Gray's Anatomy

An Effort to Simplify Shows How Complex Life Really Is. How Does It Get That Way?

KENNETH M. WEISS

On July 1, 1858, papers by Charles Darwin and Alfred Russell Wallace were read before the Linnean Society. This was the first public presentation of their ideas about how natural variation arose and proliferated into new, diverse species. The meeting had been scheduled for June, but had to be rescheduled because of the death of the Society's vice-president (see Wikipedia, "Linnean Society"). The evolution paper was shifted into the *ad hoc* summer meeting. Famously, few people were there and perhaps fewer paid any attention to the message (this may depend on how many sherries had been consumed). But the new ideas certainly *were* noticed in the following year, 1859, when Darwin's book on the subject, *On the Origin of Species*, appeared. Darwin revised his book through a sixth edition. Countless copies have been published. After 150 years, it is still *the* book on evolution, still the original in Darwin's word as well as name.

That story has been told many times. But other things were going on in London in that remarkable year, 1858. Almost to the day of the Linnaean Society meeting, the edited proofs of another book, which became "the" book on its subject, were delivered to the London publisher Parker & Son. That was *Gray's Anatomy, Descriptive and Surgical* (Fig. 1). Its story is also worth following from 1858 to the present. (The following history of *Gray's* is largely from a recent book by Ruth Richardson[1]).

Ken Weiss is Evan Pugh Professor of Anthropology and Genetics at Pennsylvania State University. E-mail: kenweiss@psu.edu

DOI 10.1002/evan.20240
Published online in Wiley InterScience (www.interscience.wiley.com).

Like Darwin vis à vis Wallace, the young anatomical star Dr. Henry Gray (1827–1861, Fig. 2a), Lecturer of Anatomy at St. George's Hospital, also had a relatively unsung partner, Henry Vandyke Carter (1831–1897, Fig. 2b). While Gray wrote the crisp descriptive text, it was Carter who drew the famously clear and esthetically beautiful illustrations that made their book a success. Carter's wood engravings are still used by artists and many of us treasure our copies of some edition of *Gray's* just for its esthetics. Unlike Darwin, however, Henry Gray was not forthcoming in giving due credit to his co-conspirator.

The young Dr. Gray undertook this project because he was dissatisfied with the existing anatomy books. One was by John Bell (1763–1820)[2]. Bell's book was noted for its realistic but gruesome figures, which accurately depicted the socially degraded people who were used in dissecting theaters at the time (Fig. 3). Those whose parts were separated for medical students had first been separated from their resting places by grave-robbing. Bell's illustrations often of villains or paupers from the dregs of society further degraded them, and rather needlessly.

However, the standard text in Gray's day was Quain's.[3] It was authoritative, but too detailed for students, who needed training as physicians and surgeons, not anatomists. Anatomy books sold very well, so with Carter's artistic help and the publisher's encouragement, Gray aimed at something that could be used effectively in class, a book with simple descriptions and clear, utilitarian drawings to train future surgeons. After about two years of intense and patient work, with Carter often carving in less than the best of light to make its 363 woodcuts, *Gray's* was published in 1858. The initial edition of 2,000 copies sold out. *Gray's* quickly went into subsequent issues and became the new standard. The result is history.

The 1901 edition of *Gray's* is still available,[4] though you'll have to spot for yourself which figures bear Carter's unique style, with its hand-engraved labeling embedded in the picture, because many new figures have been added. Also, Carter's drawings were altered when better publishing methods were developed.

It's easy to refer to traits like the "limb" or "head." But these single words belie a boggling wealth of intricacy and detail. To ask the Darwinian question, "How did the head evolve?" is but a metaphoric question, and hardly a scientific one, as is easy to see. Its anatomy alone, as seen in just a few of *Gray's* figures depicting the head (Fig. 4) is daunting. If it is even biologically meaningful to speak of a head as one structure, this one comprises a weaving of arteries, veins, capillaries, lymphatic vessels, blood, nerves, the many parts of the eyes, outer and inner ears, olfactory and taste systems, teeth, muscles, tendons, ligaments, fascia, joints, marrow, passages into and out of bones, and muscles. Then there are the many covering layers, the dura, pia, arach-

ANATOMY

DESCRIPTIVE AND SURGICAL.

