My Road to Øjvind Winge, the Father of Yeast Genetics

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THIS essay honors the memory of my very dear Danish mentor, Professor Øjvind Winge. It combines my personal recollections about him from the late 1940s with a biographical sketch that highlights several aspects of his illustrious career. I stress mainly his contributions to yeast genetics, because he is the father of this field, currently one of the key fields in molecular cell biology, genetics, and biotechnology. Despite his seminal contributions to the genetics of yeast and several other important areas, it seems to me that presently Øjvind Winge is at best only a shadowy figure, instead of being recognized as a giant in the pantheon of geneticists.

How did my path cross with Winge's, and how did I as a young student happen to recognize his greatness? The year was 1943–1944, and the place was the Polish city Lwów (also known as Leopol, Lemberg, Lviv, or Lvov), at the time occupied by Hitler's armies as a part of the Nazi General Government, created from a part of occupied Poland. I was a chemical engineering student at the Politechnika Lwowska (Lwów Institute of Technology) attending a lecture by Professor Adolf Joszt, the Head of the Department of Industrial Fermentation and Biotechnology. It was during this lecture, devoted to the industrial importance of yeast, that I heard for the first time the name of Winge in the following context: "Young ladies and gentlemen," said our Professor Joszt in very elegant Polish, "a great new discovery was made in our field of biotechnology shortly before World War II, when Professor Winge at the Carlsberg Laboratory in Copenhagen, Denmark, discovered that microorganisms, namely yeast, have sex. That permitted Winge to use genetic crosses to combine desirable fermentation characteristics into one yeast strain. "Young ladies and gentlemen, "as I would further paraphrase Professor Joszt, "this approach will revolutionize our field and will create a new field, which I venture to name genetic engineering. This approach can create limitless possibilities in modernizing the research and industries employing fermentation and other fields of biotechnology."

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Professor Joszt appreciated Winge's contribution from the point of view of an engineer, and his lecture, which exuded enthusiasm and admiration for Winge, was a turning point in my life. At that moment I decided that the new, revolutionary, and mysterious "genetic engineering," instead of traditional chemical engineering, would become the field of my endeavor for the rest of my life. I resolved that as soon as WWII passed, our enslavement by Nazis or Soviets ended, and the borders opened again, I would travel to Copenhagen and ask Professor Winge to allow me to join his lab.

After suffering waves of deportations, murders, enslavement, and occupations of my native Polish city of Lwów, first by Soviet invaders (1939–1941) and then by Nazi Germany (1941–1944), followed by reoccupation by the Soviet Union in 1944, Lwów was ethnically cleansed, without any meaningful protest by the Western Allies, including the United States, which at that time acted as silent accomplices in the Soviet inhumanities. Barbarously evicted and deported, I moved to Gdańsk (Danzig) in Soviet-ruled Poland, where I joined the newly re-established Politechnika Gdańska (Gdańsk Institute of Technology). Then in 1946, almost miraculously, all the chemistry students from Gdańsk, Warsaw, and Lódź, Poland, and their teaching staff (their laboratories so badly damaged in WWII) were invited by the people of Denmark to spend two summer months in the corresponding, but well-equipped, laboratories in Copenhagen. Dr. Stefan Rozental, a Pole who was the scientific secretary of Niels Bohr, the Nobel Laureate in Physics, and Niels' younger brother Harald Bohr, a mathematician, were the chief organizers of this remarkably generous invitation.

Soon after my arrival, I visited Professor Winge at the Carlsberg Laboratory, where three of us—Winge, his always present dog Claus, and I—met in his office. Winge made quite an impression upon me as a very gracious, elegant, and aristocratic-looking gentleman (much older than me), reminding me very much of my beloved Professor Joszt from Lwów (since "transplanted" to Gliwice in the Silesian part of post-WWII Poland). I explained to Winge how I had heard about him for the first time during Professor Joszt's lecture. Winge told me that he remembered well meeting Joszt

before WWII, that he had great respect for him, and asked whether he could help him or me in any way. That encouraged me to ask Winge whether in the future I could join his laboratory and pursue research in the genetic engineering of yeast. Winge smiled and told me that he was not aware that there was a field of genetic engineering, but that he would welcome me in his laboratory if I succeeded in the future to arrange a visit to Copenhagen. With my experience of reckless survival during all the cruel experiences of WWII (when only 14 of us survived out of my entire chemistry class of 120), I told him that I had no doubt I would succeed in eluding Stalin's talons, legally or not, and would arrange to spend some time in his lab. Starting with a private exchange with a Danish Amanuensis (assistant professor) Hakon Nord, I managed to spend the years 1947–1949 in this fabulous Danish capital, dividing my time among five laboratories. I had appointments in the Technical University of Denmark (DTH) Chemical Laboratory A (Professor J. A. Christiansen and Niels Hofman-Bang) and the DTH Mechanical Engineering Laboratory (Professor J. L. Mansa) under the auspices of the Danish Academy of Technical Sciences, and I worked as a volunteer at the Carlsberg Laboratory (Professor Ø. Winge), the DTH Biology Department (Professor S. Orla-Jensen, Erik Olsen, Inge Prange, and later Professor Henrik Dam), and the Theoretical Physics Institute (Professor Niels Bohr).

