



THE FIRST BRAIN

The Neuroscience of Planarians

ONÉ R. PAGÁN



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To my late father, Mr. Onésimo Pagán, who would have bragged endlessly about this book, and to my youngest son, Andrew (Andy), who, upon learning that I was writing my first book, immediately became its biggest fan.

Also, to my son, Reynaldo, who gave me the brightest smile when I told him about it, and to my daughter, Giselle Vanessa, whose very first words when hearing the news were: “Dad, you’re going to be famous!”

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Foreword

Robert B. Raffa, PhD

DR. PAGÁN IS a highly talented, dedicated, productive, and widely respected research scientist and teacher. I first learned of Dr. Pagán through his scientific publications. I have a long-standing interest in the use of planaria as a nonmammalian research model, and I was very impressed by his publications, in which he described several methodological innovations and novel applications using this model. His research and publications continue to impress me. I have also now come to know him and the absolute delight he takes in learning and writing about the world and our interactions with it. Dr. Pagán was trained at excellent academic institutions and programs. For example, his PhD dissertation work was done at Cornell, which is well known for its research in the field of neurobiology in general and drug abuse in particular, and was on the subject of chemical aspects of cocaine's action on dopamine reuptake transporters on brain neurons. He put this training to good use and has become a consistent publisher of his research and presenter at local, national, and international scientific meetings.

Dr. Pagán is a very active and engaged teacher in addition to his extensive activities as a research scientist. I know from my discussions with him and observations that he places teaching on a high pedestal. He goes above and beyond usual preparation and time allocation. He is even an active volunteer at "Science Day"-type events for young students. A passion to help and a caring for students at all levels are quite evident in any discussion with him.

Which brings me to this book. It is so much fun! It is written in a style that makes it equal parts educational, personal reflection, and motivational. The pure joy for the topic and the enthusiasm that exudes from the writing carry one along some well-traveled paths—but never, as one soon realizes, fully explored or fully appreciated until seen through his mind’s eye—and some new paths. The surprisingly eclectic selection of subject matter, including from the arts, literature, and social sciences, can’t fail to stimulate the reader’s knowledge and logical (or sometimes illogical) thought processes. And don’t be surprised if somewhere along the way one or more preconceived notions are challenged.

This is all presented in the most delightful manner. The style is not typical of most books written by such a distinguished researcher. It is, well, readable. And, dare I say it... fun. It is written in a way that is accessible to the beginner (yes, even to very young students), as well as more advanced students and anyone else who has even a modicum of interest in the world around us (and if you don’t think you do now, you will after you read this book). Dr. Pagán masterfully uses the seemingly lowly planaria as a magical vehicle on this inspirational tour-de-force of life, liberty, and the pursuit of happiness in the appreciation of the natural world. Who would have thought that a book about the “first brain” could lead to such a wondrous stimulation and understanding of our own brain?

So remember back to when you were a child and you hadn’t heard the word *science* yet. You were just curious about who you were, what was around you, what everything else was. So you looked, poked, or whatever else you did, to find out. Forget that this natural curiosity might have been lost, or suppressed, by school, by other demands, or by the seemingly imposing terminology of science. Want to get it back? Want to take up where you left off? Want to feel like a kid again? Then just read this book.

And, yes, it is okay to smile while reading a science book.

Robert B. Raffa, PhD
Professor of Pharmacology
Department of Pharmaceutical Sciences
Temple University School of Pharmacy
Philadelphia, PA, USA

Foreword

Harvey B. Sarnat, MD

WITH THEIR “CROSSED-EYED CUTENESS,” planarians have fascinated me since we were first introduced to them in my high school biology class. As a university undergraduate student majoring in zoology, I continued my obsession with flatworms because of their extraordinary regenerative powers and the fact that they were the first animals to exhibit bilateral symmetry as a body plan, with the three body axes of all advanced invertebrates and vertebrates. My fascination with planarians became fixed when doing a master’s of science degree in neuroanatomy and later, after medical school, when doing residency training programs in pediatric neurology and in neuropathology. I realized that planarians had evolved before the divergence of invertebrates and vertebrates and that, even if technically classified as invertebrates because they lack a notochord, many features of their nervous systems were more similar to those of vertebrates than of advanced invertebrates such as arthropods and molluscs. My ongoing research with the planarian nervous system continues to intrigue me as an origin of human life.

