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Earlier Days

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So many flies, so upside down!
Did sickness or some silly clown
Cause to be so impeded
A course of study, newly seeded?
The moral of this little tale
Is that it's quite beyond the pale
To experiment with noxious fumes
Where flies are kept in closed up rooms.

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Were I to contribute something here about Martin's favorite region of the insect brain, it would simply dilute an already abundant scientific tribute to that particular interest. So, best to consign to other vehicles observations about those enigmatic centers, the mushroom bodies. Instead, what is offered here will be, after much preamble, a reflection or two on the man himself—considerations about his patience in the face of ignorance and his strength in the face of near scientific disaster. Thus, this offering recounts observations that relate to Martin's single-mindedness and good nature. But, lest the reader is already nervous and to assure Martin and Apollonia: these reflections, such as they are, will not embarrass—at least not them. And, if there is even the slightest whiff of fantasy, even the tiniest lack of decorum, then there is always the worn excuse that, although retrievable after so many years, memories can be misshapen by the passage of time.

Before this story begins, there is a personal observation to be made about what one might call the arena of ''*Drosophila* neurogenetics,'' which was independently founded by two eminent individuals, each intent on relating genetic networks to neural networks and neural networks to repertoires of behavior (Figure 1). One of these individuals is Martin. The other was the late Seymour Benzer who, unbeknownst to Martin, happened to be working with *Drosophila* in the same building at Caltech where Martin was doing postdoctoral research on *Phycomyces* in the late 1960s with Max Delbrück. As it eventually turned out, Martin and Seymour each took a dramatically different approach to the study of the fruitfly's brain nervous system. As a consequence, with a few notable exceptions, the present community of *Drosophila* brain geneticists can be assigned as either tending to the one style or the other. The one approach, initiated by Seymour's resonant discovery of the three types of clock (period) mutants, and promulgated by many of his students (and their students, and so on), was to tackle the function of the brain from the outside in, screening for behavioral mutants that might then lead to genetic insights about the nervous system's function and development. Martin, on the other hand, separately initiated a radically different tack—one opposite and, as it has turned out, apposite—which was to generate visible mutations of the brain's structure and then ask how these might play out in terms of behavior and genetics. He and his students, and his student's students, have been stunningly successful in this despite one early, and nearly catastrophic, setback, for which a brash young novice and an eminent gentleman from Cologne were responsible. It is to this event that the present essay refers.

In the late 1960s and early 1970s, the Max-Planck-Institut für Biologische Kybernetik in the idyllic town of Tübingen was one of two great attractors (the other was in

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Figure 1. A gathering of ''neurogeneticists'' in the late 1970s. Lower left is Seymour Benzer; lower right is Martin Heisenberg.

Pasadena) for young scientists wanting to meld traditional neuroscience with the younger disciplines of modeling and systems theory. The institute was new: a handsome concrete and glass building on a modest campus that then included buildings for biochemistry and developmental biology. A plant genetics institute was a stone's throw away, just down the hill on which the main campus was perched. For the young members of these institutions, this was scientific Elysium, an ivory tower, a place to be proud of and, as many of us were, arrogant about. Not a week went by without some famous visitor giving a lecture followed by a reception in the Max-Planck Gästehaus, which looked out on pleasant gardens and a large, artificial pond where, during most of the spring and summer, its amphibian population set up an incessant din that kept visitors from getting a good night's sleep. It was, quite simply, a paradise for the young and ambitious. The Institut für Biologische Kybernetik, devoted to research on insect vision, was directed by an idiosyncratic quadrumvirate: Werner Reichardt, its founder and Executive Director, an assertive physicist who, when very young during the war, had worked on the development of microwave communication (and secretly contacted allied forces); Karl Götz, another physicist and an inspired instrumentationalist; Kuno Kirschfeld, the single card-carrying biologist (and humanist) who pioneered studies of physiological optics; and a flamboyant neuroanatomist, Valentino Braitenberg, whose love of most things Neapolitan obscured his Tyrolean origins. Each of these powerful individuals was in the position of recruiting one or two staff scientists—their ''Assistenten''—and each commanded a support staff comprising technicians and a secretary. In addition to money being no object, the institute was famous for its machine shop that produced astonishing apparatuses for measuring the tiniest deflections of the tethered flight of the house fly and its smaller cousin, *Drosophila*. It was altogether an extraordinary environment, one in which the younger staff members could work like fiends and also have rambunctious fun after hours. But, as an institution, it took itself very seriously, indeed. A hilarious reprint request from India, innocently addressed to this author at the Max Platitude Institute for Cybernautics, did not evoke mirth from the Directorate.

The Max-Planck Society, in its infinite wisdom, had also decided to expand another of its institutes, that of Behavioral Physiology in Seewiesen, Bavaria, founded in the mid-1950s by Erich von Holst and Konrad Lorenz. It would add to its campus a department devoted to the study of insect acoustic communication. Its anointed leader was to be an irrepressible professor from Cologne—a true blue-blooded Bavarian by the name of Franz Huber, whose first act on being so elevated was to contact Valentino Braitenberg to ask if he could learn neuroanatomical techniques from him or from one of his staff. And there, really, begins this tale.

