Chapter 3

WHAT *TOLL* PURSUIT:

AFFECTIVE ASSEMBLAGES IN GENOMICS AND POSTGENOMICS

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Toll! **Gate**

In the late 1970s Christiane Nüsslein-Volhard and Eric Wieschaus, working at the Max Planck Institute in Tübingen on the genetics of *Drosophila* development, developed their experimental system for producing tens of thousands of mutant fruit fly embryos (see Keller 1996, 1997). As an "experimental system," their saturation screen using chemical mutagens produced not only novel "epistemic things" but, equally important for this essay, surprised scientists (Rheinberger 1998).

One of the new "epistemic things" generated by Nüsslein-Volhard and Wieschaus was *toll,* a gene they showed to be involved in the control of dorsal-ventral polarity in the fruit fly embryo: *toll* mutants are all dorsal and no ventral, utterly one-sided. Nüsslein-Volhard has recalled gazing at this one of the thousands of mutant embryos that she and Wieschaus routinely created and then examined under the microscope, when she uttered, "Das war ja toll!" (Hansson and Edfeldt 2005) or perhaps simply "Toll!" (Weissmann 2010). Accounts differ, but there is agreement on the need to provide an exclamation mark. This has been most frequently translated from German to

English signaling pathways as “(That was) Weird!”, but “(That was) Cool!” also has currency. This is the predominant meaning, positive or affirmative across its differences.

But all signaling pathways, linguistic and cellular alike, disseminate into multiple possibilities, increasingly variant. We have to add “Crazy!” to the *Toll!* pathway, as cued by Nüsslein-Volhard herself when, in an interview for a popular website, she reflected on a more meta-scientific level:

> Interviewer: Hat es in Ihrem Leben den Heureka-Moment gegeben? *(Have you ever had a Eureka! moment in your life?)*
>
> Nüsslein-Volhard: Immer wieder mal. Das ist ganz toll! *(Again and again. That’s what’s so crazy!) (*Quoted in Weissmann 2009:2137)

Further semiotic branchings are suggested by *FASEB Journal* editor-in-chief Gerald Weissmann who, in his own rumination on Nüsslein-Volhard’s work and its affinities to Gestalt psychology, also invoked the complex network of meanings activated by “Toll!”:

> [W]ords shouted in the heat of discovery have more than their dictionary meaning. My emigré father used “toll” when he meant “crazy,” but also “curious” or “amazing;” he used it when he first treated a patient with cortisone. These days German-speakers also use toll instead of “cool” or “droll,” “outrageous” or “awesome.” (Weissmann 2009:2138)

The entry of “droll” into our pathways here is rather *unheimlich*, and reminds us of the capacity of any semiotic network to flip over into an opposite effect, just as the strange and the familiar suggest, imply, or produce each other.

I’ve digressed down these pathways early in this essay so that these multiple effects of “Toll!”—predominantly positive, but intricately riddled with tensions—will remain in readers’ memories. But I leave the conjoined translational instabilities of history and signaling pathways aside now, and note here that Nüsslein-Volhard’s and Wieschaus’s experimental system, innovative as it was, would almost certainly be described by professional historians of science as “genetic” and not “genomic,” let alone as “postgenomic.” No one at the time was talking about human genome projects, or genome projects for any other organism, for that matter. Although their overall project had a vaguely -omic intent— to catalogue, completely, all the developmentally important genes of *Drosophila*— historians would still say that their system worked in a genetic fashion, by creating and maintaining the lines that allowed for isolating the effects of particular mutant genes, characterizing them functionally or structurally at the molecular level, but with little or no use for or interest in DNA sequence.

Indeed, it wasn’t until 1988 that Kathryn Anderson (a close colleague of Nüsslein-Volhard’s) cloned *toll* and showed it to code for a transmembrane protein. It would be another five years before the next set of truly surprising results were produced. Between 1993 and 1996, Bruno Lemaitre and Jules Hoffman (among others) had established the key role of *toll* in a different signaling pathway, one that provides the

fruit fly with protection against infection by *Aspergillus* and other fungi, as well as Gram-positive bacteria: a "developmental gene" had unexpectedly become an "innate immunity gene" (Lemaitre 2004).[1] But although the Human Genome Project had by then been debated and begun (debates which resulted in the inclusion of *Drosophila* and other "model organisms" in the project), and while DNA and protein sequence information had provided a number of interesting experimental clues and theoretical insights in the research linking development to immunity, much of this work could still be called "classical" genetics and biochemistry. In a 1996 article reviewing this research and discussing the evolutionary significance of the *toll* and other signaling pathways– pathways apparently developed before the plant-animal divergence as common protective mechanisms, and only later conscripted into developmental intricacies– Marcia Belvin and Kathryn Anderson never once use the words "genome" or "genomic" (Belvin and Anderson 1996).

It was around that time that researchers in Charles Janeway's renowned immunology group at Yale cloned the first human gene coding for what would become known as a "toll-like receptor" (Medzhitov, Preston-Hurlburt, and Janeway 1997). A key part of that work stemmed from searching the human gene sequence database at the National Center for Biotechnology Information– this was three years before even a "first draft" of a full human genome sequence would become available, i.e. before "the Human Genome Project" is conventionally said to have been completed (in 2000), i.e. somewhere in the midst of the "genomic era."

Janeway's group had been expecting at the time to find a C-type lectin domain encoded in the clone they were browsing for. Ruslan Medzhitov later recalled the group's "initial disappointment" that their database search did not produce that result, but instead turned up a homology to a *Drosophila* gene (Medzhitov 2009). It was only then that they learned about the "stunning discovery" (ibid.) of Lemaitre and Hoffman; it seems that sometime in 1996 Hoffman showed Janeway a photograph (later the cover image of the September 1996 *Cell* issue which bore their paper) of "a Toll-receptor deficient fly overgrown with aspergillus hyphae" at a grant meeting of the Human Frontiers in Science in which they collaborated. Janeway had his own "Toll!"-like moment.

