The Brussels School of Embryology

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Origins

The history of the Brussels School of Embryology stretches back to 1904, the year in which the Medical School of the Université Libre de Bruxelles was looking for a new anatomy professor. The man recruited was Albert Brachet, a young doctor from the University of Liège who was currently working as assistant professor at the Institute of Anatomy under the direction of Liège histologist Auguste Swaen. Brachet moved into the facilities made available in the Warocqué Institute of Anatomy built in 1892 on the grounds of the Leopold Park in Brussels. He had already worked for many years in Liège under the direction of Edouard Van Beneden and was the author of several important works in the field of descriptive embryology. Brachet was especially interested in the development of the digestive system and serous cavities, as well as in the development of the cardiovascular system, and had been the first to describe the mid-ventral blood islet in Amphibia. In 1902, moreover, he had published a 250-page monograph on the ontogenesis of anuran and urodelan amphibians, in which he analyzed gastrulation and the formation of the trunk and head in great detail. Thus, when he took over at the Institute, Brachet was especially interested in continuing his embryological research, and eventually the service under his charge, which until then had only involved the teaching of anatomy, came to be known as the Anatomy and Embryology Laboratory, a name retained even today due to the close relations between the two disciplines.

However, Brachet did not actually take charge of the teaching of embryology until 1906, when the discipline was finally separated from its previous inclusion in physiology. So no real tradition of embryology existed in Brussels before Brachet. His only precursor worthy of mention was Polydore Francotte (1851-1916), another pupil of Van Beneden's who taught at the Science Faculty of the University of Brussels and was noteworthy for his work on the ontogenesis of the epiphysis and paraphysis and on the early developmental stages of the polyclad egg.

Albert Brachet and causal embryology

Upon his arrival in Brussels, Albert Brachet was already an expert in the methods of descriptive embryology. He considered the study of organogenesis indispensable for an understanding of anatomical complexes, such as the peritoneal cavity, and their possible anomalies. An admirable professor, whom the French called the Jaurès of anatomy, Brachet sought the total integration of anatomy and organogenesis in his classes, so that today this is one of the strong points of anatomy as taught at the Brussels Faculty.

Nevertheless, Brachet was aware of the limits of descriptive embryology as an explanatory method. An assiduous reader of *Archivs für Entwicklungsmechaniek*, he was keenly interested in the research of Roux, Driesch, Hertwig, Wilson and Morgan and closely followed the controversies that arose as a result of the work of these great pioneers. His own inclination was towards an experimental embryology aimed at elucidating the underlying causes of development — a discipline he came to call *"causal embryology"*. His stay at the laboratory of G. Born in Breslau in 1895 had introduced him to the experimental manipulation of amphibian embryos. In 1904, he had published in *Archives de Biologie* an article giving a correct account of the controversy between Roux and Oscar Hertwig over the consequences of a lesion in one of the first two blastomeres of the frog egg. He showed that the fate of the surviving blastomere

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depended on whether the plane of the first cleavage coincided with the plane of penetration of the spermatozoon, recognizable by the pigmented sperm wake.

As soon as he moved into his laboratory in Brussels, Brachet renewed his experimental research while at the same time continuing to do descriptive work, which culminated in 1914 in a series of reports mostly devoted to cephalogenesis in amphibians, fish and reptiles, an area he had mastered in 1895 during his stay at the laboratory of E. Gaupp in Freiburg. In 1906 Brachet published the results of his experimental punctures of *Rana fusca* eggs, which brought him to the conclusion that the "germinal localizations" stabilize shortly after fertilization. Next he began an in-depth study of the consequences of experimental polyspermy in the frog egg. The results of this research were eventually written up in two important papers published in 1910.

Then, in 1912, an interesting interlude began. Years earlier, Edouard Van Beneden had begun a study of gastrulation in the rabbit and bat in which he reviewed his previous ideas on germ layer formation in mammals as expressed in a report published in 1880. Van Beneden's death in 1910 caused this work to be left unfinished, however, so Brachet completed the study and published it in *Archives de Biologie*. With his interest now awakened in mammalian embryology, in 1913 Brachet attempted the *in vitro* culture of a rabbit blastocyst, using the method of Harrison and Burrows. This was the first attempt of its kind, and although the results were limited, the experiment did have the merit of showing that mammalian embryo explants could be cultured.