This popular science book of Dr. Pagán is important in bringing to public awareness the primordial role of the planarian in the evolution of animal life on Earth. From my medical perspective, their greatest practical importance lies in providing clues to regeneration that potentially might be extrapolated to the treatment of human organs and tissues that are defective in embryonic or fetal

development, show progressive loss due to degenerative diseases, or become otherwise damaged by trauma, infection, exposure to neurotoxins, or lack of adequate oxygen or blood flow. No tissue of the human body has greater need of the lessons that planarians can offer than does the central nervous system.

The evolutionary origin of vertebrates remains a highly contested issue. Even if one accepts an origin from protochordates, it is unclear whether the lineage of cephalochordates (present-day amphioxus and its Cambrian period predecessor, *Pikaia*), urochordates or hemichordates, is ancestral. The relation of chordates to echinoderms is still debated because of some shared features with chordates. A free-living ancient planarianlike organism is a very attractive candidate as the ancestor of vertebrates including man, despite a few embryonic features that do not support this theory; for example, planarians are prostomes and vertebrates are deuterostomes.

No tissue of the body makes a stronger argument in support of the hypothesis that the planarian is a remote vertebrate ancestor than does the nervous system (see chapter 9). Planarians possess a bilobar brain with commissural connections and multipolar neurones with a single axone and dendritic spines, features of all vertebrate brains but rare among invertebrates. The paired neural cords are longitudinal axonal tracts surrounded by columns of gray matter neurones, a primitive architecture that persists in some parts of the human brain. Regrettably, molecular genetic studies to date have not yet been able to resolve the important evolutionary question of the ancestral origin of vertebrates in general and the vertebrate nervous system in particular. Because so many neurotransmitters are widely shared by many classes of invertebrates and vertebrates, their demonstration in primitive nervous systems tells us something of the origin of specific secretory types of neurones but not about evolution.

The planarian nervous system, if indeed ancestral to vertebrates, further offers an explanation to the mystery of why one side of the brain controls the opposite side of the body. To develop a functional *coiling reflex*, so that the animal defensively curls its body away from an aversive stimulus, it needed primary sensory neurones on one side of the body to perceive the potential threat and the discharge of motor neurons on the other side to contract longitudinal muscles on that side. This simplest of all reflexes required the development of the *decussating interneurone* to interconnect the sensory and motor neurone on opposite sides.

I consider it a great privilege and honor to have been invited by Dr. Pagán to write a foreword to his book and an opportunity to express an additional perspective as a physician dedicated to the nervous system and its disorders in the fetus and infant. I am proud to endorse this thoughtful and insightful book by Dr. Pagán, a unique contribution to bringing an awareness that the planarian is

much more than a biological curiosity as a cute little animal with crossed eyespots for the entertainment of high school biology students. The planarian is a missing link in understanding evolution and may offer a key to the treatment and reversal of many disabling diseases of humans.

Many individuals take pride in the fact that they can trace their family pedigree back several generations or even several centuries. I can boast that I trace my family origins all the way back to a pair of flatworms!

Harvey B. Sarnat, MS, MD, FRCPC
Professor of Paediatrics, Pathology (Neuropathology), and Clinical
Neurosciences
University of Calgary Faculty of Medicine
Alberta Children's Hospital Research Institute
Calgary, Alberta, Canada

Acknowledgments

FIRST AND FOREMOST, I wish to thank my wife, Elizabeth, for her love, patience, and support, not only for this book, which she read in its entirety, giving me the most honest and useful feedback, but also because of our history together for the past twenty-odd years. Lisa, you are my dream girl, and I love you.

To my children, Vanessa, Reynaldo, and Andy, thank you for your love, for making me a proud dad, and for inspiring me to become a better man every day of my life. I love you.

Even though he is no longer with us, I want to thank my dad for so many things! I also want to thank my mom for everything. Your answer to the question I asked you when I was about four years old, “Did God create microscopes?” is still as valid today as it was forty-odd years ago. I also thank my brothers, Oscar, Alexis, and Luis, as well as my sister, Luz, for being part of a wonderful childhood. Alexis is also a gifted graphic artist and drew several of the figures of this book. He has been doing things like this for me since my undergraduate days; we make a good team.

