Article

Craig M. Story

The God of Christianity and the G.O.D. of Immunology: Chance, Complexity, and God's Action in Nature

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Many people of faith have difficulty with the idea that randomness can exist in nature; randomness is viewed as directly conflicting with God's sovereignty. Biological processes often rely on randomness to achieve important ends. The example of antibody gene rearrangement is discussed as a primary example of such processes, and the ways God can be understood to be acting in the face of apparently random processes are explored.

Much of the tension that exists between science and certain groups within the Christian faith, particularly in the United States, arises from the complete rejection by many Christians of the possibility that randomness could exist in a world created and sustained by the sovereign, all-knowing, and all-powerful God of the Scriptures. Yet, as any geneticist will tell you, random mutations provide the source of variation in populations of organisms, which are the raw material of evolution. Still, the average person on the street will find it highly counter-intuitive that something orderly and purposeful can arise through a random process. For example, author Lee Strobel, in his popular book *The Case for a Creator: A Journalist Investigates Scientific Evidence That Points toward God*, rejects naturalism because he is not able to believe that "randomness produces fine-tuning" and "chaos produces information."[1] Strobel here represents a mainstream group of believers who have trouble reconciling two ideas: (1) the seemingly random behavior of atoms and molecules in nature, and (2) God's upholding of the universe, his foreknowledge and sovereign control over events. I believe that natural systems are characterized by a kind of randomness that is a critical aspect of the way the world operates.

In this article, I define biological randomness more precisely as extreme unpredictability, and I discuss various ways of understanding the concept of randomness. I argue that randomness does not necessarily exclude purpose. In fact, such unpredictability is a necessary feature of many biological systems; it is randomness with a purpose. People whose conception of God allows for no such randomness are forced either to reject their God, or, more likely, ignore

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these observations of the natural world. I believe that this is a false choice based on a flawed understanding of God's action in the world.

A major goal of this article is to clearly demonstrate how a specific type of randomness is an essential component of some biological systems, and is compatible with belief in the biblical God of traditional Christianity. An example from my own field of immunology is the process whereby antibody gene segments rearrange to form functional genes, which I will describe below in some detail. This is just one example that illustrates how extensive and multilayered biological examples of randomness can be. In contradiction to Strobel's statement and many people's intuition, randomness, in this case, does, in fact, "produce fine-tuning." As one who upholds my college's statement of faith in "one God, the Creator and Sustainer of all things," I personally believe that randomness is compatible with God's sustaining and creative activity. The final section of this article will discuss philosophical ways to understand how God's activity relates to this kind of randomness in the natural realm.

Definitions of Randomness

It is important to define terms from the outset, since the words "random" and "chance" can have different meanings, depending on the context, and are used interchangeably by some authors, but not by others. The term "randomness" can have a precise mathematical meaning, as well as more common, intuitive meanings. The topic of randomness has come up a number of times in *Perspectives on Science and Christian Faith (PSCF)*. I refer the reader to Ronald Remmel's presentation before the California State Board of Education in 1972, reprinted in this journal,[2] in which he discussed several possible interpretations of the word, and discussed some of the quantum mechanical aspects of the issue, which are beyond the scope of the current discussion. In his speech, Remmel asked the important question of whether the world is really random or only appears that way to our limited knowledge. His personal belief was that God determines the random numbers that make the world function.

In a more recent paper, G. R. Morton and G. Simons discussed the issue of biology and chance, with respect to genome organization.[3] They point out that the Bible repeatedly describes God as being in control of chance mechanisms (such as casting lots). These authors distinguish between some meanings of randomness and chance. For instance, one definition of a random process that most people would understand is one in which the results of a procedure fall into a particular well-defined probability distribution. A well-balanced coin will yield a normal distribution with 50% heads and 50% tails, for example. A stochastic mechanism such as rolling dice may not be truly mathematically random, as would be the case if they were unbalanced. Nonetheless, even with a loaded die, the chance of rolling any given number is predictable with a certain defined degree of probability specific to that particular die. Likewise, card players can tell what the probabilities of various types of hands would be.

In my experience, when biologists describe a process as random, they usually mean that the process or result is exceedingly unpredictable. It is this kind of randomness that undergirds evolutionary processes such as gene duplication and genetic mutation. Since our genomes contain three billion nucleotides and tens of thousands of genes, the chance of a mutation occurring at any single point is a highly improbable event. It would seem impossible to predict, in advance, where such a singular mutational event would occur because of the improbability of a mutation occurring, since the mutation-generating enzyme (DNA polymerase) is extremely accurate and only very rarely makes a base mismatch during DNA replication. As Graeme Finlay summarized in a 2008 *PSCF* article on God's creative activity and randomness of DNA mutational events,

> Physical laws that describe the behavior of DNA and the way it mutates (no matter how probabilistic their operation may be) are laws that reflect God's faithful dealings with his creation. …
>
> The operation of random (probabilistic) processes in gene and species formation cannot be an alternative to divine creativity, but is an aspect of divine creativity. Indeed, because of their evident role in contributing to the formation of new genes, such random processes (chance) in the context of the directing effects of selection (necessity) lead to predictable results.[4]

Finlay then compares such systems to powerful computer programs that use "genetic algorithms" to select optimum solutions from randomly generated choices.

