About the origins of Molecular Biology and of our Department at UTD

A personal account written for my former students and colleagues

by Dr. Hans Bremer

History has its own logic, albeit dependent on a heavy dose of chance and unlikely coincidences, not unlike biological evolution. The early history of UTD Biology is closely linked to the people who created our discipline, molecular biology. After 30 years, the names of these people and their contributions tend to get forgotten. Who still remembers Delbrück? Who was Günther Stent? Carsten Bresch? What were Roy Clowes' contributions to our science? These people have shaped the concepts and conditions on which we base our work today; without them we might not be where we are now. In addition to the general significance of their scientific contributions, they have a special significance for the beginnings of UTD Biology.

The predecessor institution of UTD was the Southwest Center for Advanced Studies (SCAS), also known as Graduate Research Center of the Southwest, founded in 1964. UTD Biology grew out of the Biology Division at SCAS. The scientist who brought the first molecular biologists to SCAS and who became the first Chairman of the Division was Carsten Bresch, a phage geneticist and Delbrück's first disciple in Germany after the war. The logo on Bresch's 1964 text book "Classical and Molecular Genetics" appeared on the cover of all our Bienniel Reports until the death of Roy Clowes.

This story about our "roots" centers around those scientists who created our SCAS biology group and who have also determined my own development.

1. *Max Delbrück*

According to a discussion by Günther Stent (1968), the "structural school" and the "informational school" of molecular biology represent two different philosophies about how to approach the "riddle of life". The name "molecular biology" was defined by the "structurist" Astbury in 1952, referring to the structural organization of biological molecules, as obtained by X-ray crystallography. (In 1945, Astbury found that the DNA bases form a dense stack perpendicular to the long axis of the molecule, 3.4 Å apart.) The investigators of this school believed that physics could make an essential contribution to biology by such structural analysis. In contrast, the "informationists", led by Max Delbrück, thought that biology could make a contribution to physics by the discovery of some hitherto unknown fundamental principle or force peculiar to biology. Their starting point was not structure, but genetics. Niels Bohr had suggested that there be three *complementary* aspects of atomic existence: first, particular, deterministic; second, quantum mechanical, probabilistic, related to wave nature; and finally a suspected third state only to be found in life (*sic* Stent's "romantic phase" of molecular biology). In the 30s Delbrück had worked as a postdoc with Bohr, who inspired Delbrück to become a biologist with the words: "Biology is too important to leave it to the biologists".

In 1934, the *Drosophila* geneticist H.J. Muller, who had defined genes as

"ultimate units of life", went from Caltech to Berlin to work with Timoféev-Resovsky on mutagenesis of *Drosophila*, and to seek collaboration with physicists. As a result, in 1935, Timoféev-Resovsky, Zimmer, and Delbrück published a paper *About the nature of the gene mutation and gene structure*, in which the notions of the *gene as a molecule* and of the *mutation as a quantum jump* were put forward. The idea came to be known as the "quantum model of the gene". In 1945, in an article *What is life?* Schrödinger, while a refugee in England, called it "the Delbrück picture of the gene". Schrödinger's article stimulated a number of scientists, including Luria and Stent, who began asking about Delbrück: who is he, and where is he? Due to the war, normal connections among scientists had been disrupted.

