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Q & A

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John Bonner started working on cellular slime molds in 1940 as an undergraduate at Harvard University, and resumed those studies there as a graduate student after the 2nd World War, finishing his PhD in 1947. His first job was in biology at Princeton University, where he has remained ever since: from assistant professor to professor emeritus. He continues to pursue both his laboratory research and his book writing.

What turned you on to biology in the first place? Like so many biologists, I was first drawn in through natural history. In my early teens, birds became a passion, but then my father gave me *The Science of Life* (1931) by H.G. Wells, Julian Huxley and G.P. Wells, and I was immediately seduced into an interest in all of biology. At the age of 13 I started my first book, but as I look at it now I find it partly cribbed from *The Science of Life*, and partly made up of some remarkably peculiar prose, along with a few drawings. Later, in my university years, my interests narrowed down to two: the biology of lower organisms and the mechanism of development. I decided to combine the two and pursued the development of cellular slime molds.

Did your interests and direction change over time? The central notion of shedding light on developmental process through the slime molds has remained the same. The only change has been the expansion of the questions I have asked. Yet they all started with the peculiarities of slime molds. Their life cycles are so different from most organisms — they feed first and then develop — that I became fixated on life cycles in all organisms and how they change over evolutionary time.

This led to a life-long interest in evolution, including the importance of size in organisms. Even in a single life cycle there is a big size change from egg (or spore) to the multicellular adult, which is the period of development; this is what evolves. An interest in writing up these ideas in the form of books followed. In many ways this was a liberating experience, for one was not bound by the restrictions and conventions of journals — one was free to say what one really thinks. And with this freedom I ventured in various directions, although for the most part they were the result of thinking about life cycles. I became convinced that biology in general, and development and evolution in particular, was slighting the central role of size — a key driving force that seemed to me to be to some degree ignored and unappreciated.

Do you have any scientific heroes? The answer is many, starting with Aristotle and numerous ones in between, including of course Darwin. If I look within my own life time there again our many, including all those that made the molecular revolution come into being. Let me pick two that are slightly different. One is D'Arcy Wentworth Thompson with his book *On Growth and Form*. He did two things that are close to my heart. One is that he showed that physical forces play a fundamental role in morphology and in morphogenesis. It is not all in the genes, a point that has come to be increasingly appreciated in recent years. The other is his matchless prose; how I envy him! The other hero is Robert MacArthur. He was a pioneer who was a major player in deciphering the Rosetta stone of ecology. Using simple mathematical models he shed enormous light on the chaotic complexity of the natural environment; he gave us the way to see that light by mathematical simplification.

Do you have a favorite paper? Yes. G.P. Bidder, The relation of the form of a sponge to its currents (Quart. J. Micr. Sci. *67*, 293–323. 1923!). Not only did Bidder do some ingenious experiments on sponge hydrodynamics, but he wrote them up in an exemplary fashion. He wrote the paper in a way that, alas, would no longer be possible in a journal today.

What is your biggest mistake in your research? Some years ago I published a paper in which we showed that one slime mold mating type could, through a dialysis membrane, induce the opposite one to initiate the sexual phase; the inducer was a small molecule. A number of years later I had a graduate student who showed that there must have been a leak in our membranes for the amoebae had to touch to initiate the sexual reaction. Happily I was only subjected to embarrassment; had it happened today I might have been before a committee investigating fraud.

Any advice for someone starting a career in science? For beginners: do not be discouraged by the first negative review of a paper submitted to a journal for publication. It happens to everyone. Cool off, and see if there might be some good advice worth following.

Do you have any views on ethics? My views on ethics are based on common sense, not dogma. I have always been fascinated by the continuing discussion of when human life begins. No one seems to mention that life began billions of years ago and has been going strong ever since. I sympathize with the need to treat animals in experiments in the most humane way, but this is a matter that really does not arise in my own work. In fact when I cut up and make grafts on slime mold slugs I do not think of myself as torturing them — a sort of slime mold Doctor Moreau. But maybe I am underestimating their sensibilities.

What do you think are the big questions to be answered next in your field? When I think of developmental biology (always within the context of evolution), I find myself troubled by the increasing complexity— along with many fascinating facts among the myriad of details. We are being overwhelmed by vast quantities of information; we are on a roll and the plot keeps thickening daily. This seems to me inevitable, and even desirable, but it cannot be an end in itself. All the great advances in biology have come from simplifying the complexities; by discovering how the mass of facts are connected and how their relationship makes a new principle clear and simple. Fifty years ago ecology went through the transition from endless facts to sets of principles, sets of generalizations

that illuminated and simplified. It was through penetrating mathematical models, such as MacArthur's, that made this possible. It is my guess that development and its evolution are ready for the theoreticians to bring the morass of facts together and show that there are some basic simple rules that will flood the subject with light.

