



simple model systems and sophisticated questions

the scientific legacy of obaid siddiqi

"*Drosophila*, like the Brahmin, is born twice; first from the egg as a maggot, then from the pupa as an imago. In both its incarnations the fly behavior undergoes profound changes with age and experience. An important problem is to distinguish between innate and acquired behavior. This is difficult and, in several aspects, an unsettled issue. Understanding adaptive behavior and establishing its neural correlates is the focus of our group's interest. As a part of this effort we are studying learning and memory in larva and imago." This was the tag line Obaid Siddiqi, one of the finest scientists and arguably one the most self-effacing institution-builders in India, had on his web site in July 2013, as his group's latest research interest at the NCBS, Bengaluru when he had met with a seemingly minor road accident that happened to be fatal and ended in his demise at the age of 81. Obaid Siddiqi passed away on 26 July 2013. After establishing the Molecular Biology Unit, the first ever group of Molecular Biologists in India, at the Tata Institute of Fundamental Research, Mumbai in the early 1960s, Siddiqi became the chief architect in formulating and shaping the National Center of Biological Sciences (NCBS) at Bengaluru, Karnataka, India, in the 1990s. Siddiqi continued to do work in his laboratory till the very end.

Obaid Siddiqi too was re-born more than once, if his research work of about 60 years in biology tells us anything. First, as a molecular geneticist: in analyzing the fine structure of gene and also in developing the concept non-sense codons by identifying the suppressor of non-sense mutations during the late 1950s and early 60s. Then, as a neuroscientist at the cutting edge areas, from 1970s onward; all the while clearly conscious of the importance and the suitability of the model organisms that he was choosing to work with. In earlier times if the model organisms were fungi (*Aspergillus*) and bacteria (*E.coli*), later it was the fruit fly *Drosophila*: all easy to maintain and very amenable to work with. In one of our last meetings, Siddiqi was effusive on our proposed program of introducing collabora-

tive research at the undergraduate level vertically integrating with the schools and advanced research centers, across the country. When one of us raised the issue of poor facilities in the more than 26,000 undergraduate colleges in India, Siddiqi said leaving no scope for any pessimism: "sophistication should be in the mind; not in fancy gadgets or in laboratory space. Just look around; for a biologist, there can be innumerable lab settings; almost everywhere", he added. He was also overtly supportive and keen to empower teachers at all levels. He famously said: "teachers are at a great advantage in comparison to us, scientists. At any given time, I have only a handful of students; you teachers have them in hundreds!"

In fact, there was yet another birth he had as a student activist and organizer of protests. That was in the late 1940s when the nation was in the throes of being a republic. Which direction the Republic should take! He was arrested and sent to Jail for being an active supporter of the left movement. But, then, that was the time that was! Obaid Siddiqi also shared the family's social commitment and passion for effecting a revolutionary transformation in the country. Many from his immediate family including his sisters were in the left movement. Irfan Habib, Siddiqi's brother-in-law and a famous historian once remarked that Obaid Siddiqi must have been the only Fellow of the Royal Society (FRS) in its entire history who had spent time in jail for communist activities. That was during the "BTR period", following the party's Calcutta congress, when Obaid Siddiqi was an activist of the AISF (All India Student Federation) at the AMU (Aligarh Muslim University). According to K.Vijayaraghavan, former Director of NCBS and currently Secretary to the Department of Biotechnology (DBT), Siddiqi was 'rescued' from this field by none other than Prof. Zakir Hussain (who later became the President of India), who had persuaded Siddiqi to continue his studies in plant sciences, at the AMU. It is just another matter that later, his experimental wheat-field at the Indian Agricultural Research Institute, Delhi was destroyed by a storm and he

took that as a hint to join the famous Glasgow biologist, Guido Pontecarvo to do molecular Genetics using the fungus, *Aspergillus nidulans*.

His work on bacterial conjugation and that of suppressor of non-sense mutations are textbook material for many generations now. Between Obaid Siddiqi and the famous Caltech scientist Seymour Benzer, who incidentally started the field of Behavioral Genetics in the 1970s using the fruit fly as the model system, there is an interesting parallel; at least from the late 1950s. Though Benzer started as a Physicist, in the heady days of 1940s during the famous exodus of physicists to Biology after the persuasive writings of top Physicists among others, Erwin Schrödinger and Wolfgang Pauli, had joined the famous "Phage Group" initiated and promoted by another Physicist-turned- Biologist, Max Delbruck. He had used the model system of bacteriophage to the hilt, by genetically dissecting out the fine structure of the illustrious rII locus.