BY

HENRY GRAY, F.R.S.

LECTURER ON ANATOMY AT SAINT GEORGE'S HOSPITAL

THE DRAWINGS

BY H. V. CARTER, M.D.

LATE DEMONSTRATOR OF ANATOMY AT ST. GEORGE'S HOSPITAL

THE DISSECTIONS

JOINTLY BY THE AUTHOR AND DR. CARTER

LONDON:

JOHN W. PARKER AND SON, WEST STRAND.

1858.

Figure 1. Cover page of 1858 first edition of *Gray's*. Reconstituted from a photograph in Richardson.[1]

noid membranes, the bones, and periostial layers, not to mention the layers, hairs, glands and other structures of the skin. And of course there is that minor item inside, known as the brain.

In fact, these are just the *gross* details that can be seen with the naked eye, and only of the adult, not considering its embryological stages, which include the timing, location, size, formation, and mineralization of each component of the head. At the histological and cellular level, there is a wealth of additional structural and functional detail within each of the aforementioned structures.

Similar complexities apply to every part of the body. Anyone who can recall the dissecting room's aura of formalin knows that each of these features varies from person to person, within and between all primate species. Yet for the most part these complex structures, an arm, stomach, or head, are laid down in a very similar way among individuals and among related species. They are, for example, similar on the left and right sides, which to a great extent develop independently. What differs are the relative sizes and timing of corresponding component parts. Despite their variation, each newborn human or chimp is, after all, unambiguously a human or chimp.

Anatomy develops through a genetically choreographed embryological dance, with similar steps shared but syncopated among species. Carter's figures from the nineteenth century show how very complex the morphology of the human body is. And *Gray's* provided only a small subset of the truth, as the growth in detail in subsequent editions has shown. It is hard to imagine how much complexity is hidden just under the skin, so to speak, even just anatomically, not to mention in our physiology, behavior, immunology, and our complex sensory and other systems.

We've always been able to describe, and even test, the functional anatomy of, say, the face or the ankle bones, and to suggest possible evolutionary scenarios for it, such as what kinds of natural selection might have been involved. This was acceptable for most of the twentieth century, which saw rapid growth in anatomical and histological knowledge. (*Gray's* kept growing in size, too.) Some developmental experiments, such as manipulating embryonic tissue in experimental organisms like the frog, chick, or mouse, showed the *pattern* of development even at the cellular level, and when and how that could be disrupted. But this was largely a black-box approach, because we had few ways to relate morphological phenomena to the nature or evolution of their underlying genetic mechanisms that are presumed to be there. That's been changing dramatically as technologies in molecular development and genetics have been opening up the box.

The technological advances include the availability of largely complete genome (DNA) sequences for humans and many other species; the ability to identify the genes expressed in any type of cell at any time during embryonic development by identifying the messenger RNAs (mRNAs) that will be translated into the proteins of each gene; and the ability in a mouse or other laboratory vertebrate model to experimentally inactivate or modify the expression of any individual gene we might choose. After applying these tools for a couple of decades of intense and enormously successful research in developmental genetics, we have learned so much that the only remaining details we don't yet understand are. . . .most of the details. Nonetheless, we can see newer, better ways to approach an understanding of anatomy.