Janeway's lab thereby initiated a new phase in the understanding of the mechanisms of innate (rather than adaptive) immune response in humans, and popularized the new acronym for toll-like receptor, TLR, that "as an abbreviation" was soon "fast becoming as famous as RNA or DNA," evidenced by over 17,000 papers listed in PubMed in the following decade (Weissmann 2010). TLRs are what Janeway called "pattern recognition molecules" that are important nodes in the complex signaling pathways of cellular response, biosemiotic pathways that include numerous other proteins as well as the more widely famed RNA and DNA. Such signaling pathways are hallmarks of "postgenomics," where agency and action are distributed rather than centralized in the gene, where codes become variably interpreted signals, and an

apparently immaterial “information” is always instantiated in material processes of “transduction.”

I recount these brief stories not to demarcate genetic/genomic/postgenomic eras, but to sidestep the historical demarcation problematic altogether. My intent is to pluck out from the immense flow of events in this era, whatever we call it, a few episodes that highlight how scientific change is *affective* as much as it is cognitive, instrumental, experimental, and institutional. While those latter differences are indeed interesting and important to comprehend, the differences I am more interested in here may be summed up as: differences in “Toll!”-like expression level. A significant change in the broader genetic-genomic-postgenomic history, of which the opening narrative above is a condensed and simplified metonym, is the increasing capacity of the different experimental systems to generate two different but entwined affects, surprise and interest—surprising, interesting, unprecedented objects like toll-like receptors, and surprised, interesting scientific subjects who exclaim something like “Toll!” These affective assemblages will be difficult to assay, as we have limited methods and idioms for articulating these kinds of affective events. I also hope to develop, then, new idioms for the varied public spheres in which contemporary science is debated, evaluated, funded, and valued as a social resource, to better engage the kind of science that genomics has become in postgenomics.

Stated somewhat differently: among the many signs we might use to distinguish genetics from genomics from postgenomics– immense and ever-hoovering databases,

with higher degrees of specificity and interconnection; ever-accelerating and increasingly frugal sequencing rates; robots cheap and expensive; a plethora of job ads for bioinformaticians—there is a relatively neglected one: a complex affective response from scientists for which "Toll!" serves as a useful marker. What might we fish out of the historical archive of genomics and postgenomics using this marker, and might *we* in turn be surprised? And conversely, what might we seek to add to future historical archives of what-will-have-been-postgenomics that would further enrich those other signaling pathways, in which *the capacity for being surprised and interested* is a goal prized in the subjects of science, as well as the broader political and social worlds in which those subjects live and work?

Like genomicists mapping and sequencing a hitherto unmarked stretch of chromosome, historiographers of genomics and postgenomics depend on certain tools and tropes to establish a sequence of events or other kinds of temporal, epistemic, institutional, technological, or symbolic difference in an otherwise yet-to-be-differentiated field of events. Like postgenomicists, historiographers who rely, as they must, on ready-to-hand (even if emergent and changing) tools will be prone to reductionism, oversimplification, and even "hype" (see Fortun 2002; 2008). Like genomicists and postgenomicists, historiographers may find it productive to experiment with new tools and tropes that may seem overly speculative, insufficiently developed, unwieldy or at least unfamiliar, but may also generate fruitful new interpretive perspectives, i.e. knowledge. This essay, framed by the opening *toll*-like narrative above,

suggests that attention to affect might improve or at least add to our understanding of what is involved, or in play, in the ongoing development of postgenomics.

A brief note on hypotheses: surprise, interest, and the care of the data

In the larger work of which this is a part, I hypothesize that there are deep connections between what is almost always troped as an overwhelming "avalanche," "flood," or "rush" of data found in contemporary postgenomics (and other technoscientific fields, often grouped under the rubric of "Big Data"); and the creative and tacit "epistemic virtues" (Daston and Galison 2007) that I call "care of the data," the adroit, artful, and cautious handling of large data sets that permit both multiple interpretations and multiple errors, entangled (see Fortun, in prep.). These in turn are coupled with a palpable sense of excitement and eager anticipation that suffuse the inhabitants of the data-intense postgenomic science space. That sense of excitement, anticipation, and overall *toll*-ness is a forceful driver of scientists and sciences; however unaccountable, it deserves to be accounted for if we are to more fully understand why postgenomics (or any science) is so popular, fast, ubiquitous, and powerful.

Even a preliminary test of these hypotheses will be a long time coming, but might incorporate current behavioral/environmental postgenomic explorations of how the startle response of zebrafish may be stunted by exposure to lead (see Rice et al. 2011) or other environmental toxins. We could use the interesting results generated with that model organism work to scan human databases for promising homologous genes

involved, before moving on to extensive GWAS studies comparing the distributions of alleles associated with startle-behavior among postgenomicists to that of a control population of, say, historians. In early preparation for that work, here I begin only to briefly theorize this scientific subject as assembled from the fundamental affects that psychologist Sylvan Tomkins named "surprise-startle" and "interest-excitement" (see Tomkins 2008; Sedgwick and Frank 1995; Wilson 2000).

Tomkins described eight (sometimes nine) basic affects: interest-excitement and enjoyment-joy (the positive affects), surprise-startle (the only neutral affect), and the negative affects distress-anguish, anger-rage, fear-terror, shame-humiliation, and dissmell-disgust. The doubled terms are meant to convey the range of intensity in which the affect may be experienced. Affects are distinct from the more complex emotions that are co-assembled from the affects along with scripted cognitions. Emotions, in short, are what contemporary anthropologists would call "biocultural," while for Tomkins affects are a decidedly more physiological event, in the sense of being the property of a developing human organism as it encounters and responds, from birth, to a changing world.

"Surprise-startle" is the affect I believe is embodied in the *Toll!*-like response that I have signaled with here; it "is ancillary to every other affect since it orients the individual to turn his attention away from one thing to another" (Tomkins 2008:273). Surprise is "a general interrupter to ongoing activity"– the one-sided embryo in the long

string of normals under the microscope, the sequence match from the publicly-funded database that doesn't match the patterned expectation.

