

***CELLS AND GENES ARE PARTS OF ANIMALS: ARISTOTLE IN THE LATE 20TH CENTURY***

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### CELLS AND GENES ARE PARTS OF ANIMALS: ARISTOTLE IN THE LATE 20TH CENTURY

Ms. Braun, members of the St. John's faculty, fellow-members of the St. John's community. It is a pleasure to be your guest this evening and to return to the campus where my intellectual and spiritual life was nurtured for four years. I must begin by reassuring Mr. Michael Dink that I really do have a talk planned this evening and that this is not just an elaborately-organized scheme for me to get a bully-pulpit to regale yet another generation of St. Johnnies about events that occurred on a nearby softball field just under 20 years ago. Let me also assure those who think that the words "...mental lapse..." and "Michael Dink" can't be spoken in the same sentence that the full telling of this story will occur (yet again) during my class's 20th reunion a little more than a year from now.

This lecture has been incubating for more than eight years, since, in fact, my first introduction to biomedical science in Paul Levine's laboratory at Washington University in St. Louis. Until then, my exposure to medical research, even in medical school, had been more bookish than practical and my own view of how hypotheses are generated and tested was, I think, limited. Since that time, I have had the great privilege of participating in a first-hand way in the investigation of living matter and how it works. My primary interest in this activity has been a practical one: I have accepted the Baconian premise that understanding how the body functions or operates under normal conditions is the key to understanding what happens when it *doesn't* function or doesn't function well. I have, in effect, taken a rather narrow and what might otherwise be called mechanistic approach to living matter. More precisely, I have become interested in how cells, genes, and proteins work (this distinction between the understanding the whole and the parts, and understanding how something works versus other kinds of understanding, will be explored further in this lecture). Thus, this lecture will have something of a narrow focus. Please don't expect insights of a profound nature, either about living matter or about Aristotle. I am fully aware that there are individuals in this audience (probably sophomores, who have read just enough Aristotle to be menacing) who may even be expecting me to finish this lecture by telling you what "life", or living matter is. Please accept my humble apologies for not providing this and offering, instead, some thoughts about the *study* of living things and Aristotle's contributions to that study. During the course of this lecture I will share some of my insights into Aristotle's *The Parts of Animals*, and I will also tell you a little bit about how to clone a gene. In the process of doing so, it is my intention to awaken you to the incredible beauty and complexity of living things and enhance your respect for Aristotle's understanding of them.

While engaged in this wonderful challenge of understanding the working of nature and its relation to health and disease, I have been struck by the vocabulary of biological scientists, my friends and colleagues. Although they themselves may not recognize it, it seems to me that the language of biology is different from the language of other sciences, certainly different from the languages of geology, physics, and chemistry, three disciplines I follow at a distance as an interested amateur (largely through my perusal of the weekly journal, *Science*). What is more, that language, the language of modern biological science, reminds me of an older scientific language, a language of a discipline that my friend and mentor Leon Kass calls natural philosophy as a reminder of its pre-Baconian origins. This language of biology, I submit, still uses important concepts which have been central to the study of biology since they were articulated in *The Parts of Animals*. What I will try to point out to you this evening is how those concepts articulated by Aristotle more than 2,000 years ago are still used in modern cell and molecular biology, and I will try to convince you (as I continue to try to convince my colleagues) that the use of these concepts is appropriate and, I think, necessary. I will this evening argue that not only is the language of modern biology still essentially "Aristotelian," but that our approach to understanding

living matter and how it works differs little from the paradigm presented in the opening paragraphs of *Parts of Animals*. I will, furthermore, try to convince you that "good" and "bad" biological science rests, to a large extent, upon the investigator's ability to see the world of living things through Aristotle's eyes.

(I should point out that I am not using the words "good" and "bad" here in a moral sense. What I mean by "good science" is a shorthand for investigation that would be publishable in peer-reviewed medical or scientific journals: experiments and conclusions that would be accepted by other knowledgeable people in the investigator's field. Whether there is morally "good" and "bad" science, and whether Aristotle's system of the investigation would recognize such, is a question I will not address here but might be raised in the question period when I am finished these remarks).