After the collaboration with Timoféev-Resovsky, Delbrück decided that the approach to the understanding of the gene was a study of viruses. In 1938, Delbrück had visited Morgan's Drosophila group at Caltech, where, by chance, he met Ellis, a self-taught phage worker. Delbrück immediately realized that phage, a bacterial virus, was the model of a gene he had been looking for. Soon (1938) he published with Ellis *The growth of bacteriophage*. Despite the flaw in the interpretation ("Certain large protein molecules (viruses) possess the property of multiplying within living organisms."), the one-step growth and single-burst experiments combined with mathematical analysis represented a breakthrough in technology with far-reaching consequences for microbiology and virology research. A few years later, Luria sent his data on mutant frequencies to Delbrück. Delbrück's mathematical analysis of Luria's data decided the fundamental issue whether bacterial "variants" were really mutants or just "heritable adaptations". But Delbrück's main merit for which he received the Nobel Prize (1969) lay in his role as leader of the *Phage Group* that rapidly grew from its three founding members, Delbrück, Luria, and Hershey, to countless followers in the US and Europe who became the first molecular biologists. Delbrück originated the Cold Spring Harbor phage courses and phage meetings where the new ideas about the nature of the gene were discussed and new experiments conceived. His presence and style attracted many outstanding scientists to the new biology and focused them on fundamental questions.

Stent associated the structural and informational school with "three-dimensional" and "one-dimensional" molecular biology, respectively, referring to the 3D structure and to the 1D store of information. The members of the phage group represented 1D molecular biology. Today, structural studies and genetics are both equally accepted subdisciplines of biology. However, the solution of the 3D structure of a protein, for which Kendrew and Perutz received the Nobel Prize, did not solve "the riddle of life". Watson and Crick's *double helix* was the important breakthrough, not because of the double helix *structure* (the helix was only emphasized to emulate Linus Pauling's alpha helix; for which Pauling had earlier received the Nobel Prize), but because of the *double*, which meant *two complementary* molecules. This immediately suggested how genes might replicate. More importantly, the base sequence of the DNA contained coded information, seemingly unrelated to structure. Much later it was realized that the DNA base sequence must contain subtle structural signals for reading the information and for controlling the reading.

2. *Carsten Bresch*

Bresch met Delbrück 1947 in Berlin immediately after the war, an event described in the book "Max Delbrück and the Origins of Molecular Biology" (1988). Berlin was totally destroyed at this time and it was Delbrück's first visit after the war to see his shattered home town. Young people who had survived the war were eager to learn about scientific and other developments in the US. One of the young science students who came to Delbrück's first lecture in post-war Germany was Carsten Bresch, who became an instant believer.

A few years later Bresch became a scientist at the Max-Planck Institute for physico-chemistry in Göttingen. The director of the Institute was Carl-Friedrich Bonhöffer. The Bonhöffers had been friends of the Delbrück family in prewar Berlin. The Bonhöffer family was known for their antifascist stand and Carl-Friedrich's brother, Dietrich Bonhöffer had been killed in a Nazi concentration camp for his convictions. Many international scholars, often refugees from the Nazis, came back and visited Bonhöffer in Göttingen. Bonhöffer had an interest in biology; and many scientists in his institute worked on an iron wire model for saltatory nerve conduction. But there were also two rather isolated scientists in one corner of the building working on an esoteric subject, phage genetics: Carsten Bresch and his cousin, Thomas Trautner (now a top man in the Max-Planck Society). Supposedly Delbrück helped to bring them into Bonhöffer's institute.

In 1958, Bresch and Trautner moved from Göttingen to Köln (Cologne), where Karl Straub, a Botany professor, had been able to get funds for a new Genetics Institute to be set up by Delbrück. Delbrück had named Bresch to prepare this endeavor. Bresch designed every lab and shelf in that new institute until it was finished, with 5 stories, each housing a special division reserved for Delbrück, Bresch, Walter Harm (another early SCAS and UTD professor), Peter Starlinger (discoverer of transposons and insertion sequences) and Ulf Hennig, a nucleic acid biochemist. Delbrück arrived in 1961 and spent two years there while on leave from Caltech. In 1965 Bresch left Köln to lead the Biology Division in Dallas; in 1969 he left Dallas to become Director of the Molecular Biology Institute of Freiburg University.

3. *Roy Clowes*

I met Roy Clowes only when I came to Dallas in 1966. But I had heard of him in Berkeley, and, in fact, at a meeting in London, Roy drove some members of the meeting, including me, back to the hotel in his car, but only later I knew that this had been Roy.

