Brain, Mind and Time

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Prologue

The voice message was short and cryptic…and the caller didn't identify himself. He said simply, "If you are the Dick Ecker that used to work at Argonne, I'd like to talk to you," and left his number. It was a local number, but I didn't recognize the voice. So I called him back, little realizing that the call would begin an intellectual journey that would endure for seven years and inspire me to reflections that, otherwise, may well have remained dormant for the rest of my life.

I dialed the number and identified myself to the man who answered. He said, "This is Charles Ehret. I saw the article on you in the local paper. I didn't know you had been an infantry officer in the Korean War. I was an infantry officer in World War II. Are you a member of the VFW (Veterans of Foreign Wars)?" Charlie was not one to mince words. The year was 1997. A few months earlier, I published a book documenting my experiences in the Korean War. The local paper had featured my book in a recent issue.

In the 1960's, Charlie and I had been fellow scientists at the Argonne National Laboratory outside Chicago. We were both biologists, but our research interests were very different and we were located in different parts of the building housing Argonne's Biological and Medical Research Division. At the time, I was vaguely aware of Charlie's research activities and I expect that he knew something about what I was doing, but we seldom spent much time sharing ideas…and we certainly would not have been considered close friends. I left Argonne after nine years on the staff there. Charlie spent his entire career at the laboratory.

In our phone conversation I confessed to Charlie that I was not a member of the VFW and had never had much interest in becoming one. However, when he invited me to join him at a meeting of his VFW post the following week, I agreed, but only because I looked forward to seeing him again after so many years.

At the meeting I met a number of sincere and dedicated veterans from four different wars, but mostly I appreciated the opportunity to sit down with Charlie after the meeting. I wanted to get caught up on what he'd been doing for the past 25 years and to hear what he had to say about his experiences in World War II. He had had a stroke some years earlier, which compelled his retirement from active research. Now he had to walk with a cane and to sit with one leg propped up on collapsible tripod stool that he carried wherever he went.

After a few minutes getting reacquainted, swapping a few war stories and rehashing old times at Argonne, he announced that he was writing a book on the brain and asked if I might consider becoming a collaborator. As I said, Charlie was not one to mince words.

I had been out of touch with much of what had been happening in the world of science for most of the 25 years since I left Argonne, so to suggest that I was an unlikely candidate as a co-author of a book on the brain would be putting it mildly. But Charlie's sincerity and enthusiasm had an infectious quality about them and I found myself reluctant to simply reject his

suggestion out-of-hand as a nutty idea. So I agreed to come to his house the following Wednesday afternoon to hear more about what he was proposing.

For the next seven years, I remained totally convinced that it was impossible for us to write a credible book on the brain, but Charlie never wavered. Yet, I returned every week for all of those years simply because the atmosphere around Charlie Ehret's dining room table on those Wednesday afternoons was so unbelievably stimulating that I couldn't stay away. This is the story of those Wednesdays with Charlie. It's about a book that never got written because it was impossible to write—although some of the ideas that prompted Charlie to consider writing it were very imaginative and really should not be abandoned. I will attempt to translate those ideas for you here.

It's the story of a remarkable man—clearly one of the most brilliant I have ever worked with—and a genuine nice guy. It's about what can happen when you put a couple of old has-been laboratory investigators (and combat veterans) together with no time constraints and no agenda, and allow them to think together "outside the box." Also, in addition to being fellow scientists and fellow Bronze Star recipients, we were fellow Christians—he a Roman Catholic and I an Evangelical Protestant. This added a third dimension to our Wednesday discussions…and because we were both biologists, the issue of origins (physical and metaphysical) became a frequent proposition in those discussions.

In 2004, Charlie moved out of the home that had been our gathering place for seven years and he relocated some distance away. We did communicate occasionally after that, but we never resumed the interplay that had occupied us for those many years. His health was deteriorating—although he always said when we talked on the phone, "I'm doing fine from the neck up." He died in 2007, just short of his 84th birthday. So this will have to serve as the book he dreamed we would write together. It will not explain how the brain works, but it will certainly demonstrate what a remarkable resource his was. And, it will remain the collaborative effort he hoped for, because much of what I am about to write came directly from his imaginative spirit. Its title, *Brain, Mind & Time*, is the one Charlie originally selected for the book he envisioned us writing together. Although the contexts in which I will be using that title here will be quite different from those he had in mind for that book when he selected it, I hope you will come to agree that it remains a most appropriate way to describe our years of Wednesdays together.

When Charlie and I first reconnected in 1997, he and his wife Dorothy lived in a neighborhood of modest homes in an otherwise upscale Chicago suburb. Their home was a small bungalow on a roomy lot where their penchant for gardening was apparent the minute you drove into the driveway. There was almost no grass in the front yard. It was a mass of flower beds surrounding a fishpond. The pond was fed by a stream from a circulating pump. Across the stream was a footbridge. The side- and backyards were landscaped with equal imagination. Next to the front porch there grew and enormous ginko tree.