I clearly cannot talk about all of *The Parts of Animals* this evening, so I have and will restrict my observations to the opening chapter of the first book, in which Aristotle presents the terms and format for the ensuing discussion. I think that this is really the richest part of the book, because, at risk of stealing my own thunder, I believe that the genius of Aristotle is not his own particular observations about animals and the functions of their parts. Many or most of his observations have not subsequently been found either verifiable or generalizable. Rather, Aristotle's brilliance, at least in the field of biology, rests in his having provided the framework for all future discussions about living matter.

I will share an anecdote that introduces some of the points that I will be making in the rest of this talk. I was visiting a colleague at the University of Michigan Medical Center in nearby Ann Arbor last winter, and, like a polite and interested scientist, I asked her how her work was going. She beamed and proudly answered, "Great! I think I've found a function for my gene." This is a response that perhaps only another cell or molecular biologist could understand or appreciate. Suffice it to say that, while the modern revolution in molecular biology and medicine has given us tremendous power to clone and sequence genes from every species of living matter, including human beings, those of us engaged in this sort of endeavor are actually looking for something more than a genomic or complementary DNA library and a gene sequence. What my colleague was telling me, I think, was that she had finished the 20th century part of her work (discovering, cloning, and sequencing a gene), but that her work was seriously deficient until she had done the Aristotelian part. She understood that a gene sequence in itself is a rather paltry contribution to science and very unlikely to be published in a prestigious journal or by itself provide the basis for a grant application to the National Institutes of Health without a context for that gene sequence. That is, even after having intimate knowledge of the structure of a gene and the related DNA sequences that control its transcription to RNA and protein, there is something more that needs to be explored and considered before even one's fellow-scientists will consider the work either compelling or complete. Let us look in more detail at the type of work that my friend had done and try to define, in Aristotle's terms, what more needed to be done.

Anyone who has taken a high-school level biology course or is reasonably well-versed with the lay press is aware that living things possess within their cells the information required to replicate either identical copies of themselves or semi-allogenic copies which contain genetic material from another member of the same or a nearly-related species (we call these copies "offspring", and, for the human species, they are called "children"). However, although the discovery of deoxyribonucleic acid (DNA) as the source of genetic information and the unravelling of its marvelous code has assuredly contributed in an enormous way to our understanding of genetics and reproductive physiology, an equal impact has come in our ability to explore in a detailed fashion the functioning of cells and how the expression of particular genes is controlled in particular cell types. Thus, specific cells in specific tissues are capable of being studied in intricate detail and this, in turn, has allowed us tremendous insight into how these cells and tissues function. It is this level of study, sometimes subsumed under the heading, "Cell and Molecular Biology," that provides the core for much of modern medical research.

If you examine appropriately-stained human tissue under a light microscope, it is very clear that what you are viewing consists of an ordered arrangement, and that different-appearing cell types contribute to this pattern. In fact, the absence of pattern and the appearance or predominance of a single cell type, the pattern observed in tissue sections of malignant tumors, appears obviously pathological. Similarly, within these cells, a semblance of pattern emerges, different for each cell type, with some common patterns for all cells. DNA is largely confined to the nucleus, while RNA and the structures for protein biosynthesis can be found in the cytoplasm. These observations, which have been accepted for many years, suggest that, although every cell of a given organism contains the same genetic material as every other cell, in multicellular organisms (and especially complex organisms like vertebrates), every gene is not expressed in every cell of every tissue. That is, the different cell types and specialized functions of specific cells (for example, insulin secretion by what are known as islet cells of the pancreas) demonstrate or indicate that the transcription of encoded DNA into a messenger RNA template and subsequently into protein occurs differently in the cell types, and sometimes differently depending upon the tissue in which a given cell type might be found. This has led to the hypothesis that certain cells and tissues express genes that are not expressed in other cells or tissues, and that our understanding of the functioning of such cells or tissues in health and disease might be aided considerably by our knowledge of the genes expressed exclusively in these tissues and the factors that control their expression.