Roy was closely associated with the origins of both bacterial genetics and plasmid biology. This has its roots in some side effects of experiments that were done by Lederberg and Tatum (1946). When Lederberg prepared double-mutant *E. coli* strains for his classical bacterial crosses, he used X-ray mutagenesis (genetic methods were developed for *Drosophila*, which was too large an organism to be penetrated by the milder UV irradiation). As a result of this "rough" treatment, the bacteria accumulated many fortuitous mutations. Unknown to him, Lederberg's original *E. coli* K-12 strain happened to carry an F-plasmid, which made it "male". During the mutagenesis, one of the strains was accidentally cured of the F-factor (*F* for fertility), which made it female and allowed crosses to be performed between male and female mutant strains. Lederberg had been unaware of the preconditions for his success, for which he and Tatum received

the Nobel Prize. The scientists who later identified the F-factor and laid the foundations of bacterial genetics were Bill Hayes and Roy Clowes in England. The zero coordinate on the *E. coli* chromosome map is given by the threonine marker that is transferred first in a cross when the male strain is *E. coli Hfr*H, where *Hfr* stands for *high frequency of recombination* (due to F) and H stands for Hayes. This and subsequent work made Bill Hayes and Roy Clowes the leading experts on bacterial genetics and plasmids.

Another fortuitous mutation in Lederberg's experiments produced a slow growth phenotype. Again, this was not noticed because the strain immediately accumulated a suppressor mutation that allowed it to grow faster. During the numerous early crosses, the two loci got separated and ended up in different laboratories, where they were later discovered. The slow growth mutation had occurred in the *spoT* gene and caused the accumulation of an inhibitor of ribosome synthesis, the nucleotide ppGpp. The suppressor mutation occurred in the *relA* gene, which codes for a ppGpp synthetase. A descendent of this *relA* strain ended up with Stent, who studied it in 1960 with Sidney Brenner, when they discovered the "stringent" (*relA*$^+$) and "relaxed" (*relA*) response to amino acid starvation. Because Stent wanted to define the basis of the Rel phenotype, he needed to characterize it genetically, and the person to do this was Roy Clowes. In 1961, Roy spent a year as a Visiting Professor in Stent's lab in Berkeley to map the *relA* gene. When I arrived a year later in Berkeley, they still talked much about Roy, but since I was working on another project with Stent's student, Mike Konrad, I was not too interested in Clowes' work at that time. Only later, at UTD, I began to study the functions of *relA* and *spoT*. In 1991, Jim Hernandez in our lab showed that the *spoT* polypeptide encodes a second ppGpp synthetase activity, in addition to the ppGpp degradation activity that had been discovered earlier.

When Gordon Churchward came into my laboratory in 1975, he expressed surprise that apparently nobody at UTD knew about the importance that Roy Clowes had for the rest of the molecular biology community. Gordon's mentor in England, Barry Holland, had come a few years earlier into Roy's laboratory at UTD as a Visiting Professor. Roy was considered to be the leading expert on plasmids at that time. Plasmids are the essential ingredient of the new biotechnology industry. This industry started from Stanford, where Paul Berg had made the first artificial recombinant DNA and Stan Cohen created the first plasmid vector for recombinant DNA work. With more foresight, biotechnology could also have started here at UTD.