DISSECTING THE BLACK BOX

Modern genetic knowledge of anatomical development takes two general forms: breaking down and building up. In the breaking-down department, for most traits genes are known for which mutation has path-

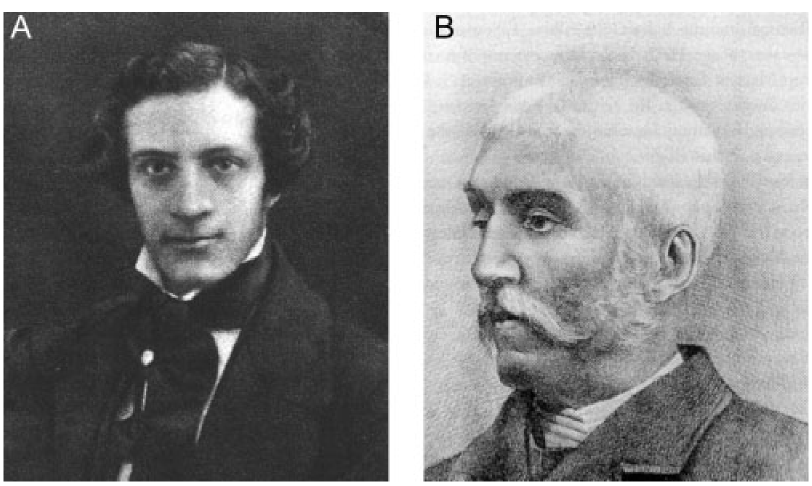

Figure 2. A brace of Henries: A. Gray, B. Carter. Public domain.

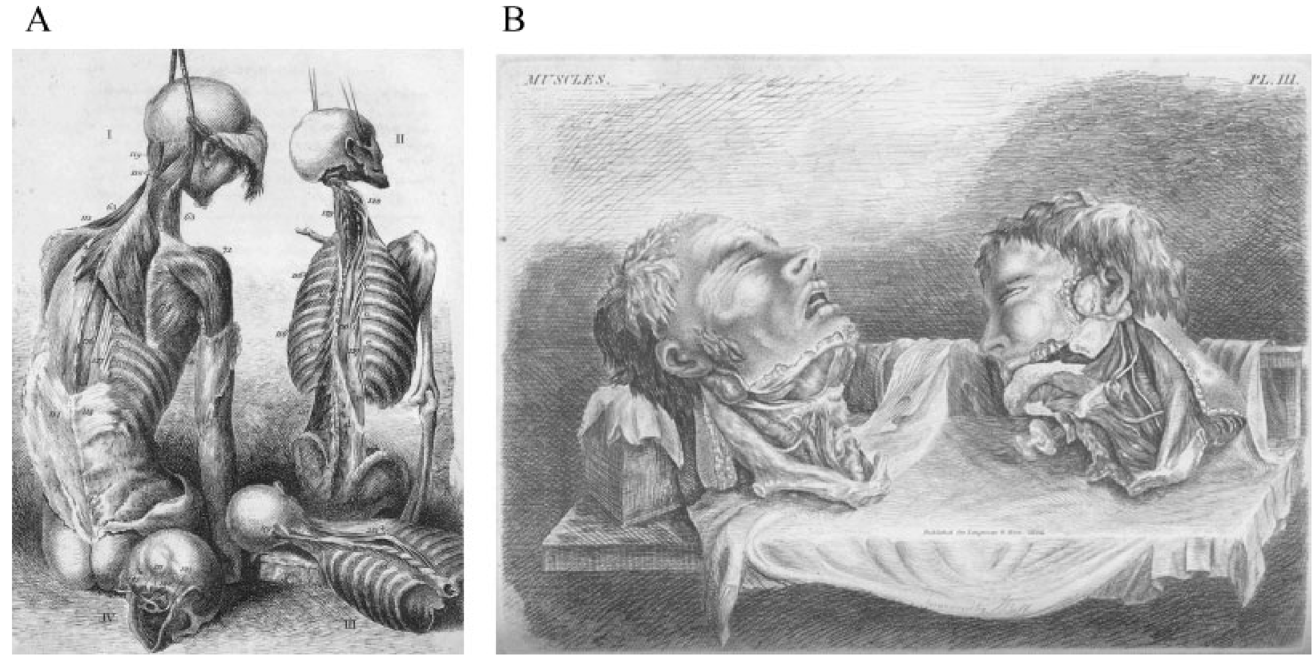

Figure 3. A gruesome representation of John Bell's version. Source: public domain, from Bell.[2]