The staff member so detailed was me, and for the next few weeks, I set about teaching the illustrious visitor all the methods I then knew, including some rather tricky silver impregnations. We were lent space in the Plant Genetics Institute, where we set up our paraphernalia. We had tremendous fun catching various insects and then

working late into the evenings, drinking liberal amounts of whisky. But, we did not exactly ingratiate ourselves with the administration when, one evening in a moment of foolishness, we placed a coplin jar of slides that were to undergo an overnight incubation at the center of a pentagram that we had drawn on the floor with some chalk, placing on one of its five points a small heap of headless *Gomphocerus rufus* (Franz's experimental animal of choice), on another a rabbit's lower jawbone, on a third some dried flowers, on the fourth a few Pfennige, and on the fifth a small glass of whisky. This nonsense was discovered the next morning by the cleaning ladies, good and devout local people, who promptly had hysterics and went on strike until the culprits of this devilish apparatus could be apprehended. Franz and I heard about their consternation and were duly summoned to the Director's office where we sheepishly confessed, a confession that was accepted by the cleaning staff after generous helpings of Sahnekuchen und Kaffee. But, we were nevertheless banned from working in the Plant Genetics building.

The laboratory we were next permitted to use was in the basement of the Biologische Kybernetik building itself. One wall of this room had been newly equipped with a lot of steel shelves that, soon after we moved in, received scores of bottles that smelt rather strongly of malt and in which lived large numbers of tiny flies, our first encounter with *Drosophila melanogaster*. These belonged to Martin, who had just arrived in Tübingen from California to take up an assistantship with Karl Götz. He was newly married and was pioneering his own future, combining his knowledge of genetics with observations of behaving fruit flies (Figure 2). But, Franz Huber and I really had no idea what Martin's research was about, although we saw him often in the laboratory doing those strange manipulations that people do when they knock down flies and transfer them to fresh bottles. To these bottles were affixed mysterious names, dates, and other obscure missives. It was all beyond our ken and we simply went about our immediate business, which was to impregnate brains with the Golgi method, at that time the only technique that could resolve single neurons.

In those days, sectioning Golgi-impregnated brains was an undeniably toxic affair. To visualize neurons demanded that the brains were sectioned, and this first required the dissolution of highly flammable nitrocellulose, otherwise known as gun cotton, in a mixture of diethyl ether and absolute ethanol. Increasing concentrations of this miasmic, volatile concoction were gradually infiltrated into the tissue. The brains, now immersed in viscous nitrocellulose, were next hardened by pouring them and that awful stuff into little paper boats floating merrily on open glass jars of chloroform. That evening, there were probably 10 such cuvettes from which fumes, mixed with those of ether, wafted into the air, for we were preparing to section a lot of material. Cutting the sections was a real kick. Each block was mounted with liquid ethereal nitrocellulose onto a boxwood platform that was periodically washed with cold chloroform to prevent shrinkage. The block was clamped to a sliding microtome, the blade of which, wickedly sharp, was kept wet by squirting ever more chloroform at it. The knife was pulled across the specimen in the direction of the operator's face peering woozily at the sections, which, as time

Figure 2. Apollonia and Martin shortly after their arrival in Tübingen in 1969.

progressed, appeared to come off the blade as identical pairs. Closing one eye seemed to help a lot. Each new section was lifted off the knife with a piece of chloroform-soaked lens paper and deposited on a slide sticky with drops of ethereal nitrocellulose. It seems incredible that Franz Huber and I did this late into the night without injury, all the while consuming generous amounts of Johnny Walker. By about one thirty in the morning, we had sectioned some hundred or so brains and had survived the inhalation of unadvisable amounts of soporifics.

Martin's flies were not so lucky.

We didn't discover this until 2 days later. Our Golgi preparations were lovely. Franz Huber had a wealth of material on his favorite grasshopper. The next day, Martin was as courteous to us as he had been from the start, although he had, unknown to us, determined that of his precious stocks of mutants very few had survived their inadvertent and terminal narcosis. It was only when Franz Huber came knocking on the door of my room in the Max-Planck guest house (I had not yet found lodgings in town) that I realized something was very wrong indeed. First, the Johnny Walker was not in evidence, which was an especially bad sign, particularly as we had planned to celebrate our success that evening. Second, Franz looked simply ghastly, quite white around the gills. He explained that just an hour earlier he had been commanded to Werner Reichardt's office—the second Directorial summons during his visit—this time to be told that we had slaughtered some thousands of fruitflies and that we had jeopardized, possibly even annihilated, the research of Karl Götz's new staff scientist. What could we do, we wondered; this was quite awful. And so, the next day, we went to Martin and shamefacedly apologized for our ignorance, for we should have realized that while we humans can tolerate such noxious abuses to our system, the little fruitfly cannot.

Martin was the perfect gentleman. Without recrimination, and with good grace, he explained that there were possibly some stocks still left and that these things simply happened anyway. We knew that they simply didn't, but were glad enough to be so generously let off the hook. What I didn't know at the time was that such good manners and generosity of spirit are second nature to Martin. Despite this almost fatal disruption to his research, he has always made light of it, even waved aside the very recollection. That he started again, repairing what we had almost destroyed, was never mentioned and I am sure that he has given it, if not a second thought, certainly not a third one. This is what I referred to at the beginning of this essay as Martin's strength: his tolerance—actually, just one strength of many but one that, in retrospect, is pretty impressive. He would probably wave that away too, so I will not embarrass him further, except to say that notwithstanding Franz Huber's and my best, albeit semiconscious, efforts at its destruction, Martin's research took off and gained huge momentum. The strategy that he introduced those many years ago is now, as we all know, pivotal to understanding how the fly's brain works.

There is one more thing to add: whisky in moderation, but best leave the ether.

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