Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

Wolfgang Beermann (1921–2000): The Man and His Science

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WOLFGANG Beermann died on January 18, 2000, in his home in Tübingen, Germany. He was 78 years old. Although it is true that his name and work are no longer familiar to many biologists of the younger generation, Beermann was one of the few outstanding pioneers who led the study of the cell into the age of molecular biology. His methods were microscopy and formal genetics, but his results, conclusions, and thoughts have fascinated and influenced many molecular biologists. Beermann's favorite subjects were chromosomes. He actually termed his field and the courses he taught graduate students "Chromosomenforschung" (chromosome research). If one were to describe his work in a few words, one could say that he studied the morphology of polytene chromosomes with the aim of understanding the mechanisms of cell differentiation.

Chromosome structure has fascinated biologists ever since Boveri and Sutton proved chromosomes to be the morphological correlates of linkage groups of genes. Numerous authors have described a linear organization of meiotic and mitotic prophase chromosomes composed of subunits, the chromomeres, which in advantageous systems, such as meiosis in grasshoppers and a number of plants, appear as individual and persisting entities. Wilson, when reviewing this evidence, stated that the chromomeres possibly align, divide, and conjugate two by two, just as do "the Mendelian unit-factors or genes of heredity" and that "these two lines of research are but dealing with different sides of the same problem" (Wilson 1925, p. 912). On the basis of thorough studies of meiotic chromosomes of lilies, Belling (1928) went so far as to hypothesize that individual chromomeres may be morphological correlates of individual genes.

A new era of chromosome research began with the detection of giant chromosomes in tissues of Dipteran insects, the midges Bibio and Chironomus, and the fruit fly Drosophila (Heitz and Bauer 1933; Painter 1933; King and Beams 1934). The patterns of numerous individually identifiable bands in these chromosomes, especially well developed in salivary gland cells, provided a basis for precise cytological chromosome maps and their alignment to the genetic linkage maps in *Drosophila melanogaster*. These studies, especially the maps of Bridges and genetic evidence provided by many authors, very soon led to the localization of specific genes to individual chromosome bands (Mackensen 1935). However, a long-lasting debate about the structure of salivary gland chromosomes in relation to mitotic chromatids and about the physical nature of chromosome bands and their relation to chromomeres and genes followed. Even the constancy of the banding pattern was often doubted, and the discussion was further impeded by the fact that very different ideas existed about the physical nature of genes.

The importance of chromosome structure was brought to the attention of a general audience by Schrödinger (1944) in his famous book *What Is Life? The Physical Aspect of the Living Cell*, first published in 1944. It contains four plates, all of which show chromosomes. In his comment on an image of Drosophila salivary gland chromosomes, Schrödinger suggested a very straightforward interpretation of chromosome structure: "The larger genes make deeper staining bands" (Schrödinger 1944, plate IV legend). Schrödinger had received part of his information from Darlington, who assumed that genes were proteins. It is not clear to the reader how Schrödinger's statement fits into his thoughts about the physical nature of genes. These thoughts did not have much influence on the progress of genetics (Dronamraju 1999), but the concept of chromosome bands "made" by genes returned many years later as the "one-band one-gene" hypothesis, based upon localization of complementation groups along the Drosophila chromosomes (Judd 1998).

Whereas the bands were useful landmarks for gene localizations, three questions remained open: (1) What is the structure of salivary gland chromosomes in rela-

