DOI: https://doi.org/10.36094/sc.v89.2023.Remembering_Seymour_Benzer_in_his_Post.Das_Ghosh.33

ARTICLE

Sci. and Cult. 89 (1–2) : 33-37 (2023)

REMEMBERING SEYMOUR BENZER IN HIS POST CENTENARY YEAR

MOUMITA DAS* AND CHINMOY KUMAR GHOSH**

The world celebrated the birth centenary of the pioneer of molecular biology and neurogenetics, Seymour Benzer in 2021. He had many feathers in his cap. On one hand he was a physicist, and then on the other he was a molecular biologist, and above all a behavioral geneticist. The most significant feature of his journey of research in science was his inter and trans-disciplinary approach. The hallmark of his brilliance was the maverick nature of his quest for the truth, which made him travel from physics to the exciting world of 'fine structure genetic analysis' to the unique application of the 'fruit fly Drosophilia melanogaster*' for the study of nervous system function and development. This article narrates the above features of the life and works of Seymour Benzer with a view to spreading awareness about his inquiry driven approach to scientific research.*

The world is celebrating the birth centenary of the pioneer of molecular biology and neurogenetics, Seymour Benzer. His endeavors have opened up these two new fields of scientific investigations, which are now growing by leaps and bounds. The knowledge about gene structure and how genes affect behavior got elucidated through the seminal work of Benzer that laid the foundation of modern genetics and genomics. Benzer was a versatile scientist, and his academic upbringing was marked with his interest and proficiency in the three major subjects, Physics, Chemistry and Biology.

Seymour Benzer was born on October 15, 1921 to Meyer B. and Eva Naidorf in South Bronx, New York, USA. His grandfather was a tailor and maternal grandfather an orchard grower in Sochaczew, Poland. Both his parents immigrated to USA in about 1910. They were engaged in tailoring and dressmaking business. Little had they known that their son will become a tailor of a different genre where his curiosity will dominate over public pressure or the fashion trends in researches with neurodegenerative diseases and so, his journey of founding the branch of science called Neurogenetics never followed the beaten track. Being the only boy among the three children, the older two were girls, he was the favourite of his parents.

Growing up in Brooklyn, he had a modest home environment where his parents conversed in Yiddish and minimal English; he went to a Hebrew school and learnt Yiddish at home. Thereafter, he attended the high school. By the time he went to the sixth grade, at about eleven years of age, he had developed a keen interest is nature studies. Around the same time, his brother-in-law gifted him a microscope and thus a whole new world opened up for him. "I looked at everything that I could find", said a reminiscing Benzer in an interview.[1] Subsequently he started dissecting frogs using his parents' sewing tools, such as scissors and needles, and making the legs of the frogs twitch with electrical wires. He was a voracious reader from a young age and had the habit of taking his Physics book along to the synagogue where he used to hold it over the Bible and read.

* Deputy Director, National Centre for Innovations in Distance Education, IGNOU, New Delhi,
e-mail: moumitadas@ignou.ac.in

** Former Director, National Centre for Innovations in Distance Education, IGNOU, New Delhi,
e-mail: contactckg@gmail.com

Studying at the New Utrecht High School, his interest in Biology grew further, but as the subject taught was mostly Classical Taxonomy with hardly any reference to advanced areas of Biology, he became disinterested. He was influenced by the Chemistry teacher there and he developed an interest in that subject. Then he joined the Brooklyn College with a Regent's Scholarship of $500 a year. This was the only college the family could afford to send him to and he was the first in his family to attend a college. At college he became interested in Physics. He graduated in 1938. At the recommendations of his college professors, he joined Purdue University.