So many people have generously and enthusiastically helped me in this adventure. I want to start by highlighting the contributions of two friends who encouraged me in this adventure every step of the way. These friends are Mr. Peter Cawdron, a fellow blogger, friend and established writer, and Dr. Robert Raffa, a fellow scientist, friend, and collaborator. They both read the entire book and gave me invaluable feedback. They made sure that whatever I wrote was understandable to the general public without compromising the science; furthermore, they

oftentimes proposed useful stylistic suggestions that improved the manuscript. I also want to thank Dr. Raffa for suggesting the title of the book: *The First Brain*.

I decided to start blogging to “test the popular science waters” after reading a two-part blogpost from Mr. Brian Switek’s *Laelaps* blog titled “So you want to write a pop-sci book?” Blogging made me think seriously about the possibility of writing a popular science book, but I actually decided to start writing it after reading an article by a professional scientist and science writer, Dr. Mark Changizi, titled “How to Write a Popular Science Book,” which appeared in *Psychology Today*. From these readings I truly believed that I had what it takes to write popular science, so from the bottom of my heart, Mark and Brian, thank you.

I thank Dr. Sina Ebnesajjad, who gave me instrumental advice to navigate the book contract intricacies and for his enthusiastic support and friendship. Every time we met at the coffee shop he made sure that I was at the computer actually writing!

I thank Dr. Harvey Sarnat and Dr. Robert Raffa, whose scientific papers made me think about planarians in terms of neurobiology and pharmacology, respectively. Also, I thank them for the forewords to the book and for their unconditional support for this project.

I wouldn’t have had the courage to go ahead and write a book proposal without the feedback and encouragement of many people that read my *Baldscientist* blog. Several fellow bloggers are regular readers who always gave me support and kind words, but most importantly, they gave me their honest feedback on my writings in general and on some of the book chapters in particular, with no sugarcoating whatsoever, for which I am immensely grateful. These regulars are Peter Cawdron, whom I mentioned above (Thinking SciFi), Sedeer El-Showk (Inspiring Science), John Jaksich (The Silent Astronomer), Sam Mason (Science in the Land), and Rebecca Trotter (The Upside Down World).

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I must make a special mention of two people that generously provided materials, insights, and professional perspective about the general field of flatworm biology. Dr. Masaharu Kawakatsu sent me quite a few rare scientific papers on planarians and some original photographs of *really* hard-to-find early work (pre-1700s) on planarians and graciously allowed me to use such pictures in the book. He also proofread the planarian chapters and gave me a unique historical perspective on “planariology,” of which he is one of the renowned protagonists. His gentlemanly character, which came through even in email communications, and erudite and enthusiastic advice proved invaluable for the completion of this book. Dr. Kawakatsu also graciously provided many original color photographs of planarians, which are included in the color plates. Also, through him I found Dr. Vida Kenk, the daughter of one of the preeminent planarian biologists of the twentieth century, Dr. Roman Kenk, as well as an invertebrate biologist in her own right. She also generously provided materials and personal insights on her father’s scientific life through documents and through a delightful telephone conversation.

My road to academia was not straightforward. I was blessed with many people that made it possible: Vesna Eterovic, Richard Hann and Pedro Ferchmin (Universidad Central del Caribe), José G. Ortiz (University of Puerto Rico) and George P. Hess, Susan Coombs and Robert Oswald (Cornell University); you know what you did for me, and I thank you.

I want to express my gratitude to my academic home, West Chester University (WCU), especially the Department of Biology and the College of Arts and Sciences. I am fortunate for working at an institution where I do not have to choose between teaching and research; I can excel in both. I am also thankful for WCU’s fine library staff and resources. Libraries are still a fundamental scholarship resource, and I do not think anyone can convince me to feel otherwise.

At the publisher’s front, my thanks go to Mr. Jeremy Lewis, Mr. Erik Hane, and Ms. Hallie Stebbins of Oxford University Press, who believed in my work and are my knowledgeable guides in the initial editorial process. My special thanks to Ms. Eli Hausknecht and Ms. Molly Morrison, project managers and to Ms. Danielle Michaely, copy editor. My special thanks to Laura Shelley, master indexer. Thank you all for making this “first book-writing adventure” a reality!