Because of this rather busy schedule, my hours in Winge's laboratory were unusual, from 7 p.m. to around midnight and often during weekends. In the beginning, I had generous guidance from Winge and also from his closest collaborator, the very quiet and unassuming but indomitable and always helpful Catherine Roberts, who, being single, liked to spend late evenings in the laboratory. However, after acquiring the necessary skills, I spent long hours at the Zeiss micromanipulator-equipped microscope, mostly alone, cutting each ascus and mating the isolated spores or cells of many yeast species with hard-to-remember names. During my years of research in Copenhagen, I also helped with teaching and published eight papers in *Nature* and *Acta Chemica Scandinavica* (on the kinetics of iodine-azide reactions, iron bacteria, microbiological corrosion of steel pipes, and Pseudomonas), but I never found time to write up my contributions to the technical improvements in the genetic analysis of interspecific crosses between various species of yeast. These included laboratory and industrial strains of *Saccharomyces cerevisiae*, *S. chevalieri*, *Zygosaccharomyces priorianus* Klöcker Nos. 120 and 181, *Z. mandschuricus* Saito No. 160, and *Z. nasdonii* Guilliermond No. 1004. (While preparing this essay, I found my "ancient" notes about these unpublished 1947–1949 experiments. Some of my results were preserved by being included in publications of Winge and also Roberts, my guiding lights.) It was not until 1990 that I published a paper on yeast, which Øjvind would certainly have appreciated as a molecular approach, since we separated all of the *S. cerevisiae* chromosomes as bands on a gel and cut only one chromosome at a predetermined site, using our Achilles heel technique (Koob and Szybalski 1990).

During these years I made several lifelong friends among students and visitors in Winge's laboratory, some of whom I introduced into the field after learning it only months earlier and who taught me new tricks. Among them were Mogens Westergaard, Urs Leupold, Giovanni E. Magni, Herschel Roman, Piotr P. Slonimski, Carl C. Lindegren, Boris Ephrussi, R. B. Gilliland, and Eric Zeuthen. Of those, probably the only other survivor is Piotr, whom I meet rather regularly in Paris or in Warsaw. Winge's physiology department was on the upper floor, but I also spent some afternoon hours visiting the chemistry department on the floor below, directed by the incomparable Kai Ulrik Linderstrøm-Lang (Holter 1976). I certainly learned to appreciate his ingenious micromethods, his wit, and his genius. I also made several additional friends among his co-workers, who were a very lively group. However, the legend that the Carlsberg beer flows from special faucets at each laboratory sink is certainly not true, although the free supply of soft and other drinks in special refrigerators was plentiful.

After this personal introduction, I shall now outline Winge's impressive life history, on the basis of a mix of my imperfect personal recollections and the "official" biographies of Winge written by Jorgensen 1965 and Westergaard 1965, Westergaard 1976. A nearly complete list of Winge's publications is provided in Westergaard 1965. The early days of yeast genetics are summarized in a volume edited by Hall and Linder 1993.

Øjvind Winge was born in Aarhus, the largest city in Jutland, the mainland of Denmark, in 1886 (115 years ago), which means that he belonged to the generation of my parents. His mother was from Trondheim, my favorite Norwegian city, and he told me that after high school he moved to Copenhagen, motivated by his parents, who wanted him to study law and in this manner to follow the prosperous career of his father, a prominent lawyer. But since in his family there were also prominent biologists, their genes must have prevailed, since he soon switched to studying natural sciences, mainly botany, the love of his boyhood. During his studies, he met most of the prominent Danish botanists and mycologists, including Emil Christian Hansen, who often is regarded as the first Director (after the very short and rather controversial directorship of Rasmus Pedersen) of the Physiology Department of the Carlsberg Laboratory, the position that Winge later inherited. [Around 1907, Emil Christian Hansen had offered Winge a position, but he declined it because he preferred to continue his studies in mycology (Westergaard 1976).]

