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Biographical Note / *Notice biographique*

Madeleine Gans (1920–2018): a pioneer in developmental genetics

Madeleine Gans (1920–2018): une pionnière en génétique du développement

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Madeleine Gans in 1987, gracious gift from her daughter Catherine.

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Madeleine Gans (1920–2018) is a distinguished pioneer of the French school of genetics whose exceptional talent and intensive dedication to research and teaching activities during her professional career (1945–1990) were most influential triggers for the emergence of developmental genetics. She was nominated professor in 1961 at the Faculty of Sciences of Paris (subsequently Université Pierre-et-Marie-Curie and, now, Sorbonne Université). In 1987, she was elected corresponding member of the French Académie des sciences.

Madeleine Gans, birth name Madeleine David, was born on June 5th 1920, in Pont-à-Mousson, France, in a family of three children. Her father was an engineer and her mother a school teacher in mathematics. She attended high school in Pont-à-Mousson where she obtained Baccalauréat in June of 1939 and entered the University of Nancy in medical and scientific tracks. She showed a great interest in the physics lectures given by Professor Marcel Laporte. In 1940, due to the Second World War, Madeleine Gans and her family left Pont-à-Mousson and Nancy to seek refuge first in Rennes, then in Larche and Toulouse, in the unoccupied south-west of France. From October 1940 to September 1945, Madeleine Gans was able to continue her university studies in Toulouse, where she graduated in medicine and science. Letters written to her brother Pierre during this period reveal that she was already very determined about the specific studies she intended to follow and that she had no interest in a medical career, preferring scientific reasoning and experimentation. By chance, in Toulouse, she met her physics professor from Nancy and his assistant, François Gans, who later became her husband. She never spoke of her participation in a resistance network during this period, perhaps out of modesty, an important trait of her personality. After the war, highly recommended by Albert Vandel (1894–1980), her professor of zoology at the Faculty of Toulouse, she contacted Boris Ephrussi (1901–1979) [1], who accepted her into his laboratory.

In 1945, on his return to France from the United States, B. Ephrussi was appointed both head of the genetics department at the Institut de Biologie Physico-Chimique (IBPC) in Paris and professor at the Sorbonne, filling the first university chair of genetics created in France. Three teams were working in the laboratory. Projects on *Drosophila* increased with the arrival of Philippe L'Héritier in 1946. At the same time, a new project began on the yeast *Saccharomyces cerevisiae*, led by B. Ephrussi, and another on the filamentous fungus *Podospora anserina*, led by Georges Rizet.

In February 1946, a lemon-yellow eyed spontaneous mutant, named *zeste*, appeared in the *Drosophila melanogaster* collection, and B. Ephrussi suggested to Madeleine Gans that she studied it because of its unusual properties: the mutant phenotype (yellow eyes) is present in females but not in males, it varies with temperature and shows variegation under certain conditions. She immersed herself in this subject with enthusiasm and five years later, on December 21, 1951, she defended her doctoral thesis "Étude génétique et physiologique du mutant *zeste* de *Drosophila melanogaster*". From the beginning of her work, it was clear that the *Drosophila zeste* (*z*) mutant was peculiar. Madeleine Gans showed that the *z* mutation is located very close to the *white*$^+$ (w^+) gene on chromosome X. She studied gene dosage between *z*, z^+, and w^+ and discovered that the *z* mutant phenotype strictly depends on the presence of two doses of the w^+ gene. She showed that this property is subject to a position effect as the *z* mutant phenotype is reversed when one of the two copies of the w^+ gene is transferred close to centromeric heterochromatin via chromosomal rearrangements. Finally, she discovered that the variegated eye pigmentation depends on both external conditions (such as temperature) and the genetic background of the strains, a novelty at the time. This work, published in French in 1953 in *Le Bulletin Biologique de France et de Belgique* [2], was later translated in American laboratories as a textbook case of genetic analysis.

While working on her thesis, she married François Gans in 1947. They had three children, Catherine born in 1948, Pierre born in 1951 and Elisabeth born in 1957. On her arrival at the Ephrussi laboratory Madeleine Gans was supported by an IBPC grant. In 1946 she obtained a position as "attachée de recherche" (Research Associate) at the then newly opened Centre National de la Recherche Scientifique (CNRS). She was promoted to "chargée de recherche" (Research Project Leader) in 1952, after which she switched to a university career, first as "chef de travaux pratiques" (Head of Practical Work) in 1953,

then as professor from 1961 until her retirement in 1990.