When Belgian universities were closed in 1914 for the duration of the First World War, Brachet answered the call of his colleague Nicolas and accepted the post of Associate Professor of Anatomy and Embryology at the Medical School in Paris. At the request of Henneguy, Brachet delivered a series of lectures in which he set forth his ideas on causal embryology. These lectures were eventually written up and brought out in book form by Doin in 1917 under the title *L'oeuf et les facteurs de l'Ontogénèse*. The high regard and admiration felt towards Brachet by his French colleagues resulted in his election in 1918 to the Institut de France, and a year later in an Honorary Doctorate awarded him by the University of Paris.

With the end of the War and his return to Brussels in 1918, Brachet took up his duties once again as professor and laboratory director. Twelve years remained to him and he lived them intensely. In 1921 he published *Traité d'Embryologie des Vertébrés*, a work written at the request of Editions Masson and considered his crowning achievement in descriptive embryology. When the War began in 1914, Brachet was working on marine invertebrate eggs at the Roscoff Marine Laboratory due to his special interest in the work of Loeb and Delage. Once the War was over, he took up this work again and in 1922 published an interesting report on the premature fertilization of the sea urchin egg, in which he described the synchronization of all the nuclear structures, both male and female, resulting from the fertilization of the immature egg. Following his experimental analysis of amphibian eggs and embryos, in 1922 and 1923 Brachet destroyed localized portions of the gray crescent of the *Rana fusca* blastula. His careful analysis of the

The Warocqué Anatomical Institute at the time of Albert Brachet's arrival in Brussels.

The auditorium of the Warocqué Anatomical Institute in 1927. 1. Albert Brachet. 2. Albert Dalcq. 3. Pol Gerard. 4. Jean Pasteels.

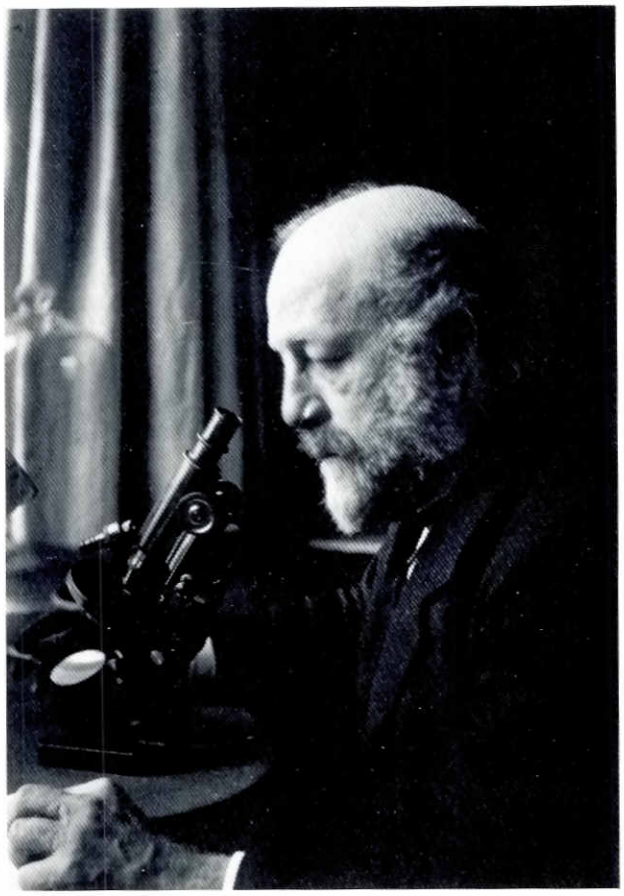
operated embryos led him to the very conclusions concerning the organizer properties of the dorsal lip of the blastopore reached simultaneously by Spemann as a result of his experiments on the newt egg. In 1927 Brachet carried out a highly advanced experiment in which he successfully made a graft of the organizer.