The front door of the house led you to a small living/dining room. The dining area consisted of a small round table next to a

large window facing the front yard. It was at that table that Charlie welcomed me every Wednesday—and where we spent our time for the next seven years. In the picture above, he can be seen seated where I found him on most of those Wednesdays. The living room was distinguished by four features that were immediately apparent to anyone entering the room. In addition to family pictures (they had had eight children), the place was strewn with *angels, books* and *clocks*. Pictures and other images of angels abounded on walls and shelves. Books were so abundant that the room could be more accurately described as a library than a living room. Clocks of every imaginable description filled the tiny space with their ticks, their tocks and their unsynchronized chimes. I will have things to say about all three of these features, because each is part of the story that developed from my years of hanging out in that room.

On that first Wednesday, wasting little time with small talk, Charlie assaulted me with a volume of printouts from his computer. In them, he had summarized the ideas he envisioned being included in the book he wanted us to write. Most of those ideas had their foundation in his years of experience as a world class chronobiologist. Chronobiology is the study of how biological systems measure time—their "biological clocks." In the study of such things, Charlie was one of the best. His book, "Overcoming Jet Lag" (with Lynne Waller Scanlon, Berkley Books, New York 1983), remains the accepted standard for resetting the biological clock during intercontinental travel…and he is credited by many in the field with providing the most credible explanation for the nuclear accident at Three Mile Island.

However, even given his prominence in his field of research, I was having some difficulty coming to grips with his confidence in setting out to write a book on the brain. I knew of nothing in his background that had prepared him to undertake such a challenge. And there was absolutely no doubt in my mind that I had no business being considered as a collaborator on the project. I was trained as a bacteriologist, and from early in my research career I had focused my interest on molecular biology. Clearly, it was this latter interest of mine that had attracted Charlie to me as a prospective co-author. His ideas on the functioning of the brain were founded on his conviction that the basis for human thought and memory could be found in the molecular biology of DNA in the brain. My problem was that, intuitively, I didn't like that idea. So, we did not have a particularly strong foundation for a collaborative effort.

Yet, what our Wednesdays lacked in agreement on the issue of how the brain works was more than made up for by our shared passion for probing for the truth, our shared interest in multitudes of topics having little or nothing to do with brain function and our mutual respect for the other guy's ability for creative thinking. Whether we agreed or disagreed, Wednesday afternoons were always amicable and intellectually stimulating, and always sent me home challenged by my curiosity to think outside the box. Often, for me, some of that thinking was devoted to developing evidence to prove that Charlie's theories for the molecular basis of brain function were wrong…and to plotting strategies for avoiding spending too much time the following Wednesday talking about the book. However, as is often the case when someone spends time thinking, I frequently found myself developing ideas of my own that would never have come up without the stimulation of my running contention with Charlie over the book.

Almost immediately after that first Wednesday, my name appeared as co-author on the pages of stuff that emerged from Charlie's computer each week. There was, of course, a time in my career when I would have balked at having my name associated with scientific writings to which I had made little or no contribution and that expressed ideas to which I could not really subscribe. However, I had mellowed considerably as I approached my eighth decade…and I

remained totally confident that Charlie's ideas—as they appeared in those frequent printouts—would never see publication.

Some of those ideas—particularly related to how the body's circadian clock could possibly influence some brain functions—were very creative and well worth pursuing, but most of them were buried in volumes of unrelated and disconnected verbiage. The simple problem was, Charlie couldn't write—at least not for public consumption. For him, everything was relevant and important. He was able to connect it all in his own mind into a completely comprehensible picture. However, he couldn't translate that picture into descriptions that would make sense to anyone that wasn't already very familiar with the details.

That problem had become an issue earlier in his career when he set out to publish his book on jet lag. The editor looked at what he had written and demanded that Charlie rewrite the manuscript using the help of a ghost author; otherwise it would not be considered for publication. Charlie reluctantly agreed, and the ghost-written book has been very popular since its release in 1983…but he hated it. Asked why, he would answer simply, "They took out all the good stuff." But most of what he considered "good stuff" were details—much of it from the results of his own research—that simply obscured the main points the book was attempting to communicate. Now I was facing the same problem with the book on the brain he envisioned our writing together…I was finding it a significant challenge to convince him to abandon the "good stuff."

Why did I go to the bother? That question has an easy answer. Charlie's was a brilliant mind. Although it sometimes took a little effort, whenever that mind could be distracted from what he considered the "good stuff"—that is, the cellular mechanisms of circadian regulation that had been the bread-and-butter of his active years in research—he had a broad depth of knowledge on an unbelievably vast variety of subjects…plus an amazing recall of details and their sources. I often described him to others, who didn't know him, as a "walking encyclopedia."

In fact, in my weekly efforts to direct his thoughts away from the book that could never be, I don't recall ever introducing a subject in which he wasn't interested or about which he didn't have some basic understanding. So, with this brief introduction to the long-running production that was Wednesdays with Charlie, I'll introduce the setting and the players and relate some of the highlights from those weekly encounters.

The Setting

As I have indicated, every wall and surface of the Ehret's living/dining room was generously festooned with things treasured by one or both of them. In Charlie's case the treasures related to three things that continued to stir his imagination and his passions—*angels, books and clocks.*

Angels

Among the multitude of pictures and figures of angelic beings that adorned the walls and shelves of Charlie and Dorothy's living room, the dominant depiction was of the angel at the bridge. Charlie acknowledged that his familiarity with that illustration dated all the way back to his days as a student at St. Martin of Tours school in the north Bronx neighborhood of New York City, where it hung over a blackboard in one of his classrooms. However, his long-term fascination with it really began in December of 1944, while he was leading an infantry platoon against the German army during World War II. To describe those events, I have extracted some quotes from a collection of reminiscences, titled "As if on Automatic Pilot," that Charlie wrote with his daughter, Julia Granton, in 1999.