Later, I explore some "surprises" of the Human Genome Project, as recollected and expressed by a number of its leading figures, as part of a more encompassing argument that the *Toll!*-like response of surprise is the affect produced by any effective experimental system when it produces what Rheinberger terms the "unprecedented." Surprise-startle, for Tomkins, is a "circuit-breaker" (ibid.), a shatterer of habits that prompts a "re-orientation"—of the individual, but eventually of a community. It is the response to what Evelyn Fox Keller (1995:22) calls "the funny thing that happened on the way to the Holy Grail"— the interruption of the expectation that "it might be a big, intricate code but it's still just code," or the realization that the code was always already broken or at least noisier and more open to multiple determinations than one dreamed, that every center and every command and every imagined mastery was decentered and disrupted and subject to deferred interpretive orders.

With the increasing amounts of bio-semiotic-substance of all kinds produced daily by the investments in, of, and around the Human Genome Project, is it any wonder that funny things would happen– that interruptions and surprises would mount? Why were *we* surprised? Maybe we wouldn't have been so startled if we had learned to pay attention to the affective register of scientific developments.

"Interest-excitement" is the other related affect animating the postgenomic subject. Re-oriented by the surprise-startle affect, a postgenomicist becomes interested

in the accumulating information, which reinforces the interaction, driving the entire experimental system forward into new unprecedented futures. Like surprise, interest is elicited by something that couldn't be simpler– difference, as registered by "neural firing:"

> It is our belief that it is possible to account for excitement on a single principle— that of a range of optimal rates of increase of stimulation density. By density we mean the product of the intensity of neural firing times the number of firings per unit time. (ibid.:187)

We postgenomicists are interested by difference. The greater the difference– in intensity, or in number– the more neural activity, the more interest-excitement. And the more interest-excitement, the more one cares, and the more one cares, the better one thinks:

> The interrelationships between the affect of interest and the functions of thought and memory are so extensive that absence of the affective support of interest would jeopardize intellectual development no less than destruction of brain tissue. To think, as to engage in any other human activity, one must care, one must be excited, must be continually rewarded. There is no human competence which can be achieved in the absence of a sustaining interest, and the development of cognitive competence is peculiarly vulnerable to anomie. (ibid.:188)

Excitement can be “massive,” but need not be; it is “capable of sufficiently graded, flexible innervation and combination to provide a motive matched to the most subtle cognitive capacities” (ibid.189).

In this extremely condensed version of my hypothesis, then, the giga-scads of difference produced routinely in postgenomics are not just neutral information uploaded , downloaded, regarded dispassionately; it excites, and incites a desire for still more difference, faster. There are, of course, many more sources of interest-excitement in postgenomics than raw sequence-difference, and the social, cultural, and cognitive contexts in which those differences are read (interpreted, differently) are enormously productive of scientific desire as well. I do not mean to disregard or discount those, but I am here exaggerating the more bodily, affective drivers of *Homo sapiens genomicus*, *Toll!*-kin of Drosophila, to remind us to account for affect when we are accounting for the many drivers of any “Big Data” science like postgenomics. That brightening of the eyes, that contraction of the facial muscles pulling the sides of the mouth upward into a growing grin that I’ve seen so many times on the face of a postgenomicist at the merest hint of a new data set or increased throughput rate, is is not just an effect of sober rational assessment.

In the remainder of this essay, I analyze some episodes in which startle-surprise and interest-excitement are drivers of, or are assembled along with “subtle cognitive capacities” in some important developments in postgenomics– indeed, it may be a fairly good heuristic to think of postgenomics as what results when the comparatively coarse,

crude, boorish and "boring" genomics becomes somehow more subtle. One strand in this story is how DNA sequence information, as an object in itself, went from "boring" to *toll!*

Avoid boring projects

Twenty years ago I wrote a history of the U.S. Human Genome Project as it was then emerging, focusing on the narrative structures and different kinds of work (scientific, social, political) scientists and others had to engage in to make genomics happen (Fortun 1993). Taking the affective register seriously has required a re-valuation of statements and events that I once overlooked, or dismissed as unimportant in my previous writings on genomics. The main examples I take up here are expressions from the latter part of the 1980s, when the Human Genome Project was first being discussed and then initiated, concerning the "boring" quality of DNA sequencing as a form of scientific work and, somewhat less expressly, the boringness of DNA sequence data itself, moving from there on to more recent events in postgenomics.

Let's begin with perhaps the most frequently read and referenced of statements regarding the "boringness" of DNA sequence and sequencing, from Walter Gilbert's 1991 *Nature* opinion-piece, "Toward a paradigm shift in biology." The opening paragraph conjured a mood, albeit a somewhat complex one:

> There is a malaise in biology. The growing excitement about the genome project is marred by a worry that something is wrong– a tension in the

> minds of many biologists reflected in the frequent declaration that sequencing is boring. And yet everyone is sequencing. What can be happening? Our paradigm is changing. (Gilbert 1991: 99)

In his own effort to historicize his then-current location, Gilbert provided an important reminder to subsequent historiographers grappling with similar questions of change: if we are to map affects and their shifts, we will always be presented with complex amalgams. Malaise will be mixed with excitement, excitement will be marred by worry, and any of these component affects will be growing or diminishing, becoming more or less intense, but in any case always in some kind of tension with other elements.

So something was changing already in 1991, provoking the scientist to ask the historian's question: what can be happening?[2] "And yet" (there is always the "and yet" that marks the simultaneity of difference if not contradiction): sequencing is boring, "and yet" everyone is sequencing. There is excitement, "and yet" there is worry, boredom, malaise. Genomics is *toll*!, and yet it is *toll*!

Maybe Gilbert's statement simply begs for differentiation and specificity: *some* biologists in 1991 were bored with genomics, *some* were excited by it, and these different subject positions and their affects correlate with their social position: Nobel laureates, full professors at elite institutions, and (ex-)CEO's of successful biotech corporations may have enjoyed more freedom and privilege to find more excitement in genomic speculation than the assistant professor, post-doc, or technician worrying

about the tedious and repetitive demands of grantwriting, marker characterization and development, and quotas of DNA sequence to be fulfilled. Your *toll*-age may vary.

Some such social analysis is certainly possible and necessary, as will be seen below. But we shouldn't explain away too quickly the force and logics of complex affective states, and their possible importance for understanding scientific change over time.