All these people helped me to create a much better book than the one I would have written without their input. Any mistakes, of course, remain my sole responsibility.

Finally, I want to thank my barber, Mr. Heath Brewer, who is always in the mood to talk science.

When we're in college, we think about our future as a direct line from now to then, from here to there. . . . But if you look at the careers of many successful people, you'll find that their route is often far more sinuous. And if you look at happy people, you'll find even fewer who traveled a straight line.

—LEONARD MLODINOW

INTRODUCTION

FIRST AND FOREMOST, thank you for reading this book! As an avid reader myself, I have always thought that reading is a little bit like a conversation—granted, a somewhat one-sided conversation, but in my mind, a conversation nonetheless. Moreover, what is lost in this type of conversation in terms of direct interaction is more than compensated for in terms of the number of people who can converse with the author, as well as by the elimination of the time factor. You see, when we read, we are in a sense hearing the voices of authors we may never meet in person for a variety of reasons, including that they may no longer be with us. With this book, for the first time I will be on the proverbial “other side” of the fence in this type of conversation. This is very exciting for me, so again, whether you are reading this right after publication or whether you are reading these words a hundred years from now and wonder about the childish state of science in my time, from the bottom of my heart, thank you.

I absolutely love science, always have, always will. I am in awe of the natural world and of the methodology of science that allows us to uncover nature’s secrets. Nature is majestic; I know of no better way to describe it. I feel quite privileged and even grateful of being able to try to understand some of it, however little I can really understand in my limited time, ability, and opportunity on this planet. Like the great Isaac Newton, many times I feel like “. . . a boy playing on the sea-shore, and diverting myself now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me.”

On a related note, I feel incredibly lucky that I work as a scientist and educator. I hold an undergraduate degree in general natural sciences, a master's degree in biochemistry, and a doctorate in pharmacology, with a strong emphasis on neurobiology. There is a point in stating this. In a way reminiscent of the sentiment stated in Dr. Mlodinow's quote at the beginning of this introduction, I did not follow the direct route to pursue my academic dreams. You see, I was a nontraditional student. After college, I was a high school teacher and I worked in a casino (not at the same time) for a couple of years. After that, I got a job as a research technician at a medical school, where I worked for about nine years. I would say it was there that I learned how to be a scientist, for which I will always be grateful. I then got the opportunity to get my PhD at a top research university and now I am having the time of my life because I teach and do research.

I love my job. Do you want to know why? In what kind of job do they pay you explicitly for reading and learning about the topics you love? It gets better; as a science professor, a big part of the job is to talk (usually to students) about scientific subjects, and the best thing about that is that you have a captive audience: *they have to listen to you!* I am also a practicing scientist, which is a sometimes overlooked way of learning and teaching. After all, when you do research, it is like having a front seat while learning about nature directly from the source. As part of this, I run an active research laboratory in which I have had and still do have the fortune of interacting with many dedicated undergraduate and master's degree students who learn about science firsthand under my direction. I have been very fortunate in the sense that by far, most of these students have what, in my opinion, they are supposed to have to succeed in life: enthusiasm, responsibility, and a pristine work ethic (a good mind, while quite convenient, is just icing on the cake). That said, remarkably, without exception, each of my past and present students has taught me something. Along those lines, many of my past research students have gone on to develop very productive careers of their own, which understandably, makes me a very proud mentor.

Even though I am very familiar with the topics I will talk to you about and in many cases I even have direct, firsthand experience on the subject matter, keep in mind that in science, you are free to verify—actually, you are *encouraged* to verify—anything that any scientist says about science, no exceptions. Nowadays, this is easier than ever! Even more importantly, one of the most beautiful things about science is that all of us, whether we are aware of it or not, are innate scientists. Allow me to explain. Without exception, humans are curious creatures. In that sense, we are like many other organisms with which we share this planet. However, only we humans have built upon that curiosity by developing methods

and ways of thinking that permit us to understand nature a little better, a little beyond what we can immediately perceive through our bare senses.