4. *How I got into molecular biology*

In 1951, I had transferred from the University of Marburg to Göttingen to study with the neurobiologist Jochen Autrum in the Institute of Zoology. The first thing every graduate student in Autrum's laboratory had to learn was soldering and to build an oscilloscope for the study of nerve impulses. Since I originally wanted to become an electronics engineer, this seemed exciting and exactly the right thing for me. As a high school student, I could never afford to get my hands on a "Brownsche Röhre" (now called picture tube or TV screen), an essential part of oscilloscopes. But fate had decided differently. Since I had some background in developmental biology from my training in Marburg, Autrum thought I was just the right person for a project he had conceived with his fellow professor and developmental biologist, Karl Henke. They wanted me to study

the development of blood vessel patterns in chick embryos by means of measuring redox (reduction-oxidation) potentials and pH gradients that might precede the differentiation of blood vessels. To do so, I needed micro redox and pH electrodes. To learn how to make them and measure those parameters, Autrum proposed to send me to Bonhöffer's institute. There I spent a year learning to make rhodium-plated micro-electrodes, Wheatstone's bridges and other nice gadgets. They turned out to be totally useless for my study, since the development of blood vessel patterns has nothing to do with redox and pH gradients. Even if it had, the question would have remained: what determines the pattern of pH gradients that were supposed to determine whether a vein would be here and not there in the embryo? Apparently Henke did not know much physics, and Autrum did not understand development. They had supplemented their ignorance rather than their knowledge, and I was the victim. But I was excited; I had survived the war, there was no more military, we had food again, and there seemed to be interesting things in science to discover. When I went to the Bonhöffer institute, I did not meet Bresch and Trautner, but I went to a lecture that Delbrück gave there. He talked about the "invention" of the "Herren Watson and Crick", and whether there had to be a break in the DNA at every turn of the helix to separate the two daughter strands during replication. I even got a reprint of the famous Watson-Crick paper in *Nature* out of Delbrück's hand.

Delbrück had received his Ph.D. in Göttingen, and since he was interested in the progress of Bresch's studies, he often returned to Göttingen. In 1954, Delbrück gave a lecture series at the Zoology Institute. In his first lecture he pointed out the difference between physics and biology textbooks. A physics textbook, he said, always begins with rock-hard fundamentals, but when it comes to the details, he found large gaps in our knowledge. In Biology, on the other hand, it is quite the opposite: whereas the beginnings are vague and there is nothing solid to build on, there is a lot of solid knowledge in the details. Delbrück wanted to change this state of affairs and write "Page 1" of the future biology textbooks. One evening Delbrück joined our research discussions in the Zoology department (which were held from 8 to 10 pm) to answer questions. We had a strong *Drosophila* genetics group in our department and we already knew about DNA in the chromosomes. But we did not know what a gene was. Is it a DNA molecule? Delbrück thought that DNA with many genes was a continuous molecule. Dimitrij Lang (with Kleinschmidt) proved this later, before he came to Dallas, with his famous picture of T4 phage DNA that appeared on the cover of several new biology textbooks.

By the time I had finished the Ph.D. research, my thesis advisor Henke had died and Autrum had moved to another university. I wanted to change direction. From Delbrück I **knew** of the existence of an emerging new biology. In 1958, I applied to Bresch in Köln for a postdoctoral position. Although we had been in the same institute in Göttingen together, Bresch and I had never met. When he took me as a postdoc, the new Genetics Institute in Köln was not yet ready; we worked as guests in Straub's Botanical Institute. (Straub later got his own Max-Planck Institute and one of my UTD students, Nancy Shepherd, has worked there as a postdoc). The move to Köln was the first step on my way to the US.

5. *How I got into Stent's laboratory*

Ole Maaloe, a microbiologist in Copenhagen, became an early believer in Delbrück's new biology. Around 1950, several young scientists in the US who had met Delbrück and wanted to learn about phages and bacteria had come to Copenhagen. Günther Stent came from Berkeley, and Luria in Nashville had sent his student Jim Watson. Also Bresch came; all wanted to experience the Bohr-inspired "Copenhagen spirit". At that time it was thought that genes are proteins, not DNA, but Watson wanted to get away from proteins and Copenhagen and moved on to the Cavendish Laboratory in Cambridge (England) to work on DNA. Stent thought Watson was dead wrong. Stent and Bresch became friends during this time and happened to date the same Icelandic girl in Copenhagen, whom I later met as Inga Stent.

