A WONDROUS TALE OF A SPERM TAIL

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Ever since graduate school, which is now some forty years ago and counting, I have had to live with the stigma of devoting my life and creative energies to the study of sperm tails. It has always been, and still is to this day, a minor source of embarrassment whenever I have been asked outright what it is that I research. In addition to its minor value as a conversation starter at the right kind of parties, it has also been good for me in some significant ways. It enforces a measure of humility on me to accept that I have a less- than-bragworthy avocation, and a measure of self-confidence to get comfortable with it. It also repels some small-minded people I am glad to keep at a distance. Most importantly, it has taught me the connectedness of the biological world.

I did not seek sperm research as my calling in life. In fact how I got into it was rather pragmatic. I saw a sign posted on a campus bulletin board to attract physics students to a summer job in a biology lab. The job was to build electronic equipment for use in research, and the employer was one Dr. Robert Rikmenspoel. I applied for and subsequently landed the job. I later found out that my great good luck stemmed from the fact that I was the only applicant. Even so, good fortune had indeed smiled upon me, for I discovered that I absolutely loved (*i.e.* adored), the eccentric and brilliant Dr. Rikmenspoel. He was a Dutch physicist who was doing very cutting edge and un-

usual research, applying math and physics to biology. It was also lucky for me that he found my skills sufficient and liked my temperament (mainly my sense of humor). He encouraged me to go into research, and put in a good word to get me admitted into graduate school in Biology. This meant that I could officially enroll in a Ph. D. program and continue to work in his research laboratory, and that is more or less the happy ending of the story. With every real happily-ever-after comes some baggage, and in my case it was sperm tails. That is what he worked on, and what I have worked on ever since. I can say with no false modesty that I have "proudly" carried on this legacy (he left this world in 1984). I am now a recognized authority on sperm tails with all the attendant honors and benefits, if any.

For a very long time I labored patiently and persistently, investigating what it is that makes the sperm swim. I explored the role of the cell membrane, the signals that turn the sperm on (cyclic AMP does), and what makes them tumble in the female oviducts (calcium). I even got a "big idea" about how the insides of the tail work like a little machine to produce the swimming action. I built the idea into a computer model and published it as the "geometric clutch" model of flagellar beating.

By the way, the tail of a sperm is called a flagellum and there are lots of flagella (that is the plural form) in the biological world. All the while that I was doing these things, I had to be content with the idea that if we understand how a flagellum works it may be good for something. After all, it is basic knowledge about a biological organelle (little organ) of living cells. I have always valued scientific knowledge as having some inherent value in and of itself. Nonetheless, friends and family, even some intelligent people, always want to know, "will this cure something"? I was getting tired of saying "well . . . er . . . maybe . . . infertility, or ah . . . maybe birth control" when what I really wanted to say was "no, it will not, you small-minded cretin."

Now, I am pleased to report that things have taken a turn

for the better in sperm tail research. A professor in Sweden, Dr. Bjorn Afzelius, a fellow sperm tail guy, discovered that defective sperm tails can be linked to disease. The good doctor noticed that some male infertility patients also had in common that they were suffering from a group of additional symptoms. These symptoms included chronic bronchitis, and situs inversus, the latter meaning that their heart was on the wrong side of their chest. This grouping of symptoms was a known disorder called Kartagener's syndrome. When he checked out what was wrong with their sperm he found that they were missing the motor proteins (called dynein arms) that make the sperm flagella able to swim. Apparently this was what was wrong with them; their flagella had no motors inside and could not move. It not only made them infertile, it also made the cilia in their lungs unable to clear the junk out of the air passages and made the cilia in their brains unable to pump fluid properly. These cilia are really also a kind of flagella, only going by an alias, so when the sperm are screwed up, so are the cilia found elsewhere in the body. This even accounted for their hearts not being in the right place, as the cilia determine the left-right body pattern during the development of the embryo. So, all of a sudden, it became obvious that flagella (and their alter ego, cilia) were more important than merely as the propellers for sperm cells.

Once a new door is opened, you can never tell what you will find in the room. The number of "ciliopathies" that cause human diseases is now in excess of 30. The list includes certain types of mental retardation, some cases of hydrocephalus, a hearing disorder and at least one type of blindness. The grand prize discovery was that the commonest genetic kidney disorder, polycystic kidney disease, is caused by improper assembly of the primary cilia in the kidney tubules. These cilia share many of the same components and are assembled by the same chemical machinery that assembles the sperm tail.