Øjvind graduated from the Copenhagen University in 1910 with a Master's degree, which in Scandinavia closely approximates our Ph.D. degree, and subsequently spent some time in Stockholm, Paris (Sorbonne), and Chicago studying mainly chromosomal cytology. When Øjvind then returned to Copenhagen, the position of the Directorship of the Physiology Department of the Carlsberg Laboratory had already passed from the yeast physiologists [Emil Christian Hansen (see the most interesting biography by Klocker 1976), considered by some as the "Danish Pasteur," who introduced pure

cultures of yeast in breweries, and Albert Klöcker, Director extraordinary and yeast physiologist], to Ernst Johannes Schmidt, whose main interest was the study of the migration of the eel and who is regarded now as a distinguished oceanographer (Ege 1976). Schmidt, who among geneticists was best known because of his diallel crosses, using either fish or the domestic fowl (Schmidt 1922), hired Winge, probably because he shared with Øjvind the earlier interest in Lebistes (guppies) and hops, but with the purpose of helping him in oceanography and also in other more genetical fields. Thus, Winge studied the breeding of hops and the genetics of fish, worked on improving aquaria, and participated in the study of ocean currents by cataloging the messages recovered from champagne bottles thrown overboard from various ships. In 1917, he published his advanced (Scandinavian) Doctoral thesis, "The chromosomes: their numbers and general importance," which contained the theory of speciation by polyploid evolution (Winge 1917). Winge was interested in interspecific hybrids and studied hybrids of Tragopogon, Geum, Sambucus, and even between animal species. He also published on cytoplasmic inheritance in hops and on the inheritance of eye color in humans and of coat color in horses.

In 1921, Winge was appointed to the new chair of genetics at the Veterinary and Agricultural University in Copenhagen and Lyngby. Despite the heavy teaching load, he wrote *The Textbook in Genetics* (three Danish editions in 1928, 1937, and 1943; see Winge 1928) and published papers on the cytogenetics of sex determination and on the inheritance of color genes in guppies. He also made seminal contributions to the cytopathology of tumor cells, describing the first cases of hyperploidy among other chromosome abnormalities.

Winge has told me that one of his main ambitions at that time was to establish a Chair of Genetics at the University, but since that was not realized, he accepted in 1933 an offer to become the Director of the Physiology Department of the Carlsberg Laboratory. He also told me that, since the Carlsberg Breweries had established and funded this institution since 1876, he decided to study only three organisms, all important for the brewery industry, namely, yeast, hops, and barley. Thus, the mission of the laboratory moved away from oceanography and returned to the field of the early Directors of the Physiology Department, especially Emil Christian Hansen (Klocker 1976). The first task, starting in 1933, was an attempt to recover the stock cultures of yeast from the collection of Hansen and Klöcker. These cultures were up to 46 years old! Winge remarked to me that he had trouble believing it and then felt almost "religious" about it, when he found that a large percentage of those cultures could be revived, although they had been kept in 10% sucrose solution or in wort and were not even refrigerated. He felt elated realizing that this would permit easy, safe, and inexpensive long-term storage of all the valuable mutants and genetic constructs. This remarkable recovery of cultures, nearly half a century old, was described in Winge's first paper on yeast (Winge and Hjort 1935).

Thus began the era of Winge's contributions as the Father of Yeast Genetics. Although Øjvind told me a few stories about his research on color inheritance and sex determination, and I saw, as late as 1949, aquaria with guppies near his office, most of his work after 1947 was devoted to yeast. [The exceptions were a publication on the salmon (Winge and Ditlevsen 1948) and a widely read book on dog genetics (Winge 1950).]

At the time when Winge started to work with yeast, his approach was to treat this microorganism in the same way as he had worked with higher organisms. There was no mass mating as is done presently with microorganisms, but cells were treated as individuals, with each ascus cut with a handmade fine glass needle while watched under a microscope equipped with a Zeiss micromanipulator. Spores were isolated into separate droplets, and the process of spore germination and individual matings between the germinal tubes was followed under a microscope. Winge's approach was a combination of tetrad and pedigree analyses, a very slow and laborious but precise approach. Using a binocular low-power microscope, a micropilot flame of a Bunsen burner, and a very steady hand, I remember preparing scores of fine glass needles, which unfortunately broke too easily when used for cutting the rather tough asci. Frustrated as an engineer, I asked Winge why we could not develop and use selective markers to screen or select for recombinants, as I had just heard was done for bacteria, but his attitude was that this was like "cheating" and he preferred to see the actual copulation process and hybrid formation with his own eyes, because otherwise one could not trust whether the product was a hybrid or a new mutant. (He originally believed that the claim of gene "conversion" by Carl Lindegren, the American yeast geneticist, could be explained by mutations, as discussed below.)