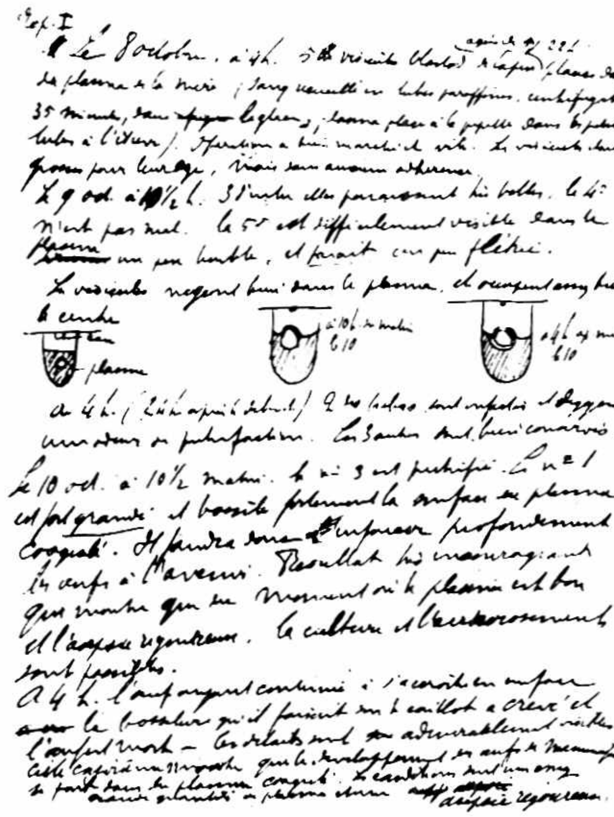
This was his last achievement in his old laboratory at the Warocqué Institute, since in 1928 he moved to the new Porte de Hal facilities built with funds made available by the Rockefeller Foundation. As Rector of the University of Brussels from 1923 to 1926, Brachet played an important role in drawing up the curriculum for the new School of Medicine in which he had served as Dean from 1911 to 1914. His last years were devoted to encouraging and promoting the research of his students and collaborators, and to preparing a new edition of *L'oeuf et les facteurs de l'Ontogénèse*, which came off the press in 1930. A few days after the publication of his final work, Albert Brachet died at the age of sixty, after a long illness endured with great courage. Although his untimely demise was a serious blow to the laboratory, Brachet had been especially concerned to secure the future of his School. His successor was his senior pupil, Albert Dalcq, at the time Assistant Professor of Anatomy, who had been carefully groomed by Brachet to take over as director of the laboratory when the time came.

The pupils of Albert Brachet

Several young researchers, drawn by Brachet's reputation, came to the laboratory to begin embryological research under his guidance. Here we can only cite a few of the scientists who went on to brilliant careers in many different disciplines. Albert Dustin (1884-1942) studied the origin of gonocytes in amphibians, was named to the Chair of Pathological Anatomy at the University of Brussels and was especially noteworthy for his discovery of the blocking effect of colchicine on mitosis. Pol Gerard (1886-1961), Brachet's first assistant, carried out in the laboratory what is still regarded as a classic study of spermatogenesis in the acridian *Stenobothrus*. Later, Gerard was named Professor of Histology and became known for his interesting research on the fetal membranes of lemurs. He succeeded Dustin to the Brussels Chair of Pathological Anatomy. Together with one of his pupils, Robert Cordier, he studied the histophysiology of the renal tubule, thus making an important contribution to the Brussels School of Nephrology.

The first of Brachet's pupils to complete his university studies in the laboratory was Maurice Herlant (1887-1920), although his career was tragically ended at the age of 33. Named an assistant in 1911, he was drawn by Brachet towards the cytological study of





Albert Brachet (1869-1930) and a facsimile of his protocol sheet describing the first attempt to cultivate a mammalian embryo *in vitro*

fertilization and experimental parthenogenesis. He elucidated the action of the hypertonic solution used in Loeb's chemical parthenogenesis and revealed the permeability cycles linked to fertilization and to the first cleavage mitoses of the sea urchin egg. Together with Brachet, he carried out a detailed study of polyspermy in frog eggs and described the cytological mechanisms of cleavage in eggs subjected to the traumatic parthenogenesis described by Bataillon in 1910. Maurice Herlant was without any doubt headed for a brilliant career in science, but his premature death deprived the Brussels School of a representative who surely would have reached international standing.