ological effects. Thus, mutational bashing of genes named *Shh* or *Pax2* can lead to various forms of holoprosencephaly, facial midline defects such as cleft lip or palate, only a single central upper incisor, or cyclopia, the state of having only one central eye. (Gene names may appear dauntingly technical but they are just names, no more obscure than, say, Aloysius or Ethelberta). Mutations in genes called *Fgfr1*, *2*, and *3*, or *Twist1* can alter head shape or cause premature fusion of the cranial sutures (craniosynostosis).

Explanations of anatomic traits from the building-up perspective requires a bit of background. The hundreds of cell types in the body change their behavior rapidly during development. They do this by changing the genes they use at any given time. We have about 25,000 different genes, each capable of different expression depending on context. There also are many other kinds of functional units in our genomes that affect how genes are used, and may actually comprise the majority of genomic functions. Identifying these genetic elements yields very long lists that, like Victorian beetle collections, are the cynic's archetype of mindless data collection.

To account for this complexity in any simpler way is a challenge. The explosion of research findings in developmental genetics has occurred long since *Gray's* became too big to hold except on your lap (to the immense annoyance of your displaced cat). Indeed, *Gray's* has more *pages* just to describe anatomy than I have remaining words in which to try to explain how it works. But let's try to think in a more general way. What we'll see is that development produces things, like sphenoids, eyes, and braincases, but is really about relational principles, or a kind of "logic" that is shared, along with greatly overlapping lists of genetic contributors, by *all* such structures. Thinking in terms of genetic processes provides a reduction in what we might call the dimensionality of causation, or the number of different things we have to keep track of. This is because, unlike long lists of genes, there is a short list of basic principles by which development is achieved.

Experiments have identified many kinds of *networks* of interactions among tens of genes that are used to build anatomical structures. For many purposes, we can determine when and where a network is active by testing for the expression of one of its genes, taken as an indicator, without needing to consider each of the network's participating members. This helps reduce our lists. We might still be in some trouble if we could not generalize even further, but we can.

Gene networks are, to a large extent, involved in "signaling", by which information is passed among cells, causing them to differentiate by, for example, changing their gene-expression patterns. Signaling, a dynamic process in embryonic space and time, is the most important means by which cells build complex organ structures like heads and feet and everything in between.

The use of signaling networks is both combinatorial and hierarchical. Growing tissues are isolated from each other except when connected by signaling, so that each can form its respective organs. Once a cell has changed, it "remembers" its gene-expression state and thus becomes receptive to further change by being ready to detect and respond to subsequent signals. Signaling is spatial, because it relates cells in different locations to each other; it is temporal because one cascade of differentiation leads subsets of those cells to differentiate further. The result is