It is quite likely that the antibody gene shuffling processes described below are not actually random in the mathematical sense, since some rearrangements may occur more than others. In fact, the shuffling of antibody gene segments should be seen as a very complex stochastic system whose final result, the three-dimensional shape of the final antigen-binding site, cannot be predicted in advance. Not only is the particular amino acid sequence of the resulting protein not determined in advance, but also the precise three-dimensional folded structure of the final antibody is itself highly unpredictable, and beyond the capabilities of today's most advanced computers to predict. Christians should work to understand what biologists mean when they speak of events as being random, and accept that these do, in fact, occur every day in our bodies. The more challenging philosophical issue remains, to determine what role God plays in these events. A number of different viewpoints held by theologians and other Christian writers will be discussed in the final section of this article.

Antibody Gene Rearrangement

To some it seems obvious that chance events are incompatible with God's sovereignty and omnipotence. Phillip Johnson, a key player in the intelligent design movement, has been quoted as saying that the important question about evolution is "whether there's an intelligence and purpose behind our existence—or our existence is random and accidental."[5] Here, the word random and accidental are conjoined and therefore stated as having no purpose. How can God be truly in control of the world if randomness exists and accidents happen? In the following example, we will see that the system for generating antibodies involves a number of distinct steps, each of which is highly "accidental" or random in nature, yet I hope to demonstrate that it is this very randomness which provides the defense against disease that keeps new viruses and bacteria from invading our bodies.

In the antibody gene rearrangement system, widely separated segments of DNA join together in unpredictable ways, forming functional genes capable of producing antibody proteins that bind to the surfaces of invading pathogens. The great diversity of potential pathogens in the world demands that our bodies contain an equally diverse pool of antibodies to combat them. Yet, rather than encoding tens of thousands of different antibodies of predetermined binding specificity in our genome, the antibody-producing cells rearrange several antibody gene segments to produce in the range of 10^9 different antibodies. The raw material here is a collection of hundreds, rather than thousands, of gene segments. The result is a sufficiently diverse pool of antibodies such that, at any given moment, at least a few of them are capable of binding to and inactivating any bacterium or virus encountered.

Though I have provided enough detail below to entertain a senior biology undergraduate or possibly also a biologist in a field outside of immunology, I encourage those readers unfamiliar with immunology to feel free to skim through some of the immunological details and history below, once the main point being made on how the genes rearrange is understood.

The G.O.D. of Immunology

The vertebrate immune system can produce an extremely large number of structurally distinct proteins known as antibodies, which are distinguished by the antigen they recognize. Like all proteins, they require assembly instructions encoded in the DNA. Antibodies are produced in response to a triggering substance, an antigen. The problem that plagued scientists was that there seemed to be far too many types of antibodies produced by the immune system. The number of antibody specificities is exceedingly large. This would require either a huge amount of genome devoted to antibody genes, or a diversity generation mechanism. In fact, a diversity generating mechanism does exist, and it involves several highly unpredictable (random) steps, which, in combination, greatly raise the diversity of the antibody specificity pool. Exactly how this antibody diversity is *encoded* in the DNA has been ironically called immunology's G.O.D. problem—and searching for the Generator of Diversity (G.O.D.) was a central mystery in immunology for many decades.

The chief job of an antibody is to bind tightly to and inactivate, or mark for destruction, foreign substances that enter the body. The ability of these antibody proteins to bind to the surfaces of viruses or bacteria that have never before been encountered, is critically important for survival. A defensive army of blood cells, called B cells, secrete antibody proteins into body fluids such as blood, lymph, and

milk, and also into the intestine. People who lack B cells due to a genetic disorder or medical treatments such as chemotherapy become repeatedly afflicted by bacterial, viral, and fungal infections that a normal person would fight off easily.

Antibodies are arguably among the most important proteins for immune defense. These Y-shaped proteins mysteriously and suddenly (within a week) appear in the blood following exposure to a foreign substance. This foreign substance could be the protein or sugar antigens contained in a vaccine (a flu shot), or the actual pathogen itself (influenza virus). Long before it was known *how* these specific antibodies were produced, it was understood that a vaccine could provide long-lasting protection from disease, if it contained antigens similar to those of a pathogen and was delivered in a weakened or non-infective form. For simplicity, the following discussion will focus on the antibody diversity generation mechanism. However, a parallel (homologous) G.O.D. system is found in the T cell arm of the immune system for the generation of T cell receptors.

The search for mechanisms used by the body to produce such a diverse immune repertoire began with Paul Ehrlich around 1900. The problem was amplified after Karl Landsteiner's demonstration that laboratory animals could produce antibodies against man-made organic compounds not found in the natural environment (experimental work around 1917, discussed in Tauber[6]). Starting in the 1970s, using the tools provided by the recombinant DNA revolution, the solution to this puzzle of antibody diversity has been revealed in great detail.