The discovery of gene sequences expressed only in specific tissues is undertaken by the construction by what are called gene libraries. This was the process that my colleague in Ann Arbor was engaged in when I visited her last winter, and because the process by which this is accomplished is relevant to the discussion that follows, I will share some of that with you. I apologize in advance for the somewhat technical nature of this exposition, realizing that I am about to provide you with something that is almost certain to squelch fruitful discussion at St. John's: factual information. Please bear with me, however, because I believe your understanding of the process through which data is generated in the modern biological sciences will help you to understand what I have to say about understanding this data from Aristotle's point of view. I should also say that I believe the process itself would have been interesting to Aristotle, and that I believe that it's the sort of thing he himself would have delighted in had he had the means to do it.

The construction of gene libraries from specific cell or tissue types begins again with the "First Law" of modern biology: that DNA contains information that encodes specific protein sequences, and that the protein is synthesized from a template molecule of RNA, whose synthesis serves as the intermediary step. You will recall (again, please forgive my pedantry) that proteins are composed of smaller building blocks called amino acids. Each amino acid is specified within the DNA molecule by a three base-pair sequence called a codon. The DNA code is somewhat "degenerate", as the currently-used jargon has it, in that some of the amino acids are specified by more than one codon. In the normal sequence, a gene is activated by the binding of certain proteins to a region of DNA called the promoter, which results in the transcription of an RNA molecule whose sequence is complementary to that of the DNA template (remembering the Second Law of modern biological science: adenine pairs with thymine [or, in an RNA molecule, with uracil] and guanine with cytosine). The newly-synthesized RNA molecule is processed further in the cell cytoplasm and used as a template for the biosynthesis of a new protein.

Because of the complementarity of DNA or RNA, gene libraries can be constructed from either, those using DNA referred to as genomic libraries (containing all the genes of the specific species from which they were obtained and therefore identical whether the starting tissue was brain or skin) and those starting with RNA being designated "complementary DNA libraries," as they begin with a RNA which is then synthesized *in vitro* to a complementary strand of DNA. Complementary DNA libraries contain only the gene sequences are expressed in the tissue or cells from which they were obtained.

The next steps in cloning involve the digestion of the DNA into smaller fragments that can be analyzed



in a practical way, and the insertion of the fragments into a host (usually a virus) that will allow its insertion into a cell (at this stage, usually, a bacterium) that will propagate and produce multiple copies of the gene fragments. This is necessary in order to have an adequate amount of DNA to manipulate and analyze. After millions of copies of each gene are produced, the gene fragments can be isolated from the bacteria, which grow as colonies on agar plates. Selection of the specific colonies which contain the genes or genes of interest can be accomplished by examining products secreted by the bacteria or by techniques which rely upon the binding of related DNA sequences to the DNA within the bacterial plasmids. The bacteria containing the genes of interest can then be selectively grown, the plasmids containing the cloned DNA isolated from the rest of the bacterial DNA, and the sequence and structure of the cloned genes ascertained (the techniques used to sequence DNA are in themselves rather interesting but not within the purview of a talk like this one). Using complementary DNA libraries, unique genes expressed in specific tissues in response to specific stimuli or at specific times in development can be identified, isolated, and their sequence determined.

I want you to note that up to this point all we have is a gene sequence, a structure, a very minute part of an animal (or plant). Furthermore, although there is some marvelous technical wizardry involved in obtaining this sequence, the process through which the sequence is obtained is more or less mechanical and, with some exceptions, more or less the same no matter what cell type, tissue, or even species the scientist is working with. This is the equivalent, more or less, of doing what Aristotle describes in lines 15-18 of the first chapter: taking a lion, or ox, or human being and describing the parts in infinite detail. No attempt is made (yet) of relating the minute DNA sequences to commonly-expressed cell, tissue, or organism functions. The reason for this relates, in part, to the method through which genes are isolated and cloned. It should be clear from how I have described the method of cloning and sequencing that the manipulation of DNA required for this process involves the almost complete separation of that particular gene or DNA sequence from the *context* in which it is normally found. However, it is just that context that is crucial to our understanding of the role of that gene within the cell and, subsequently, its role in the function of that particular tissue or organism. The rest of the process, the activity that makes cloning and sequencing truly interesting, involves the understanding of how the protein encoded by that gene functions or what it does (which is why my colleague was so excited about having a function for her gene). To put it another way, one seeks the *telos* for that gene. Until that is found, the mere gene or protein sequence is singularly uninteresting to either the natural philosopher or the molecular biologist. To put it in language that my peers might understand, it would be very difficult to publish a gene sequence by itself without a *context* for that sequence which suggests a *functional* role for that gene in a cell or tissue or in a particular biological process. My knowledge of that function might be limited or vague, but publishable molecular work invariably contains and requires a context without which the gene sequence is neither useful nor enlightening.

