BIOGRAPHICAL MEMOIRS

John Tyler Bonner

May 12, 1920–February 7, 2019
Elected to the NAS, 1973

A Biographical Memoir by Vidyanand Nanjundiah and Simon Levin

John Tyler Bonner ranks among the great biologists. He was beloved by his colleagues for the example he set as a scientist and as a friend, colleague, and mentor and was known as an inspiring teacher. By developing the cellular slime molds as models for studying developmental processes and social evolution, John built bridges between evolution and development that helped launch a field, inspiring generations of experimentalists and theoreticians to explore the connections more thoroughly. In graduate studies at Harvard, Bonner identified the slime mold *Dictyostelium discoideum* as his primary experimental organism because of its great potential to ask a range of questions at the core of studying evolution and development: How do individual organisms organize themselves into multicellular assemblages that can perform more complex tasks? What triggers switching in behaviors from "selfish" consumption of resources to cooperation, and what signals serve to organize collective ensembles? In a landmark experiment, John identified the signal, showing that when amoebae had run short of food, they exuded a diffusible chemical attractant, later shown (through his efforts) to be cyclic AMP. It was the key to the emergence of multicellularity. His discovery that chemotaxis rather than cell-to-cell contact underlay this process was transformational, attracting the attention even of Albert Einstein, and inspiring later development of sophisticated mathematical theories. Bonner's autobiography *Lives of a Biologist* conveys a delightful picture of his growing up and becoming a scientist.

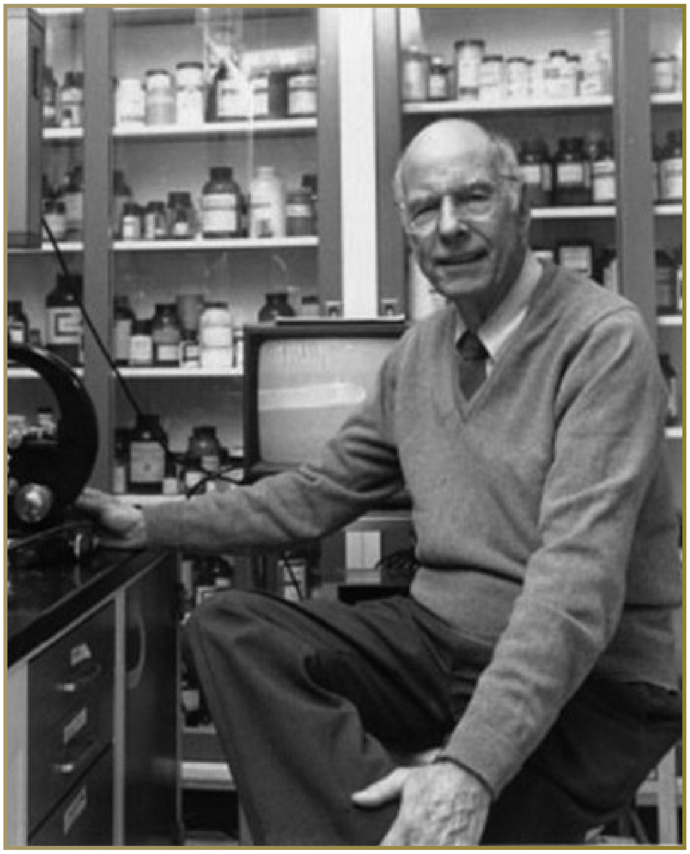

Figure 1 Portrait of John Bonner taken in his laboratory in Princeton University, USA, in 1990. *Courtesy of the Indian Academy of Sciences*.

Early Life, Education, and Career

John Bonner was born in New York City on May 12, 1920, and also spent time as a youth in France and England. In 1934, the Bonners returned to the United States, and John and his three brothers enrolled in Phillips Exeter Academy, like their father Paul Hyde Bonner, who was at various times a banker, soldier, singer, diplomat, and best-selling author; his mother Lilly Marguerite Stehli belonged to a wealthy Swiss family. He graduated from Harvard University in 1941 and stayed on for graduate work. During this period, he married Ruth Anna Graham and also served in the U.S. Army Air Forces from 1942 to 1946, returning to Harvard to finish his Ph.D. in 1947 under the tutelage of William H. Weston. He would go on to spend his entire career at Princeton University, occupying the George Moffett Professorship and acquiring a reputation as a great researcher, teacher, mentor, and department chairman. Princeton awarded him an honorary degree in 2006 to recognize his legendary contributions to the university and science more generally. In all, he received four honorary degrees and was a member or fellow of the American Academy of Arts and Sciences (1969), American Philosophical Society (1972), National Academy of Sciences (1973), and Indian Academy of Sciences (1992).