The diversity generating mechanism is summarized in the following, and provides a clear example of a kind of randomness that is often observed in biological systems. Lennox and Cohn coined the phrase "generator of diversity" (and the catchy abbreviation G.O.D.) to describe the process whereby antibodies obtained their diversity. The portion of their 1967 review in which G.O.D. is first mentioned is shown below, and despite the use of some terms unfamiliar to the non-immunologist (v for variable gene region, c for constant gene region), it should be apparent that, at the time, they did not have much to go on in formulating a mechanistic explanation. These authors were trying to explain the observation that antibodies have portions of their sequences that are very consistent (constant) from one to another antibody, and other regions that are highly different in amino acid sequence (variable). The DNA encoding these segments has a very defined region wherein the variability is found. This variable region, we now realize, is the part of the antibody that binds antigen, and the source of this variableness is what Lennox and Cohn were speculating about in their review.

> One can imagine models in which variety is introduced into v, not c. An example is that proposed by Brenner & Milstein. Whatever the detailed mechanism, one must suppose a region in DNA which signals the start or stop for the generator of diversity. This is abbreviated GOD … Diversity could be generated by an error-prone DNA polymerase or an error-prone DNA template. Included must be a mechanism to assure that the portion of the v gene coding for V in the protein is varied throughout its length, i.e., there must be a stop as well as a start signal. The reason for assuming this is the failure to find a gradient of variability along V … A mechanism which introduces random variation in V must waste chains and, therefore, cells since not all amino acid residues introduced into V are compatible with a functional subunit. Controlled variation would eliminate waste, but no simple mechanism for this, consistent with the facts we are trying to explain, presents itself.[7]

The point that Lennox and Cohn were making was that they suspected that the region of DNA encoding the variable, antigen-binding portions of the antibody gene was produced by an error-generating mechanism that was targeted to a part of the DNA. Here, "error" is a necessary aspect of the production of antibodies. Such errors were seen at the time as a necessary feature driving the diversity of the antibody population. Lennox and Cohn's speculations were partly correct, as we will see below.

Competing Theories to Explain Antibody Diversity and Specificity

For the first half of the twentieth century, prior to the discovery of T lymphocytes, the field of immunology focused heavily on theories of antibody formation. In addition to the diversity problem, scientists were also puzzled by the basis for self-nonself discrimination—stated another way, this is the immune system's nonreactivity to its own antigens (self-

tolerance). We not only need a diverse pool of antibody specificities, but we also need to avoid self-reactivity; the antibodies we produce must be directed against pathogens or foreign antigens, and not against self antigens. When the immune system produces antibodies against its own tissues, the result is autoimmune disease, something immunologist Paul Ehrlich appropriately termed *horror autotoxicus*.[8] Examples of common autoimmune diseases include rheumatoid arthritis, lupus, and type I diabetes. In each case, the immune defenses are directed against normal body tissues.

Understanding the physiological basis for self-nonself discrimination and antigenic specificity was helped along by a short paper published in the little-known *Australian Journal of Science* in 1957. It was here that Frank Macfarlane Burnet proposed his clonal selection theory (CST).[9] CST appeared in the context of competing ideas of antibody formation, between those favoring instructionist and those favoring selectionist models for the origin of antibody specificities.[10] Burnet's CST posited that *individual cells bearing single receptor specificities were subsequently selected by antigen to divide and expand clonally*—a revolutionary idea. This theory potentially resolved a number of questions, including immunological memory (a long-lived clone), tissue specific responses (clones residing in different tissues), autoimmunity (clone with a mutated antibody), and tolerance (self-reactive clones deleted early in development). As mentioned in a recent review celebrating CST's fiftieth anniversary, a corollary of CST is the requirement of a diversity of receptors present on the surface of B cells upon which selective forces may act.[11]

In principle, there are two ways antibodies could end up detecting antigen and proliferating to quell an invasion. In an *instructionist* model, an antibody's shape is directly influenced by contact with antigen, whereas in a *selectionist* model, a pre-existing antigenic specificity is chosen (selected) by antigen from a presumably diverse pool. That is, either the antibody changes as it contacts antigen or else the body is making many types of antibodies even before it is exposed to antigens. The history of instructionist vs. selectionist models is rather convoluted, with individual researchers changing their views over time, as new experiments became known. One of the earliest instructionist models was Paul Ehrlich's "side-chain" theory.[12] The side-chain theory persisted through the 1960s and seemed to agree with Jacques Monod's findings in bacterial enzymology: just as bacterial enzymes seemed to adapt to alteration in their sugar fuel, as understood at the time, pathogens were thought to imprint their shapes onto the immune-globulin proteins, inducing them to change shape in response. The demise of instructionist models largely came about as the result of an increasing understanding of molecular genetics and molecular biology, which began in earnest following Watson and Crick's discovery of DNA's structure in 1953.

