed that my claims about irreducible complexity would have suffered quite a blow.

Now, one cannot have it both ways. One cannot say both that intelligent design 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 intelligent design (whether successfully or not) shows that intelligent design is indeed falsifiable. What is more, it is wide open to falsification by a series of rather straightforward laboratory experiments such as those that Miller and Doolittle pointed to, which is exactly why they pointed to them.

Now let us turn the tables and ask: How could one falsify the claim that a particular biochemical system was produced by a Darwinian process? 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 to be falsified. 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 Barry Hall started with the wrong bacterial species or 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. 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.

The danger of accepting an effectively unfalsifiable hypothesis is that science has no way to determine if the belief corresponds to reality. In the history of science, the scientific community has believed in any number of things that were in fact not true, not real, for example, the universal ether. If there were no way to test those beliefs, the progress of science might be substantially and negatively affected. If, in the present case, the expansive claims of Darwinism are in reality not true, then its unfalsifiability will cause science to bog down, as I believe it has.

So, what can be done? I do not think that the answer is never to investigate a theory that is unfalsifiable. After all, although it is unfalsifiable, Darwinism's claims are potentially positively demonstrable. For example, if some scientist conducted an experiment showing the production of a flagellum (or some equally complex system) by Darwinian processes, then the Darwinian claim would be affirmed. The question only arises in the face of negative results.

I think several steps can be prescribed. First of all, one has to be aware—raise one's consciousness—about when a theory is unfalsifiable. Second, as far as possible, an advocate of an unfalsifiable theory should try as diligently as possible to demonstrate positively the claims of the hypothesis. Third, one needs to relax Darwin's criterion from this:

> If it could be demonstrated that any complex organ existed which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down.

to something like this:

> If a complex organ exists which seems *very unlikely* to have been produced by numerous, successive, slight modifications, and if no experiments have shown that it or comparable structures can

be so produced, then maybe we are *barking up the wrong tree.* So, LET'S BREAK SOME RULES!

Of course, people will differ on the point at which they decide to break rules. But at least with the realistic criterion there could be evidence against the unfalsifiable. At least then people like Doolittle and Miller would run a risk when they cite an experiment that shows the opposite of what they had thought. At least then science would have a way to escape from the rut of unfalsifiability and think new thoughts.

NOTES

[1] C. Darwin, *The Origin of Species* (1859; reprint, New York, Bantam Books), p. 154.

[2] M. J. Behe, *Darwin's Black Box: The Biochemical Challenge to Evolution* (New York: Free Press, 1996), p. 39.

[3] C. de Duve, *Vital Dust: Life as a Cosmic Imperative* (New York: Basic Books: 1995), p. xiv.

[4] D. J. DeRosier, "The Turn of the Screw: The Bacterial Flagellar Motor", *Cell* 93 (1998): 17–20.

[5] W. A. Dembski, *The Design Inference: Eliminating Chance through Small Probabilities* (Cambridge: Cambridge University Press, 1998).

[6] K. R. Miller, *Finding Darwin's God: A Scientist's Search for Common Ground between God and Evolution* (New York: Cliff Street Books, 1999), p. 145.

[7] Ibid., pp. 146–47.

[8] B. G. Hall, "Experimental Evolution of Ebg Enzyme Provides Clues about the Evolution of Catalysis and to Evolutionary Potential", *FEMS Microbiology Letters* 174 (1999): 1–8.

[9] B. G. Hall, "Evolution of a Regulated Operon in the Laboratory", *Genetics* 101 (1982): 335–44.

[10] B. G. Hall, "Evolution on a Petri Dish: The Evolved β-Galactosidase System as a Model for Studying Acquisitive Evolution in the Laboratory", in *Evolutionary Biology*, ed. M. K. Hecht, B. Wallace, and G. T. Prance (New York: Plenum Press, 1982), pp. 85–150.

[11] P. L. Foster, "Mechanisms of Stationary Phase Mutation: A Decade of Adaptive Mutation", *Annual Review of Genetics* 33 (1999): 57–88.

[12] B. G. Hall, "On the Specificity of Adaptive Mutations", *Genetics* 145 (1997): 39–44.

[13] Hall, "Regulated Operon".

[14] Hall, "Experimental Evolution".

[15] Ibid.

[16] Ibid.

[17] Hall, "Petri Dish".

[18] R. F. Doolittle, "A Delicate Balance", *Boston Review*, February/March 1997, pp. 28–29.

[19] T. H. Bugge, K. W. Kombrinck, M. J. Flick, C. C. Daugherty, M. J. Danton, and J. L. Degen, "Loss of Fibrinogen Rescues Mice from the Pleiotropic Effects of Plasminogen Deficiency", *Cell* 87 (1996): 709–19.

[20] Doolittle, "Delicate Balance".

[21] Bugge et al., "Loss".

[22] Ibid.

[23] T. T. Suh, K. Holmback, N. J. Jensen, C. C. Daugherty, K. Small, D. I. Simon, S. Potter, and J. L. Degen, "Resolution of Spontaneous Bleeding Events but Failure of Pregnancy in Fibrinogen-Deficient Mice", *Genes and Development* 9 (1995): 2020–33.

[24] T. H. Bugge, Q. Xiao, K. W. Kombrinck, M. J. Flick, K. Holmback, M. J. Danton, M. C. Colbert, D. P. Witte, K. Fujikawa, E. W. Davie, and J. L. Degen, "Fatal Embryonic Bleeding Events in Mice Lacking Tissue Factor, the Cell-Associated Initiator of Blood Coagulation", *Proceedings of the National Academy of Sciences of the United States of America* 93 (1996): 6258–63; W. Y. Sun, D. P. Witte, J. L. Degen, M. C. Colbert, M. C. Burkart, K. Holmback, Q. Xiao, T. H. Bugge, and S. J. Degen, "Prothrombin Deficiency Results in Embryonic and Neonatal Lethality in Mice", *Proceedings of the National Academy of Sciences of the United States of America* 95 (1998): 7597–7602.

[25] National Academy of Sciences, *Science and Creationism: A View from the National Academy of Sciences* (Washington, D.C.: National Academy Press, 1999), p. 25.

[26] Bugge et al., "Loss".