Is teaching important to you for your research? Very. The main reason is that it forces me to think beyond what is going on in the lab, or what I am writing. Were I in a think tank with no teaching I would definitely have fewer thoughts. Even in laboratory work, teaching research has often expanded my own vision of what to try next.

What do you think of the state of biology today? It has indeed changed in many ways, and to the good. Molecular biology has come into its own and provides enormous power to answer new and old questions in such areas as development, physiology, and cell biology. The use of mathematical tools has become increasingly effective in shedding light on ecological and evolutionary problems, and other matters, such as the functioning of the nervous system. And there have been increasing applications of physical principles to biological problems. This has changed the way we teach, or rather what we teach. Biology is indeed evolving, yet I like to think that we are not throwing out where many of us started: the fascination with natural history.

Do you like to take time off? For many years my schedule has been laboratory work during the academic year and writing in the summer up in Nova Scotia. There my daily schedule is being chained to the desk writing in the morning and time off in the afternoon. It used to be salmon fishing every afternoon, but now it is more often walking in the beautiful local woods. The latter helps me in my writing; I often plan the next morning's composition.

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Quick guide

Bacterial flagellar motor

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What does the motor do? It rotates a thin helical filament (a propeller) that powers swimming motility. There are one or several motors per cell, each with its own filament. The filaments extend out from the surface of the cell into the external medium (in common bacteria) or run beneath the cell's outer membrane (in spirochetes). As the helical axis of the filament generally runs at an angle different from that of the motor axis, the two are coupled by a flexible coupling or universal joint (the hook).

What does the motor look like? In electron micrographs, it appears as a series of rings mounted on a rod surrounded by an array of studs embedded in the inner cell membrane (Figure 1). These sub-assemblies are built from about 20 different kinds of parts (proteins), each with a distinct name (given in Figure 1). The names (also applied to the genes that encode the proteins) were devised by bacterial geneticists according to the defects that resulted from null mutations, for example, *fla* (no *fla*gellum) or *mot* (flagellated but non-*mot*ile). Genes with similar mutant phenotypes were labeled A, B, C, and so on. Eventually, *fla* became *flg, flh, fli,* and *flj,* because there turned out to be more *fla* genes than letters in the alphabet. The third letter (*g*, *h*, *i*, *j*) denotes different clusters of *fla* genes on the chromosome.

How is the motor assembled? The motor is built from the inside out, component-by-component. The MS- and C-rings are assembled, a transport apparatus is added that controls the export of the axial structures, and then these are assembled in the order: rod, hook, hook-associated proteins, cap and filament. Genes encoding these components are expressed in a similar sequence. P- and L-ring proteins transit the inner membrane by a different export pathway. There are a number of checks and balances in this process, the most dramatic of which involves an antibody-like factor that blocks expression of late genes, which encode the filament protein FliC, the Mot proteins A and B, and the various components of the chemotaxis pathway. When motor assembly reaches the level of the hook, this factor is pumped out of the cell by the flagellar transport apparatus, relieving suppression of late-gene transcription. At about the same time, the export apparatus switches from transport of components of the rod and hook to the hook-associated proteins and filament. Ingenious mechanisms are involved in supplying raw material at the base of the motor, in rod and hook-length control, and in pumping hook and filament subunits through a 2 nm pore along the motor axis. In *Escherichia coli* and *Salmonella*, the energy required for this export is supplied by an electrochemical proton gradient (protonmotive force). Remarkably, the filament grows at its distal end.

Does the motor turn only one way? No, it spins either clockwise (CW) or counterclockwise (CCW) at about the same speed. These are the directions that you see when looking down at the drive shaft as it emerges from the cell wall. In the best-studied system (the gram-negative bacterium *E. coli*), the motor changes direction on average about once per second (in the absence of an external stimulus.) The intervals between reversals are exponentially distributed: there is a constant probability of reversal per unit time.

How does the filament generate thrust? The viscous drag on a thin stick in water is about twice as large when it moves sideways than when it moves lengthwise. Propulsion depends upon this asymmetry. In common bacteria, the normal filament is long and thin: the pitch of the helix is about five times its diameter. Think of this helix as a series of sticks moving slantwise in the aqueous medium, rotate the helix about its long axis, and add-up the forces due to the viscous drag on each stick. You will find that the helix generates both thrust and torque (axial force and circumferential twist). Suppose you hold such a helix in front of you and turn it CW: it will push you backwards and try to twist you CCW. An observer looking at you from the far end of the helix will see the filament rotate CCW, your body rotate more slowly CW, and the pair of you