Ultimately, the solution to the diversity question, and the identity of immunology's G.O.D., provided some insights into the development of self-nonself identity within the immune system, and a convincing confirmation of the clonal selection theory. By the late 1970s and early 1980s, the realization that antibody-producing cells were clonally selected focused attention on what was happening at the genetic level. Was there something special about the antibody genes that allowed for production of such a large potential pool of different specificities to be manufactured? Indeed, there was, and sequencing the genes eventually told much of the story of what was going on.

Explaining Receptor Diversity

A number of ideas were put forth to explain the great diversity seen in the antibody proteins. The nature of the problem was extended when it was realized that antibodies could be generated against compounds not found in living cells or in the natural environment, such as 2,4-dinitrophenyl[13] or 2-phenyl-oxazolone.[14] One explanation for the great diversity is that our DNA, passed down through the generations, might encode many different antibodies, enough to bind every conceivable antigen, and the appropriate ones are selected when needed. But this proposal requires that a very significant proportion of the genome be devoted to antibodies.

Research over the past forty years has uncovered many details of the genetic mechanism that produces diversity in the receptors of B cells (antibody molecules). Indeed, it has proven true that much of the raw material for the antibody repertoire is encoded in the genome, and yet the antibody repertoire is also distinctly molded by the environment, but not in the way the instructionists had proposed. The G.O.D. mechanism began to be revealed when

methods for determining the amino acid sequence of antibody proteins were developed, in concert with DNA sequencing technology. The key discovery—one totally unprecedented—was that *multiple combinations of gene segments are assembled to form the final antibody gene.* The precursors of antibody-producing B cells are continually produced from the bone marrow, and in the process of B cell development, the antibody genes are rearranged to generate novel specificities. This is unlike most genes, in which the genetic code is read off as a blueprint for assembly of a single, defined amino acid sequence of the protein. These changes in the DNA, which are randomly generated as described below, produce the variability seen in the antibodies.

How Antibodies Are Formed

Antibodies are Y-shaped proteins made of a light chain and heavy chain paired as shown in Figure 1. The heavy and light chains fold together so that their amino terminal ends (NH_3^+) form the antigen-binding site.

As mentioned above, amino acid sequencing, and later DNA sequencing, revealed a high degree of sequence diversity in the variable domains of both the heavy and light chains. The observation that there was a variable end and a more constant region led Dreyer and Bennett, in 1965, to propose the existence of a large number of variable "genes" which would rearrange and join with a fewer number of constant genes.[16]

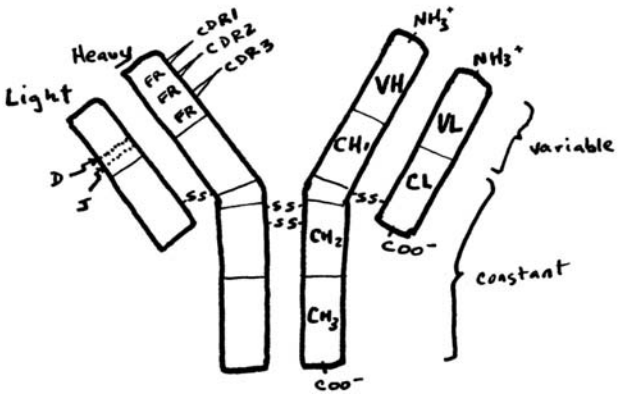

Figure 1. The basic structure of an IgG antibody protein.[15] The structure is composed of two light chains and two heavy chains. The three constant domains of the heavy chain are denoted (CH_1, CH_2, CH_3). Disulfide bonds (S-S) hold the structure together in a H_2-L_2 stoichiometry. The variable domains of light and heavy chains (VL, VH) are the parts of the antibody that are encoded by gene segments which undergo the sorts of rearrangements described in the text, giving rise to tremendous diversity in the amino acid sequences and, therefore, antigen-binding specificity. The D and J segments are shown in their approximate positions along the variable domain. Less variable parts are known as framework regions (FR) and are involved in the protein's folded structure, rather than in antigen binding. CDRs are complementarity determining regions that loop out and contact antigen.

In 1970, amino acid sequencing of the amino termini of 64 different antibody light chains revealed a significant degree of diversity, with a degree of similarity such that variable segments could be grouped into families. This prompted the authors, Hood and Talmage, to propose the possibility that 10,000 light chain genes, in combination with 10,000 heavy chain genes, could produce 100 million specificities.[17] With some back-of-the-envelope calculations, they figured that this would only require 0.4 percent of the 3 billion basepairs of the human genome. Hood and his colleagues would have been surprised to learn that less than about 1.5% of the entire human genome actually encodes protein, as revealed by sequencing the entire genome,[18] and that we actually have somewhere in the vicinity of 25,000 protein-encoding genes total.[19]