First, an introduction from the Preface of that document…

> *"Included in the stories is one that I hold dear to my heart. It is a very special personal "revelation" about the truly remarkable power of the idea of "Angels"…My encounters with angels consisted not of visions but of actual pictures. First in the Alsace, and later in Malvern. Angels reminiscent of my childhood taught me later on, and after much reflection, meditation, and investigative study, about the wisdom and utility of some of our metaphorically enriched mythologies. Especially about the latent power of our inner resources; the capacities hidden deeply, but which surface when needed, to place us in an almost non-volitional, yet indeed creative and quasi-heroic mode. As if on automatic pilot."*

…and then—from a manuscript submitted to Notre Dame University's Scholastic Magazine in 1995—the description of his remarkable encounters with the angelic image that so dominated his living room half a century later…

> *"The east face of the Alsatian farmhouse, near the Saar border, had been sliced clear and away, as if by some giant woodsman with surgical skill. The table was set for supper, and looked more like an exhibitor's display of rural life, than a family meal abandoned on the eve of battle. But what froze me in my tracks, in the deep snow outside, was that huge picture on the west wall: a two-meter tall familiar rendition of the 'till now 'hackneyed' Guardian Angel of my youth. It was all there: the cutesy Hansel and Gretel kinder, crossing a broken bridge above the torrent below, and beyond, the lightning bolts and hints of wolves in the dark background…*

"I finally got mine on the Sigfried Line near Prum, and on that same day in February, only three men remained out of over 50 in my original platoon. I was evacuated on the hood of a Jeep by heroic aidmen to a field hospital, and then transferred by ambulances to hospitals in Liege, Paris, and finally Malvern, in Worcestershire, England. A backlog of letters and V-mail caught up with me there. The first I opened was from 'Ma Hague,' mother-in-law of my brother Harry (then with the 8th Air Force at a base close by). It was a 'God Bless You' card with that same 'till then corny picture of the Guardian Angel at the Bridge."

Angels were seldom a dominant feature in our discussions over the seven years Charlie and I met in that room, but their influence on him and his thinking remained palpable throughout those years.

Books

Charlie Ehret gave new meaning to the term bibliophile. The multitude of volumes in his living room was, by his own admission—and Dorothy's frequent chagrin—only a small sample of the collection he had amassed over the years, had squirreled away in every available nook and cranny in that little house and had continued to expand with addictive fervor.

Few were the Wednesdays that I did not arrive to find a box left by the mailman on the front stoop—the most recent shipment from one of the discount booksellers whose catalogs he voraciously devoured. Because there was almost nothing that did not interest him, the subject matter of these volumes varied widely. Certainly, nothing even remotely related to how the brain works ever escaped his attention, and I could always look forward to finding—as I sat down at the table for our afternoon by-play—a stack of new books with pages already dog-eared and marked up with his marginal comments. (It was his firm contention that, if a book was worth reading, its highlights needed to be clearly identified. He did not buy them to look attractive on some shelf.)

He seldom, if ever, read any one of these books from cover to cover. Yet, he always seemed to be able to extract the important (at least, important to him) details from each and have them clearly in mind when we sat down to talk. And, seldom could I find any reason at the time for disputing his selection of the things he considered important for us to consider. Often he would suggest that I read one of these volumes, which I usually did. But not having his facility for extracting the meat of the subject from cursory examination—and being unwilling to depend solely on his dog-ears and markups—I typically read the book from the beginning.

Frequently, he would discover he had purchased the same book twice and I would become the owner of the extra copy. In fact, some of the most treasured volumes in my library were the result of Charlie's over-zealous bibliophilia. Although I cannot claim to anywhere near the range of interests my friend possessed, I was usually delighted to expand my knowledge in unfamiliar fields. And, those that dealt with how the brain works usually helped equip me to keep up my end of discussions on the book that would never be—and to counter what I

considered to be his wrong-thinking on the possible molecular mechanisms of brain function.

Clocks

Of all the paraphernalia that adorned the living room it was probably easiest to understand why they included a multitude of timepieces. For almost his entire research career, Charlie had been studying biological clocks—how living systems keep track of time. For him, however, it was more than simply a research career…it was an all-consuming passion. If you could understand that passion, then you could perhaps understand what he meant when he talked about "the good stuff"—the fundamental principles of time regulation in biological systems.

I don't propose to probe very deeply into "the good stuff" here, but it will be useful for me introduce you to the subject of chronobiology, explain a little about what it involves and define some terms that most likely will come up in later discussions.

The time keeping mechanism in the human body is usually referred to as the "circadian clock." The term circadian is derived from two Latin words that translated mean "about a day." Every day the body goes through sequences of processes that occur—or at least reach maximum (or minimum) activity—at certain times. So, under normal circumstances, your body always knows what time it is—even though your consciousness may not be able to translate the occurrence of these chemical cues into hours and minutes on your alarm clock.