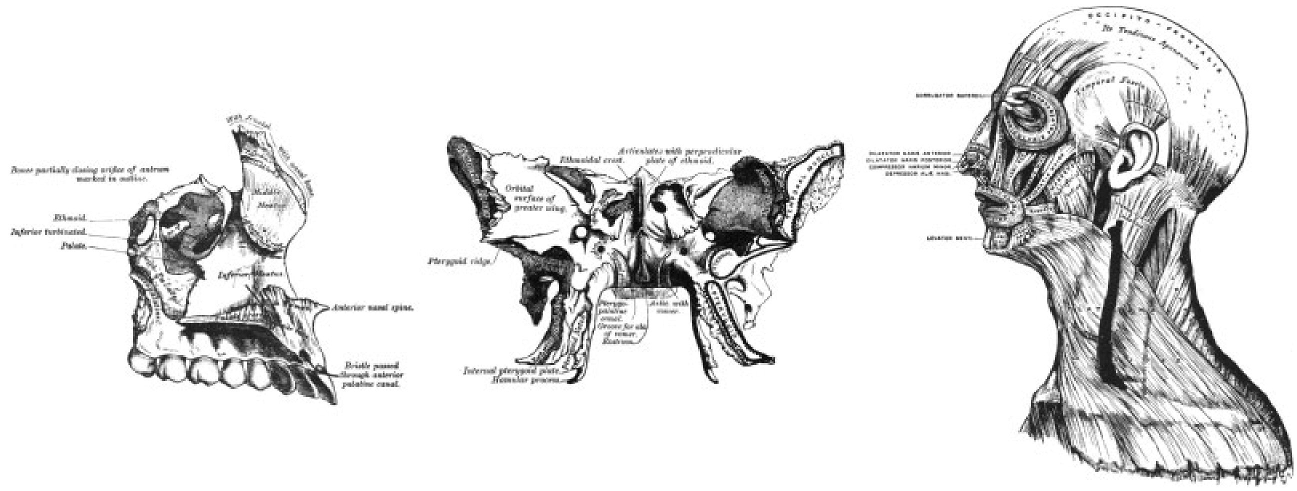

Figure 4. The complexity of the head à la *Gray's* Anatomy (1918 Edition): a sampler, Left to Right: Inner face, sphenoid, superficial head and neck. Additional images are on the cover.

locally nested, modular structures, layers, repeated units, and branching, as Henry Carter's drawings showed in the lobular structure of lungs or salivary glands, the different numbers of bones from shoulder to finger, different numbers and types of teeth or vertebrae, and segmental variation within brains.

Even within a developing organ, like an eye or stomach, different tissue layers respond to their local signaling environment, so that muscle, bone, nerve, vessels, and their own corresponding histological structures can develop. Cells expand into new areas by division by clustering together, by recognizing the signal receptor molecules on each other's surfaces, or even migrating through a surrounding tissue by using their signal receptors to detect the appropriate environment. These processes are used all over the developing embryo, employing different combinations of signals and receptors. While one cell may be actively producing the signal, entirely different cells may express a gene that codes for a signal-receptor protein that enables them to react to the signal. This is what keeps an embryo a coherent whole.

Starting with a single fertilized egg cell, polarities, axes, and tissue layers, as well as their respective branches, segmented, modular, and repetitive structures, ensue in cascade after cascade of these signal-based processes. Like any drama, one act sets the stage for the other, all of them sequestered segments of the whole developmental play, but without intermissions. Each cell maintains its inner environment and adjusts in response to its outer environment.

NESTED, HIERARCHICAL, REPETITIVE COMBINATIONS OF GENES

I can illustrate these principles with a description of one simple part of the head, the teeth. As shown in Figure 5, teeth form in the first branchial arch, the mammalian descendant of the first gill arch in ancestral fish. When the arch first appears, its covering ectodermal layer broadly expresses a signal gene named *Fgf8*, but this area is narrowed through the inhibiting action of another signal gene, *Bmp4*, resulting in separated spots along the jaw where teeth will grow. The outer layer will form enamel in these areas, while the underlying tissue, called mesenchyme, interactively responds with the ectoderm and will eventually produce the tooth's pulp and dentine. Mesenchymal cells expressing a gene called *Pax9* respond to the ectoderm, while neighboring areas are inhibited by *Bmp2* expression. Subsequently, a series of patches of expression of specific combinations of signal and responding genes specify first the location of future *types* of teeth (incisors, canines, or molars), then their numbers, and then their surface cusps. During this process, many of the *same* signal combinations are reiteratively used (Fig. 5D), reducing the list of things we must consider to get a general sense of how teeth are made.

This patterning occurs in soft tissue. The result is then put in stone, so to speak, as a cascade of mineralization gene expression occurs, with different members of the same family of genes used to form the enamel and dentine, respectively.[8]

Teeth provide a good example of developmental processes because they have been studied in great detail and are visible and accessible. But the same kinds of simple relational processes, and many of the same signaling combinations, are involved in the other structures of the head (and elsewhere), keeping Carter and Gray burning the midnight oil to produce their book.