During the three years following her thesis defence, Madeleine Gans continued her investigations of the *zeste-white* interactions. However, after the departure of Philippe L'Héritier and his team to the new CNRS Centre in Gif-sur-Yvette, she decided to switch to another research subject and teamed up with Georges Prévost, a new young scientist recruited in 1955 as "chef de travaux pratiques", to develop a new model in the laboratory. Interested in the relationships between the nucleus and the cytoplasm, they chose *Coprinus radiatus* because this Basidiomycete exhibits a long and stable dikaryotic phase during which two haploid nuclei coexist in the same cytoplasm, constituting a valuable tool for genetic analyses.

Research quickly followed two main avenues: the isolation of metabolic mutants [3], and the use of the dikaryotic phase to adress fundamental questions of exchange between nuclei [4]. A collection of one hundred mutants was created, leading to the first large-scale genetic mapping of a Basidiomycete [5]. In 1957, Madeleine Gans and Georges Prévost left the IBPC in Paris to establish their team in the Laboratoire de génétique physiologique at the new CNRS Centre in Gif-sur-Yvette. There, they conducted studies on somatic recombination [6], sexual incompatibility loci [7], and biosynthetic pathways (pyrimidine and arginine), all using genetic methodology. In particular, they showed that the *ur-1* locus is composed of two genes belonging to a single transcription unit [8] controlling the first two steps of the pyrimidine biosynthetic pathway, a novelty at the time. Results with *Coprinus* [9] and *Neurospora crassa* led to a model in which carbamyl-phosphate is produced by two enzymatic complexes: a mitochondrial one for the arginine chain and a cytoplasmic one for the pyrimidine chain. However, under certain conditions, "decanalization" of the carbamyl-phosphate from arginine biosynthesis could take place [10].

Until the late 1980's, genetic methodology was used to study a variety of other biological topics, resulting in no less than 27 original articles often published in the "*Comptes-Rendus de l'Académie des Sciences*". However, as they largely ignored the molecular biology methods that were rapidly emerging at the time—in addition to being often published in French—they received insufficient international recognition, and it was another closely related fungus, *Coprinus cinereus*, that became the prominent model for this group of organisms [11].

Madeleine Gans and Georges Prévost were very dedicated to teaching genetics at the University. As early as 1956, they were involved in the creation of a new postgraduate course, the DEA de Génétique [12], and until 1990, Madeleine Gans continued to actively teach genetics to numerous undergraduate and postgraduate students who went on to successful careers in this field. In 1968, when Georges Prévost joined the new Faculty of Science at Orsay, Madeleine Gans moved her team to the new Centre de génétique moléclaire that the CNRS had just opened in Gif-sur-Yvette and decided to return to the *Drosophila* model of her early years.

This was a new beginning. The application of the genetic methodology to the understanding of developmental processes had just been proposed [13], but nothing existed in France. Madeleine Gans decided to immerse herself and her whole team in the identification and analysis of mutants involved in animal development, with a special focus on the polarity and pattern of the *Drosophila* embryo [14].

It should be remembered that the *Drosophila* oocyte is a large cell that is polarised along its anteroposterior and dorso-ventral axes, prefiguring the axes found in the embryo, larva and adult. This polarisation, present before fertilisation, was postulated to result from the presence in the oocyte cytoplasm of substances deposited under the control of genes acting during the female oogenesis, the so-called "maternal-effect genes". In addition, germ cells are the first cells to form at the posterior pole of the oocyte and this depends on the integrity of the posterior plasma; removal of this polar plasma leads to flies devoid of germ cells and thus to sterile adults (grandchild-less mutants). Madeleine Gans and her collaborators undertook several systematic mutageneses to screen for such female-sterile mutations linked to the X chromosome, which could lead to specific anomalies in the embryo, larva or adult [15]. The mutants obtained were analysed in her laboratory [16–20] and in collaboration [21]. At the time, very few teams in the world had undertaken the screening of female-sterile mutations in *Drosophila*, placing Madeleine Gans's team in an enviable pioneering position. Subsequently, other screens for maternal-effect mutations and systematic screens for

zygotic mutations affecting embryonic pattern formation were performed by others, confirming the strength of the genetic approach for developmental analysis [22]. This was universally recognized with the awarding of the 1995 Nobel Prize in Physiology or Medicine to Edward Lewis, Christiane Nüsslein-Volhard and Eric Wieschaus.