Winge was convinced that the micromanipulation of spores and cells is the only "honest" way to study the genetics of yeast, and practically all of his experiments were done in this manner. Using this approach, he showed clearly that several Saccharomyces species alternate between haploid and diploid phases. Spores are haploid, and their germination establishes a haploid phase (which was rather unstable in Winge's strains of *S. cerevisiae*), which then leads to diploidization by conjugation between two haploid cells derived either from two different spores (which permits genetic crosses) or from the same spore (self-diploidization). The first article on yeast genetics (Winge 1935) was the result of these studies and was followed by an article on tetrad analysis (Winge and Laustsen 1937), where morphological markers were used. Subsequently, Winge 1938 (and oral presentations) and Winge and Laustsen 1938, Winge and Laustsen 1939 used fermentation markers. (These must have been the pre-WWII results that so much impressed my teacher in Lwów, Professor Joszt, when he stressed that Winge's finding corresponded to the birth of genetic engineering.)

During WWII and after, until 1961 (Winge *et al.* 1961), there was a steady stream of papers on yeast genetics emanating

from Winge's laboratory. Since all this has been very thoroughly summarized and discussed by Westergaard 1965, Westergaard 1976 and especially by Mortimer 1993A while Roberts 1950 describes her and Winge's methods and Forsdyke has prepared a Web page (Forsdyke 2001), I see no reason to repeat all that in this short essay. Instead, I highlight only some of Winge's seminal contributions to yeast genetics and conclude with a few additional reminiscences.

Winge provided a foundation for both the basic genetics and the industrial applications of yeast, by developing the micromanipulation methods that allowed reliable ascus dissection and tetrad analysis. He demonstrated that yeasts alternate between the haplophase and diplophase and showed that various yeast strains could be mated and, therefore, that their industrially important fermentation characteristics could be manipulated. He also showed that many traits follow simple Mendelian rules, permitting linkage studies, whereas others are more difficult to analyze, being polygenic traits. By chance, he started his studies with homothallic, self-diploidizing yeast strains, but recognized that *S. ludwigii* is heterothallic. That allowed him later to demonstrate that his strains of *S. cerevisiae* could behave both as homothallic and stably heterothallic, with only one gene, *D* (*diploidizer*)—presently designated as *HO* (homothallism)—controlling the switch between these traits. This opened the field of mating-type switching and sex determination in yeast, an area always of great interest to Winge, since he had previously studied it in Lebistes and other higher organisms.

The recognition of mating types in *S. cerevisiae* was developed through famous running arguments between Winge and Carl Lindegren of the Southern Illinois University (see Mortimer 1993B). Carl discovered the **a** and **α** mating types and later applied to yeast the gene conversion hypothesis of Winkler 1930. I well remember their arguments during Carl's visits to Copenhagen especially in 1949, culminating during the discussion after one of the Lindegren lectures, when Winge commented: "Carl, I enjoyed very much your lecture, but I could not force myself to believe most of what you have just said." Winge, a careful and critical Mendelian geneticist, could not tolerate Lindegren's capacity to generate or adapt ever new iconoclastic *ad hoc* theories based on only one or very few experiments with seemingly aberrant results. Øjvind relished good arguments (he had several during his scientific career) and was a good fighter; he would rather fight than compromise the "truth." However, in a few cases Lindegren's intuition prevailed, even in the absence of critical data, when Winge confirmed heterothallism in *S. cerevisiae* and when the concept of gene conversion was generally accepted (Winge 1960). The Winge-Lindegren disputes are discussed by Westergaard 1965, Westergaard 1976 and in the volume edited by Hall and Linder 1993. To me, Winge will always remain a father figure of the field of yeast genetics, a great and critically precise scientist.

Throughout his life, Winge's interests were broad and certainly not limited to yeast genetics. As already mentioned, as a mycologist he was interested in mushrooms as found in nature; I remember that when we were walking in the woods near the summer estate of Professor Henrik Dam, the Nobel prize winner for the discovery of vitamin K, I happened to notice a luxurious growth of *Agaricus deliciosus* (in Polish, rydz), my favorite wild mushroom. We collected it, fried it in butter, and relished its delicious taste, while Henrik was convinced that we would soon die in pain, poisoned by "these terrible toadstools." In the world of woods and forests, one should also remember that Winge had an indirect impact through his pupils on the genetics of trees and was also interested in hunting and hunting dogs. He published a book on the genetics of dogs (Winge 1950) and loved them. His beloved Claus always followed him everywhere. He asked me much about hunting customs in pre-WWII Poland, knowing that my father had been a president of the Saint Hubertus Hunting Club in Lwów and that I had a multitude of hunting experiences.