So what does all this have to do with Aristotle? Because this is early in the year, I think I should say a few things about the reading of Aristotle to the freshman, who should be engrossed in and captivated by Homer at this time and have probably had little no exposure to Aristotle's scientific books. In this way I will also reveal some of the prejudices that I have brought to this book as I read and reread it over the past 8 years. I was once told that a key to reading Aristotle is the understanding that many of his books seem to be written as answers for which the reader must supply the question. I have found this insight very useful. Furthermore when reading *The Parts of Animals*, I have found it helpful to pause after every sentence or two and ask, "As opposed to what?" We are fortunate that Aristotle sometimes gives us alternative explanations or possibilities, but I think that one appreciates the genius of Aristotle only after considering the explanations or alternative ideas that he has rejected without his having belabored the point in writing (lest the freshmen should be misguided, let me quickly point out that Aristotle is not above belaboring points).

To begin this discussion, we have to confront, first and foremost, our archnemesis. I believe that understanding *The Parts of Animals* requires some insight into the alternative point of view about

living things, which Aristotle attributes to Empedocles. I feel unfortunate that most of what I know about Empedocles comes from Aristotle, and I think that we at St. John's, especially, have to be cautious in judging a philosopher's thought simply on the basis of what somewhat else says about him. I certainly would not want to judge Aristotle's system of natural science on the basis of what is said about him in modern science textbooks, for example. However, be that as it may, whether fairly or unfairly, Empedocles is used as representative of a school of thought that suggests that the coming-to-be of living things has occurred by chance, that their formation has occurred haphazardly, and that the compelling force in this process is *necessity*, in Greek, *anangke*. For example, the process of the formation of the backbone, Empedocles is said to argue, occurs by necessity, a consequence of the fetus becoming twisted in the uterus.

This approach is one that, on the surface, seems attractive to modern scientists. It is certainly consistent with classical physics and mechanics and the so-called scientific ideal exemplified in Newtonian physics. When I was a junior here at St. John's, I remember reading a quote by French biologist Andre Lwoff attempting to support a role for Empedoclean necessity in biological science:

"The machine is built for doing precisely what it does. We may admire it, but we should not lose our heads. If the living system did not perform its task, it would not exist. We simply have to learn how it performs its task."<sup>1</sup>

This same mechanistic approach seems to have been what Claude Bernard had in mind when he stated that:

"...a created organism is a machine that *necessarily*<sup>2</sup> works by virtue of the physico-chemical properties of its constituent elements."<sup>3</sup>

At a certain level, this seems to remain a deeply-cherished belief or prejudice of modern scientists, who, even after the demise of classical physics in the early 20th century seem to yearn for a world more like Newton's than Einstein's. However, when I confront this belief, as I often do when I encounter other colleagues, particularly those who work exclusively in the laboratory rather than at the bedside, I recall the words of Marcel Proust:

"Error is more obstinate than faith and does not examine the grounds of its belief."

I do believe that in biology and experimental medicine, the Newtonian/Cartesian model is erroneous, or at least incomplete. The problem with this approach, is, ironically, a practical one: it simply doesn't work. It may very well be true that the coming-to-be of living matter occurred as an accident in the "primordial soup" billions of years ago, requiring neither the direction of a beneficent deity or even directedness from the impersonal forces of nature. It may very well be that what transpired was

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<sup>1</sup> Quoted from *The Cell* Carl Swanson. Prentice-Hall, Inc., Englewood Cliffs, NJ, 3rd Ed., 1969, p.7.