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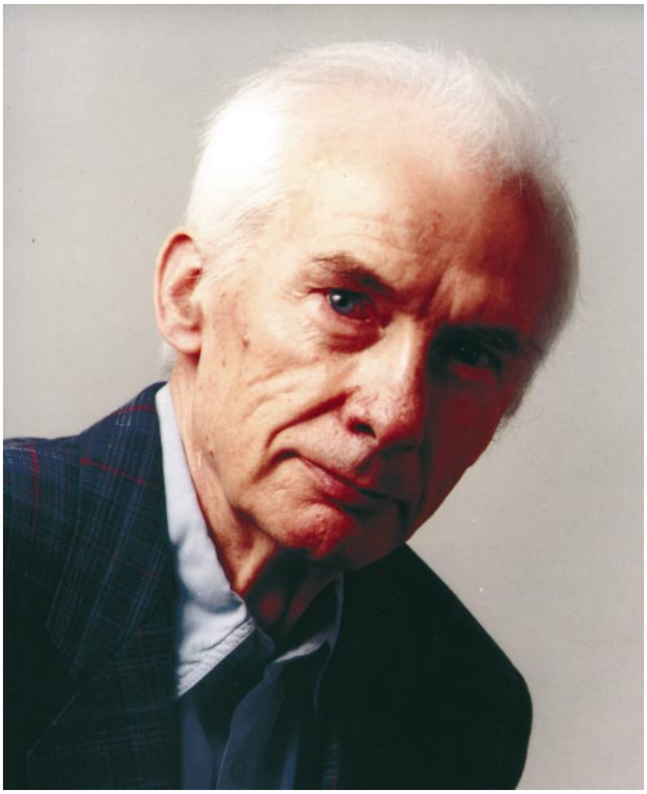

Wolfgang Beermann around 1990. Photo courtesy of Dr. Anke Beermann.

tion to chromatids?, (2) What is the structure of bands in relation to chromomeres?, and (3) Is the banding pattern a constant structural feature of a chromosome region in different nuclei and in different tissues?

The simplest and most straightforward interpretation of giant chromosome formation, by repeated rounds of replication of chromatids that remain paired after polyploidization (polyteny), was supported by Koltzoff, Bauer, Bridges, Painter, Koller, and others. However, convincing direct cytological evidence was still lacking. On the other hand, cytological observations caused others to suggest a honeycomb structure (Metz) or a swelling of ordinary chromosomes by bloating with their own products (Darlington). Fibers observed as longitudinal chromosomal elements were considered to be artifacts. Chromosome bands were reported to vary between different nuclei or cell types; they were interpreted to arise as turns of spirals of chromosome subunits arranged parallel (Ris and Crouse) or to become rearranged during development after an earlier fragmentation of the chromosome (Sengün and Kosswig).

The first two questions were solved by Hans Bauer and Wolfgang Beermann (1952) in a careful analysis of salivary gland chromosomes of Chironomus, which develop into a size much larger than Drosophila chromosomes. They also exhibit local sites of decondensation that protrude laterally from the chromosome body: the Balbiani rings, first observed in 1881 by the Italian cytologist E. G. Balbiani. By using a chromosome inversion that, upon somatic pairing with the noninverted homologue, created a torsional power on a Balbiani ring site and thus forced it to spread out into a position lateral to the chromosome body, Bauer and Beermann clearly demonstrated that the chromosome was composed of bundles of longitudinal subunits in the Balbiani ring that spread out locally into increasingly thinner sub-bundles. Accordingly, chromosome bands adjacent to the Balbiani ring locus were seen in the periphery, split into latitudinal subunits of increasingly smaller size. This was a clear and convincingly obvious demonstration of the polytene nature of giant chromosomes, as well as of the formation of chromosome bands by a side-by-side alignment of homologous condensed regions in the chromatids, the chromomeres (Bauer and Beermann 1952). In his doctoral thesis for his supervisor Bauer, Beermann also established the constancy of the chromomere pattern. In a most careful analysis of the chromosome structure in four different tissues of the larva, he found a precise morphological correspondence of the individual bands in these tissues, the chromosomes of which exhibit large differences in their degrees of polyteny (Beermann 1952).