Once antibody genes began to be sequenced, it became apparent that large numbers of genes was not the answer. One clue to the source of diversity came with the findings of Susumu Tonegawa, that the DNA encoding the antibody genes found in antibody-secreting B cells was markedly different from the same region of DNA isolated from sperm cells or body cells of the same animal (the germline DNA). Something unprecedented had happened to the immunoglobulin genes during the process of B cell development—parts of the genes had rearranged, confirming the Dreyer-Bennett hypothesis.[20] This finding was significant enough to earn Tonegawa a Nobel Prize in 1987. By the early 1980s, DNA sequencing of numerous light and heavy chain genes from B cells, as well as the entire germline region, had revealed the presence of gene segments which were joined together (rearranged) to form the final productive antibody heavy and light chain genes.[21]

By comparing DNA sequences of germline, unrearranged DNA with the sequences of rearranged antibody genes, it became clear that there were three distinct types of gene segments that combined to encode the antigen-binding part of the antibody heavy and light chain genes. These are now known

as V (variable), D (diversity), and J (joining) segments. Once the variable region had rearranged, a final step of recombination brought the rearranged variable segment in contact with the C (constant) gene region, and a complete antibody gene was then ready to be transcribed and translated into protein. A rearranged light chain gene is formed by a recombination event in which a single V gene segment combines with a J segment. Next, this V-J is joined with the remaining invariant portion of the gene, the constant region (C region). A rearranged heavy chain gene is similar but slightly more complicated, as it involves the additional diversity (D) segment, with D→J joining first, then V→DJ joining, followed by VDJ→C joining. Immunologists have been known to say unusual-sounding things like "V to D-J" and "V-D-J to C," and they actually know what they are talking about. (You may need to read those last few sentences again, or just skip ahead.) The layout of gene segments for the heavy chain genes in mice is shown in Figure 2. Humans have a similar arrangement.

This process of gene rearrangement is known as V(D)J recombination, and is supported by a mountain of experimental evidence, including identification of the targeting sequences flanking each of the gene segments, and the rules which ensure that the segments assemble in the proper order (not V to V, for example), as well as the identification of the specific recombination genes (RAG1 and RAG2) that accomplish the rearrangement with help from several DNA housekeeping enzymes.[22]

An important component of V(D)J recombination that injects a significant degree of additional randomness (unpredictability) into the process is the *imprecision of the joining mechanism*. During the cutting-and-pasting process, each double-stranded DNA end is temporarily held in a closed hairpin configuration. This hairpin is then enzymatically cleaved, often off-center, which, upon extending outward, can add several additional nucleotides. (These are called palindromic "P" nucleotides, since they spell out a short DNA palindrome as a result of the hairpin mechanism.) In addition, several non-templated nucleotides, known as "N" additions, may be added by the enzyme terminal deoxynucleotidyl transferase (TdT).[23] These additional P and N nucleotides added at the junctions between V, D, and J segments add a significant amount of diversity to the repertoire, as the greatest amount of variation is seen precisely at this junction. (CDR3 in Figure 1.)

Tonegawa noted that the imprecision of DNA end joining produces diversity which comes at the expense of significant losses because of shifts in the reading frame, which result in a nonviable protein upon translation.[24] Since amino acids are encoded three at a time, if one or two nucleotides are inserted at a junction, the ribosome will be shifted to a new reading frame, and amino acid "nonsense" will be produced until a stop signal is reached, which usually prematurely truncates the amino acid chain. Since there are two copies of each genetic locus, the B cell has two opportunities to arrive at a productive rearrangement for each antibody chain.

At this point, it may be helpful to summarize some of the contributions to generating diversity in the antibody repertoire. Each of these steps involve a degree of unpredictability and chance:

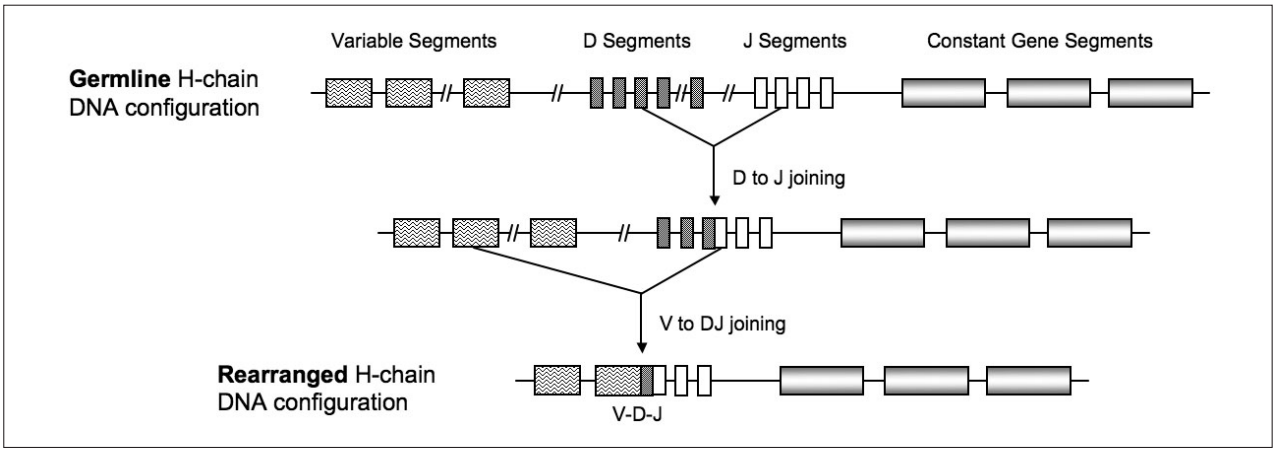

Figure 2. The process of V-D-J joining in the heavy chain of antibody is illustrated. There are hundreds of V regions, dozens of D segments, and several J segments. The VDJ junction thus created will then join with one of the C region gene segments to form the complete antibody gene.[25]