<sup>2</sup> My italics

<sup>3</sup> Claude Bernard, *An Introduction to the Study of Experimental Medicine*, trans. Henry Copley Green. New York: Dover Books, 1957, p. 93.

inevitable based on the laws that govern large molecules that we now call "organic" and the chemistry of carbon and nitrogen. That does not negate the fact that what *has* come to be is organized matter, and that our *understanding* of that matter requires our understanding of that organization and the relationship between structure and function. As Aristotle points out, the Empedoclean view falls short because of its lack of *logos*. It does not provide a framework which makes the phenomena understandable. Aristotle follows this by gleefully pointing out that Empedocles, too "...being led and guided by Truth itself, stumbles upon this..."<sup>4</sup> and is required to recant and retract, admitting, for example that bone is more than its elements *per se*, but that there is a *logos* (which, in this context, I believe might be translated "understandable feature" or "...understandable features...") that requires several layers of explanation for us to discern.

Thus, while the mechanistic language borrowed by modern biologists from classical physics might sometimes be used in the biological sciences, that is not the common language and certainly not the language used in published research. Let me add that this is not because, in their heart of hearts, modern biologists don't wish to have a language reminiscent of classical physics. Indeed, one of the prejudices common among biological researchers is that the laws of biological science (dealing, as they do, with the macroscopic world) are or will be shown to be more like classical mechanics, with orderly phenomena of cause and affect occurring in time, than like the topsy-turvy world of quantum physics and relativity. They have learned however, that the language of classical physics and mechanics has limited practical usefulness in modern biological research.

I will here therefore submit that there are several critical concepts in Aristotle's biology that remain in common use in modern biological science (although in a somewhat disguised form), that remain crucial to how we understand living matter. I will spend the rest of my time examining two of these concepts in more detail. They are *telos* and *anangke*. My list is intentionally limited to these two, but before I proceed I should state that a complete understanding of Aristotle's biological works and their relevance to modern biology should also include a deeper discussion of cause and all its layers of meaning. Similarly, *eidos* is clearly a unifying concept in Aristotle's physics and metaphysics and any discussion of his natural works that does not address this concept is incomplete. However, both of these topics are by themselves suitable lecture material and I have decided to avoid them in this discussion. I envy the sophomores, however, who will be able to immerse themselves in Aristotle's *Physics* later this year and will have, therefore, a rich and ample opportunity to think about these issues.

There is, among modern scientists, perhaps no more greatly-misunderstood concept than that of *telos* as Aristotle understood it. Indeed, "teleologic" thinking is often apologized for in "serious" research seminars and can subject its user to a measure of skepticism (if not scorn) by other investigators. This is, of course, due to a misunderstanding of the concept of *telos*. We are, in this instance, partly at the mercy of St. Thomas Aquinas, who brilliantly engrafted Aristotelian thought (physical and metaphysical) into Christian theology. Thus, the Christian view of a beneficent Deity ordering Nature to His own (sometimes inscrutable<sup>5</sup> but unquestionably beneficent) ends has clearly influenced, or tainted, the reading of Aristotle ever since. No such world view informs the *Parts of Animals* or the concept of *telos* as used in Aristotle's works in the natural sciences. As used in the *Parts of Animals*, *telos* is intended to describe the predictable culmination of natural processes. A robin's egg *predictably* hatches a robin. A seed *predictably* grows into a plant. Thus, the end of the egg is the mature robin; the end of the seed is either growth or the mature plant. These ends exist without either striving on the part of the organisms or intervention from the deity. They do, however, provide the foundation for our

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<sup>4</sup> Aristotle, *Parts of Animals*, trans. AL Peck. Cambridge, MA; Harvard University Press, 1983.

<sup>5</sup> "...where were you when I laid the foundations of the earth?" Job

understanding of the egg or the seed, their *logos*, as Aristotle says.<sup>6</sup> Furthermore, while they can be thought of separately, *telos* and necessity (*anangke*) are clearly co-existent and inter-related, just as matter and form are. If an egg is to grow into a mature robin (its *telos*) it must, of necessity, have certain characteristics which will protect it during gestation (e.g., a hard shell). None of this sort of thinking, which is central to Aristotle's way of looking at living things, is completely foreign to cell biology or experimental medicine. In the example of our gene sequence, the *telos* of the gene is two-fold: the transmission of genetic information to progeny and the encoding of information required to synthesize a protein, which, in turn, has its own its own *telos*. The second part of the molecular biology in which my friend in Ann Arbor was engaged required that she put her gene *back into context*, both literally and mentally, to discern the function of the protein encoded by the gene and factors regulating its expression in different cells.