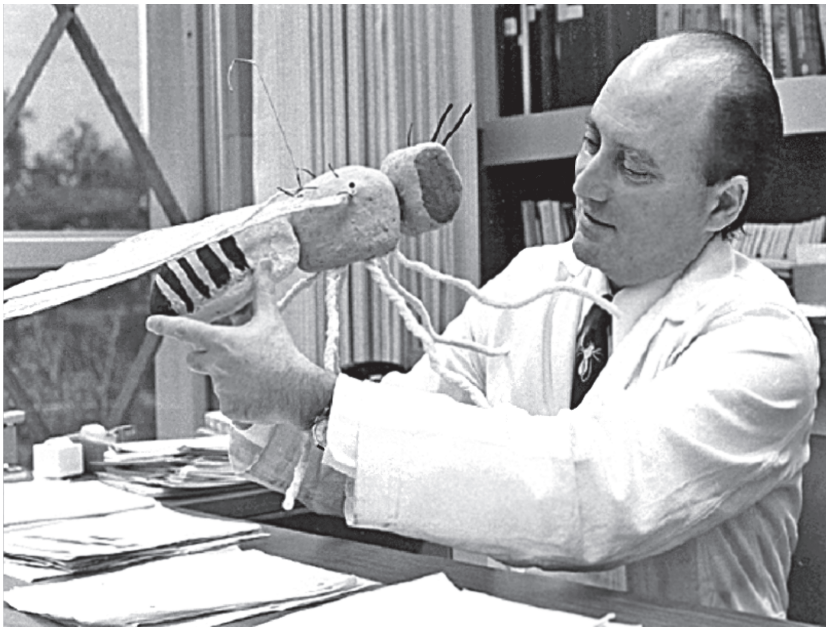
At Brooklyn College, when Benzer was sixteen years old, he met Dorothy Vlosky. Dorothy (nicknamed Dotty) was a twenty-one-year-old nursing student. They had been dating for three years. In 1942, at his father's behest, just before joining Purdue University he married Dorothy. Benzer's father had told him "I want you to marry the girl". Reminiscing the event, Benzer said "We had an orthodox wedding at her home, and we left the people dancing while we went to catch a train to Indiana. That was our honeymoon." When Benzer's stipend was raised from $70/month to $120 per month at Purdue, Dorothy could afford to complete her graduation. They had two daughters, Barbara and Martha Jane. When Barbara was born, Benzer's father accompanied the family to babysit the child.

During his career as a physicist and behavioral geneticist, he travelled to France and England with his wife and children. They had a few instances of difficult times in Paris and England with their living conditions as they faced a lack of central heating. In Paris, his daughter Barbara developed diarhhoea due to the deploring living conditions. She had eventually recovered when they moved to better locales. In England, "Being warm was a constant preoccupation" as Benzer had recalled in an interview. They, however had wonderful time with food as the English "have wonderful ingredients", as Benzer put it.

Benzer had a side of personality that was fun loving. Together with his scientist colleagues, he used to indulge in mischievous acts. Once while staying in Pasadena, he wanted to listen to Arturo Toscanini, a famous Italian conductor, who was visiting for two days. As he could not get the tickets, he decided to sneak in during intermission with Dorothy. They were thrown out during intermission. When he narrated this incident to Max Delbrück (the biophysicist), he was excited at the prospect of sneaking in, and along with their wives they sneaked in during the intermission the next day. Needless to say, all of them were thrown out. However, as Benzer recalled, "the ushers took pity on us; so, when it came to the encores at the end, they let us go in and stand in the back to hear the encores."

Benzer was fond of good food. He was "in love with Japanese food", especially sushi. He used to visit ethnic restaurants to try out exotic food.

After about 23 years of married life, Dorothy passed away after losing a prolonged battle with cancer. For two years, Benzer mourned the death of his wife. Then he married Carol Miller, a Professor of Neuropathology. They had a son, Alex. They also had several step-children, and grandchildren. They developed a close relation until the death of Benzer.



Source:https://upload.wikimedia.org/wikipedia/commons/thumb/3/39/Seymour_Benzer.gif/800px-Seymour_Benzer.gif