There is an informative take on the trajectories of these two: some say it as the tale of two scientists! Seymour Benzer and Obaid Siddiqi, though apparently from different background, they addressed very similar research questions in biology and their paths crossed many a time. When H.J. Muller came up with the concept of a gene as a mutable, heritable unit of function that can be separated from other such units by recombination, even in the late 40s, people started wondering: what, physically, was a gene? Was it made purely of nucleic acids, or was it part protein? Was it simply a linear stretch of DNA, or was it a globular one? These were questions waiting to be addressed when Seymour Benzer was propelled into Biology research in the US and when Obaid Siddiqi joined Guido Pontecarvo in Glasgow for his doctoral program. It is interesting that Siddiqi took up such a challenging question for his degree and made major contribution to arrive at the concept of the gene as a linear structure by means of intra-genic recombination studies using *Aspergillus nidulans* at a time when Benzer started dissecting the rII locus of the bacteriophage through the

same procedure, but obviously with much more robust a model system like the bacteriophage which reproduces in large numbers. Siddiqi had made his name in scientific circles through his work first in Glasgow and later on in Clod Spring Harbor Laboratory and in the University of Pennsylvania. India beckoned and in 1962, Siddiqi took charge to establish the Molecular Biology Unit at the TIFR, Mumbai that gave a much needed push to research in frontier areas of biology in India. This also was the beginning of a new paradigm of interdisciplinary collaborations in biology in the country, though Siddiqi felt, more needed to be done in this front.

Around the same time, both Benzer and Siddiqi started getting interested in the biological basis behavior or rather in the molecular basis of behavior. Siddiqi was soon to contact Benzer and both of them started studying the electrophysiology of the historic *ts* (temperature sensitive) mutants, at Caltech. To this day, *ts* (temperature sensitive) paralysis remains one of the most dramatic demonstrations of nerve function in an intact organism.

"I got interested in this general problem of personality and behavior—how much is genetics and how much is environment?" Benzer stated in his famous Oral History Project at Caltech. "If you're doing genetics, it's important to work with an organism where you can work on *populations*, because if you run a rat through a maze over and over again, it takes weeks to get any significant amount of data that would be statistically significant. But if you have a bunch of flies, they all have the same genotype, and when you run them through a maze, you immediately get to do with hundreds of flies at once". Obaid Siddiqi could not have agreed more!

It was much later though Siddiqi started addressing the question of learning and memory and the role of genes in this 'meta-behavior', i.e learning. The so called 'memory mutants' and the 'sleep mutants' from Benzer's laboratory were well-

known for quite some time, now. One can only speculate, why it took so many years before Siddiqi attempted at this question of learning and memory using the fly, frontally. Perhaps, he may have been concerned about the genetic deterministic slur attributed to such gene-centric studies on behavior. It was Punita Panchal, a masters' student who had done certain studies earlier on learning and memory in a garden snail in one of the colleges with whom Siddiqi started his work on learning studies in *Drosophila*, using olfactory cues as the conditioned stimuli in mid 90s. Siddiqi's focus till then, at the TIFR, has been largely to dissect molecular pathways of chemo sensation by using *Drosophila* mutants.

In the learning and memory studies, though Benzer's group had isolated several genes as early as in the 1970s, Siddiqi's interest was to address the plasticity question much more subtly: he was interested to ask how much of the early experiences influence in later behavioral manifestations. Nothing could be better than the fly model system with its "twice-born" characteristic to be used as a model. Siddiqi had done interesting studies on larval learning and memory. He never forgot to emphasize that such a simple model system should be a boon for teachers looking for innovative teaching-learning programs that would take their students to the frontiers of Biology research thus bridging the existing wide gap between what is being taught in the class room and what is practiced by scientists in research centers.

Siddiqi's group at the NCBS had some early successes in learning and memory studies in *Drosophila* larvae, though we will restrict referring to a few cases here. In one case, they were able to dissect the forms/stages of memory. In a fine piece of analysis of the work on electroshock conditioning (Research Report 2004-05, NCBS) he wrote: "...one part of the long-term memory was insensitive to cooling.

There are thus, at least three different components in larval memory of shock treatment, short-term, middle term and a cooling insensitive, long-term. A kinetic analysis of the larval memory of electric shock should lead to a better understanding of the underlying neurological mechanisms." This is quintessential Siddiqi: simple systems and sophisticated analysis of meticulously collected data! He used to quip: working with the fast changing larval instars demands fast work, the full day and "then, you have the whole night to mull over on your observation"!

Most interesting was the finding reported in 2010 that while early exposure to multiple odors (when the freshly emerged flies were reared in an enriched medium) improves the discriminatory ability against classes of odorants as well as develops high acuity to odors later on in life, it also confirmed that the exposure to limited odors act as a handicap for the fly. Most strikingly, electrophysiological recording showed that this alteration in function is located at the periphery, in the olfactory receptor neuron (ORN) itself. That Obaid Siddiqi and Seymour Benzer at a later stage started taking substantially different trajectories while addressing behavior and especially, neuronal and behavioral plasticity questions, is interesting. Siddiqi is surely holding hope for an enriched environment for millions of people who are in deprived situations, till the end. Would this not also be a case of early environment influencing the manifestation of behavior at later stages?

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