In my own career I was blessed to work with an outstanding molecular scientist (Dr. John Atkinson, now chair of the Department of Medicine at Washington University in St. Louis) who was singularly unapologetic for his use of teleologic language and thinking. From Dr. Atkinson I learned how serious scientific problems can be approached in a practical and illuminating way if the Aristotelian concept of *telos* is applied creatively. Indeed, posing questions in cell biology that start with *telos* is often the best way to start an inquiry into structure and mechanism, form and function. In this sense, *telos* remains the prior or primary concept in much of cell biology, just as in Aristotle's biology.<sup>7</sup> Let me provide some examples.

In both cell and molecular biology, the discovery of new genes and/or structures, or the finding that a certain gene or protein is unexpectedly expressed in a certain cell or tissue, is one of the exciting and rewarding events in the life of any investigator. However, insight into the significance of such a finding is often provided only by an understanding of its *telos*. Scientists refer to this work and thought-process as the elucidation of the function of the new gene or protein. This is nothing more or less than an understanding of its *telos* and it is considered to be an essential part of the understanding of new genes and proteins. They provide, I submit, the only means by which their biological significance can be discerned, or, if I may speak in Aristotle's terms, the *telos* provides rational ground, or *logos*, for the subsequent inquiry. That other scientists agree with my assessment of the importance of this process is measured by my friend's excitement at finding a "...function for her gene." What my colleague was asserting was the importance of the Aristotelian concept of *telos* in modern biology.

A question that Dr. Atkinson often used to ask at the beginning of his work was, "Why would this cell express this protein (or gene)?" Or, "Why would this cell express this protein (or gene) under these conditions?" I learned by watching an experienced scientist begin his work this way that a tremendous amount of experimental biology can be undertaken if such questions are asked and allowed to provide the rationale for a series of well-designed experiments. Thus, the concept of *telos* provides not only a theoretical framework which allows a scientist to understand the meaning of certain phenomena produced in the laboratory, but it also provides a valuable starting point for further investigations. In this very real sense, *telos* is the practical and logical starting point for the investigation, as Aristotle has pointed out.<sup>8</sup>

Necessity (*anangke*), is another concept that is used in modern biological research with some of the same breadth of meaning as in Aristotle's biological works. Christianized Aristotelianism has attempted

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<sup>6</sup> *Parts of Animals* I, i, 639b 15-17.

<sup>7</sup> *Parts of Animals* I, i, 639b, 15.

<sup>8</sup> *Parts of Animals* II (1) 646a25 - 646b5



to elevate *telos* above necessity, maintaining that God's will and the mechanisms by which His world operates are separable in fact and in thought. This allows, among other things, provision for laws of nature to be suspended for the benefit of the Church, as Edward Gibbon stated. While this is a convenient world view for the structuring of a politically-powerful church on earth, it had devastating effects on the understanding of living creatures, and allowed the evolution of the concept of vitalism that so seriously stymied biological thinking in Europe into the nineteenth century (I should also point out that it made theology tough, too. The distinction between God's foreknowledge versus foreordination, Grace versus Free Will, etc. are innate, I believe, in this dualistic approach to Nature and Nature's God). This distinct separation of *telos* from *anangke* is clearly excluded from Aristotle's natural works, and *The Parts of Animals* in particular. Rather, *anangke* and *telos* go hand in hand, and provide a basis for the understanding of one-another. Thus, while *telos* is primary for Aristotle, in that it provides the framework through which biological processes are understood (again, the *logos*), it is also clear that both the coming-to-be and the maintenance of living things obeys the laws of *anangke* in the physical and logical way that Aristotle understood this term.