The scientific power of these generalizations can easily be seen by the way they guide research all across the spectrum of life, from plants to animals.[9] Even an enormously complex trait such as the skull makes genetic as well as developmental sense. It's an exciting time, but it is only a beginning that, like *Gray's* for surgeons, represents a simplified plan which developmental genetic research can be built.

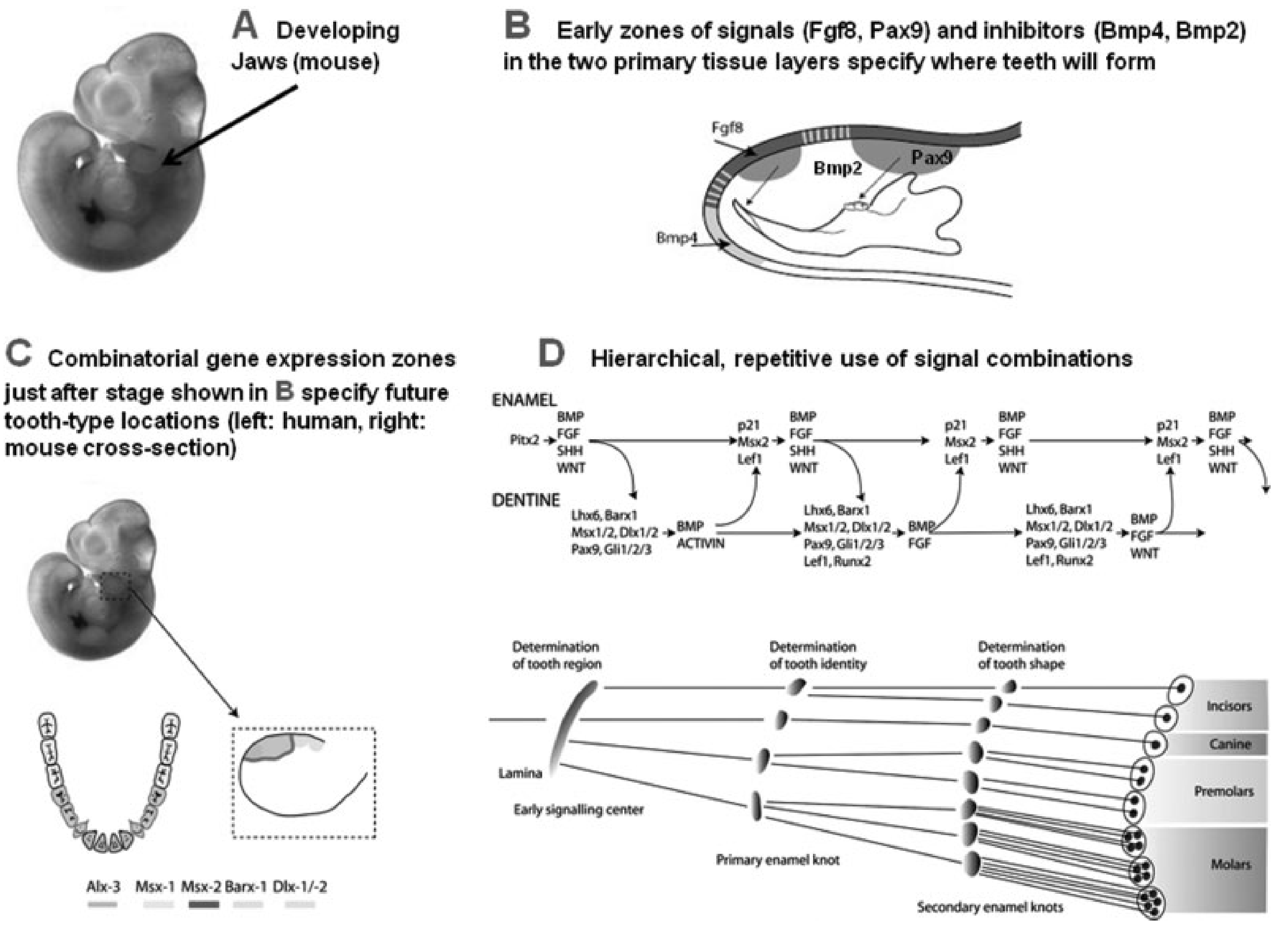

Figure 5. A few of the genes and processes involved in tooth development. A. Early embryo showing future jaws. B. Combinations of expressed genes specify future tooth initiation zones, as shown by the inset adult mouse jaw. C. Subsequently, combinations of different genes specify where each tooth type will form; redrawn after McCollum and Sharpe.[5] D. Nested, repeated combinatorial expression of a few of the known signaling and responding genes in the upper (enamel) and lower (dentine) tooth layers, as teeth and their cusp structures form. Arrows show time passage; genes named at left of arrow induce expression of genes on the right. Communication between the two tissue layers is shown; modified after Jernvall and Thesleff.[6] Final mineralization involves additional signaling, not shown. The specific gene names are unimportant here. For details see online dental development data base, http://bite-it.helsinki.fi/, as well as McCollum and Sharpe,[5] Jernvall and Thesleff,[6] and Kawasaki and Weiss.[7]

However, a ground plan of developmental processes does not tell us how much of the genetic mechanism we actually need to understand. That depends on the question one is asking.[9] To what extent a knowledge of the genetic mechanisms involved is relevant to understanding how the morphology is used, how it affects behavior, how it relates to past or present ecologies, or the way selection and drift molded the differences, is up to each investigator. Genetics may be at the root of all of life, but we don't all have to be geneticists. It may suffice to know that, sure enough, the genetic mechanisms we assume are there can be worked out, and this is sure to affect future editions of *Gray's*. But genetic knowledge will not change the what-structure-goes-over-what of anatomy, even if it helps account for how it got that way when it matters to know that. We should, at least, understand and respect both the complexities and the regularities of genetic mechanisms, because we're no longer just dealing with a genomic or Darwinian black box.

THE RECEPTION OF *GRAY'S*