Øjvind and his wife Julie were always very gracious hosts, and I enjoyed immensely many visits in their home. Julie was very gracious and always animated, the first lady in my experience who enjoyed smoking cigars. We often discussed politics, and Øjvind was very interested in my WWII experiences under both the Nazi and Soviet occupations, the political systems that he detested. He was genuinely sad when he learned from me that several of his Polish scientific friends, whom he knew from meetings before WWII, had been deported, arrested, or killed by Soviets or were among the forty Lwów professors murdered in 1941 by the Nazi SS Sonderkommando. His feeling of horror was sincere, especially when he heard that many professors were evicted from their labs and prevented from teaching and to survive had to "lend their legs" to feed the lice used in manufacturing the typhus vaccine (Szybalski 1999).

Øjvind also liked to discuss the arts (he was a very skilled artist and made many oil paintings), but our conversation somehow always returned to the field of science, his reminiscences about oceanography and eel migration, or the latest "unfounded and irritating" theories of Carl Lindegren. When in 1949 I decided to emigrate to the United States (when Stalin took still firmer control in Poland, while Denmark was in too close proximity to the Soviet empire, for my comfort), Øjvind gave me some very helpful advice about the best places in the States to continue my interest in DNA and genetics. He first mentioned two "promising young geneticists," Ed Tatum at Yale and Francis Ryan at Columbia University, and one "old timer" M. Demerec, the director of the Cold Spring Harbor Laboratories. I wrote to each of them. Ed Tatum answered that he was just moving to Stanford and was temporarily out of funds, while Milislav Demerec invited me to join the Biology Laboratory at Cold Spring Harbor, where I spent almost five of my best, most inspiring, and enjoyable years. I am very indebted to Øjvind for such good advice.

One of my last memories of long conversations with Øjvind and his charming wife, Julie, was during a week

we spent together in Villa Serbeloni in Bellagio, Italy, during and after the International Congress of Genetics in 1953. We discussed the presentations at the Congress, and Øjvind asked me about my research on the genetics of antibiotic resistance. He also told me then that after serious stomach ulcer surgery in the previous year, he now felt his age and failing health. However, to me he appeared very fit, physically and especially intellectually. In the ensuing years, I made a point to see him even briefly in his office or home during my periodic travels to Copenhagen, until I sadly learned, during the summer visit of 1964, that Øjvind had passed away on April 5, 1964, of a lung embolism.

My two most recent encounters, but this time only with the spirit of Øjvind, were during the first two months of 2001. The first was the invitation to write this essay, as one of the last survivors who actually worked in his laboratory and had many not only scientific but also social encounters with him. This stimulated me to get in touch with a few survivors of the Winge era and with presently active yeast geneticists, to refresh my memories, and to realize how many honors were bestowed upon him during his life, including memberships in 10 academies, six honorary memberships in learned societies, two honorary doctoral degrees, and several medals, prizes, and decorations.

The most recent encounter was at the February 7, 2001, Genetics Colloquium in Madison, by David Page of MIT on "Mammalian sex chromosomes and germ cells: a 300-million-year experiment." With the cooperation of the audience, we were reminded about the seminal contributions of Winge 1927 on linkage between determinants for mating and 18 male color genes in guppies. Winge 1927 had shown that there was a single sex-determining locus. All but one of the dominant male color genes map to the Y chromosome and, although the X and Y chromosomes sometimes cross over, colored females are never found in nature. Fisher 1931 (p. 362) proposed that the color trait was intrinsically deleterious, because of predators, but that strong female preference for colorful males caused its sexual selection in males. Fisher argued that there would be strong natural selection to increase linkage between color factors and the sex-determining locus (on Y), to prevent the color genes from being transferred to the X, where they would be harmful in females. This was a typical Fisherian response to an impressive contribution by Winge!

We should never forget that Winge catalyzed key steps in the formation of the modern fields of genetic engineering and biotechnology through the creation of yeast genetics by his fundamental contributions to this new field. Appropriately, he developed these contributions of nearly 150 papers in the context of the Carlsberg Laboratory, one of the grand research institutions in the tiny country of Denmark. His generosity of spirit extended to young investigators from many countries, as illustrated by my own experience when I unexpectedly arrived from war-torn Poland. In short, Øjvind Winge was a great biologist in the broadest sense.

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