Benzer's Career

At Purdue he worked on Physics projects that were mostly war related, such as semiconductors and cyclotrons. Working on semiconductors, Beuzer used purified germanium and doped it with selected elements and characterized the properties. He discovered that in some cases there was a photoelectric effect and negative resistances as well. His group developed various devices that employed these properties and they obtained patents. Six patents were in his name while he was still a graduate student. He got

his PhD in 1947 on his thesis titled "Photoelectric Effects in Germanium (1947)". He was hired as Assistant Professor at Purdue as soon as he completed his PhD. However, he was already interested in Biology by then. He left Purdue and joined the laboratory of Max Delbrück at the California Institute of Technology (Caltec), California, as a Post Doctoral Fellow in a project on bacteriophages. Recalling the incident, he shared an interesting anecdote about how he had made up his mind when he met James Watson at Purdue and inquired him about a suitable lab, the options being the labs of Max Delbrück and Salvador Luria. Watson said, "Well, if you come to Luria's lab, he won't leave you alone. He's very good, because every day he'll ask you what you've done. Whereas, if you go to Delbrück's lab, you may not see him for two weeks at a time, because he likes to go to the library and look up something and go his own way."[1]

Afterwards, he went to the Pasteur Institute in Paris for research in 1951 with his wife Dorothy and four-year-old daughter Barbara. He joined the laboratory of Andre Lwoff, working on bacteriophages. Subsequently he returned to Purdue, where he resumed his work on bacteriophages. In 1956-57 he went to Cambridge University on a post-doctoral fellowship with his wife and two daughters, Barbara and Martha. Eventually, after returning to Purdue, he started working in the field of Molecular Biology, on the *r* mutants of bacteriophages, and he published one of his most notable discoveries, the fine structure of *rII* gene, in 1959.

By the sixties, he was getting more and more interested in Behavioral Genetics. In 1967 he left Purdue and joined Caltech as a Professor, and began his work on Behavioral Genetics using *Drosophila melanogaster*. At Caltech he studied behaviour using *Drosophila*, treating individual flies as a "molecule of behavior". He continued to work on *Drosophila* mutants to elucidate the genetic cause of behaviour. He mentored many research students who went on to become eminent scientists in future. His endeavors opened up an entirely new field of research that later became known as Neurogenetics[2].

To understand the significance of Benzer's discovery, it is important to take a step back and look at the historical background. It all began with the discovery by Gregor Mendel in 1865 that the behavioral characteristics or traits are transmitted from one generation to the next through discrete units, which he called "hereditary factors". He also stated that these "hereditary factors" segregate or randomly separate from each other independently during the production of gametes[3]. These "hereditary factors were named "genes" by Wilhelm Johannsen in 1909. Meanwhile, the DNA had already been discovered in 1869, cell division in 1879[4] and the chromosomes in 1882. In 1902, Mendel's "hereditary factors" were linked to chromosomes by Walter Sutton and Theodor Boveri[5]. By 1911 it was shown that the genes, linearly arranged on chromosomes, were the units of heredity by Thomas Hunt Morgan using the fruit fly *Drosophilla* and its mutant variants as a model[6]. In 1928 Morgan established his laboratory at Caltec, where his student Alfred Henry Sturtevant joined him. Sturtevant developed the mechanism to map the genes on the chromosomes based on the frequency of crossing over (chromosome breakage and reunion during cell division). Scientists were able to produce new variation of the gene (mutants) using X-rays and chemicals, which helped in artificially mutating *Drosophilla* to produce new variations, which enabled gene mapping. The fact that one gene got coded for only one protein (enzyme) was demonstrated in 1941 by George Beadle and Edward Tatum[7]. That the genetic material was the DNA was established by Alfred Hershey and Martha Chase in 1952. The structure of DNA was elucidated by James Watson and Francis Crick in 1953.

The eminent quantum physicist Erwin Schrödinger, intrigued by the fact that X-rays could cause heritable changes to genes, and thus life itself, wrote the book *What is Life?* He was introduced to this book at Delbrück's lab when he was a post-doctoral student there. This book became the inspiration for Benzer[8].

Mapping the Fine Structure of the rII Gene

Benzer was interested in the structure of the linearly arranged genes, as described by Morgan, and how they reproduced themselves. He believed that a gene had "sub-elements" and questioned if these sub-elements were linked in a linear way to form the structure of the gene[9]. To seek answer to his questions, Benzer needed the necessary tools and techniques that would give him the right answers.