The Developmental Biologist and the Evolutionary Biologist

Bonner played two distinct, though overlapping, professional roles representing different strands of his science. One was that of an experimentalist, a developmental biologist, who as a graduate student happened upon the unusual life cycle of *Dictyostelium discoideum*; the organism was to occupy his attention for the rest of his working life. In this role, he probed fundamental questions through simple experiments, making use of extremely elementary apparatus. His techniques, indeed his style of research, harked back to the great embryologists of the late nineteenth and early twentieth centuries; he admired them a lot and became personally acquainted with two of them, Edwin Grant Conklin and Thomas Hunt Morgan, late in their lives. Bonner's other role was of an evolutionary biologist. Today the area to which he contributed is better known as evolutionary developmental biology (evo-devo). In fact, he can be counted among its founders. The field has had a long gestation time, dating back to Darwin as well as D'Arcy Thompson, though those two had divergent explanations for how evolution took place. Here too the roots of his interest went back to questions that were initially raised during the late nineteenth and early twentieth centuries, to a period when development and evolution were viewed as processes involving related aspects of change, except that the change was perceivable over enormously different time scales. In evolutionary biology, Bonner was a theorizer. Except towards the end, when he showed himself open to a radically new possibility, he continued to maintain a neo-Darwinian view of evolution.

As a developmental biologist, Bonner's focus was on basic questions. What properties of single cells account for their collective behavior? What factors lie behind a defining feature of multicellular organization, namely the differentiation of the mass into a well-proportioned structure? Except that they are embedded within a conceptual framework that involves genes, DNA, RNA, and proteins, these are the very questions that engage developmental biologists to this day. He was constantly alive to the classically posited dichotomy between the mosaic (pre-differentiated) and regulative (spontaneous differentiation of a homogeneous unit) modes of differentiation. Bonner the developmental biologist mostly communicated with fellow scientists in the conventional manner, through published articles. The influence he had thereby on cellular slime mold biology research was fundamental. On the other hand, the field of developmental biology as a whole was moved more by findings on large, obligatorily multicellular animals. Marine invertebrates, amphibians, and much later, fruit flies, were typical objects of study. It took a long time for *Dictyostelium* to acquire the status of a "model," which is to say a fashionable organism for study; now that it has, the picture has changed.

Bonner's discovery of cellular slime molds was serendipitous. While waiting for an appointment, he was glancing through a Ph.D. thesis by Kenneth Raper that dealt with *Dictyostelium discoideum*, one of the cellular, or dictyostelid, slime molds. This group of organisms is special in that, depending on the stage at which they are observed, the cells can be solitary or form part of an integrated group. They go through the same cycle that all so-called higher organisms (including us) go through: one cell becomes many cells and then one again. But in their case, the many-celled phase results, not via successive cell divisions, but from the spontaneous aggregation of spatially separated amoebae that are starved of food. Importantly, just as in "higher" organisms, the constituents give the impression that they have forsaken their individuality; they act like members of one social group. In particular, the multicellular stage that is known on account of its sausage shape and motility as the slug, exhibits division of labor. Finally, the amoebae in it differentiate into specialized cell types and form a fruiting body resembling that of a fungus. A ball of stress-resistant spores at the top enables the transition into the next generation; the number of cells remains about the same. That makes the slug and fruiting body ideally suited for the study of single-cell properties that initiate and sustain multicellularity. Bonner carried out experiments that picked up one regularity after another in the collective state; more importantly, he identified quantitative relationships to characterize them. In spite of the simplicity of the system, the majority await detailed understanding.

The most famous of his observations became a Ph.D. thesis. Using unbelievably simple techniques and elementary apparatus, he managed to pin down chemotaxis as the reason why cells come together. The amoebae moved towards the source of a chemical attractant that was secreted by one or a small group of cells, to which the rest responded. He imaginatively named the attractant acrasin after the enchantress in Edmund Spenser's poem who lures unwary men to

Figure 2 Bonner in the late 1940s or early 1950s, in his laboratory in Princeton. *Courtesy of Rebecca B. Roberts.*

their doom. (After it emerged that cellular slime molds also had a sexual cycle involving cannibalism, the naming seemed prescient.) Many years of work, punctuated by false leads, culminated in a simultaneous discovery with Theo Konijn, a much younger fellow cellular slime mold researcher based at the Hubrecht Laboratory in Utrecht. The Bonner and Konijn groups found that the long-sought acrasin, the "first messenger" in *D. discoideum,* was none other than cyclic AMP, the same molecule that was gaining prominence as a "second messenger" that mammalian cells made upon stimulation by certain hormones.