Albert Dalcq (1893-1973) gained assistant status in 1919 after earning his M.D. degree that same year. Before summarizing the career of Brachet's direct successor, however, we must first take note of the arrival at the laboratory of two young students, both of whom were to become assistants following the death of Brachet: first, Jean Pasteels (1906-1991), whose career was to be closely linked to that of Dalcq, and Jean Brachet (1909-1988), who took his first steps as a researcher in the laboratory of his father. We should also mention the stays at the laboratory of two Americans — Leigh Hoadley, later to become Director of the biology laboratories at Harvard, who did research on chick blastoderm sections in Brussels, and Edmund Hall, who studied the consequences of macromere puncture at the 8-cell stage in *Rana fusca*, and went on to become Director of the anatomy laboratory at the University of Louisville.

Albert M. Dalcq and Jean J. Pasteels: morphogenetic potential

The names of these two scientists will always be associated with each other. Until the outbreak of war in 1940, their work was remarkably complementary. When Dalcq succeeded to the post left by Albert Brachet in 1930, his scientific achievement was already considerable. Interested in continuing the research on the sea urchin egg so brilliantly begun by Maurice Herlant, Dalcq concentrated on the egg of another echinoderm, *Asterias glacialis*. During successive stays at the marine laboratory at Roscoff, he had analyzed the role of sea water cations in egg activation and described a type of experimental parthenogenesis in which the first cleavage results from depolarization of one of the maturation divisions.

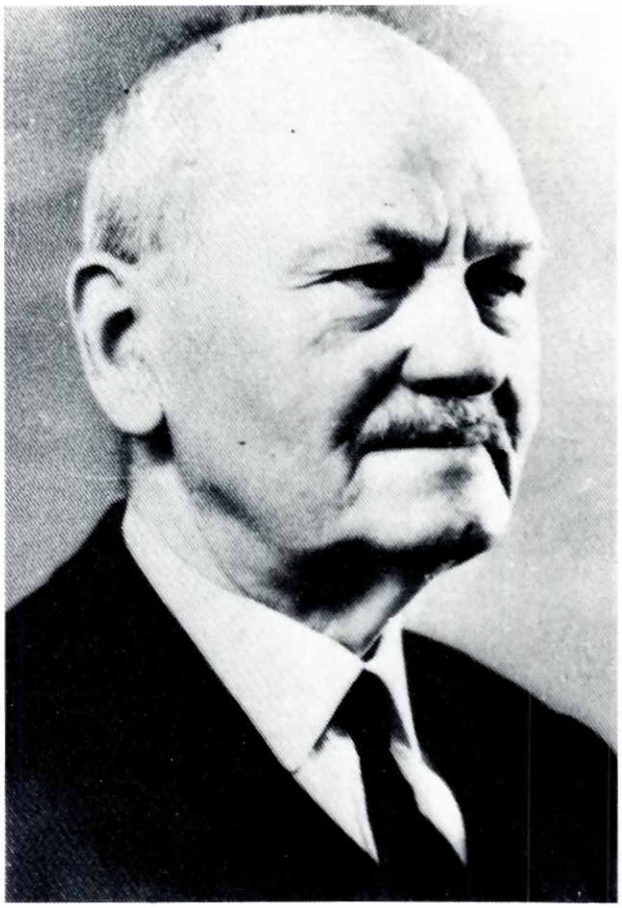
During this same period, Dalcq directed the young Pasteels — at the time still a student — in a parallel study of the egg of the spiralian mollusk, *Barnea candida*, making it possible for Pasteels to extend to this species the conclusions reached by his mentor. The joint work of these two men drew attention to the importance of the Ca^{++} ion in the maturation, activation and fertilization of the egg. Moreover, this was a pioneer work in the field of cell physiology. As a conclusion to these studies, Dalcq published his first book, *Les bases physiologiques de la fécondation et de la parthénogénèse*, brought out in 1928 by Presses Universitaires de France. Already in this work, the reader perceives that the author has set himself the goal of laying the bases for a theory of development, a goal he was to reach ten years later in his work with Pasteels.

After being named Director of the laboratory, Dalcq decided to continue the experimental research on morphogenesis in amphibians which had been interrupted due to the death of Albert Brachet. He worked in this field from 1929 to 1932, publishing numerous reports on his study of the consequences of chromatine elimination or intoxication in *Rana fusca* gametes. His aim was to distinguish the respective parts of the "nuclear sap" and the chromosomes during dicentric cell division. During this same period, he renewed his study of marine eggs and in 1932 published the now classical results of his merogony experiments on the virgin *Ascidiella aspersa* egg, known since Chabry's time as a "mosaic" egg. Using his experimental technique, Dalcq was able to verify that this egg can be shown to be endowed with important regulating faculties, as long as the experimenter manipulates it early enough.