Once giant chromosome structure had been established as an amplification of “ordinary” chromosomes owing to polyteny, the field was open for functional investigations that were of general importance rather than being valid for just a few exceptional cells. In his thorough study of the chromomere patterns in homologous chromosome regions of different larval tissues, Beermann detected local decondensations of individual bands that occurred in certain tissues but not in others. Some of the structural modifications also were specific for the larval or the prepupal stage. Beermann interpreted these structures as indicating gene activity and their tissue-specific patterns as indicating a differential genetic activity in different cell types, “the first direct cytological indication for the single elements of the genome reacting differentially to internal and external conditions” (Beermann 1952, p. 196; my translation). Bridges (1937) had observed similarly modified bands in Drosophila chromosomes and had termed them “puffs” without offering an interpretation. Beermann found that puffs always originated from single bands, including the Balbiani rings, which he showed can appear at very different degrees of development, from a slight decondensation of the band or a small puff to conspicuous unfolding of the chromosomal elements. He assumed that they were sites of especially high metabolism.

The interpretation of puffs and Balbiani rings as morphological indications of genetic activity was soon strongly substantiated by two important findings. Beermann’s student Pelling showed that pulses of tritiated uridine were incorporated in puffs and Balbiani rings and exhibited in autoradiographs a specific pattern of rapidly labeled chromosomal RNA, just as was to be expected by active gene loci (Pelling 1959). Beermann (1961) detected a group of special cells in the salivary gland of *Chironomus pallidivittatus* that produce a type of secretion different from the secretion of the other gland cells. In crosses with *C. tentans*, he could localize the gene(s) for this trait to either of two short sections in chromosome IV. In one of these sections he then detected an additional Balbiani ring that is specific for the special cells and does not occur in the other gland cells of *C. pallidivittatus* or any gland cell of *C. tentans*. In crosses with *C. tentans*, the secretion trait was linked to the Balbiani ring. Furthermore, when the Balbiani ring locus was transferred by crossing over into the *tentans* chromosome IV, and the stock was crossed to a *C. tentans* strain with a chromosome IV inversion that prevented further crossover, exceptional larvae that did not produce the special cell type of secretion were obtained. These phenotypes were much too frequent to have arisen from double crossover or mutations. Beermann showed that the phenotype was correlated with a preponderance of the *tentans* genome and interpreted it to have arisen by suppression of manifestation of the *pallidivittatus* secretory gene. In all these animals, the extra Balbiani ring was not developed, indicating a causality of its activity for the expression of the secretory product.

These findings provided strong evidence for a general concept of cell differentiation based on differential activities of genes. It was this conclusion that made Beermann's work so attractive to the scientific community of his time. Though it was generally accepted that genes were DNA molecules that were transcribed into RNA, the basis of cell differentiation had been far from clear. Selective amplification of the DNA in part of the genome during development; chromatin diminution, first considered by Weismann as a general mechanism for endowing different cell types with different subsets of genetic information; or rearrangement of chromosome fragments during development that could create new positional relations between genes are just a few examples of the mechanisms that had been suggested for understanding the differentiation of cells. Beermann (1956) returned to Boveri's concept of the nucleus reacting to subtle cytoplasmic influences by reversible changes when he stated in his contribution to the 1956 Cold Spring Harbor Symposium: "The phenomenon of differential structural changes in giant chromosomes will probably help to put the classical theory of differentiation on a detailed cytological basis comparable to that provided for the chromosome theory of heredity when the true nature of giant chromosomes was first discovered" (p. 229).