Ten years later, during the time I was a postdoc at Delbrück's institute in Köln, Günther Stent came to visit his friend Carsten. Stent had spent a sabbatical with Sidney Brenner in Cambridge, England, and was on his way back to Berkeley. With Brenner, Stent had discovered the "stringent response" of bacteria to amino acid starvation, which laid the cornerstone to the still ongoing research on the regulation of ribosome synthesis in bacteria and which was to become my main research topic at UTD. Stent talked about his Cambridge work in Köln, but I do not remember anything from his talk, except that I can still see Stent smiling during the round table discussion that was our form of seminars. I was too shy to participate much in any discussion, but I vaguely remember that Stent and I shortly talked together the next day. After he had left, an invitation arrived from Stent for someone in Bresch's group to join his laboratory in Berkeley, but it was not clear whom he meant. I was much too unimportant to feel concerned about it. It seemed to be forgotten until Bresch happened to visit in Berkeley, when they agreed to send pictures of all Bresch's people to Stent. Then came the letter: "It is Bremer, whom I wanted". I could hardly believe it. In 1962 our family boarded an ocean liner to New York, and from there to San Francisco by plane, where Stent's graduate student Mike Konrad and his wife Carol brought us in their car to Berkeley.

6. *Goals for Dallas*

In the early 60s, when Texas Instruments (TI) grew to international prominence in North Dallas, the founders of that company, Eric Johnson, Eugene McDermott, and Cecil Green, had difficulties to persuade physicists to come to Dallas and work for them, especially after the Kennedy assassination. So they thought about "producing" their own PhDs here in Dallas. As part of a master plan called "Goals for Dallas", they created the Southwest Center for Advanced Studies (SCAS). They got Loyd Berkner, former President of the International Geophysical Year in 1957 (when several nations divided up the antarctic among them), to organize the new research facility. It was pointed out that Dallas-Fort Worth had a similar economic structure, with aerospace and electronics industry, as the San Francisco Bay area, but whereas the California metroplex "produced" about 1000 PhDs per year, the Dallas area produced none. They considered giving money to existing institutions, but were persuaded that it is better to start something new than to try to upgrade a second-rate institution.

Berkner joined with another geologist, Larry Marshal, who contacted the first scientists about SCAS. Larry Marshal had the idea that pesticides and DDT in the oceans might gradually kill the blue-green algae (now called cyanobacteria) that are the major

source of our oxygen in the atmosphere. He warned that there could be a catastrophic disrupture of the oxygen cycle and that the issue needed to be studied urgently. Apparently, Loyd Berkner supported this view, which gave some priority to the hiring of biologists. Naturally, TI was more interested in physics. Geologists were also needed, because of the suffocating oceans, the Texas oil, and because Berkner and Marshal were geologists. This is why SCAS originally centered around physics, geology, and biology.

I believe Marshal had approached Delbrück for advice, who referred him to Stent and Bresch. Stent, who would not exchange Berkeley for Dallas, suggested Clowes. Both Bresch and Clowes came, Bresch only for two years after which time he planned to move to Freiburg.

Either Bresch or Stent must have suggested Thomas Trautner's and my names; Thomas Trautner was a Visiting Professor in Berkeley during the time I was there. Some day in 1964, Larry Marshal was sitting next to me at my bench in Stent's lab in Berkeley and talked to me about SCAS. In 1965, Trautner and I went to Dallas to be shown around. The Founders Building had already been built, and we were in the seminar room that later became the room in which I taught "Methods I" for many years. I had several offers for positions, one from Stent in Stent's new Max Planck Institute in Berlin, one from Delbrück to come back to the Genetics Institute in Köln, and one from Larry Marshal to come to Dallas. I was so fascinated by Berkeley that I thought every lab in the US must be like Berkeley. I took Stent's advice "If Clowes is coming it's going to be good" and went to Dallas, while Trautner became a Division Head in Stent's institute in Berlin. Unlike Delbrück, who spent two years in Köln, Stent made only short visits to his Berlin institute. (Both Delbrück and Stent were born in Berlin and were very fond of the city as it was before 1933.)