This same concern to understand the nature of the compromise between morphogenetic predetermination and regulating tendencies was what led him, during the thirties, to conduct experimental research on the blastulas and early gastrulas of amphibians. One of the issues then being raised was whether presumptive neurectoblastic material must necessarily be induced to organize itself into a neural tube. Despite certain clues, such as those offered by the work of Yamada on pronephros, the causes of the regionalization of the chordomesoblastic envelope and of the central nervous system remained an enigma. Dalcq performed three types of operation: partial ablation of the organizer, transplantation of the upper part of the gray crescent and, especially, equatorial translocations causing the animal pole to rotate 180° relative to the vegetal half, so that part of the organizer, which varied according to the level of the section, was now placed in ventral position.

The results of this painstaking analysis were completed by the parallel results obtained by Pasteels using a totally different method. After devoting several years to the study of gastrulation in meroblastic vertebrates and establishing, by means of a colored mark technique learned during a stay with Walther Vogt in Zurich, the presumptive fate maps in the blastoderm of fish, birds and reptiles, Jean Pasteels took up the inversion experiments on uncleaved amphibian eggs carried out by Schultz in 1894 and developed further by Penners and Schleipe in 1928. These authors' observations had not enabled them to account clearly for the fact that bilateral symmetry, the position of the organizer and the direction of gastrulation can be modified at will by the experimenter. By perfecting the techniques of his predecessors, completing them with centrifugation and with exceptional analytical expertise, Pasteels reached the following logical conclusions:»...the preliminary steps of morphogenesis (organizing center, morphogenetic movements and local predispositions) start as a consequence of some metabolic changes which involve: a) a cortical substance dispersed in a decreasing gradient in the dorso-ventral direction, b) a factor linked to the yolk material (1938)».

Although Dalcq and Pasteels used entirely different experimental approaches, the conclusions to be drawn from their work coincided on all points and resulted in a new concept — that of *morphogenetic potential*. This was a truly quantitative theory of embryonic development, and was presented in 1937 and 1938 in two articles written jointly. According to this theory, the triggering and coordination of gastrulation kinetics resulted from two interacting factors: an internal gradient linked to the distribution of yolk material and a



Albert Dalcq (1893-1973)

cortical field decreasing from the center of the gray crescent. The first is labile and can be modified by displacing the yolk material, while the second is stable and not susceptible to experimental treatment. The topographical changes that occur as a result of gastrulation give rise to the dorso-ventral and cephalo-caudal gradients whose interaction determines, for each cell group, the level of morphogenetic potential that will determine its features and fate. The unique principle resulting from this interactive metabolism was called «*organisine*». During this period of intense activity, Dalcq, true to his penchant for synthesis, published two new books: *L'organisation de l'oeuf chez les Chordés* (Gauthier-Villars, 1935) and *Form and Causality in Early Development* (Cambridge University Press, 1938). These two works preceded his masterpiece, *L'oeuf et son dynamisme organisateur,* a remarkable synthesis of embryological knowledge as it stood at the time of its publication, edited by Albin Michel, in 1941.

The War of 1940-1945 caused laboratory research to stop. The University of Brussels refused to submit to the orders of the Nazi occupying forces and closed its doors in November 1941. With the return of peace, work was rapidly renewed. A description of the post-War period, however, should not be attempted without first mentioning the principal pupils and collaborators of the thirties. In 1934, Tung, a Chinese scientist, took up Dalcq's work on *Ascidiella* and

Jean-Jules Pasteels (1906-1991)

in a series of elegant experiments isolated and translocated blastomeres. Once back in his own country, Tung was destined to play an important role in politics.

Like Tung, Dalcq's assistant, Julien Fautrez, also studied the first stages of the ascidian egg, but immediately became interested in the development of the nervous system in amphibians. After the War, he was called to occupy the Chair of Anatomy and Embryology at the University of Gent.