It deserves to be considered why Beermann's early work, on an organism unknown to most biologists and all published in German, had such an enormous impact. He studied at the University of Göttingen, which had lost most of its scientific reputation after the expulsion of Jewish scholars, and wrote his doctoral thesis at the Max-Planck-Institut für Meeresbiologie in Wilhelmshaven, a place known only as a navy base that, of course, no longer existed. But Beermann had excellent teachers. In Göttingen he was most influenced by Karl Henke, who studied the development of pattern formation in Lepidopteran wings and was especially interested in differential mitosis as a basis for cell differentiation in groups of interacting cells that he termed "Kleinorgane." In Wilhelmshaven his supervisor was Hans Bauer, who with Emil Heitz had rediscovered the giant chromosomes and who was an expert on chromosome morphology and Drosophila genetics. Both Henke and Bauer had been students of Alfred Kühn, whom August Weismann had considered "one of my best students." Beermann was thus under the influence of a great tradition and of two teachers who were both intellectually and experimentally creative scholars. But he appears to have been rather independent from the beginning. As a young schoolboy, he spent so many hours with his microscope and produced so many cytological preparations that his mother was driven to despair because of his lack of exercise. He appears to have known his profession very early. He also had a vivid interest in botany, an interest encouraged in many ways by his grandfather, a schoolteacher, who, for example, gave him a professional excursion flora on his 11th birthday. Beermann mentioned later that both Bauer and Henke were familiar names to him during his high school years.

Wolfgang Beermann was an outstandingly keen observer, a very thorough and skillful cytologist, a man who investigated a problem to the last detail. At the same time, he was able to recognize the essence of a phenomenon and common principles among a wealth of details. He also was a master of formal genetics, a competence not found too often among cytologists. He described his results convincingly and could get others to recognize their general importance. He did not hesitate to draw far-reaching conclusions. However, these could be experimentally tested and were later proven to be correct. For example, he realized immediately that the decondensation of chromatids in Balbiani rings offered a model for the structure of lampbrush chromosomes and the functional meaning of their loops. Although he came up with the right results at the right time, part of his early success in winning the attention of the scientific community was the result, I am tempted to assume, of his personality.

He loved America. He had been a prisoner of war in a camp in Kansas until released in 1947, but this first exposure to the United States obviously was a positive and very stimulating experience. He returned many times in his later life to present his results at conferences and seminars and as a visiting professor in Berkeley (1962–63) and in Tallahassee, Florida (1967–1968). He was enthusiastic and was met with sympathy. He owned a large number of American books and knew a great deal of American literature. I remember him, immediately after returning from Berkeley, reading with comic devotion for the members of his lab a persiflage in the style of Longfellow (whose work he, of course, knew from high school) on Hiawatha's adventures at the International Biochemistry Congress in Moscow, from the newest catalogue of Calbiochem. His membership in the Genetics Society of America meant much to him. When he was elected a member of the National Academy of Sciences in 1975, he was deeply moved. In his laboratory, over the years he hosted a large number of young American postdocs, out of a wish to give back something of what America had given to him.

The number of places where Wolfgang Beermann worked during his scientific life is small. After receiving his doctoral degree from the University of Göttingen in 1952, he spent a year in Stockholm as a postdoctoral fellow in the laboratory of Caspersson at the Karolinska Institute. He then joined the Department of Zoology at the University of Marburg as a research associate with the developmental biologist Friedrich Seidel, also a former student of Kühn. Beermann was appointed a lecturer at Marburg University in 1955. After offers from Columbia University and the Max-Planck-Institut für Biologie in Tübingen, he decided to move to Tübingen, where he was appointed director at the Institute in 1958, a position he held until his retirement.

Beermann's Department at the Max-Planck-Institut für Biologie was a small but very active center of research. Of his associates, I mention only two scholars whose research grew directly out of his own. In 1959, Claus Pelling (1959) had shown that puffs and the nucleolus are the sites of rapidly labeled RNA. He also developed a precise map of the puffs in the salivary gland of *C. tentans* and found that ~15% of the visible chromomeres could be active in RNA synthesis in this tissue, with up to two-thirds observed within one gland. Pelling also provided a direct cytological proof for polyteny. Chironomus embryos were labeled with tritiated thymidine and raised to last-stage larvae. Preparations of salivary glands then yielded autoradiographs which, after 2 years of exposure, exhibited single subtle traces of silver grains that extended over the entire length of giant chomosomes and obviously were images of individual chromatids (Beermann and Pelling 1965). Ulrich Clever thoroughly analyzed the alterations of the puffing pattern in development and identified chromosome loci whose activation was an indication of early steps in metamorphosis. At the same time, Peter Karlson had purified the molting hormone ecdysone. Clever (1961) and he then demonstrated that injecting ecdysone into Chironomus larvae was followed by immediate activation of a small number of metamorphosis puffs. Clever and Karlson (1960) concluded that there probably was a direct interaction between hormone and hormone-dependent gene, an early concept that has stimulated much of the wealth of work with other steroid hormones.