Given this rather tight circadian regulation—that is, the tendency of the body to routinely emphasize certain processes at certain times of day—it becomes easier to understand how things that might upset the schedule of these processes can have profound effects on health and well-being. When this schedule is "out of sync," the condition is termed "dyschronism," and Charlie liked to compare it to an orchestra in which the different instruments are all playing the same tune, but not at the same measure in the score at the same time.

The effects of dyschronism can be anything from mild to devastating, and jet lag is only one of a multitude of circumstances in which those effects can be experienced. I expect that it was the importance of some of these other effects that ultimately inspired Charlie to want to write a book on the brain. Primary control of circadian regulation occurs in the brain…and the brain can experience some of the most devastating effects when that regulation malfunctions.

So, a room full of clocks became a perpetual reminder that, wherever our conversations took us, the business at hand was how the body handled—and mishandled—time. And, wherever this particular account of those conversations takes us, we will ultimately find ourselves returning to the business at hand.

The Players

Lest I be viewed as a totally uncooperative participant in the effort to write a book on the brain, I need to emphasize that—at least early in the collaboration—I made efforts to write some material that I thought might contribute to the project. One of the earliest of those was an introduction that identified who we were and captured the essence of our collaboration. Following is the text of that introduction:

Among the earliest discoveries to be made by authors who contemplate writing a book on the workings of the human brain has to be the vast abundance of recent works already available on the subject. Following that discovery, most prospective writers are likely to pursue one of two possible options. Either they will abandon the undertaking as superfluous or they will ponder the reason the subject matter has attracted so many expositors and, based on that understanding, boldly join the debate. Obviously, we find ourselves to be followers of the latter option.

New books on the brain continue to accumulate simply because the subject matter remains refractory to any explanation that can attract a significant consensus among those who qualify to be considered authorities. Mystery attracts the curious--and the fundamental mechanisms of human cognition remain a mystery. The only way to solve such a mystery is for the curious to debate its issues. The publication of ideas is, after all, the lifeblood of scientific inquiry.

We certainly find ourselves numbered among the curious, but we also find ourselves unwilling to add a volume to the debate without also being able to add some significant new ideas to the discussion. Our purpose here is not to contest any or all of the proposals that occupy the many volumes others have contributed, but rather to add a dimension that has been essentially neglected up to now in the dialogue.

In many respects, it is easier to offer a contribution in a subject area that defies consensus than in one in which the dogmas are more universally accepted. That is, as long as no one really understands what's going on, some would argue that no speculation should be considered too far out to be included. Perhaps some have made contributions based on that point of view. We would not like our offering here to be so considered.

We bring to the debate a body of qualifications that combine to offer some unique new insights into the matter of human cognition. These insights are offered not to add another definition to an already crowded accumulation in the literature, but rather to provide those who are active in the business of definition some new perspectives that may make that business easier and more fruitful. We are, in many respects, particularly well suited to assume that role.

Although we may not be quite so bold as to posit that a collaboration such as ours could not have occurred if our ages did not average out to more than three-score and ten, we are prepared to suggest that our collective antiquity has had a significant positive influence on the outcome. Of course, a part of our conviction in this regard derives from the simple fact that, in more than 140 cumulative years, we have been afforded the opportunity to accumulate many insights that only time can engender.

However, there is an even more significant age-related reason that we were able to combine our efforts in this project with so much personal satisfaction and so much confidence that our efforts would flourish. When a scientist is put out to pasture, his corpus may be banished to the rocking chair, but his curiosity is freed from the demands of the laboratory environment to

pursue questions that can only be tackled by concerted cerebration. In our days as active investigators, we were not at all unique among colleagues in the scientific community in our tendency to disdain quiet contemplation (omphaloskepsis, to use a favorite term of one of those former colleagues) in favor of a day at the bench. Now age, infirmity and the social security system have combined to offer us the luxury of becoming what our degrees have said we were from our investiture as scientists. We have become full-time philosophers—and happily so.

No longer captive to the call of the laboratory, we now have the opportunity to sit in private seminar and contemplate the current state of understanding of the subject matter we have elected to pursue, to apply what we recall both from our own work as investigators and from our many years observing the passing parade, and to formulate new ideas based solely on synthesis from those sources. Our only regret is that it has taken us a 140 collective years to discover this most rewarding endeavor.

As I re-read this text now, I continue to believe that it expresses accurately the heart of our collaboration, irrespective of whatever differences in point-of-view our weekly encounters may have generated. And, as Nobel laureate Andre Lwoff suggested in the following extract from his classic 1953 review on lysogeny (a term that doesn't need to be defined here), reflections on discoveries from earlier work can often be a more productive endeavor than designing and undertaking your own experiments.

"For many young scientists the future is more important than the past and the history of science begins tomorrow. Nowadays,…, many facts and theoretical views are gloriously discovered which were known a long time ago. It has seemed, therefore, desirable to credit early workers for their achievements and also to spare unnecessary efforts directed to later rediscoveries. Moreover, it is interesting to know how phenomena were discovered, how the problems were born, attacked and solved, and how and why our ideas have evolved. The danger of parachuting young enthusiastic scientists into a flower bed of selected data and fully bloomed conceptions should not be underestimated…" Andre Lwoff, *Bacteriological Reviews*, 17:269-337, 1953.

