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INTRODUCTION

JANE MAIENSCHEIN
School of Life Sciences, Arizona State University

"Embryology," naturally enough, evokes images of embryos. Certainly at the beginning of the Carnegie Institution of Washington Department of Embryology in 1914, there were embryos in abundance. These were human embryos: preserved, sliced and studied in order to construct models that became the basis for human embryology textbooks and medical school training. Primate studies then provided information and understanding of embryo implantation in the mother's uterus, of material exchanges between mother and embryo, and of the entire developmental cycle through studies that would have been impossible with humans. By the second half-century of the Department's work, embryos had receded in importance. Tissue and cell cultures provided new histological information about development. Biochemistry, molecular genetics, and relations of genetics to embryogenesis took center stage. Yet, unlike other university departments, professional societies, and journals, the Carnegie Department did not rush in the second half of the twentieth century to change its name from "embryology" to "developmental biology" or "molecular biology." At heart, the research group remained concerned with the processes of development. And, yes, with embryos, through experimental embryology and then through development and genetics. Now, embryos are in vogue again, vaulted onto the front pages of local newspapers by a cloned sheep named after Dolly Parton, by stem cell research, and by the hopes for improved reproductive medicine.

This book explores the Carnegie Institution of Washington (CIW) Department of Embryology since its inception. Who did what, where, how, and why? What contribution did this department make to the development of biological understanding of embryos, and what is this group doing to lead the way into the future? In this chapter I draw especially on the annual reports from the CIW and on the papers in this volume to provide an introduction to the Carnegie philosophy and to the personality of an institution that is distributed across different places and with people who move in and

out of the story. The CIW could have become an anachronism, a sort of monument to the hopes of the progressive era, frozen in time with the vision of a late nineteenth century rags-to-riches man who made good. But it has not become that. The Carnegie Institution has remained vital because of the underlying principles and the selection of good people to guide programs. The Department of Embryology has helped to keep embryos scientifically alive in the many senses that this volume discusses.

Andrew Carnegie and his Institution

The story begins with Andrew Carnegie, and indirectly with Carnegie's mother. His mother's dominance in his life undoubtedly shaped Carnegie's own drive to succeed and to concentrate on business and community, since she kept him from marrying and developing strong independent ties during her lifetime. Considered a "robber baron" by his critics or a "captain of industry" by his supporters, Carnegie made money in steel – a lot of money. When he succeeded beyond even his imagination, he resolved to put that money to good use. His philosophy of "scientific philanthropy" called for not just scattering funds to individual isolated causes or leaving large sums to one's heirs but rather for investing in the future. Outlined in his "Gospel of Wealth," Carnegie's ideas rested on the assumption that it was better to educate and support than to give handouts on which recipients might become dependent. Wealth must be properly administered, he insisted, and "It were better for mankind that the millions of the rich were thrown into the sea than so spent as to encourage the slothful, the drunken, the unworthy."[1] He gave library buildings, but left it to the community to provide the books and the librarians. He gave to universities, particularly to the Tuskegee Institute, Hampton College, and Berea College rather than to better established schools and made sure that the programming was top quality and the money well invested. And he established the independent Carnegie Institution of Washington to promote scientific research (Fig. 1.1).

In 1901, Carnegie concluded that it was time for an "institution of higher learning" in Washington. Yet he decided against establishing a university there that would compete with other universities. Instead, he settled on an independent research organization. The lovely centennial volume by James Trefil and Margaret Hindle Hazen, entitled *Good Seeing. A Century of Science at the Carnegie Institution of Washington, 1902–2002*, outlines those early discussions and the history of the institution overall. Clearly, Carnegie was inspired by John D. Rockefeller's new medical research institute in New York. His enthusiasm for supporting the individual "genius" pointed to an institution that would allow those individuals to try new ideas in a climate unfettered by the needs to teach or to sell ideas to industry. His goal was to promote both basic research, with "investigation, research, and discovery 'in the broadest

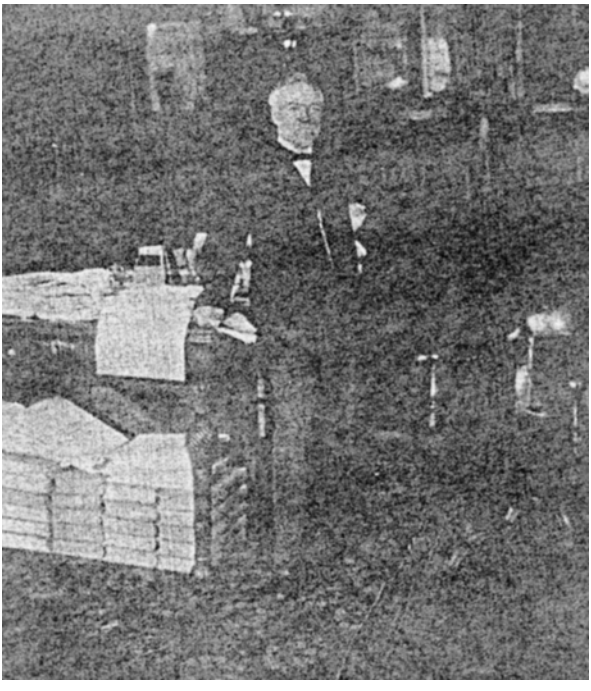

Figure 1.1 Andrew Carnegie "America's Most Eminent Business Man."

and most liberal manner,'" and application, fostering "the application of knowledge to the improvement of mankind."[2] Given Rockefeller's emphasis on medical research, Carnegie resolved to look in other directions and not to include clinical medicine.