Francois Twiesselman and Joseph Brandes used Tchakotine's ultraviolet microbeam to provoke localized lesions, first on the chick blastodisc and second on the blastula and young gastrula of amphibians. Twiesselman, who was also Dalcq's assistant, went on to a brilliant career as an anthropologist at the Belgian Institute of Natural Sciences.

Special mention must be made of Allyn Waterman, an American scientist who, during the course of a stay in Brussels, showed that it was possible to reproduce in the sea urchin the same effects as those caused by lithium (fusions, exogastrulation) through the action of various physiological ions. Waterman, who was to become a professor at Thomson College, was, together with Waddington, a pioneer in experimental embryology in mammals.

But the student with the most brilliant career ahead of him was the son of Albert Brachet himself. Having entered the laboratory as a student researcher in 1928, Jean Brachet earned his M.D. degree in 1933 and was immediately appointed Dalcq's assistant. By that time, he had already published five works devoted mainly to the study of DNA — then called thymonucleic acid — during oogenesis in various species and during the development of the sea urchin egg. Seeing how irresistibly his pupil was drawn towards biochemistry, Dalcq put Brachet in charge of a special unit set up in his laboratory. But the young Brachet was not at all eager to become an anatomist, and the teaching of osteology — the course to which he was assigned — was especially unappealing to him. In 1939 Brachet left the Medical School for the Science Faculty where he founded, together with the physiologist Raymond Jeener, the laboratory of animal morphology, which today has become the Department of Molecular Biology of the Université Libre of Brussels. Before leaving the laboratory, Jean Brachet published a series of articles in which he addressed various issues in the biochemistry of development, one of which was written in collaboration with Waddington and Needham on the chemistry of the organizer. The biology courses assigned to him as a member of the Science Faculty fit in much better with his interests as a researcher. One of the articles in this special issue on "Developmental Biology in Belgium" is devoted to the career of this great pioneer of modern molecular biology, who died in 1988.

The post-War period

During the first years of the post-War period, Dalcq and Pasteels continued their study of morphogenesis in amphibians. This was the occasion for updating the notion of morphogenetic potential, which was being refuted by proponents of a qualitative theory proposed by Toivonen based on experiments using heterotypic inductors. Later, the principal elements in the quantitative theory of Dalcq and Pasteels were incorporated into the «double gradient» theory of Toivonen and Saxén (1955).

Many young foreign researchers participated in this last phase of research on amphibians: Lallier and Dollander (France), Minganti (Italy) and Huang (China). For his part, Jean Pasteels studied the effects of centrifugation on the blastula and early gastrula, showing that in these simple experimental conditions, the ectoblast is spontaneously capable of forming not only neural structures, but also various chordomesoblastic components, which in normal development is only possible in the caudal region, and which can also be produced under the influence of certain xeno-inducers. He was also interested in the morphogenesis of the tail and demonstrated that the mechanisms governing the individualization of the caudal structures did not differ in any fundamental way from those of gastrulation.

With time, however, the scientific activities of Dalcq and Pasteels began to diverge. Aware that the embryology laboratory of a medical school cannot ignore the development of mammals, Dalcq decided to orient research in this direction. Since he felt it would be premature to undertake experiments on germ cells that still resisted culture *in vitro,* he used cytological and cytochemical methods, focusing especially on cytoplasmic RNA, the importance of which had been surmised by Jean Brachet. He entrusted the first such projects to a young American biologist, Alberta Jones (later to become Mrs. Seaton). The Ph.D. thesis she presented in 1950, together with Dalcq's own research, led to the «segregationist» theory that was long considered the most coherent interpretation of the differentiation of the two fundamental cell groups in the mammalian blastocyst: trophectoderm and inner cell mass. Having found in the structure of the cytoplasm and in the distribution of the ribonucleic particles of the rat ovule the equivalent of the two gradients of the amphibian egg in the form of a "dorso-animal field" giving bilateral symmetry to the undivided egg, Dalcq postulated that the plasma of this region undergoes, during the first three cleavages, a segregation in a group of dorsal blastomeres at the origin of the inner cell mass, with the ventral blastomeres moving up to the surface to completely surround and form the trophectoderm. Both groups are determined at the 8-cell stage. This theory was first supported by the experimental work of Friedrich Seidel on the rabbit and of Andrzej Tarkowski on the mouse, as well as by the histoenzymological research of Jacques Mulnard. Soon, however, the new experimental research made possible by progress in *in vitro* embryo cultures showed that, in the case of the mouse at least, the segregationist theory could not account for the considerable regulating capacity of the mammalian embryo. Although their conclusions failed to withstand the test of time, it is undeniable that the work of Dalcq and his collaborators gave decisive impetus to causal embryology of mammals, a flourishing discipline today.