Origins

One vital interest Charlie and I shared in common was the matter of how things got started. Although we were both committed Christians—and believers in biblical revelation—we shared a common conviction that the earth was some 4 billion years old and that it had become populated with flora and fauna over those billions of years by some still poorly understood gradual evolutionary process. Neither of us was prepared to simply ignore the biblical account of origins, but we both felt that the scientific evidence of an old earth and some kind of progressive developmental process was overwhelming and required us to consider the biblical account as a metaphor. I'll have more to say about that a bit later.

Of course the stated purpose of our weekly get-togethers was the proposed book on the human brain, so the developmental processes that attracted most of our interest were those leading to the emergence of human beings. Yet, the primary human attribute that had attracted Charlie to this enterprise in the first place was the circadian clock, so it was essential to begin our search for the physiological basis of that clock back at the time when it first came into existence in our primordial forebears. It turns out that the search took us back a very long way.

Without getting disgustingly technical, I'll introduce you to the forebear that we speculated was the most likely creature in which the circadian clock first arose—and to some of the terms we used to describe the primordial players and their properties. Since many of those players have survived the eons since their inception, scientists today have been able to investigate those properties under the assumption that they have remained the same as they were at their origin. This is, of course, a substantial assumption, but there are reasons to believe that it is not unreasonable.

The class of organisms we proposed as the original bearer of the circadian clock is called the "blue-green algae." They are the most primitive organisms that have been shown, in modern day experiments, to possess properties of circadian time regulation. And, Charlie—in his perpetual scouring of obscure references for anything relating to the subject of his passions—had unearthed (no pun intended) a paper showing that fossils of these algae had been found in deep-drilling cores from Australia that were estimated to be almost three billion years old.

The "blue-greens" are the most primitive photosynthetic entities; that is, organisms that are capable of using energy from the sun to convert carbon dioxide (from the air) into organic compounds in the cell. Because they do not have their hereditary material organized into a distinctly identifiable nucleus, they are normally classified—along with bacteria and fungi—in a group called "prokeriotes." Another term used to describe organisms like these—that are so primitive that they cannot be identified either as plant or animal—is "protist." Organisms that do have identifiable nuclei are called "eukeriotes."

Among the blue-green algae, one genus in particular has been studied extensively in regard to its capability for circadian regulation. This genus is called C*yanobacterium*. So our speculations about the possible mechanism by which the circadian clock first came into existence focused on the cyanobacteria—and I wrote those speculations into a prospective chapter for the book. Following is the text of that chapter as I wrote it. It was my last attempt to contribute any writing to the project.

In Search of Green Grandfathers
Speculations on the Ultimate Progenitor of Eucariotic Evolution

As evolutionary historians debate the significance and timing of events leading to the development of today's geobiota, one characteristic common to all eucariotes has been conspicuously neglected as a potential contributor a better understanding those events. That characteristic is the circadian clock. In fact, it may well be that circadian periodicity will ultimately become identified as an even more reliable indicator of the metabolic distinctions between the eucariotes and their ancient ancestors than the "true nucleus" from which they acquired their name.

All eucariotic organisms (at least all of those that have been studied for this characteristic) tend to follow regular cycles of activity that have periods of roughly one day (circa = about; dian = a day). If this attribute of eucariotic life is so totally ubiquitous—and is not to be found in any of the procariotes—then perhaps its acquisition played a critical role in the events that led to the development of eucariotes from their procariotic ancestors. And, if we can identify a molecular basis for such a critical evolutionary event, we may be able to gain significant insight into the molecular mechanisms that compel its continued existence in higher life forms today. That is the speculation we offer here.

To appreciate the importance of circadian periodicity in the progress of evolution, we first need to consider some of the problems that had to be overcome as the simplest one-celled organisms evolved the necessary complexity to become what we are today. Paramount among those problems was the necessity for an ever-larger quantity of hereditary determinants. The genome of simple protists exists as a single strand of DNA, most of which is read in sequence, as the genetic code is transcribed during the cell cycle. However, if more complex structures and functions were going to become possible, a genome with more capability would become necessary. And as that capability increased, there would arise increasing constraints on the ability of a single strand of DNA to accomplish the necessary transcription in the time required to allow the organism to survive and compete.

So, relatively early in evolutionary history, it became necessary for genetic expression to become a synchronous process in which multiple strands of DNA were transcribed in concert. However, this acquired capacity for phased transcription carried with it the seeds of its own destruction—that is, the potential for the loss of synchrony over time. Although perfect transcription synchrony was probably not required for survival, increased complexity undoubtedly carried with it the necessity for some coordinated use of gene products from segments of the genome that were on different DNA strands. Loss of synchrony in these processes would prejudice survival very quickly.

Perhaps an analogy from the computer world will help illustrate the critical importance of synchrony in coordinated processes. We plan to output this page to a printer that will be expecting to receive the data bits "in parallel." That is, each of the eight bits that the computer uses to code for each letter and character in the text will be sent to the computer through a separate wire. It is essential, of course, that all of the bits representing a given character arrive at the printer at the same time. If they do not, the output will be printed as nonsense. To make sure that this does not happen, parallel printer cables are generally limited in length. The only way you could assure the integrity of the output over greater distances would be to place a device at regular intervals along the cable to somehow re-synchronize the bits.