It is pretty evident that I am rather enthusiastic about this book; it is expected. However, at this point the most important question to you, my dear reader, is, *what's in it for you?*

Well, the first thing that comes to mind is that if you are interested in science, it is a safe bet that you are interested in its progress; you want to learn as much as possible of a particular subject, especially where it is going, while being careful at the same time of not losing sight of where it came from. You will have an easier time predicting a possible future trend or application of a specific discovery if you understand how it came to be.

Also, we science types are fascinated by facts, but facts by themselves are simply not enough; we also want to know whenever possible the “why” behind those facts. If you care about this—in other words, if you are even peripherally interested to find out about the “whys” of nature—you are implicitly interested in the organ that makes you feel interested. That organ is, of course, your brain.

In this book I will tell you a story with science, especially neurobiology and pharmacology, as the unifying theme. The book consists of ten chapters organized into four parts. What's different about this book is that its main character is a certain type of flatworm, commonly called planarians. Before meeting these interesting little guys, I'd like to offer you a brief introduction about science in general; after all, this is a popular science book. In part I, “Fundamentals,” we will first go over a series of science-related concepts in two chapters that will make the understanding of the rest of the book much easier.

The main theme of this book is to explore aspects of nervous system anatomy, physiology, and pharmacology from the premise that the planarian brain is an early, if not the earliest, example of an actual brain in the animal kingdom. Moreover, we explore the concept of the planarian brain as the first vertebrate-style brain that appeared in our planet and how the study of the planarian brain may throw light on the human brain, helping us understand ourselves a little better.

Before we do that, though, we must have a working understanding of neurobiology. Part II of the book, “The Science of the Brain” (chapters 3, 4, and 5), explores the neurobiology- and pharmacology-related concepts that are necessary to understand the rest of the book. These topics include the similarities and differences between “neurobiology” and “neuroscience,” among other topics. In this part we will also talk about what is often called the most complex system in the known universe, the human brain.

In part III, “Planarians,” we finally meet the main character of this book. In chapters 6 and 7, I will formally introduce you to some of my favorite (nonhuman) organisms: the *flatworms*, specifically the *planarians*. These worms have a distinguished place in developmental and regeneration biology; you may remember them as the little guys that grow a new head when decapitated (more on this later!).

Planarians have captured the imagination of people of all walks of life, not only scientists. In chapter 8 I offer you an interlude in which I explore a series of curious connections between planarians and popular culture. Just to give you a preview, these guys have inspired works of art, they have appeared as characters in comic books and other kinds of literature, and there are even some interesting links between flatworms and very popular science fiction and fantasy works.

Part IV, “The First Brain,” is kind of the “flagship” of the book. It is also about neuroscience, but exclusively from the perspective of planarians. In chapter 9, we will see that bits and pieces of what constitute the modern nervous system are found in much simpler living organisms. Also, we will explore in more depth the case for the planarian brain as the first actual example of a brain, as well as some intriguing neurobiology research done in these flatworms.

Psychology can be seen as applied neuroscience. One of the most interesting episodes of the history of psychology also has planarians as the main characters. In this chapter I also explore this interesting history, where planarians were for a while a favorite animal model to study learning and memory. In fact, for a very brief period a new discipline, “protopsychology,” did show a lot of promise, was intensively studied, and then simply faded away, in that order.

More recently, certain species of planarians have become a favored, popular, and somewhat surprisingly useful animal model in pharmacology and toxicology. We deal with this emerging “planarian pharmacology” field in chapter 10. Among other topics, I will talk about the experiences of several fellow planarian researchers, some of whom are also colleagues and friends. More specifically, we will talk about the effects of naturally occurring products on drug-induced behavior using the planarian model. Interestingly, several research groups, including my own, have uncovered a series of parallels between planarian pharmacology and vertebrate pharmacology, which provides evidence in favor of the usefulness of these invertebrates in pharmacological research.

Whenever I talk (or write) about science, I try to stress the fact that science is done by people, with everything that goes with the territory. In any scientific discovery the human factor and its historical background are factors that need to be taken into account to understand the full story. For this reason, in all chapters I have tried to include historical and character anecdotes that help present the human factor in science.