Needless to say, this has put sperm tail researchers in a much more favorable light. But that is not the most phantasmagoric part of the story. The discovery of the cause of the kid-

ney disorder resulted from sperm tail research on *Chlamydomonas,* better known outside the esoteric circle of research geeks as a type of pond scum. You have probably on at least one occasion tried to kill it in your swimming pool (for shame!), not knowing it was giving the human race important medical knowledge.

Chlamydomonas gametes (their equivalent of our sperm) have perfectly fine flagella and since they (the *Chlamy*, not their flagella) grow prolifically in fresh water, they have become a favorite of sperm tail researchers. The *Chlamydomonas* worshipers have their own cult-like meetings in the late spring and do heaven only knows what secret rituals. I certainly don't know because they don't invite me. So far my work has been carried out on mammals or sea urchins, and the snooty "Chlamy group" doesn't think that it belongs at their meetings.

However, personal feelings aside (no really, I even have friends who are *Chlamy* people), they *do* deserve credit for discovering that the assembly system that builds the flagellum is what was defective in the kidney disorder. Now you are probably wondering HOW it is possible to discover ANYTHING at all related to a human being by looking at the flagella of a pond scum organism. This is the second wonderment of my sperm tale. Dozens, and possibly even hundreds, of the proteins that are found in the *Chlamydomonas* flagellum are recognizable as components of our own flagella and cilia. How can this be? Our nearest common ancestor, as far as can be determined, dates back to about 500 million years ago. These *Chlamydomonas* are single-celled green **plants**; they are more closely related to rose bushes than to you or me!!

Here is the deal: each and every one of us was produced by the fertilization of a female gamete (an egg) by a male gamete (a sperm). That male gamete could only accomplish this if it had a working flagellum. If its flagellum was defective, in even the smallest way, that sperm would not have succeeded in fertilizing the egg. This is Darwinian selection of the severest kind. If the sperm tail did not work right even ONCE in the chain of fertilizations that led up to you from your ancestor of

500 million years ago, you would not be here! Further, the same exact thing is true for the *Chlamydomonas* cell in your swimming pool. Somewhere back in time we both had a common ancestor, and because of that, and because both organisms use flagellated sperm to pass on their genes, the DNA that codes for sperm tails is very similar. You see, it has to be, because if the sperm did not work properly, even once, there would be no descendents from that lineage. The functionality of the sperm acts as a kind of quality assurance, guaranteeing that no change will be permitted in the DNA coding for the sperm flagellum unless the change does not impair the functioning of the sperm. As a result the amount of change in these genes even over millions of years is very limited. Only good or neutral changes can be passed on to the next generation. HA! Now you begin to see just how important sperm tails are!

The sperm tail is the gatekeeper for the continuity of life. It insures us that we receive a good functional set of the core of genes that builds a flagellum. There are more than 250 protein components built into a functioning sperm flagellum, and dozens more proteins play a role in the assembly process that constructs the flagellum. So, the number of genes that must work right to get a good sperm tail is quite large.

The ciliopathies show us that some of these same genes have been put to use building other components of our bodies besides the sperm tail. For instance, the same genes build the lung cilia that keep our lungs clean and clear. This connection is easy to understand, since the lung cilia are basically a type of flagella. Less obvious, but just as true, the genes that assemble the sperm tail play a role in building the tubules of our kidneys, forming the convolutions of our brains and constructing the sensory cells for vision and hearing. The long list of ciliopathies that have so far been discovered shows us that the sperm tail genes are used to build many organs in the human body. Although some unfortunate individuals do get defects in these genes, they will usually not pass the defects on to the next generation because their sperm don't work very well. This is why ciliopathies, though diverse, are not very common in the

population. The sperm tail genes come to you with an evolutionary quality guarantee!*

What does this sperm tail tale teach us about the connectedness of the biological world? What could be more compelling evidence for the continuity of the tree of life than the amazing conservation of the genes of the sperm tail in so many distantly related organisms? We find the same proteins are recognizable in the sperm of humans, rats, mice, fish, sea urchins, and even *Chlamydomonas,* a green plant! Creationists fret that Darwin's theory of evolution reduces us to the descendants of apes. Sperm tail researchers have glimpsed a more humbling truth; we are the direct linear descendants of pond scum. It explains a lot.

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* This "evolutionary quality guarantee" does not cover maternal mutations or mutations occurring during or after spermatogenesis. Such mutations render the warranty null and void and expiate God, Charles Darwin, and especially Dr. Lindemann from all obligations pursuant to the development of subsequent ciliopathies and costs that may be incurred by the zygote, or caregivers of the zygote, resulting from such conditions.