I have mentioned before the wistful engagement of classical (Newtonian) physics and modern biology, an engagement that is ever-prolonged while the wedding is continually postponed. I believe that there is still a yearning among many biologists to believe that, because living things adhere to the laws of chemistry and physics (or, more correctly, that novel laws of chemistry and physics are not required to understand either the coming-to-be or the functioning of living matter), that all of the biological sciences will be eventually be focused on understanding laws of absolute necessity which are the direct descendants and consequences of the original Big Bang. However, in many cases, this concept of absolute necessity (because "A" happened, "B" absolutely must happen) is only one of the ways in which the concept of necessity is used in biological science and medicine. Furthermore, such logical thinking is seldom the starting point in the practical world of modern medical research. Rather, modern biologists, working with concepts of structure and function (*telos*, if you will), are more often fruitful when they operate in the world of what may called "...conditional necessity." That is, the argument that if "A" is to be formed, then other things must also occur. For example, if health is to be produced, then certain actions are necessitated by the physician or the healer. This may still seem somewhat abstract, so let me use an example from my own experiences at Washington University.

The complement system is a series of proteins that provide one of the important defenses of higher organisms against invading micro-organisms. However, unlike other parts of the immune system, complement proteins do not, in themselves, discriminate "self" from "non-self." Once activated, there is nothing in the biochemistry of these proteins that precludes their amplifying on and destroying host cell or tissues instead of the invading viruses or bacteria. This discovery that the complement system is non-specific was made simultaneously in St. Louis and San Diego and much of this early work was done by my mentor, Paul Levine. These discoveries led to the hypothesis that *if* the biochemistry of the complement proteins is such that they can activate even on host cells, then *by necessity* there must be some mechanism through which host cells can *deactivate* them. This is a very Aristotelian approach, and it was the beginning of a series of investigations, carried out in St. Louis, Baltimore, and Cleveland, that elucidated a new family of cell-surface proteins with a common genetic structure. These proteins were shown on mammalian cells but not on bacteria or viruses (at least not under normal circumstances) and were shown to deactivate complement on host cells exactly as would be predicted. An understanding of these proteins and how they function has provided new insight into rheumatic diseases such as rheumatoid arthritis and systemic lupus, as well as some understanding of how cells of the immune system are destroyed during the course of HIV infection (the latter is work from my own laboratory). Thus, the concept of necessity, as used in its broader, "Aristotelian" sense, provided the foundation not just for a theoretical approach to mammalian cells but for practical advances in the science of immunology.

This is not to say that so-called "absolute" necessity is not used in modern biology. We know, for

example, that if the pH or hydrogen ion concentration of the intracellular fluid drops below a certain "physiologic" range, that certain predictable consequences will occur to in the efficiency with which intracellular enzymes will function. We know that, eventually, prolonged lowering of intracellular pH will eventually have profound disturbance of cellular energy metabolism and eventually lead to cell death. However, in these cases, the concept of absolute necessity is still informed by the concept that the enzymes in question *do*, in fact, have functions that relate to their roles in cellular processes. The dysfunction of the enzymes is made more intelligible by the understanding that they are involved in a process that we call intracellular metabolism. In the absence of this understanding, we have hydrogen ions and a denatured polypeptide that can no longer catalyze the transfer of electrons. Even the most ardent Newtonian would concede that such an understanding is incomplete.

These two concepts, *telos* and *anangke*, are ubiquitous in modern biology and appear to be unavoidable. They provide the core of work appearing in peer-reviewed journals as well as an important aspect of any grant application to agencies such as the National Institutes of Health. They remain in use, as I have said, not because, in the deepest hearts, modern experimental biologists are enamored of Aristotle, but because they are unavoidable. Furthermore, they have been shown to be practically useful, especially when linked to the modern techniques of cell and molecular biology. The admission that these concepts are essential to the biological sciences is different from saying that unusual laws of chemistry and physics are required to understand living things. What I am saying, and what Aristotle has said, is that these concepts provide the framework through which the laws of chemistry and physics can be understood in living matter.