In this vein, I want to point out that each chapter has a number of (not too many, I hope) endnotes in a separate section at the end of the book. I encourage you to take a look at them. They will not only oftentimes point you in the right direction for further reading but also clarify and put in perspective the discussed topics. In some of them I even included humorous anecdotes and miscellaneous tidbits related to the topic at hand. Also, by reading the notes as you read the text, it can help you go around a problem that I myself have. You see, all of us were raised in the era of television. This means that most of us are accustomed to paying close attention for a few minutes and then being interrupted by commercials. Many of the notes will serve this purpose by shifting your attention ever so briefly so you can go back to the text with refreshed concentration.

The end of the book features an epilogue that tells the fictional story of two characters (one historical, one imaginary) linked by a single planarian over more than a hundred years.

I would say that there are two main purposes of this book. The first one is to share with you my fascination with this subject matter. The second is to inspire you to learn more about the topics you will read about, to go beyond what I say here and hopefully enrich your mind in the process. In this respect, I will try to follow the distinguished example of some of my favorite writers/scientists, including Stephen Jay Gould, Carl Sagan, Richard Dawkins (when he writes about science) and, of course, the author who introduced me to the popular science literature in the first place, the one and only Isaac Asimov. I hope you find my writings at least a fraction as entertaining and inspiring as these authors' works have been to me.

I wrote this book with interested laypeople in mind; however, I would be very happy if biologists and other scientists find something of value in it too. My hope is to try to make my readers curious enough that they may want to expand their knowledge in these and other related areas. To help you go beyond the scope of the book, I have included notes and selected references for each chapter as I said earlier, as well as a general bibliography. Each chapter can be read independently, but I suggest you read them in order, as I often refer to previous chapters, depending on the topic. In general, when I introduce a concept for the first time, I will define and/or explain it. Some chapters include material and original ideas that first appeared in my blog, *Baldscientist* (<http://baldscientist.wordpress.com>). However, any material from the blog is significantly expanded and updated.

I want you to be aware of something before starting this journey with me. No single book, especially a popular science book, can say all there is to say about any particular subject.

I have tried to do justice to the wealth of information about planarians available in the scientific literature. This has been a process full of difficult choices, as there is simply not enough space in a single “normal size” popular science book to include a comprehensive account of these interesting organisms. In all fairness, this is true of any life form in this wonderful planet of ours. That said, in no way am I implying that the contributions that did not make it into the book are of lesser importance than the ones that did. Planarians are experiencing a true renaissance as important animal models in biology. There are many laboratories led by brilliant scientists working on various disciplines, including but not limited to molecular and developmental biology, biochemistry, regenerative biology, neuroscience, and pharmacology. These research groups are continually generating data and adding important findings to the field. I want to apologize in advance to all my scientific colleagues whom I do not explicitly mention in this book due to space considerations, both those I know personally and those I know by reputation.

Now, would you like to know about the first planarian I ever met?

Life can be full of surprises and amusing coincidences. As I was in the process of researching and writing this book, I remembered an episode of my childhood that describes the very first time I ever saw a planarian.

It was around 1975; I was ten years old and, like many kids, loved to play outside, an activity that sadly, for many complex reasons, is not as common anymore. My elementary school yard was huge, or at least I remember it that way. When it rained hard, a couple of small ponds usually formed, which were rapidly colonized by the wonderful critters that children love to play with. Alongside my friends, I loved to collect tadpoles; they were “my thing.” Sometimes I even brought them home and watched them for several days as they sprouted legs and eventually became small toads who happily hopped away.

I vividly remember this one time when I was looking for tadpoles and I saw this whitish, ribbonlike wormy. I took it to my classroom and showed it to my science teacher. We put it in a small fish tank we had in our classroom. In retrospect, that was not a good idea. I could not find it in the tank afterwards; I am sure that a fish ate it. I do not remember if it was my teacher who told me that the wormy I brought her was a planarian or whether she gave me a book so I could try to find out what it was by myself, but at any rate, it was right then and there that I learned about planarians for the first time.



HENRY THE PLANARIAN.

Illustration by Nathan Scheck (<http://www.albinokraken.com>). Used with permission.

I never imagined that thirty-odd years after my first encounter with a planarian I would be doing scientific research with these wonderful beings, much less writing a book about them! I hope you enjoy reading this book as much as I enjoyed writing it.