Having used affect and collective mood to set the historical stage and open his essay, Gilbert never again invoked it. Affect faded into the background and became invisible, giving way to an equally complex amalgam of arguments about the reigning biological paradigm and the one Gilbert glimpses emerging from it. This complex amalgam of arguments was framed by a statement that is neither inside nor outside Gilbert's text, an exclamation that appeared only in the subtitle, and emanated from an editorial rather than authorial position: "The steady conversion of new techniques into purchasable kits and the accumulation of nucleotide sequence data in the electronic data banks leads one practitioner to cry, 'Molecular biology is dead– Long live molecular biology!'" (ibid.) Gilbert's "own" trope for paradigm change (that is, the one that clearly occurs inside his authored text) was more definitive in its invocation of a "break," and more Chinese than French in historical connotation: "…the view that the genome project is breaking the rice bowl of the individual biologist," he suggested, was a view that people had to get over. (ibid.)

Despite his attunement to the revolutionary potential of genomic kits and data, Gilbert did not envision increased surprise, excitement, or similar *toll*-like affect as one of the outcomes characterizing the new era. "The tenfold increase in the amount of information in the databases will divide the world into haves and have-nots," Gilbert predicted, "unless each of us connects to that information and learns how to sift through it *for the parts we need*" (ibid.; emphasis added). Genomics or postgenomics is, in this view, predicated on fulfilling what we already know we need and want, just faster and more efficiently. There is not really a sense that the *needs* themselves could, should, or would be transformed.

"Sequencing is boring" was indeed a frequent declaration in the debates in the mid- and late-1980s leading to the institutionalization of the Human Genome Project. James Watson's personal aversion to anything boring, especially boring people, has been well broadcasted (Watson 2007). Still, his concerns about boringness are worth taking into account, reflective as they are of broader cultural patterns. Early in his brief directorship of the HGP, Watson spoke in 1990 (around the time of Gilbert's article) about the problem of non-excitement at the American Academy of Arts and Sciences in Cambridge, MA:

> [T]he people who wanted to do it [the HGP] were all old and almost retired, and everyone young was against it, because they figured if we did it, it would take money away from their research. So all the people you normally would expect, because they're going to do something, were

> against it, and all the people, you know, who really almost stopped [doing] science, were in favor of it. Now that includes me: I was really in favor of it, as was Paul Berg. And you could say that the objective was a wonderful objective. What's more important than this piece of instructions? But everyone else felt essentially frightened. It was going to be big science, it was going to be very boring-- just determine all these letters-- so anyone who would do it is someone you wouldn't really want to invite to dinner anyways.

And it wasn't simply sequencing that was regarded as boring, in Watson's view; the development of high-resolution genetic maps provoked a similar affective response:

> … The trouble about getting these genetic maps, was that doing it was very boring, and in fact David Botstein had put in a grant application and had been turned down by NIH: it was too dull to be good science. But in fact it was a sort of tool that you really needed.

Not only are affects always amalgams— here, it should be evident that Botstein, at least, found some excitement in the boring work of developing better genetic maps— but these affect-amalgams are always assembled to epistemic objects and their larger cultural webs. This is part of the reason why affects tend to disappear from view: debates about *tools* and *big science*, for example, are well-recognized concerns of historians, sociologists, and philosophers of science and technology– and of scientists

and engineers, too. So what does it really matter if Watson, Botstein, or any other scientist is bored, when more social and collective things are at stake?

I promise to return to such questions, which are anything but boring (to me, anyway). For now let's follow Watson's remarks, which prompted an interesting exchange with Matthew Meselson:

> Matthew Meselson: Jim, in *Drosophila*, I don't know of a single gene that has been gone after intelligently, that hasn't been cloned with a little effort, even though we don't have the complete sequence of *Drosophila*. So I gather that with humans, it's different, because we can't do genetic crosses and certain other manipulations as well with humans-- but they might come along. So I would like to hear you explain why [this project is so] necessary for humans...

Watson's initial response– "I think it's necessary in *Drosophila*, just because to get them all to cost— if we can do it at one-tenth the cost that it's being done in your lab, eventually it will be cost-effective. It won't be cost-effective if you do it at five to ten dollars a base pair, but if you do it at fifty cents a base pair, you'll get it out…"— was hardly satisfactory to Meselson: "That's a different reason," Meselson argued back, one having little to do with doing science "intelligently"— i.e., not by boring rote brainless mechanical means— so he re-stated his objection:

> Meselson: Not a single important gene that anyone has gone after intelligently has failed to be cloned and sequenced.

> Watson: Yeah, but there is a lot until we do it that you don't know the existence of, and the question is if you actually see the total thing, will you be surprised and get interesting scientific insights? And my guess is you will, but that's my...
>
> Meselson: That's a different reason than the one you gave. That's a good reason.

Unlike Gilbert, for Meselson productivity and efficiency are not particularly good reasons for dedicating $3 billion in public monies to something like the HGP– but to "be surprised" by "the whole thing" and get new "interesting scientific insights"? *That's a good reason*.

Now "good reason" may mean only a reason shared widely (enough) in the scientific culture of which Meselson and Watson are (elite) members– "Unexpected surprises? Sounds good to me!" But what if it *really is* a good reason— meaning, what if there were a shared understanding of a good society as one which contained, and cultivated, scientists wanting to be surprised?

It's also worth remembering that even non-(elites) enjoy their affects, so I use my *Toll!*-like probe to pull up one more remembered event concerning these pre-postgenomic years. Going into my basement and accessing my dead-tree database, I found an interview I did as a pre-posthistorian of science graduate student with Robert Moyzis, then a leading scientist in the U.S. Department of Energy's genomics programs.