Similarly, the synchronous genetic transcription imposed by increases in the size of the

genome during evolutionary development required the concomitant imposition of some kind of mechanism to assure that transcription did not get out of phase. Mechanistically, that would appear to be a very tall order—a substantial leap in metabolic complexity at a relatively early stage in evolutionary progress. However, that leap would become a reasonably modest evolutionary step if the challenge could be met by applying a mechanism of periodicity already in place in the developmental environment—even in the earliest evolutionary times—namely, the regular periodic appearance of the sun.

There is some significant appeal, therefore, in the speculation that evolutionary complexity advanced necessarily through those primitive life forms that had already acquired a dependence on the sun for their survival—the primitive photosynthesizers. This theory suggests that the evolutionary development of plant life did much more for the ultimate existence and survival of higher life forms than provide the oxygen needed for aerobic metabolism. It also assured a mechanism of regular periodic renewal needed to permit those higher forms to possess larger and more complex hereditary components.

Each day when the sun arose on our early green grandfathers, a new cycle of metabolic activity began, originating from a reinitiated transcription from the genetic code and leading to the synthesis, growth and reproduction needed for continued survival. Who might those grandfathers be? The ideal candidates—should they continue to exist today—must be shown to have both photosynthetic activity and circadian periodicity. Our own suggestion for such a progenitor would be the cyanobacteria.

Granted that the cyanobacteria are not considered to be eucariotes, but as we suggested earlier, this cytological criterion for distinguishing between lower and higher forms of life is probably less a dependable indicator of key differences in complexity than the presence or absence of a circadian clock.

We are no more prepared at this time to suggest a molecular mechanism by which that solar-initiated, daily renewal process first came into being than we are prepared to propose such a mechanism for the circadian periodicity that occurs universally among eucariotic organisms today. Our argument is simply that, because even the most primitive of present-day eucariotes exhibit some circadian periodicity, the mechanism had to have arisen at some point very early in evolutionary history. What could be more reasonable to suggest than that its origin was somehow tied to the one early metabolic process that was, by necessity, circadian—photosynthesis.

Because circadian function has been retained throughout evolutionary history as a universal property of any and all life forms more advanced than the simplest protists, it is also reasonable to suggest that it has been and remains an absolutely essential mechanism for maintaining homeostasis and ensuring survival. This is no supernumerary process. It is as essential to metabolic integrity as protein synthesis or oxidative phosphorylation.

So when, after billions of years, the processes involved in producing ever-more-complex life forms finally evolved a creature with the biological characteristics we identify as homo sapiens, the roots of those characteristics continue to be traceable directly back to the age-old process of daily renewal. And, if we expect to ever have any hope of understanding the mechanisms that regulate the complex inter-workings of the human body, it will only come by including an appreciation of the role that circadian mechanisms play in the process.

Over evolutionary time, those mechanisms have probably undergone substantial modifications, some of which undoubtedly added levels of complexity to the process itself. But the fundamental role of circadian regulation—a role that has helped insure evolutionary

progress for billions of years—has remained the same; that is, the avoidance of metabolic chaos through daily restoration of operational synchrony.

Whether or not I might write this chapter differently today than I did back then is really irrelevant. It accurately reflects the way we were thinking at that time and it lays some groundwork for an exposition on some of the other things we discussed on origins—particularly the origin of the human race. These discussions necessarily carried us into the realm of theology—and onto the interface between science and religion. In this regard, Charlie had a considerable head start over me, although it had also been a passion of mine for many years.

Charlie had been one of the founding members of what was originally called The Chicago Center for Science and Religion (now called The Zygon Center for Science and Religion), located at the Lutheran School of Theology of Chicago. The Center assembles theologians and scientists from a wide variety of disciplines to grapple with issues related to the conflicts or concord between what we read in The Bible and what scientific inquiry tells us about our origins. By the time Charlie and I began our Wednesday sessions, however, he was no longer active in the affairs of The Center. And, although he remained in contact with some of the people there, our occasional speculations about the interface between science and religion seldom strayed beyond his dining room table.

As the weeks around that table grew into years, my personal interest in the subject of human origins was furthered to a very considerable degree by Charlie's steadily accumulating library. One book that he recommended to me, in particular, set me off on a journey into the business of paleoanthropology that has endured right up to the present. The book was *The Prehistory of the Mind* by S. Mithen (Thames & Hudson, Ltd., London 1996.). The reason Charlie wanted me to read it was pretty obvious. It was an attempt, using fossil evidence, to propose a mechanism for the development of cognition in the human brain as the species developed during hominid evolution.

However, the reason that this book was pivotal in the development of my interest in paleoanthropology was not because I liked Mithen's theses, but rather because I didn't like them. A critical question in evolutionary biology—particularly in the progression of hominid development from our earliest stone-age ancestors—has been, and remains, how and when the capacity for rational thinking came into existence. Mithen proposed a model patterned after the construction of a cathedral. He saw hominid brain capacity being evolved in a series of small developmental steps—like the construction of areas in a cathedral under construction—with each step investing the brain with the capacity for slightly expanded cognition. He attempted to validate these speculations using evidence from the fossil record—a considerable challenge, considering that all he had to work with were stones and bones.