Reviews of the first *Gray's* were mixed. *The Lancet*[10:283] and *British Medical Journal*[11] were initially gushing, but some months later a lengthy review in the *Medical Times & Gazette*[12] blasted Gray for essentially taking from others without attribution and producing nothing new. In fact, as with many ambitious authors, Gray wanted credit and went out of his way at this time, as he had in an earlier collaboration on a book about the spleen, to reduce recognition given to Carter.[1] He insisted, for example, on less than equally prominent billing for Carter on the title page; his name had to be in a smaller font (Fig. 1).

Since then, in its many editions, *Gray's*, has ballooned. The latest British edition is 1,576 pages (small print, 2,000 images), and 'written' by a large board of authors and editors.

There have even been efforts to try to cut it back, though the future versions probably will be mainly online, in which case contributors may not be able to resist the unlimited cyberspace they might use up. The name's the same, but the original purpose is gone, perhaps replaced by market rather than instructional considerations. Perhaps also there is the feeling of authorial pride that this legendary book must remain *the* definitive source on anatomy, rather than the basic tutorial for mere students that *Gray's* was intended to be.

In attempting to envelope the human body in all its glorious complexity, the authors and publishers have lost sight of the bigger—or perhaps I should say littler—picture. Yet, for many purposes, perhaps for most purposes, it is the simpler cogent facts that are most useful and even the most informative. The best ideas of the future, about the development, functioning, and evolution of the body will probably arise from syntheses based on simpler principles rather than the plethora of more complex facts.

Things have turned out differently with Darwin. There has, of course, been a similar inundation of relevant facts in genetics and evolution since *Origin of Species*. But instead of serial editions of *"Darwin's Origin of Species"* edited by large teams of contributors, it has remained literally the same book with the same single author, providing the same source to go to to for an understanding of Darwin's own thinking. Of course, newer texts in genetics seem as driven as the publishers of *Gray's* to present every fact, detail, technological method, and promise that one can dream up. As with *Gray's*, the deeper truth of the bigger picture, sometimes seems to be becoming lost in the detail.