We had been talking— this was also in 1991— about the history of early meetings sponsored by DOE that are often credited as "precursors" to the HGP (see Fortun 2002):

> MF: Can I just interrupt here for a second? It sounds from what you're telling me that the sort of standard account we get about mutation rates, and the technologies for detecting very small mutation rates, was almost on the side-- or not as much of a concern or a goal as building resources.
>
> Robert Moyzis: …I think in some ways that was an after the fact justification, in the sense that-- I mean, keep in mind that DOE has always been historically interested in those problems… So that's not incorrect to say that that's what DOE's interests are, because that's always been DOE's interest and probably will remain DOE's interest…
>
> [But] I think the history was more, "Hey, I'm real excited about this, this is a good idea; some aspects of this maybe are bigger science by biology's standards, therefore we're going to need organization, structure; average academic lab doesn't have that, DOE does." And then lastly, "Why the hell is DOE involved in this?" "Oh, well, you know, we want to study mutation, etc. etc." And I don't really think that that business about "gee, we want to understand mutation etc. etc.," really started happening until the criticism started. That when NIH started saying "what the hell is DOE doing this for? why is DOE interested?," that the sort of intellectual justification-- which isn't an incorrect one. That does fit in with the

> mission, and I still believe that that's true, but you can't kid yourself that-- I don't think it was that [sort] of a process…[I]n fact in my mind, the kind of fruitcakes who kind of dreamt up this project, myself included, that's not where they were coming from... I mean, the genome, or DNA-- it was kind of like this challenge to see if you could put the jigsaw puzzle together, as sort of an intellectual challenge. And many of the people at that Santa Fe meeting, I think, had that kind of mentality.
>
> ...I think it's really after [the 1986 Cold Spring Harbor meeting] that a lot of the apologizing and sort of re-writing of history to say, what's the scientific justification that the Department of Energy is involved in this, really began. So you've got a stretch there of perhaps almost months where, from my viewpoint, that issue wasn't even discussed. It was still, we can do this, it's worth doing, and it might actually be some fun doing, for a lot of crazy reasons. And I think it was certainly always discussed that there would be all these biomedical payoffs, but a lot of the initial players I don't think were even looking at it from that perspective.[3]

For Moyzis, the "intellectual justifications" for doing a Human Genome Project, while clearly "not incorrect," were nevertheless secondary to "fun" and related "crazy [cool/awesome/exciting/*toll!*] reasons." Promises of "biomedical payoffs" and other such rational justifications were certainly crucial to packaging, branding, and selling the HGP to its funders in the U.S. Congress, but it was the "intellectual challenge" of

assembling a massive "puzzle" that causes it to be "dreamt up." (It's worth recalling that in the Kuhnian paradigm of scientific change, "puzzle-solving" is the mundane, perhaps boring work of "normal" non-revolutionary scientists, not a challenge for fruitcake revolutionary ones.)

I've used these few episodes and recollections to characterize one aspect of resistance to a centrally-organized effort to develop the sciences and technologies of genomics in the 1980s as predicated on its being "boring"– i.e. not eliciting the affect of interest-excitement. Such resistance to the Human Genome Project was fairly widespread, with a far more complex quality that simply "it's boring," and with its own history, in which *some* resisters who were critical of *some* aspects of *some* of the project definitions that were put forward in the mid-to late-1980s, came to be supporters of the HGP as its institutional and scientific definition emerged from various expert committees and bodies (see Fortun 2002). These affect threads were woven together with institutional turf politics and their attendant mix of scientific and ideological arguments about the shape and form of the HGP. In those expert discussions, which resulted in a less sequence-obsessed and more mapping-inclusive project as well as the inclusion of various "model organism" genomes along with the human, the Department of Energy and its scientists were often troped as rather mindless, good only for tool-building or engineering-type technological problems (sorting cells, building and shipping chromosome libraries, banking but not analyzing data, etc.) while the forces of the National Institutes of Health were ones of creativity, able to pose and answer actual

biological research questions. Because the DOE=boring and NIH=interesting in these assessments, NIH would come to control twice as much money as DOE and be regarded as the 'lead" agency. The affects associated with different sciences and scientists matters to socio-political events.

One of the most persistent strains of criticism at this formative time concerned the perceived threat that an expensive, centralized genomics program posed to individual RO1 research grants, the mainstay of the NIH extramural program. Thus, scientists like Bernard Davis were asked to testify at a U.S. Senate hearing fairly late in the process, where U.S. Senator Pete Domenici (Democratic senator from New Mexico [home of Los Alamos National Laboratory] and one of the key congressional advocates of the Human Genome Project) confessed that he was "thoroughly amazed...at how the biomedical community could oppose this project:

> I cannot believe that you are going to insist on business as usual in this field. It is beyond my comprehension, I repeat, beyond my comprehension...
>
> [Y]ou cannot sit here and tell me that in all of the research that is going on with the marvelous individual investigators... you cannot tell me there is not more than $200 million, that if we even asked you to go look, you would say probably went for naught... People had a lot of fun. Scientists had a lot of exciting mental activities. But it is inconceivable that out of $7 billion in grants in this very heralded RO1 peer review approach... that

> there is not at least $200 million or $300 million that even one as dedicated to the field as you are could not go out there and look at and say, maybe we do not have to do this... [There] are too many scientists in other fields that are using hardware and new technology and new techniques that support this as a tool, that I cannot believe that you really oppose it. (U.S. Senate 1990:130)

The statement can be read as indirect confirmation that "fun," or the more clumsily phrased "exciting mental activities," is an important driver of scientific activity. Even senators— whose understanding of science (among other things) is notably limited— understand this. But Domenici also understood that playtime, in which "marvelous individual investigators" got paid with public dollars to try to surprise themselves— even if playtime was also its opposite, "business as usual"— that playtime was now over, and it was time to get on with the more serious, un-fun, and boring work of tool-making, manufacturing the "hardware and new technology and new techniques" of the Human Genome Project.

Genomic mandala

If the idea of loads of DNA sequence information in the mid-1980s elicited a *Toll*!-like affect in which "boring" predominated over "interesting," it didn't seem to take long for that affect-amalgam to invert its composition. By the mid-1990s, only a few years into the distributed, dedicated, federal tax revenue supported, multi-organismal sequencing and mapping efforts shorthanded as the Human Genome Project,

being hit with a flood of sequence information— and it indeed seems to have been dramatically physical— would elicit surprise and excitement, with barely a tinge of boredom.