1. Two Chains: The antigen binding site is a combination of one light chain with one heavy chain which are encoded separately in the genome;
2. Many V Regions: Each antibody gene is formed by selecting one from among many variable region-encoding genes (hundreds);
3. Additional Gene Segments: Each of the variable regions is actually a combination of multiple gene segments; for the light chain, V+J; for the heavy chain, V+D+J;
4. Junctional Diversity: The junctions between the gene segments are joined in an imprecise manner.

For completeness, I should mention one other mechanism that introduces diversification of antibodies through continued, targeted mutation within the rearranged antibody genes. This happens when clones of stimulated B cells are rapidly dividing in the immune organs such as the spleen and lymph nodes. Here, single base mutations are introduced within the antibody genes, which may or may not result in amino acid changes. There is apparently a competition within these immunological organs for B cells with increased antigen-binding affinity, and those cells with mutations resulting in higher affinity have a selective advantage over their nonmutated siblings. This final level of antibody diversification, known as somatic hypermutation, has been reviewed in detail recently, and the chief enzyme responsible, a cytidine deaminase, has been identified.[26] This mechanism helps explain so-called *affinity maturation*, in which antibodies appearing after multiple booster immunizations have greatly increased binding affinity compared to those arising after a single immunization. This is another example of randomness with a purpose; it is a microcosm of evolutionary competition and survival of the fittest on a cellular scale.

A mathematical formula expressing the contributors to this diversity was presented by Tauber and is as follows:

$$s_m\ (f_1V \times J \times f_2V \times D \times J)$$

with the factors V x J and V x D x J being the light and heavy chain combinatorial diversity, f_1 and f_2 representing the factor of light chain and heavy chain junctional diversity due to flexible joining mechanisms, and s_m being the factor due to somatic point mutations involved in affinity maturation.[27] This system is remarkably economical from a genetic standpoint, as it is theoretically capable of generating on the order of 1×10^{10} different antibodies from only approximately 500 gene segments.[28] No matter what the precise value is, clearly it is a very high number, and the mechanisms shown provide a satisfactory explanation for the ability of animals to make specific antibodies against practically any appropriately sized molecule.

In describing the above system, I have shown that random, or highly unpredictable events occur at a number of points in the process whereby mature antibody encoding genes are formed. This process involves the imprecise joining of gene segments chosen from a pool of possible choices. As a result of this mechanism, the way the final light and heavy chain polypeptides will come together as a folded protein is absolutely not specified in advance, and seems left to chance. Superimposed on this system is the requirement that the antibody produced not be self-reactive. Self-reactive B cells self-destruct early in development before they escape into the peripheral tissues, which solves the problem of autoimmunity. Also, many antibodies that could potentially be useful are produced and then die naturally without ever being stimulated or "called to action" by disease. Our bodies continually manufacture novel specificities to fight off new invaders, and also rely on the memory of past battles to fight the same disease more quickly when it is again encountered, by setting aside a cadre of long lived memory cells.

Without the chancy and random nature of the recombination process, it would not be possible to generate the diversity required to protect from disease with the amount of DNA allocated to this function. Of course, we should not think of this randomness as complete chaos, since the joining process is tightly controlled and mutations are targeted to the appropriate parts of the genome. Yet it would be hard to argue that randomness plays no role in the system. Not only is there a clear role for randomness, but randomness is also the key secret to the success of the recombination process in generating extremely high levels of diversity with a modicum of DNA raw material. Since only the useful and non-self-reactive specificities are selected for clonal expansion, the system, in the end, *seems* more intelligent that it actually is. At this point, let us consider the role that God may be playing in the immune system, and by extension, in the natural world more generally.

Philosophical and Theological Implications

A considerable amount of literature addresses God's role in creation, and most traditional Christians (such as those attending and teaching at my college) would agree with the basic statement that God, indeed, did create the cosmos, which is the sum total of all we observe (and even that which we do not observe) in our universe. On the subject of God's role in creation, the *Westminster Larger Catechism* (1647) states: "God executes his decrees in the works of creation and providence, according to his infallible foreknowledge, and the free and immutable counsel of his own will." I have found much agreement among believers that God is the Creator of all things, including the very large, such as the distant galaxies and the solar system, and the very small, including atoms and macromolecules like DNA or antibody proteins.