Unusually for Bonner, the announcement was preceded by a dispute over who had made the discovery first; as one might have expected with him, the matter was soon settled amicably. Bonner and Konijn agreed to announce the landmark finding in two joint publications. Following the work on chemotaxis, he went on to demonstrate that the slug exhibited phototaxis and that its sensitivity to light was concentrated at the tip. A more dramatic discovery was that the slug was thermotactic as well and could respond to a temperature difference of as little as 0.0005°C between its sides.

The cyclic AMP work burgeoned into an entire new area of investigation involving enzymes that degraded cyclic AMP, surface receptors, intracellular signal chemicals, motile proteins, and the regulation of gene expression. The last was sparked by Bonner's finding that high levels of cyclic AMP could transform amoebae into stalk cells (which are dead), but the crucial insight came from work by Robert Kay that showed that under the right conditions, much lower—and physiological—levels could induce spore cell differentiation. The sensorimotor biology of phototaxis and thermotaxis remains to be explored in depth. A further remarkable property of the slug was that its speed of movement scaled approximately linearly with length. Early on, Bonner uncovered an astonishing range of sizes, amounting to about three orders of magnitude in numbers, over which the proportions of differentiated cell types in *D. discoideum* and related species remained nearly unchanged. Another observation he made must be seen in parallel: the size of an aggregation territory is invariant over an equally impressive range of cell densities. Quite late, he accomplished something that awaits exploitation, not least by theoreticians and modelers. He discovered that by using simple manipulations, it was possible to get planar (that is, two-dimensional) slugs, in effect a two-dimensional embryo. Even a single line of cells, a one-dimensional structure, could mimic the slug in certain respects. As mentioned, almost the entire corpus of Bonner's work in developmental biology appeared in the form of publications in journals. Two exceptions were his books *The Cellular Slime Molds,* which soon became a classic, and *The Social Amoebae: The Biology of Cellular Slime Molds.* The latter began as an attempt to revise the earlier book, but Bonner soon realized that the wealth of molecular detail that had accumulated in the intervening forty-plus years made that impossible. He decided to produce something entirely new on the cellular slime molds by focusing on their social behavior and evolution.

In contrast to Bonner the developmental biologist, the bulk of the output of Bonner the evolutionary biologist came out in books. These books share elements in common. Almost always, natural selection is taken as the predominant, if not sole, explanation for organismal evolution. Single adaptations find mention, but what interested him most was the organism as an integrated whole. Thus, the life cycle—the concatenated series of events leading from one fertilized egg to another in the next generation—was not just a feature of the organism, it was the defining feature. It embodied the essence of how a genotype and an environment gave rise to a phenotype. The developmental biologist in him saw that organisms had to be viewed as ever-changing entities, not as a number of distinct snapshots frozen in time; the conventional view of the phenotype had to be replaced by a consideration of life-cycle dynamics. Bonner was an early thinker in the area of life history evolution. In the books, he describes life cycles in members of several groups, identifies similar features, and goes on to infer the common evolutionary principles behind them. In short, the approach is to identify convergent evolution in a broad sense and to account for it, not in terms of similar genes acting via similar pathways, but in terms of similar chains of selectively advantageous steps. The reasoning is by analogy, and the attempt is to distill a common logic behind life cycles. At the same time, he points out how non-identical selective demands might lead to qualitatively different life cycles.

He was particularly attentive to divergences that can result when similar stages in the life cycle occupy relatively longer or shorter times in different species, to what is called heterochrony. Heterochrony essentially draws attention to what may be called the temporal phenotype of an organism (J. B. S. Haldane and Gavin de Beer were two major figures who initiated the field). Significant outcomes followed. One was the organisation of a workshop by John in Dahlem, Berlin, at which the field of evo-devo received formal recognition, so to speak; another was a paper by him on heterochrony as the way to look at species differences in the cellular slime molds. He thought the unit of natural selection could be the individual or the group and was open to the idea of group selection. This way of dealing with evolution is already evident in one of his earliest books, *Cells and Societies.* The first chapter, titled "The Sameness of Living Things," more or less says it all. The book begins by making the point that similar activities—the assimilation of food and energy from the environment, self-perpetuation via reproduction, and integrated behavior—underlie coordinated activities among the individual cells that make up plants and animals, colonial organisms in which integration develops in another way, and social groups. It goes on to probe more deeply into the similarities in how group life is organized, draws attention to how, if the duration of early development is prolonged, it becomes possible for learned traits to become a significant component of the phenotype. Again, he concludes that similar evolutionary principles may lie behind varied lifestyles.