In 1861, at the age of only 34, Henry Gray died of smallpox. He apparently believed that he would be protected by a vaccine he received in childhood and volunteered to tend his nephew who had fallen ill to the disease. Gray's death was noted at the time because he was prominent in his own right and his book had quickly become the standard.

Henry Carter had moved to a major position in the Indian health service in Bombay before their book was published. He did not see the proofs or the title page through their final editing; transportation at that time was slow and so was the mail. Although Carter was pleased with the final product, his new mission was to help the Indian medical services as a physician and eventually as Deputy Surgeon-General, not as an artist. He served successfully in India for 30 years before returning to the UK, where he died in 1897 at age 65. He was not a celebrated figure.

Even for those who have no direct interest, or are impatient, a browse through *Gray's*, perhaps especially an earlier and simpler edition, can be a sobering experience. It shows how very much we have yet to explain in genetic and developmental terms, just about the parts of the body we can see with the naked eye. But think of anatomy from the cell's-eye view. Each cell only knows its own immediate environment and is blind to the bigger picture; yet the embryo organizes itself without an outside coordinator. In every organ in every part of the body, it does so by cascades of hierarchical signaling, each local stage partially sequestered from its antecedents and neighbors so that it can differentiate in new ways, modifying the scenery on the stage that was set for it.

Generalizations like those I've outlined account for each cell's experience as it sends, detects, and responds to genetic signals. You and I are the result of countless cells acting together in space and time, each only knowing and responding to its immediate external conditions. A few simple principles applied again and again from the molecular to the organismal level provide the kind of *general* explanation we need. In a sense, the rest is just (a lot of) specific details. For any given structure, like the limb, dentition, or head, we will have to work out those details specifically. That is being done in laboratories around the world, including an increasing number in anthropology. Somehow, each individual cell, groping only in the light of its immediate neighborhood, plays a part in the intricate dance that generates the beautifully complex material that the unsung Henry Carter so lovingly and patiently drew for us to see.

NOTES

I welcome comments on this column: kenweiss@psu.edu. My frequent co-author Ann and I maintain a blog on relevant topics at EcoDevo.blogspot.com. I thank Anne Buchanan, Nina Jablonski, and John Fleagle for critically reading this manuscript. This column is written with financial assistance from funds provided to Pennsylvania State Evan Pugh professors, and NSF grants BCS 0343442 and Hominid Project BCS 0725227.

REFERENCES

1 Richardson R. 2008. The making of Mr. Gray's anatomy. Oxford: Oxford University Press.

2 Bell J. 1810. Anatomy of the bones, muscles and joints. London: Longman.

3 Quain J. 1837. Elements of anatomy. London: Taylor and Walton.

4 Gray H, NetLibrary Inc. 1974. Anatomy, descriptive and surgical. Philadelphia Running Press Book Publishers.

5 McCollum M, Sharpe PT. 2001. Evolution and development of teeth. J Anat 199(Pt 1–2): 153–159.

6 Jernvall J, Thesleff I. 2000. Reiterative signaling and patterning during mammalian tooth morphogenesis. Mech Dev 92:19–29.

7 Kawasaki K, Weiss KM. 2006. Evolutionary genetics of vertebrate tissue mineralization: the origin and evolution of the secretory calcium-binding phosphoprotein family. J Exp Zool B Mol Dev Evol 306:295–316.

8 Kawasaki K, Buchanan AV, Weiss KM. 2007. Gene duplication and the evolution of vertebrate skeletal mineralization. Cells Tissues Organs 186:7–24.

9 Weiss KM, Buchanan AV. 2009. The mermaid's tale: four billion years of cooperation in the making of living things. Cambridge MA: Harvard University Press.

10 The Lancet. 1858. Issue II. 9:282–283.

11 The British Medical Journal. 1858. Issue 13.II:949.

12 Medical Times and Gazette. 1859. Issue 5.3:241–244.