An informative marker for this shift is the 1995 publication of the full sequence and map of *Haemophilus influenza*, signifying for some "the real launch of the genomic era" (Nelson and White 2010:172). Popular science writer Carl Zimmer notes that the publication of the 1.8 million base pair sequence landed "with a giant *thwomp*," disrupting what he wryly called "the dark ages of the twentieth century, when a scientist might spend a decade trying to decipher the sequence of a single gene" (Zimmer 2010). Even though there weren't "a lot of big surprises" about the microbe itself, Zimmer recalled that "what was remarkable was the simple fact that scientists could now sequence so much DNA in so little time." Moreover, that remarkable fact was transmitted in an instant, through the "kaleidoscopic wheel" mapping all 1740 genes: "It had a hypnotizing effect, like a genomic mandala," reflected Zimmer, and "looking at it, you knew biology would never be the same" (ibid.)

"And yet"— sameness always returns to level surprising difference; boredom re-asserts its persistence in the interest affect-amalgam. Even as genomicists "witnessed aspects of microbial diversity beyond what had been previously appreciated" in the years following the kaleidoscopic hit of the *H. influenza* genome, the mounting number of these "surprises" generated by the new sequencing capacities did not take long to simply become "widely accepted" features of the increasingly post- genomic landscape

and lifeworld. Zimmer dubbed it the "Yet-Another-Genome Syndrome" (Zimmer 2010). *Toll!/*cool had flipped to *Toll!/*droll.

Surprises of the HGP

And so, pointing out genomic surprises became something of a dull routine by the time the HGP had been ritually marked as completed in 2000. "It appears now that hardly a week passes without some new insight into the "genome" taking us by surprise," noted biologist Richard Sternberg (Sternberg 2002:155). But despite their frequency, and the growing frequency with which they were thus noted, surprises still remained largely anomalous or background "color" to the main story.

Here I note a few of the other objects or events that elicited surprise and interest among genomicists; sequence information itself was an important but not the only part of these surprises. To its credit, when Cold Spring Harbor introduced an oral history collection on "Genome Research" to its webpages, in addition to topical sections like "Mechanics of the HGP," "Challenges of the HGP," and "Gene Patenting," it also saw fit to ask its interviewees (all male on this topic) "What surprised you the most?" The affective register on display here is right on the surface– postgenomics turned out to be surprising, interesting, exciting, *Toll!,* anything but boring.

Perhaps the biggest and most publicized surprise was the number of human genes in the genome coming in much, much lower than expected. Sequencing-innovator

Bruce Roe, who led the group at the University of Oklahoma that first sequenced an entire human chromosome (22):

> [T]hat's an easy question. I put my dollar down on 120,000 genes. And for somebody to tell me that we only have twice as many genes as a worm, twice as many genes as a fly, you know, that's kind of disconcerting… So that's one of my big surprises. The other big surprise was that there are genes overlapping genes. And genes inside of genes. Here we have this huge genome that only one and a half percent encodes for, and these genes overlap each other, you know. Why would you ever do that? Well, you know, I didn't design it. We're just looking at what the designer did.[4]

Robert Waterston mentioned another now well-known surprise of post/genomics, "that fifty percent of the worm genes are shared with people, and fifty percent of human genes are shared with worm or something like that. It's just astounding."[5] The re-orienting of evolutionary history and theory is a big part of my opening story of toll-like receptors, as researchers followed genes, gene functions, and gene sequences from fly to human and beyond, re-orienting much of immunology in the process.

In this series of fireside chats (metaphorically and literally– these interviews were mostly shot over a few days in front of a Cold Spring Harbor fireplace), Eric Lander departed the most from sequence-centrism and waxed Weberian:

> What surprised me most?

In the end, how satisfying it was personally. That I went into the project as a relatively young scientist. I began to get into the human genome project at the age of thirty. At that point, you do things cause you're young and hotheaded and competitive and all sorts of things. Having now devoted fifteen years of my life to this, it's a very large piece of it and at some point I came to have-- maybe about half way through-- just a tremendous affection for the people, my colleagues doing it. A tremendous feeling like this was a purpose much greater than any of us, much bigger than me. It was the first time I felt like I was a part of something much more important than I was and with a much greater purpose and something that would live far beyond me. That was why when the Celera thing came along and Craig [Venter] came along aiming to kill this, I probably reacted more strongly than anybody in the project, more violently in my reaction than anybody in the project because this mattered. It mattered to get right. It mattered because for me this was, you know, this was a calling in life and a purpose in life and nobody was going to go and screw it up like that and turn it into some private thing and not let us get the benefits from it… I can't imagine a more wonderful thing to have done in life. And that surprised me. I guess I didn't ever imagine that it would end up meaning so much.[6]

Just to clarify: I admire that Lander waxed Weberian, and I would shout *Toll!* if there were more of a *Wissenschaft-als-Beruf* tone to our public discourse of science now. Maybe I just have a soft spot for Lander; in 1990 he was the first person I ever formally interviewed when I was a larval historian of science, and I was impressed then by his generosity, honesty, and his insistence that the metaphor most appropriate to the Human Genome Project was not the "Holy Grail" but the less exciting, more public-infrastructure-oriented "Route One of Genetics." So in re-reading this interview decades later I am surprised, in turn, that *he* was surprised that boring infrastructure would "end up meaning so much." Watching the video is a necessary supplement to reading the transcript; Lander pauses, appears to take the question quite seriously, ponders, and responds with spontaneity and enthusiasm.

Some of the most honest and reflective perspectives, and most resonant with our signaling pathways here, came from Maynard Olson:

> There are a lot of things that surprised me about it. You know, history always looks so clear in retrospect, but not so clear in prospect done. I thought that it went much more rapidly and much more smoothly than I could have imagined. And it did so for a whole bunch of reasons. I mean, the problem was enormous. … Not conceptually difficult but practically an immensely difficult problem… We were just mismatched. We didn't have good enough techniques. We didn't have any where near enough strong investigators. The whole computational infrastructure didn't exist.