What made Beermann's department unique in the field in Germany and probably in Europe were the incredibly many visitors from the United States and other countries, among them numerous eminent scholars, who stayed for days, weeks, months, and even years, and who were instrumental in bringing about the singular atmosphere that lives forever in the memory of Beermann's graduate students and postdoctoral fellows. I mention only one visitor: Curt Stern, who had been a member of the department himself (then a department of the Kaiser-Wilhelm-Gesellschaft at Berlin-Dahlem), before he left Germany in 1931, and who transferred to the young generation the spirit of a German scientific tradition that had been expelled and extinguished by the Nazi government.

Toward his students, Beermann showed much tolerance and understanding. He wanted them to work and think independently, and he would rarely put his own name on a publication to which he not had contributed with personal work. He thus continued a tradition from which he had himself benefited as a student: his own doctoral thesis had been published with him as the sole author. Hans Bauer, his supervisor, stated in his review of Beermann's thesis: "Auf die innere Entwicklung habe ich keinen Einfluss ausgeübt" ("I have not exerted any influence on the mental development of this thesis").

His own work he summarized in a book, *Riesenchromosomen*, published in 1962. Later experiments led into molecular biology and were performed in collaboration with others. An early result obtained by Jan-Erik Edström and Beermann (1962), using Edström's elegant method of nucleotide base microelectrophoresis, was that Balbiani ring RNA had a base composition quite different from that of nucleolar or cytoplasmic RNA. Subsequently, Edström, Bertil Daneholt, and Bo Lambert analyzed the properties of Balbiani ring genes. Finally, the genes that encode the secretory proteins of the gland cells were sequenced. Beermann did not actively participate in these experiments, but he took part in their interpretation. Also, he detected a new, additional Balbiani ring in the gland that could be experimentally induced. The transcriptional activity in this locus was followed, as his Swedish colleagues showed, by the appearance of a novel protein in the gland secretion. The early problem of the relationship between chromomeres and genes was again addressed in collaboration with Melvin Green and Veikko Sorsa in a cytological analysis of deletions at the *white* locus in Drosophila (Sorsa *et al.* 1973). Genetics and electron microscopy provided clear evidence that *white* occupies not more than a small part of the band 3C2-3.

As chromosome research became more and more molecular, appropriate methods and equipment were established in the department. Beermann realized this to be necessary and accepted it, but he did not develop a desire to run gels, centrifuges, and scintillation counters himself. His principal instruments remained his Leitz Ortholux microscopes, with a type of phase-contrast device he liked, but which nobody else in the lab could master. After his retirement, these microscopes were transferred to Germany's leading technical museum, the Deutsches Museum in Munich, where they are on exhibition with their original label "Abteilung Beermann."

Around 1970, he began to suffer from Parkinson's disease, which in later years more and more impeded his motor abilities. In spite of that, he continued for many years to publish (Beermann 1973), to serve as an editor of Chromosoma, as he had been since 1964, and as a reviewer of manuscripts for Genetics and for the Proceedings of the National Academy of Sciences. In his very last days, he continued to read science and The New Yorker magazine, and his brain worked as brilliantly as ever. He is survived by four children, two of whom are biologists. He lives on in the memory of his numerous colleagues, friends, and former students.

I thank Dr. Anke Beermann and Dr. Claus Pelling for personal communications.

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