Christians can also agree in the biblical concept that God is not only the Creator but also the Sustainer of all things. God "upholds the universe by his word of power" and "in Christ all things hold together" (Heb. 1:3; Col. 1:17). Yet, it is important for us to examine these terms more carefully. What do we precisely mean when we say that God sustains and creates? How does he sustain, and through what means or mechanisms is creating accomplished? For example, a plain reading of Scripture gives the impression that God's creative acts occurred in the blink of an eye:

> And God said, "Let the waters teem with living creatures, and let birds fly above the earth across the expanse of the sky." So God created the great creatures of the sea and every living thing with which the water teems …
> (Gen. 1: 20–21).

This description of God's activity in creation is quite different from the accepted scientific explanation. Any discussion of how God acts in the world must consider the fact that science has made great progress in understanding a great many details about the inner workings of not only the stars and planets, but also of living systems—something that would have been utterly unimaginable in biblical times.

Science has been so successful that, for a number of increasingly outspoken atheist scientists, this scientific level of understanding is, for them, sufficient in and of itself. A small but vocal number of these scientists have forcefully argued that a scientific understanding should be sufficient for Christians as well. One does not need to search very hard to find a quote from a prominent scientist deifying random processes, or at least suggesting that randomness plus time is a complete explanation. One well-known and possibly apocryphal example is from biologist Richard Dawkins: "Life results from the nonrandom survival of randomly varying replicators."[29] At this point, I would like to keep in mind the title of a popular book on the controversial subject of origins: *God Did It, but How?*[30] Fischer's book, which I first read as an undergraduate, underscores the essential and important point on which all Christians can agree: God is ultimately responsible for the existence of the universe and all that it contains. God did it.

Now we come to the more interesting discussion of God's role in the kind of chance processes such as those I have described for antibody gene rearrangement, but which are also found in many other biological processes. Again, I am defining random in the sense of highly unpredictable, highly contingent processes. One of my goals here is to raise awareness of work in philosophy addressing the issue of randomness in nature. My opinion is that this issue of randomness, chance, and seeming unpredictability found in nature lies near the heart of the struggle that many believers have with evolutionary science. It is particularly problematic if any kind of chance-based mechanism is dismissed out of hand as simply incompatible with a biblical worldview. I hope that I have clearly painted a picture of how chance and stochastic processes are important to the normal functioning of the immune system. However, this still leaves open the question of God's role in the process, and whether or not he is limited in his future knowledge.

The late theologian and biochemist Arthur Peacocke directly addressed philosophical and theological questions of how God acts in the world. Peacocke was critical of his fellow biologist Jacques Monod's view that "only" chance was responsible for the world, stating that he saw no reason to elevate the observations of chance events to a metaphysical principle.[31] In his monograph, Peacocke provided a helpful explication of two meanings of chance. There is, on the one hand, the kind of chance seen in flipping a coin. In this instance, if one knew all the variables of force,

friction, and so forth, one could predict the landing as heads or tails. This really is not chance at all, but simply lack of precise knowledge. The second kind of chance he discusses is, I think, more applicable to antibody rearrangement. This is the kind of "accidental" intersection of two (or more) unrelated causal chains. The example he uses is one of a hammer falling from a building and hitting an unfortunate passerby on the head. One event is unrelated to the other, and it is a pure accident that they occurred together. As Peacocke states,

> There is no connection between these two causal chains except their point of intersection, and when the hammer hits you on the head could not have been predicted from within the terms of reference of either chain taken by itself.[32]

I think it is this second type of randomness that occurs in V(D)J recombination in antibody genes. For example, first one particular V region joins to a particular J region, and in the process, the hairpin loop of DNA then happens to be opened at one particular position, followed by the insertion of, say, six nucleotides, each of which could be A, C, G, or T. This is indeed a collection of independent events that together may (or may not) eventually produce a single product, a functional antibody gene. Despite Peacocke's acceptance of accidental events in biology and in the world of falling hammers, he viewed all events, including the random ones, as God's hand at work. His view "posits that God exists and interpenetrates every part of nature, and timelessly extends beyond as well."[33] In this scheme, if God were not to exist, so also all matter and energy of the universe would cease to exist; however, God is also transcendent over the universe.

In David Bartholomew's recent book, *God, Chance and Purpose: Can God Have It Both Ways?* he argues that chance events, rather than running counter to the idea of a sovereign God, are actually an essential component of the world. Chance events should be seen as *within* the providence of God. As he writes, "chance is a necessary and desirable aspect of natural and social processes which greatly enriches the potentialities of the creation."[34] In the example of antibody diversity, it should be apparent that without the random nature of its mechanism, the cell would require a much more bulky system, involving dramatically more actual nucleic acid content (numbers of genes).

Not all Christians agree with Bartholomew's view. In a review of Bartholomew's book, intelligent design theorist William Dembski outright rejects the possibility that uncertainty (randomness) exists in the universe, at least from the point of view of God, the idea being that we only *think* certain things are random, but they really are not.[35] Dembski further criticizes Bartholomew for a "surprisingly shallow" view of chance, saying that he does not tell his readers what chance is. I hope that my example of antibody rearrangement has clearly indicated, at the very least, what I mean by the terms randomness and chance.