I hope I have provided you, in this very brief way, with some insight into how certain ideas articulated in Aristotle's *Parts of Animals* remain in use in modern experimental medicine. Furthermore, I hope that I have convinced you that these ideas are not just part of a theoretical framework, but that they provide a very practical starting point for the process of modern biological research. Let me also say that I believe that if Aristotle were alive today, he would find very little in modern laboratory research that is in direct conflict with his approach to living things as articulated in the *Parts of Animals*.

Let me close by saying a word about what modern experimental medicine has not borrowed from Aristotle and something about how this may limit, or at least define, our understanding of living things. Of all the concepts in modern biology, evolution is the one most clearly foreign to Aristotle's biology. To Aristotle, the species were permanent, more or less immutable, and eternal. To the modern biologist, species are what's left over after a process called natural selection. In its most extreme case, evolution is so totally lacking in either direction or permanence that, ultimately, the theory of natural selection is just as appropriately described as "...survival of the survivors..." rather than "...survival of the fittest." *Eidos* (species) and *telos* are conspicuously absent from modern evolutionary theory. It is thus hard to find common ground between evolutionary biologists and Aristotle. The two world views are clearly not compatible.

However, in modern experimental medicine, the concept of evolution is, ironically, partly-informed by the concept of *telos*. For example, the existence of certain structures or proteins in lower animals (for example, fish) and humans is often used as an argument for their physiological importance. That is, structures or proteins highly-conserved through evolution are considered significant. For example, the fact that fish have complement proteins is used as an argument for the importance of this primordial wing of the immune system. To put it another way, the *telos* of a structure is considered vital to the extent that it is conserved in evolution. Thus, even with modern evolutionary theory as an overlay, experimental medicine still derives tremendous power from essentially-Aristotelian ideas.

Another aspect of Aristotle's biology that is lacking in modern experimental medicine is its scope. By this I mean that Aristotle's physics and metaphysics are essentially inseparable, and that they are part of a system of thought that addresses human beings and their relationship to the world around them.

While the world of clinical medicine may take a person into many parts of the world of man and display some of the best and worst of human life, the world of experimental medicine is, in the end, neatly circumscribed. People engaged in medical research are, in the end, focused on understanding how things work. The final goal of this is, of course, to find out what's happening when something doesn't work (that is, when someone is ill) so that remedies can be found. The answers given to the questions raised by modern biologists will, therefore, reflect the form in which the question was asked. That is, our answers will always only tell us how something works, not what it is or what our relationship to it should be. We are, in essence, like the Lilliputians, who could dismantle Gulliver's watch and could understand its mechanism perfectly, but were unaware of its purpose (believing, as they did, that it was the god that he worshipped).

I will close as I began, with an anecdote, or actually, two anecdotes. Let me take you, on a cool sunny November afternoon, into the delivery room of an upstate New York hospital, where I, a third-year medical student, am spending my first afternoon in labor and delivery. I want you to see a wet, blue infant who takes her first gasp, utters her first cry, and begins to wiggle and squirm, her cries becoming more vigorous with each passing second. I want to see the beaming father and mother as they hold their first-born daughter, call her by her name, and put their cheeks against her soft pink skin. I also want to take you into the pediatric intensive care unit on a frosty November evening. I will take you to the bed of an eight-year-old boy dying of infectious complications of AIDS. I will tell you that this boy was the only child, the adopted son of an otherwise childless couple, and that I had come to respect this couple's sorrow and struggle as one of the most profoundly sad and noble chapters I had witnessed in my career. When the time came to accept that we had nothing left to offer but the prolongation of suffering, when decisions were made to remove noxious tubes and hardware, when I watched this child gasp his last breaths in the arms of his tearful parents, I understood the profound ignorance of doctors, biologists, philosophers, and clergy. My experiences at the bedside, and with birth and death in particular, have taught me that there is a great deal about life that I cannot explain. I fully understand that the method of inquiry that I have inherited by Bernard, Bacon, and Descartes was not designed to probe into the more compelling questions that raised by my experiences as a physician. Thus, while my own career remains focussed in the understanding of the human body and how it works, I remain profoundly humbled at how inadequate even a complete understanding at that level would be. For all of our knowledge and our attempts at knowledge, we...

"...are here as on a darkling plain  
Swept with confused alarms of struggle and flight,  
Where ignorant armies clash by night."