Three dominant female-sterile mutants obtained in one of the mutagenesis screens mentioned above immediately caught Madeleine Gans' attention because of their striking properties [23]. These sex-linked dominant mutations, named *ovo*^{D}, lead to complete sterility of females, while mutant males are entirely fertile. The mutations are only active in the germ line, not in the somatic line of the female ovary. Madeleine Gans understood the great advantage of these *ovo*^{D} mutations for studying the role of other sex-linked mutations in oogenesis. An advantage that was exploited by Norbert Perrimon, first as a pre-doctoral student in Madeleine Gans' laboratory [24] and then during his PhD in Anthony Mahowald's laboratory. Norbert Perrimon made two major improvements to this technique: one allowing induction of germ-line clones at a much higher frequency [25], the other allowing the extension of germ-line clonal analysis to autosomal mutations [26, 27]. These genetic tools have subsequently been used by all teams working on developmental genetics in *Drosophila*.

During her thorough analyses, Madeleine Gans uncovered an unexpected phenomenon: some viable flies among the progeny did not result from mitotic recombination but rather from phenotypic reversion of *ovo*^{D} mutations in the female germ line [23]. The high reversion rate and the simultaneous occurrence of numerous lethal and morphological mutations suggested the mobilization of a transposable element. Indeed, in 1989, Madeleine Gans and her collaborators showed that the mobilisation of *gypsy* and *copia* transposons was able to induce *ovo*^{D} reversions [28]. It was also shown that this mobilisation depends on the genotype of the mothers of *ovo*^{D}/+ females. A new genetic element was discovered, named *flamenco*, localised in the heterochromatin of the X chromosome [29]. In most strains, *gypsy* is stable and repressed under the control of *flamenco*, but in some strains *flamenco* is in an inactive permissive form, *flamP*, which cannot repress *gypsy* [30, 31]. It was later shown that the *flamenco* locus is composed of repetitions of fragments of retrotransposon sequences extending over a region of 179 kb in the heterochromatin of the X chromosome [32], from which small RNA molecules are produced and then charged by the Piwi protein, those piwi-RNAs (piRNAs) being involved in transposon silencing.

From 1970, Madeleine Gans' laboratory expanded considerably. Numerous doctoral and postdoctoral students joined her laboratory. Madeleine Gans' notoriety attracted brilliant young researchers such as Eric Wieschaus and Norbert Perrimon, who spent several months in her laboratory. She also welcomed foreign researchers to enrich her own research with their particular expertise, namely Marco Zalokar, Pedro Santamaria, Patricia Simpson, Hermann Denis and Maurice Wegnez.

Madeleine Gans led her team in a non-hierarchical way. Her sole motivation was science, experiments, and discoveries. She had a special and quick intelligence for genetics: she could visualise the results of complicated crosses over several generations, often leaving her collaborators far behind. She was a very cheerful and optimistic person, transmitting her enthusiasm to all the people working with her, researchers, students, technical assistants, thus creating a congenial atmosphere in the laboratory. She had a high regard for ethical and humanist considerations. She was always very aware of the personal difficulties that her students or collaborators might be experiencing and tried to help them.

Madeleine Gans retired from teaching at the university in 1990 and from the laboratory in 1994. She spent the rest of her life in a small, pleasant house full of plants and flowers in Gif-sur-Yvette, not far from the laboratory. She died on the 18th of April 2018 at the age of 97. A few months later, a scientific symposium entitled "Developmental genetics: the impact of *Drosophila*" was organised in her memory by the French Genetics Society in the new CNRS buildings in Gif-sur-Yvette. Several generations of students and eminent biologists, recalling their interactions with Madeleine Gans, presented the latest advances along the scientific paths she had helped to initiate.

Conflicts of interest

Authors have no conflict of interest to declare.

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