Dembski argues that if God were to allow randomness, then he is no longer able to know all things, and could not know the future because it would be a random outcome. I prefer to leave open the possibility that what we perceive as chance or random events really are God's doing. This is consistent with Remmel's view, mentioned earlier, wherein God chooses the random numbers that drive natural events. He is "doing" it, and it is random (to us). I am comfortable accepting the seemingly contradictory ideas that God can both allow randomness and also know the future. Since God operates and exists in a dimension where time has no limitation for him, he is in the past, present, and future all of the "time." He knows the future, because he has been there (and is there). We, who cannot know the future because we are "stuck" in the present, are only projecting our limitations on God when we say he is limited by present randomness and uncertainty. If the randomness that we see is merely an illusion, as Dembski seems to suggest, I suppose that is one way to resolve the paradox. For all practical purposes, however, and from our human perspective, we may as well consider randomness to be *100% real*. We should work diligently to understand how randomness may be involved in natural processes, and, at the same time, understand that God is carrying out his ultimate ends as revealed by Scripture.

God is answering prayer, creating divine appointments and coincidences for those who are under his mantle of care and who call on his name. Critics of evolutionary science such as Phillip Johnson have argued that "methodological naturalism" is an all-encompassing worldview which is contrary to biblical Christianity. He sparked the intelligent design

movement as a way to detect the supernatural or to inject the designer into the daily bench work done by working scientists, an effort which will be doomed to failure if random processes are, in fact, a major part of God's way of working in the world. The challenge therefore remains, to explain the randomness theologically. We must not stick our heads in the sand and pretend that randomness does not exist, or try to define it away. In a pre-Darwinian world, the knowledge of randomness in nature was greatly diminished. In the twenty-first century, theologians may be playing a catch-up game with science. And despite the good work that has already been done, many lay people remain unaware, and often see science and faith at odds with each other.

This discussion has done little to resolve how we are to understand God's precise role if randomness is the normal way nature works. It may be as John Polkinghorne has suggested, that the existence of quantum uncertainty is what allows God room to work.[36] There are two extreme viewpoints. In one, God is continually moving every individual atom, every raindrop. As John Calvin wrote, "it is certain that not a drop of rain falls without the express command of God."[37] This view is seen even today in the lyrics of popular worship songs such as "Indescribable," by Chris Tomlin, in which God is described as playing a very active role in natural events:

> Who has told every lightning bolt
> where it should go
> Or seen heavenly storehouses
> laden with snow
> Who imagined the sun
> and gives source to its light
> Yet conceals it to bring us
> the coolness of night?[38]

The opposite extreme is that of a strictly material world in which each atom goes about its business with no room whatsoever for God's action. Peacocke's view has the atoms going about their business, but God being intimately involved in the process. In Finlay's article on random process and divine purpose, he points to a third option, that nature has *relative autonomy*. This means that God allows nature to have a self-sufficient mode of operation, but that this autonomy is completely dependent on God conferring it on the natural realm.[39] I should mention that this autonomy can be seen as parallel with free will of humankind. If God is able to be sovereign in the face of humans' free will, it seems to me that he is also able to be sovereign in the face of molecules' random behavior. I realize that the topic of free will is a deep one, itself open to debate among various branches of Christendom, and we should not be sidetracked by this fascinating and potentially irresolvable topic. I would note that the topic of free will in nature has been explored by Polkinghorne and others.[40]

The inside front page of Arthur Peacocke's 2004 edited volume entitled *"Evolution: The Disguised Friend of Faith?"* contains a fascinating quote from Aubrey Moore, one of the first clergymen to openly accept Darwinian evolution by natural selection and incorporate it into his theology. These words were published about thirty years after publication of Darwin's *On the Origin of Species*.

> The one absolutely impossible conception of God, in the present day, is that which represents him as an occasional visitor. Science has pushed the deist's God further and further away, and at the moment when it seemed as if He would be thrust out all together, Darwinism appeared, and, under the disguise of a foe, did the work of a friend … Either God is everywhere present in nature, or he is nowhere.
>
> A. L. Moore (1848–1890)[41]

Given these options, I would emphatically agree that God is everywhere present in nature, even though he may seem disguised behind events that to us seem very random, chancy, and uncertain. To me, it is glorious, indeed, to consider that from the randomness in the world of biology arise the many good things we enjoy, and for which we give God thanks. The combination of chromosomes in sexual reproduction gives rise to the variation we see among living organisms; random combinations of gene segments allow us to defend against every bacterium and virus that comes our way. There probably is no way, humanly possible, that we will ever fully grasp how God is able to know the future, yet still allow nature to have autonomy; yet I am personally comfortable with that paradox. I believe and trust that God is at work in the world, and not distant, faithfully bringing about his ultimate aims, while, at the same time, allowing raindrops, lightning bolts, and antibody genes to operate with their own economy, under his all-knowing care and ultimate authority. ❋

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Notes

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