If there was one theme at which Bonner plugged away in all his writings, it was the centrality of size—or the number of units that made up a whole—in evolution. He put it succinctly in a book written in his eighties: "Size is a supreme regulator of all things biological." For him, the primary driving force for the evolution of multicellularity, as also for the evolution of group living, was that increased size was very likely of selective advantage. That soon led to selection for division of labor (or cell differentiation in a multicellular organism). From there, selection acted to build and strengthen the myriad pathways of intercellular (or inter-individual) interactions that improve the efficiency of multicellular (or social) life. Increased size eventually led to selection for increased complexity. Size determined not only strength, but also the physiology of organisms and their abundance. Taken separately, these ideas were not original, but he may have been the first person to show their applicability across the entire biological domain, including social life. He drew attention to several regularities in the manner in which properties of the whole varied with size, regularities that took the form of "scaling laws" (Julian Huxley's "allometry"). But he was careful to point out that although they expressed trends, too much should not be read into linear correlations between the logarithms of two variables.

In addition to heterochrony, Bonner was a strong advocate for the role of behavior as an evolutionary driving force. He repeatedly emphasized the importance of the Baldwin effect, a way for an environment-dependent trait to become internalized or constitutive. This way, not only could evolution be led by behavior (as James Mark Baldwin had proposed), but evolutionary change in development could originate from recurring environmental modification (as suggested originally by Stuart Newman). He went on to propose that the difference between regulative and mosaic development could be explained analogously as the consequence of genes "seeping in" to fix the steps leading to mosaicism. The explanation deserves to be probed in depth, keeping in mind that the distinction between mosaic and regulative development is not cut and dried, but depends on when and how the test is made, meaning on the timing of gene action. His final foray into evolutionary biology came at the age of ninety-three with the publication of a slim book titled *Randomness in Evolution.* To some it seemed that he was taking a radical step away from being the advocate of natural selection that he always had been, but that was not true. He was merely expanding on what he had been advocating for long, that natural selection for variation in size and form was a stronger force in large organisms than in small ones. That hypothesis was tied up with the idea that a plausible repercussion of natural selection for size increase would be future selection for complexity. The argument went thus. The larger and more intricately interconnected a well-adapted organism, the more likely that a genetic change would be detrimental; on the contrary, a small organism would be more tolerant of change. The conclusion he drew was that the smaller the organism, the more likely that its phenotype could evolve neutrally, that is, through changes that were neither advantageous nor disadvantageous. In support of the contention, he pointed to a number of examples. They included protists such as foraminifera, radiolarians, and diatoms that had been categorized into a huge number of species based on their morphologies and yet appeared to occupy overlapping if not identical niches. There were his pet organisms, the cellular slime molds, too. The notion of neutral phenotypic variation overlapped with an old idea of his, which was that quantitative variation of non-genetic origin (he termed it "range variation") could provide a springboard for natural selection to act.

Final Thoughts

Bonner passed away on February 7, 2019, just short of his ninety-ninth birthday, as a major figure in twentieth-century biology. His influence on developmental biology, in particular on the developmental biology of the cellular slime molds, was significant and immediate. In evolutionary biology, his ideas will take longer to percolate. He was a founding father of evolutionary developmental biology, but the manner in which he presented his ideas may have made it difficult to appreciate their power. He did not lay down hypotheses and argue out their consequences, but made his case by way of illustrations drawn from hugely diverse forms of life. Ironically, the clarity of his writing and low-key style of presentation, often accompanied by a telling anecdote, led some to overlook the profundity of his ideas. He was an exceptional theoretician, but not mathematical (even though he constantly stressed the importance of mathematical reasoning and rated the contributions of Ronald A. Fisher, J. B. S. Haldane, and Sewall Wright to evolutionary theory very highly). Like D'Arcy Thompson, whom he admired greatly, he was an advocate of the importance of mechanical principles for understanding biological form. But apart from a single collaborative work on slug movement in *Dictyostelium,* he did not have much to say about it in detail. He did not like being pigeon-holed either as a reductionist or a holist and asked why one could not be both at the same time. The ability to think over vast scales was his forte.

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