The study of genes requires experimental models that can produce offspring in large numbers and that too in a very short period of time. This is because gene manipulations are done in the parent organisms through chemicals or radiations to mutate their genes. These mutations are expressed in the offspring, which are then studied and mapped on the chromosome. Another feature, namely the recombination of genes is also studied in the offspring to assist in mapping the gene. It is taken that with the lesser frequency the genes recombine during meiosis, the closer they are linked to each other, and are inherited and expressed together.

While in Purdue, Benzer had an eureka moment when he was working with the *r* mutants of the K-12 bacteriophage. The K-12 bacteriophage is a T4 virus that infects the K-12 strain of the bacteria *Escherichia coli*. In laboratory conditions, the bacteria *E. coli* is grown in the pertri dish and these can be seen in the form an opaque lawn (a growth of bacteria). When the bacteriophage is added to the lawn, the virus attacks the bacteria and kills it. This can be seen as clear portions in the otherwise opaque lawn. This behaviour of the virus is called rapid lysis (designated as *r*). A normal bacteriophage produces small clear zones, whereas an *r* mutant bacteriophage produces big clear zones. These clear zones are called bacteriophage plaques. There are a variety of *r* mutant bacteriophages that produce fuzzy plaques and differently patterned plaques. Scientists had recombined these mutants with one another in many ways and had developed an area for a genetic map of the bacteriophage. The *r* mutant viruses have three regions (loci) in their chromosomes associated with the mutation, namely *rI*, *rII* and *rIII*. He also used two different strains of *E. coli*, namely B and K. Strain B allowed the growth and completion of life cycle of *rII* mutants as well as the wild type, but strain K allowed the growth and life cycle of only the wild type. He used these strains of bacteria to select his *rII* mutants.

Benzer realized that this was a system in which he could do very fine gene mapping, even at a single nucleotide level. This was because he could put 100 million plaques on one plate and the number of nucleotides in the DNA of the bacteriophage was already known by that time as it was in 1954-55[1]. He could resolve mutations in the gene even if these were one nucleotide apart.

He decided to focus on the *rII* loci. He observed that there were some *rII* mutants that did not form a big plaque, as they should have. These produced small clear zones, which were similar to the "Wild type" mutants. These were designated as "defective" mutants. He deduced that it was possible because of the genetic recombination between the chromosomes of the normal *rII* mutant parents. It was possible that both the parents would have some part of the intact *rII* genes which recombined in the offspring to produce a "defective" offspring that exhibited characteristics that were similar to the "wild type". His experiments demonstrated that this was due to a phenomenon known as complementation[10]. Complementation is the ability of two different mutations to restore wild type function when they are in different DNA stands (trans), but not when they are on the same DNA strand (cis). Benzer coined the term "cistron" for these genetic units[11].

Benzer crossed hundreds of *rII* mutants and found about 2000 mutations in the same gene. He calculated the recombination frequency and found out that in some pairs, the recombination frequency was as low as 0.02 centimorgan, which meant that the smallest unit of recombination and the smallest unit of mutation in the bacteriophage was a single base pair of DNA. The mutations in a single base pair was called point mutations. In other cases, there was a deletion of a single nucleotide in the mutant gene. The semutations were called deletions. The viruses with deletion mutations in *rII* showed no recombination with other mutants or genes and did not back-mutate. He used these deletion mutants to map several genes.

Benzer was of the thought that the *rII* loci could be broken into different fragments. Indeed, he was able to show that the gene had a structure that could be split into a unit of recombination (recon), mutation (muton) and function (cistron).

Experiments with Drosophila

His interest in Behavioral Genetics stemmed from his observations on his two daughters. One was serene and the other was lively, in spite of living in the same environmental conditions. This phenomenon intrigued him. Also, he had read a book by Dean E. Wooldridge named *The Machinery of the Brain*. This made him think "how do you get from a set of genes and chromosomes to a brain that thinks and behaves. How do you get from a gene to behaviour?"[8] Benzer was intrigued by the question of how the one-dimensional information encoded in a gene becomes translated into the multi-dimensional complexity of behavior; when an individual develops from an egg, the one-dimensional information contained in the linear sequence of genes on the chromosomes is somehow translated into a two-dimensional blastula, which later folds to produce a precise three-dimensional array of sense organs, central nervous system, and muscles. Finally, the ensemble interacts to produce behaviour, a phenomenon which requires four dimensions, at the least, to describe[8]. To seek the answer to his questions, he started an investigation with *Drosophila*. In this instance too, he took the same approach as with the bacteriophages. He selected *Drosophila* because in his own words, "If you're doing genetics, it's important to work with an organism where you can work on populations"[1]. With *Drosophila*, he could get a large number of progenies in a relatively short duration and he had planned to study mutations with large populations. His research question was "What is the simplest kind of behaviour you can think of for which