I expect that the reason Mithen chose the rather complicated cathedral model to illustrate his theories was because of what happened suddenly after hominid evolution had been under way for more than five million years. About fifty thousand years ago, cognitive ability in the developing human line increased precipitously from that of a stone-age cave man to that of modern humankind…apparently the same as we possess today…all in an evolutionary instant. This event is what paleoanthropologists call "the cognitive explosion." So, Mithen had to employ some kind of model that would allow for this precipitous conclusion to the "prehistory of the mind." In his model that conclusion was the completion of the cathedral. Of course, he had no biological mechanisms to propose for how that could have happened. For good reason! There are none—at least as I see it. And this is where the interface between science and religion comes into

play.

For some years, I had been nursing the idea that the so-called cognitive explosion marked the instant in time when the first human became "the image of God" as proclaimed in the first chapter of Genesis (Gen. 1:27). However, I knew that my suggestion that the sudden investment of mankind with fully-developed cognition was a metaphysical, rather than a physical, event—and that it occurred at an identifiable instant in evolutionary history—was going to be unpopular with proponents on both sides of the interface. So, while Charlie pursued his ideas for the book that could never be, I set about to develop a rationale for my thesis on human origins. Of course, we continued to share our respective ideas on these and other topics, many of which will be the subject matter of subsequent chapters in this book. My work on human origins ultimately resulted in a monograph titled "The Image of God and the Biology of Adam" which can be found on the internet at www.ocomm.org/adam.

Symphony

Earlier, explaining some of the rudiments of chronobiology, I used Charlie's favored metaphor of the symphony orchestra. Now I'd like to return to that metaphor to help describe some of the thinking that most likely led him to undertake the "book on the brain" adventure. Of course, there is no way that I could ever translate that thinking with clarity at anything but the most basic level. The fact is, I spent seven years trying to understand how his thought processes worked and only succeeded with partial success. And, in many cases, when I did understand where those processes were leading, I did not agree with the direction they were taking us. Yet, the basic theory behind his symphony metaphor is very sound and well worth my effort to describe it here.

In that chapter on "green grandfathers" I attempted to contribute to the project, I summarized the fundamental role of circadian regulation as "the avoidance of metabolic chaos through daily restoration of operational synchrony." That is, some of the metabolic processes that contribute to stable daily life in humans are not all necessary at all times. So, there have to be in the human body mechanisms that regulate those processes to assure that they operate when needed and remain inactive when they are not required, like an orchestra under the diligent direction of the conductor. And, just as an orchestra with members that play at the wrong measure at the wrong time will produce discords that are unpleasant to the ears, so a metabolism out of circadian regulation will produce discordance in the processes that maintain health and well being.

This failure of circadian regulation is termed "dyschronism," and Charlie was convinced that it is responsible for a lot more than simply the effects of jet lag or the inability of shift workers to adjust adequately to their work schedules. In fact, he and other chronobiologists had contributed research suggesting that the time of day the body is exposed to various stimuli can influence markedly to effects of those stimuli. For example, it has been suggested that, when patients are given chemotherapy, the timing of its administration can significantly influence its effectiveness. Similarly, many other drug therapies or metabolic manipulations were thought by Charlie to be most effective at certain times of the day.

Perhaps his most intriguing speculation—at least to me as a professional observer—was the idea that many instances of depression in humans have their origins in dischronism. That is, in some people that are particularly sensitive to imbalances in circadian regulation, the resulting metabolic disparities can produce unwanted but unavoidable feelings of depression. The best evidence in support of this theory comes from studies of a manifestation of depression called "seasonal affective disorder (SAD)." People with this kind of depression tend to be more severely and more often affected in winter, when light levels are lower—and they are often able to overcome these episodes by sitting under special lights that attempt to mimic the spectrum of sunlight. However, this "photo therapy" is most effective only if it is undertaken in the early morning hours.

To understand how these observations of people with SAD support the theory that some—and possibly much—depression is caused by dischronism, we need to look at how the human body resets its clock. In my earlier discussion on the evolution of circadian mechanisms, I suggested that these mechanisms became necessary to keep an increasingly complex metabolism in some kind of synchrony…and that the logical signal to re-establish synchrony is the daily appearance of the sun. Triggers—like the dawn of the day—that reset the biological clock are

called by chronobiologists "zeitgebers," which is a German term meaning literally "time givers." Light is one of a number of zeitgebers that have been identified, but it is clearly the one that has the greatest beneficial influence in cases of SAD…and that influence clearly supports the idea that dischronism may well be a significant influence in the cause of this condition.

As I promised not to make this into treatise on chronobiology—which I have never claimed as an area of expertise—I will avoid stretching Charlie's symphony metaphor beyond this brief introduction. I invite readers interested in more detailed explanations to seek out the abundant scientific literature on the subject—including Charlie's copious bibliography.

Although it may be a bit of a stretch to include the following under the heading "Symphony," it is about music and it describes what became a very significant Wednesday afternoon debate that lasted more than a year.