7. *Biology at SCAS*

The molecular biologists at SCAS included many phage geneticists (Bresch, T1; Marsch, T4; Lanni and McCorquodale, T5; Hausmann, T7; Kemper, P22 and λ). In addition, we had biochemists (Harris, Krone, Meyer-Coval, Witonsky), organic chemists (Bujard, Werbin), physicists (Gray, Lang), yeast and *Physarum* geneticists (Hefner, Gutz, Güttes), microbiologists (Bauerle, Clowes, Heumann, Müller), a protozoologist (Heckmann) and a strong UV biophysics group (Rupert, Jagger, Harm, Patrick). Several members were trained in classical biology (Güttes, Gutz, Heckmann, Heumann, Kemper and I). Texas Instruments money seemed to flow freely; every faculty member had at least one technician and most had postdocs. All in all, we were a happy group with much scientific and social interaction. We were constantly inviting guests and discussing new candidates to hire. At the peak, we had about 20 faculty and an equal number of postdocs. Herman Bujard, Karl Müller, and I organized the first "Journal Clubs" and "Research Discussions", which later became the glue that held our department together.

Biology was the largest division of SCAS, and the only molecular biology department in the "Southwest" (which includes many other states besides Texas). Departments at other more ambitious Texas institutions, including UT Austin and Southwestern Medical School in Dallas, were afraid that we were preempting their future development. Scientifically, the Southwest was rather bare at that time (when UTD managed to hire the Nobel laureate Polycarp Kusch, he was heralded as the first Nobel

laureate in the Southwest).

The year 1968 brought a change. First, Bresch and other scientists he had brought to Dallas had planned to stay only for two years, which caused the "exodus" of a large segment of the faculty. Second, Texas Instruments had to lay off many workers because of lagging defense contracts, so that SCAS, with the large biology group they never really wanted, had become too expensive. After many deliberations and negotiations, they donated SCAS to the UT system.[1]

8. *Transition from SCAS Biology to UTD Biology*

When we had become UTD and Hermann Bujard decided to leave Dallas, I tried to persuade him to stay, arguing that Dallas needs a great university and that UTD is bound to become one. Hermann was not convinced. He had the right foresight; soon he was director of a new Molecular Biology Instititute in Heidelberg.

The transition from SCAS to UTD has been a difficult period for the department. We were asked to drop the "molecular" from the name of our department and degree, because of fear of adverse public relations (creation of "Frankenstein monsters"), and it was declared that our department was not only overstaffed, but staffed with the wrong persons. We were to teach biology (for many this means dissecting cats), not molecular biology. However, despite many setbacks and shrinkage in faculty numbers, some of the original spirit and enthusiasm of the SCAS biology faculty was still preserved during the early years of UTD. I hope that some of it has spilled over to our first generations of graduate students and postdocs.

Reminder

Today the world envies the US economy, and foreign politicians understand the connection between Stanford and Silicon Valley that epitomizes our high-tech-driven economy. For that reason, nearly every politician in Europe and Asia (and even in Texas) promises to spend more money on education. However, they don't realize that Stanford's success was not based on money, but on individual, exceptional scientists. The US spends more money on education per student than any other country, but all comparative tests of student achievements show the US near the bottom of the list. SCAS had built a megadollar supermagnet facility next to our Founders Building that was supposed to foster "Graduate Research". It was never used and has recently been trashed, because the scientists to use it did not come. This ought to be a reminder for anyone who plans to build up a scientific department. First, one has to create an intellectual atmosphere that attracts outstanding individuals. This cannot be substituted by money, "goals" and "vision statements".

[1] Footnote: not all of the individuals listed in section 7 were hired prior to Bresch's departure.