> Most of our ideas about how to proceed were wrong. There was no overall organization that we had any kind of experience with. There was just the idea of building one. The problems just seemed rather overwhelming but, of course, exhilarating. I was never pessimistic although I was always restraining people that said, you know, this is going to be easy… I think that if you had asked me how long it was going to take I would have been off by a decade or so. And even then I would have felt I was being optimistic. Because again I just couldn't see the path. And I couldn't see the path because the path wasn't there. A lot of other people thought that they could see the path but if you go back and read in detail what they said, that didn't turn out to be the path. Those were a lot of dead ends.[7]

Genomicists were surprised by themselves.

In the conclusion, I return to this labyrinthine dimension of scientific work, in which the amazement generated in the doing of science is an affective effect of its maze-like qualities, and one is alternately overwhelmed and exhilarated (as with any encounter with a sublimity). But next I consider how these brief, fragmentary glimpses of the affective dimension of postgenomics become difficult to account for, hard to assimilate into a system of historical or social value.

Accounting for genomics

Leapfrog again now to ten years after the ceremonial "completion" of the Human Genome Project. The *New York Times,* which had long exuded nothing much short of unalloyed enthusiasm for the HGP and every milestone discovery within that vast enterprise, conveyed a tone of disappointment that suddenly seemed to be everywhere in a 2010 editorial:

> 10 years later, a sobering realization has set in. Decoding the genome has led to stunning advances in scientific knowledge and DNA-processing technologies but it has done relatively little to improve medical treatments or human health. (New York Times 2010)

If the "advances in scientific knowledge" and technology here said to be "stunning" were, in fact, stunning, it would be hard to imagine the sentence and the editorial moving on so quickly, in the same sentence, to that dismissive "but…" of accountability. I hardly expect the editorial board of the *New York Times* to be truly stunned by anything, including their own role in building enthusiasm for wreckless invasions that kill millions, but I wonder how an editorial written within a culture which had a greater capacity to convey and truly share in the scientist's sense of stunningness might read differently? Instead it's just: *stunning, yeah sure, but they haven't exactly cured anything like they promised to when they cashed that $3 billion check we gave them, have they?*

Nicholas Wade echoed the judgment and the rhetoric in an accompanying article:

> For biologists, the genome has yielded one insightful surprise after another. But the primary goal of the $3 billion Human Genome Project— to ferret out the genetic roots of common diseases like cancer and Alzheimer's and then generate treatments— remains largely elusive. "Genomics is a way to do science, not medicine," said Harold Varmus, president of the Memorial Sloan-Kettering Cancer Center in New York, who in July will become the director of the National Cancer Institute. (Wade 2010)

It is as though surprise and insight were a dime a dozen, last year's news, and could not really disturb the calculations of worth that were being eagerly assessed. And it would do little good to point out the– irony? *Schadenfreude*?— that many historians, feminist philosophers, sociologists, and more than a few postgenomicists themselves had been making almost exactly that prediction about the expected medical benefits of the Human Genome Project for any number of years. *They* were not surprised when the relationship between genomes, illness, and medicine turned out to be more complicated than hoped or predicted by the more hardcore genome-as-Grail advocates.

What new genre of science writing could take account of the *Toll!*-like emergence– both and/or neither science and/or medicine, both and/or neither immunology and/or genomics– of the family of toll-like receptors, and their fantastic evolutionary history that binds human to halibut, a history that includes the evolutionary repurposing (surely *that* is "the designer" which Bruce Roe invoked

above?) of "genes for" innate immunity into "genes for" embryonic development? Public discourse on postgenomics– and similarly multi-scale, distributed, complex, public-resource dependent scientific projects, such as the sciences of climate change (Edwards 2010)— needs new genres of science writing that are patient with the difficult demands of interpretive multiplicity and openness, transparent toward and tolerant of complexities and ambiguities (marked here by my disseminated *Toll!* sign), yet resolute in their recognition and embrace of genuinely creative, *better* science.

Postgenomics has indeed gotten to be "better science" (Fujimura and Rajagopalan 2011) than genomics was: more subtle, less determinist, more attuned to the flexibilities and limits of its own categories, techniques, and analytic concepts. I read Fujimura and Rajagopalan's article-ending evaluation of how the developing theories and practices of genotype variation in large-scale populations have, over time, become "better science" on these multiple registers: "better" scientifically, ethically, affectively. "Better" for me also means "more careful," with that term again amalgamating the cognitive with the ethico-pragmatic with the affective.

In the larger project of which this essay is a part, I'm re-orienting my positive affects toward a better ethnography of these better sciences, focusing on asthma researchers incorporating postgenomic findings and practices into a larger ecology of diverse sciences, from air quality modeling to psychosocial stress measurement to environmental and anti-poverty activism. In that story, no gene ever came anywhere near to master-molecule magic-bullet holy-grail territory, yet postgenomicists have

found much of interest. Toll-like receptors are one small part of that interest-network, and like all the other multitudinous distributed parts, their signaling-effects are always partial, sometimes contradictory, dispersed in unexpected ways between and within thoroughly mongrel populations, in play only at certain stages of development and under the sway of variable environmental conditions from the microbial flora of the gut to the ozone and particulate matter levels of U.S. cities maintained at deadlier-than-necessary. Yet I admire the postgenomicists of asthma, even as their efforts and knowledges are swamped by the sublimity of asthma's causes and exacerbators. I admire that they, like so many other postgenomicists, have networked themselves into consortia that share data, results, materials, analytic techniques-- as well as their misgivings and uncertainties about all of these. And I particularly admire how they, like so many other postgenomicists, have transvalued even the "boring" work of curating and caring for materials/data sets, materials/data banks, and materials/data techniques (see e.g. Leonelli and Ankeny 2012) so that these infrastructural activities have their own rewards, virtues, recognitions, and even surprises and interests far beyond what any dreamer of genomic futures had in the 1980s.

The amazement of experimental systems and the public sphere

To revisit and re-sound my opening story: "Toll!" the expression, like *toll* the gene, should register multiple effects in multiple signaling pathways, altered by multiple contingencies of context– environmental, temporal, developmental. "Weird!" and

"Cool!" are only the first two dominant registers probed by the various translators of Nusslein-Volhard's speech act; "awesome," "crazy," "droll," and "mad" can also be activated.