Dalcq immersed himself entirely in this new line of research, tirelessly pursuing his work until well after his retirement in 1963. His last years were devoted to an exhaustive study of spermatogenesis, and the results were published, following his untimely death in 1973, in a voluminous monograph published by the Royal Academy of Medicine of Belgium, where Dalcq had served as Permanent Secretary since 1957.

For his part, Pasteels diversified his activities, concentrating on both embryology and cell biology. He continued his research on the gastrulation of meroblastic vertebrates, publishing in 1956 and 1957 a table of the development of Chelonians and Lacertilians that has remained a valuable reference work for anyone interested in studying ontogenesis in reptiles. From 1950 to 1953, he published a dozen articles devoted to the quantitative analysis of DNA in the nuclei of various cells in mitosis and interphase, using the histophotometer prototype designed by Lucien Lison. Together with Lison, in 1950 Pasteels made a major contribution to knowledge of the cell cycle by demonstrating that DNA synthesis (S-phase) occurs after mitosis and not during the prophase as believed until that time. By 1958, Pasteels understood the future importance of the electron microscope for the exploration of morphogenetic processes, especially in the early phases of development. He thus began a remarkable study of the ultrastructural aspects of fertilization, taking for this purpose the material that had launched his career: the mollusk *Barnea candida*. He verified that in this species, the membrane of the male pronucleus is formed at the expense of the endoplasmic reticulum of the egg.

The diversification of their respective work did not at all affect relations between Dalcq and Pasteels. In 1954 they jointly authored the important chapter on vertebrate embryology for Grassé's *Traité de Zoologie*. Following his retirement in 1976, Pasteels practically abandoned embryological research, and wrote only a few review articles, devoting himself almost entirely to insect morphology, for he was also a renowned entomologist, specialized in parasite hymenoptera. He published numerous articles in this field, and museums and entomological institutes the world over consulted him regularly on problems of determination. Jean Pasteels died on August 24, 1991 at the age of 85, following a long illness borne with great courage and dignity.

The successors of Dalcq and Pasteels

Jacques Mulnard became Jean Pasteels' successor as director of the laboratory. Trained in *in vitro* culture techniques under Honor Fell at Cambridge, under Pieter Gaillard at Leiden and under Clifford Grobstein at Bethesda, he focused most of his experimental research on the problem of precocious differentiation of the mouse embryo. The unit created by him in 1958 is still active and working in close collaboration with Jean Brachet's cytology and molecular embryology lab, today directed by Paulette Van Gansen, and notably with Henri Alexandre, a disciple of Brachet's. In 1987, following Mulnard's retirement, another pupil of Dalcq and Pasteels' was appointed director of the laboratory. This was Jean Milaire, who had earned an international reputation in the fields of organogenesis and teratogenesis. Initiated in the methods of developmental genetics during a long stay at the laboratory of Hans Grüneberg at the University College of London, he is today considered one of the world's leading experts in limb development.

If the tradition of causal embryology has remained alive, it is because the laboratory has been able to adapt to the rapid evolution of biomedical science. With the introduction of each new research technique, the nature of research has gradually been modified. Aware of the importance of developmental biology to modern medicine, the laboratory is open to the collaboration of clinical scientists from many fields, including gynecology, radiology, genetics and pediatrics, a tendency which is helped by the recent concentration of the Medical School on the new Erasmus campus at Anderlecht. Despite present financial restrictions and the difficulties involved in recruiting future embryologists from among young doctors and subjecting them to the rigors of full-time lab work — the norm until recently — continuity appears assured thanks to the enthusiasm of certain young scientists, such as Marcel Rooze and Stéphane Louryan, who have succumbed completely to the appeal of basic research. We are therefore convinced that the flame lit in 1904 by Albert Brachet shall never be extinguished.

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