DNA Music

Charlie attended graduate school (at Notre Dame) in the late 1940s and he had little or no training in molecular biology. His field of study was protozoolgy—the science of one-celled animals. However, this did not deter him from pursuing speculations about possible molecular mechanisms of things he observed in his one-celled specimens. And, because he was such a voracious reader, reports relating to those mechanisms seldom escaped his notice—particularly mechanisms involving DNA, which he was convinced were the key to everything. So, when he discovered in the scientific literature some papers reporting that the sequence of subunits in DNA could be translated into music, he climbed on board in a big way—and he couldn't wait to share his enthusiasm with me.

The papers he had found were from the late1980s and were the work of Susumo Ohno of the Beckman Research Institute of the City of Hope in Duarte, CA. In one such paper, Ohno had translated portions of Bach's Prelude No. 1 for the well-tempered clavichord into DNA sequences using a translation rule that assigned different notes on the scale to specific DNA subunits. Charlie was enthralled with the idea. I thought the whole thing was totally preposterous. It made no sense chemically. It made no sense musically. But of course, that didn't deter Charlie. It supported his idea that DNA sequences in the brain were the key to brain function and that was sufficient—at least for the year or so that this research remained a occasional topic of discussion on Wednesdays; that is, whenever I couldn't succeed in steering the discussion in some other direction. Then, I would again offer my arguments as to why I couldn't support this work being included in the book that would never be and we would finally move on to other things.

I don't recall now which of those arguments finally convinced him that DNA music would not provide credible support for his theories about brain function, but he continued to pursue the idea that gene sequences in the brain were what needed to be studied if you hope to discover how the mind worked. Meanwhile, I continued to treasure the less frustrating aspects of my weekly exposure to this extraordinary mind.

Cannon Fodder

Interestingly, although we were both research biologists and had at one time been colleagues in the same laboratory, the common interest that first drew Charlie and me back together at the end of the millennium was our shared experience at The Infantry School at Ft. Benning, GA—he in 1944; I in 1951. That common alma mater—known affectionately by the inmates as "Benning's School for Boys" —was where GIs selected to be trained as infantry platoon leaders ("cannon fodder" in the common parlance of the day) attended Officers Candidate School (OCS).

Charlie's tenure at the school was a scant three months—hence the term "ninety-day wonders" commonly used to describe officers produced there during WWII. By the time the school was reactivated for the Korean War, those of us who became candidates had to endure the rigors of officers training for almost twice as long—although I'm not at all sure we became that much better officers as a result of it. Both Charlie and I were agreed that the training was useful and necessary, but that nothing can really prepare you for the responsibility of leading men into combat. Combat leadership is 99 percent on-the-job training. What that gold bar on our collar did was simply identify who was responsible.

Although experience in combat for some ex-GI's remained a subject too traumatic for discussion, in my experience that has been the exception rather than the rule. Typically, if you put a couple of combat vets together, the result will inevitably be an exchange of war stories. Charlie and I were no exceptions. He was justifiably proud of his military service, served actively as a member of the VFW and of VBOB (Veterans of the Battle of the Bulge), attended their meetings and reunions and maintained contact with comrades from his days in the war. Meanwhile, I continued to resist his invitations to join him in the VFW—at least for a while. As it turns out, Charlie's membership in that organization set me off on another unexpected adventure.

Being a member of the VFW included a subscription to VFW Magazine, the official publication of the organization. So, whenever one of our Wednesday meetings occurred in a week in which he had received his copy of the magazine, he was prepared to point out to me whatever his copy had that month on the history of the Korean War. By that time in our marathon of meetings, the magazine was beginning to publish articles celebrating the 50th anniversary of notable battles in the Korean War, which had begun in 1950. Routinely, these articles included statistics on combat losses in those battles. When I checked out those statistics, I discovered that they were usually wrong.

Some years earlier, I had put together a database including all of the casualties in the war. At the time, it was the only reliable database available, having taken me about five years to compile and verify. So, I contacted the editor of the magazine, pointed out the errors and provided him the correct data. What followed was an invitation by the editor to do research for the magazine as it documented the battle history of the war each month for 37 months, marking the 50th anniversary of that month's combat. At the end of that time, the editor suggested that I write a comprehensive battle history of the war, documenting the combat losses for each unit by casualty type.

This book, "Korean Battle Chronology," McFarland and Company, Inc, Jefferson NC, was published in 2005 and contained the following dedication:

To my friend, Charlie…fellow scientist, fellow combat infantryman, Purple Heart veteran of "The Big War" and, for the last seven years, esteemed accomplice in our Wednesday afternoon brain games.

I was pleased to be able to present a copy of the book to Charlie while he was still spry enough to welcome my visit…and to swap a few more stories.

Epilogue

In 1997, when I sat with Charlie Ehret in the VFW hall in Hinsdale, Illinois, the idea of writing a book on the brain was as outlandish a proposal as I could imagine. Yet, I now find myself writing the epilogue to a book that would not exist except for what took place at that meeting. This book, which I'm sure is a lot shorter than he imagined at the time—and missing a lot of the "good stuff" he would have liked to include—bears the original title he chose and is, in most respects, the collaborative effort he conceived that day. Although I have done the writing, his imprint on the author and on the message will show through very clearly. Although they were years of my dotage, the time I spent at Charlie's dining room table were among the most stimulating years of scientific and philosophical inquiry I have spent in my entire professional career. And I will remember him fondly for the rest of my days.