Hence my preferred expression, as in my essay's title echoing Francis Crick's autobiographical *What Mad Pursuit*: genomics became an increasingly *Toll*! pursuit—cool and awesome, but at the same time also a bit weird, boring, and more than a little mad.

These amalgams are essential: whereas genomics was *mostly felt to be* a boring machine tool, overcoded by the code discourse it directed at genomes to straightforwardly translate or decode them, postgenomics is *mostly felt to be* cool and awesome and crazy and weird and droll and mad, excitedly exceeding all its coded channels. Attending to affect should offer a complex of surprises and interests, often out of synch, not a simplified understanding of postgenomics.

"I couldn't see the path because the path wasn't there," Maynard Olson recalled about the paradoxically even-sooner-than-expected completion of the Human Genome Project. This view of the entire history of the Human Genome Project can be read as a confirmatory signal for Rheinberger's view of experimental systems as a maze:

> An experimental system can be compared to a labyrinth whose walls, in the course of being erected, simultaneously blind and guide the experimenter. The construction principle of a labyrinth consists in that the existing walls limit the space and the direction of the walls to be

> added. It cannot be planned. It forces one to move by means of checking out, of groping, of *tatônnement…* The articulation, dislocation, and reorientation of an experimental system appears to be governed by a movement that has been described as a play of possibilities *(jeu des possibles).* With Derrida, we might also speak of a "game" of difference. It is precisely the characteristic of "fall(ing) prey to its own work" that brings the scientific enterprise to what Derrida calls "the enterprise of deconstruction." (Rheinberger 1998:291)[8]

In an age of austerity, it seems easy to forget, and easy to devalue, that postgenomics is a game that provides its players with a high degree of surprise and excitement— tempered by tedium. Why should we as a society pay (a lot!) to boost their levels of interest-enjoyment? I'm mostly marking the question here, and acknowledging its difficulty and its risks. I am not comfortable with it, which means that the question boosts my level of interest-enjoyment, even as it leaves me prey to my own work, groping in the labyrinth for a path that is always only emerging.

"And yet…"

Genomics and postgenomics have received plenty of hyperenthusiastic adulation and plenty of deflationary critique– both of which, it bears stressing again, are well warranted. But these rather one-dimensional alternatives need to be doubled, at least, read together and against each other, if they are to do justice to the crazy, cool, awesome, exciting, boring, droll, and mad pursuit of postgenomics. As genomics shaded

into postgenomics, it became more and more *toll!*— and that surprised everyone, including its chroniclers– at least this one. Attending to toll-like expressions of surprise and excitement will enrich our own styles of "dynamic objectivity" in historical and ethnographic analyses of postgenomics, binding our own account to the fuller range of the forces shaping this scientific field. Yes, postgenomicists can be seekers of profit, affirmers of baseless "racial" categories, purveyors of problematic personalized medicines, and all the other personas implicit or explicit in so many ethical, legal and social studies of this ever-emergent ensemble of scientific practices. But, as a necessary supplement to these necesssary accounts, we could stand to come to better terms with the surprise-seeking, creativity-affirming, excitement-purveying dimensions of postgenomicists' personas– even, perhaps especially, if those terms include *toll!*-like amalgams.

I think there is also a politics to the pursuit of *toll!*-like affect in contemporary science that is also a necessary supplement to the necessary politics of critique. There is a need in American culture for a greater collective capacity for the surprise-startle and interest-enjoyment that comes through engagement with complex scientific systems, complex arguments, and complex realities. In a time of austerity, compounded by a pervasive devaluation of many kinds of knowledge spiked by elements of outright anti-scientism (in the U.S. at least), re-reading a genealogy of postgenomics could contribute to a cultural need for new idioms for a re-valued science that extend beyond its pragmatic applicability, to encompass its ability to provoke widened, shared curiousity

about complex biological, cultural, and environmental conditions. My experimental hope is that adding a complex *toll!*-like amalgam of affects to the diversity of receptors through which we make sense of postgenomics' untimely course of continued emergence will produce, as it has for at least some postgenomicists, surprising effects driven by and embodying of attentive care.

Notes

1. Lemaitre notes the element of serendipity involved in these experiments: "I now realize that our success in identifying the function of Toll in the *Drosophila* immune response was partly because we routinely used a mixture of Gram-negative and Gram-positive bacteria to infect flies, whereas other groups only used Gram-negative bacteria. The Gram-positive bacteria strongly activated the Toll pathway and enabled us to discern the role of Toll…" (Lemaitre 2004: 524-25)

2. It is also a philosopher's question, or at least those philosophers similarly attempting to make some sense of that which has not yet arrived but is in another sense already here: "What Derrida refers to as the 'to come' and Foucault as the 'actual,' Deleuze calls absolute deterritorialization, becoming, or the untimely. It is the pure 'event-ness' that is expressed in every event and, for that reason, immanent in history. It follows that every event raises with greater or lesser urgency the hermeneutic question, 'what happened?'" (Patton 2009:42)

3. Author's interview with Robert Moyzis, October 22, 1991. See also Fortun 2002 for my re-reading of other comments by Moyzis, regarding his "surprise" at the readiness of many scientists in 1985 to entertain the idea of completely sequencing a human genome.

4. http://library.cshl.edu/oralhistory/interview/genome-research/surprises-hgp/roe-surprises-hgp/; recorded 29 May 2003.

5. http://library.cshl.edu/oralhistory/interview/genome-research/surprises-hgp/surprises-hgp/; recorded 1 June 2003.

6. http://library.cshl.edu/oralhistory/interview/genome-research/surprises-hgp/lander-surprises-hgp/; recorded 2 June 2003.

7. http://library.cshl.edu/oralhistory/interview/genome-research/surprises-hgp/olson-surprises-hgp/; recorded 01 June 2003; last accessed March 15, 2013.

8. *Tatonnement* is the term of Francois Jacob, who is also the source for Rheinberger's "play of possibilities" (he notes that the English translation of Jacob's book *The Possible and the Actual* (Seattle: University of Washington Press, 1982) does not convey this connotation from the French title, *Le Jeu Possibles*). The Derrida quote is from *Of Grammatology*, trans. Gayatri Spivak (Baltimore: John Hopkins Press, 1974, p23-24.

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