you could make mutations and changes, and work out the relationship between the gene and the behaviour"[1]. He zeroed on the behaviour of phototaxis, i.e., going towards light. This is one of the strong behavioral responses in a fly. To test the behaviour, he devised a countercurrent distribution procedure to ensure that his results were statistically correct at least ninety five per cent of the time. Using his device, and mutagens, he could isolate many different types of phototaxis mutants that showed a wide spectrum of behaviour. It was later found that the differences in the behaviour were due to changes in the structure of the compound eye or visual degeneration. He studied a mutant named "drop dead" where the fly drops dead after a few days of hatching. Using these mutant and normal flies, he produced mosaic flies. He found that the mosaic flies were normal, which suggested that "if half the brain is normal and half the brain is mutant, the normal half can supply some factor that keeps the other half from degenerating".[1] He, along with his team made maps for these genes on the chromosome. He coined the term "sturts" for a unit of distance for behaviour. Arrangements were made in his lab to study circadian rhythms and the behaviour of "learning and remembering" using *Drosophila* as the experimental model.

From a trained physicist to a molecular biologist to a neurogeneticist, Benzer donned many intellectual hats in his eventful career as a scientist. His curiosity, ability to design his experiments, combined with his multiple scientific skills enabled him to achieve what he had set out to do. He left a deep impression on many scientists whom he had mentored. For his contributions he received several prestigious awards and prizes. Seymour Benzer continued to run a vibrant laboratory at Caltec till he had a stroke. His last words (to his physician) were "I have two questions." He breathed his last on November 30, 2007 at the age of 86 years[11] leaving behind a legacy of holistic view towards scientific investigation. His scientific temper got vividly revealed through his inquiry driven approach and the inter- as well as trans-disciplinary nature of his research. His works have been a journey of bridging the theory-practice divide which happens to be a general malady of dissemination of science education. Let the legacy of Seymour Benzer kindle the interest in his life and works which are worth emulating for rejuvenating teaching-learning transactions in science at the academic institutions of our country. ❐

References

1. California Institute of Technology. 2002. http://oralhistories.library.caltech.edu/27/1/OH_Benzer_S.pdf (Accessed on 26.12.2021)
2. Mark A Tanouye, M. A. 2008. https://www.nature.com/articles/ng0208-121 (Accessed on 30.12.2020)
3. National Human Genome Research Institute. 2013. https://www.genome.gov/25520230/online-education-kit-1865-mendels-peas. (Accessed on 30.12.2020)
4. National Human Genome Research Institute. 2013. https://www.genome.gov/25520234/online-education-kit-1879-mitosis-observed. (Accessed on 30.12.2020)
5. National Human Genome Research Institute. 2013. https://www.genome.gov/25520242/online-education-kit-1902-chromosome-theory-of-heredity (Accessed on 30.12.2020)
6. Allen, G. E. 2020. https://www.britannica.com/biography/Thomas-Hunt-Morgan. (Accessed on 29.12.2020)
7. Winchester, A. M. https://www.britannica.com/science/genetics/The-work-of-Mendel#ref936973. (Accessed on 29.12.2020)
8. Bonini, N.M. 2008. https://www.genetics.org/content/180/3/1265. (Accessed on 26.12.2021)
9. Benzer, S. On the topography of the genetic fine structure. *Proc. Natl. Acad. Sci. USA*, 1961, **47,** pp. 403–415.
10. Anon. 2014. https://www.biology-pages.info/B/Benzer.html. (Accessed on 30.12.2021)
11. Quinn, W. G. Seymour Benzer's life, *Fly*, 2008, **2:2**, pp, 55-57, DOI: 10.4161/fly.6102