The new Carnegie Institution began in 1902, with Daniel Coit Gilman as President. Gilman had served as first president of the University of California from 1872 until he moved to become first president of the newly founded Johns Hopkins University before then accepting the new challenge of heading the CIW and developing its mission. At first, the institution awarded individual grants. In the biological sciences, some of the most visible funding went to the individualistic Luther Burbank, and some of the most important early support went to George Harrison Shull at the Cold Spring Harbor Laboratory. Burbank was the sort of "genius" Carnegie sought to invest in, but was idiosyncratic and unable to share his individualist approach with others. The Carnegie sent Shull to study with Burbank to learn his scientific methods, but Shull concluded that they were actually not scientific at all and perhaps not very methodical. The resulting "Burbank problem," where Carnegie favored Burbank while the trustees were more skeptical about what Burbank actually offered for the longer term, clearly influenced

the selection process and the organizational structure for further Carnegie awards.[3]

The Carnegie Institution opted for a combination of individual awards to selected geniuses for short-term support and with the apparent expectation that there would be results in the form of reports and publications. Carnegie had written that "You know my own opinion is that no big institutions should be erected anywhere." Instead, "exceptional men should be encouraged to do their exceptional work in their own environment." Carnegie had concluded that "There is nothing so deadening as gathering together a staff in an institution. Dry rot begins and routine kills original work."[4]

Yet this did not mean that the Institution had no place. In 1909, the trustees dedicated an administration building at 16th and P Street in Washington. In addition, various research laboratory sites have come and gone over the century, as appropriate for the work at hand and often in partnership with other institutions and individuals. Genetics found a home at Cold Spring Harbor Laboratory, on Long Island, and in other places like Thomas Hunt Morgan's laboratory at Columbia University. Embryology centered in a sequence of at first borrowed, and then specially-designed, laboratory buildings associated with the Johns Hopkins University.

The Department of Embryology

In 1913 Franklin Paine Mall applied for Carnegie support for his work on human embryos. As Nick Hopwood has documented in an outstanding study, *Embryos in Wax*, close examination of human embryos had gained considerable attention in the preceding decades, notably through the work of Wilhelm His and Franz Keibel.[5] These researchers sought through detailed anatomical and histological studies to trace the changes in structure from the very beginning of embryonic life. That is, rather than just assuming that life really begins at the traditional forty days or at the point when germ layers are well defined as many morphologists had assumed, these embryologists believed that it was at least important to assess the significance of the earliest stages. Presumably, the importance of structure does not begin all of a sudden at a later point, but exists from the beginning. At the very least, we should know more about the entire embryological sequence. To that end, they collected, described, and modeled as many stages of the developmental process as they could find, though initially these necessarily focused on later stages since those were the ones most easily available. Embryos in the earliest stages are nearly invisible, and it took more experience to know even what to look for or to know what the tiny embryonic thing was once it was observed.

Following other leading American anatomists, Mall went to Leipzig to study with anatomist/embryologist Wilhelm His and in his role as anatomist at the Johns Hopkins Medical School began to amass his own collection of

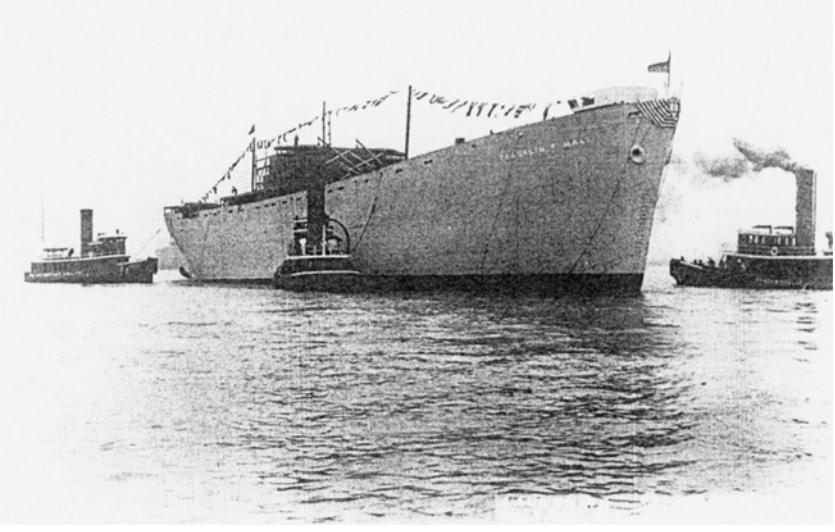

Figure 1.2 The "S. S. Franklin P. Mall," named after the first Director of the Department of Embryology.

human embryos. There is no better way to learn than by doing, he argued, and no better way to teach than with observations of models and specimens to inform study of the static textbooks. On February 20, 1913, Mall received Carnegie Grant No. 874 for $15,000. Work began right away to catalog the existing collections and to secure the collections and records in fireproof facilities. As Mall put it, "A vigorous campaign has been carried on for new specimens of human embryos," reaching half the physicians in the USA and many internationally.[6] This aggressive strategy paid off with new specimens and increased visibility for the collection, presumably helped by the stability afforded by a substantial grant and institutional support from the Carnegie Institution generally (Fig. 1.2).

Mall was made director of a new Department of Embryology, a position he held until his death in 1917. By 1916, Mall was reporting in the annual *Year Book* that while it had taken ten years to get his first 100 embryos, five years for the next 100, three years for the next, and two years for the next, 400 specimens per year had been pouring in since Carnegie support had begun in 1913. He noted that over 500 persons had contributed to the collection (apparently not counting all the mothers who were obviously but in many cases obliviously involved).[7] With Carnegie visibility and authority, the project attracted support from the medical profession generally and even from the State Board of Public Health of Maryland, which instructed physicians in the state to send their specimens to the collection for the purpose of advancing our collective knowledge.

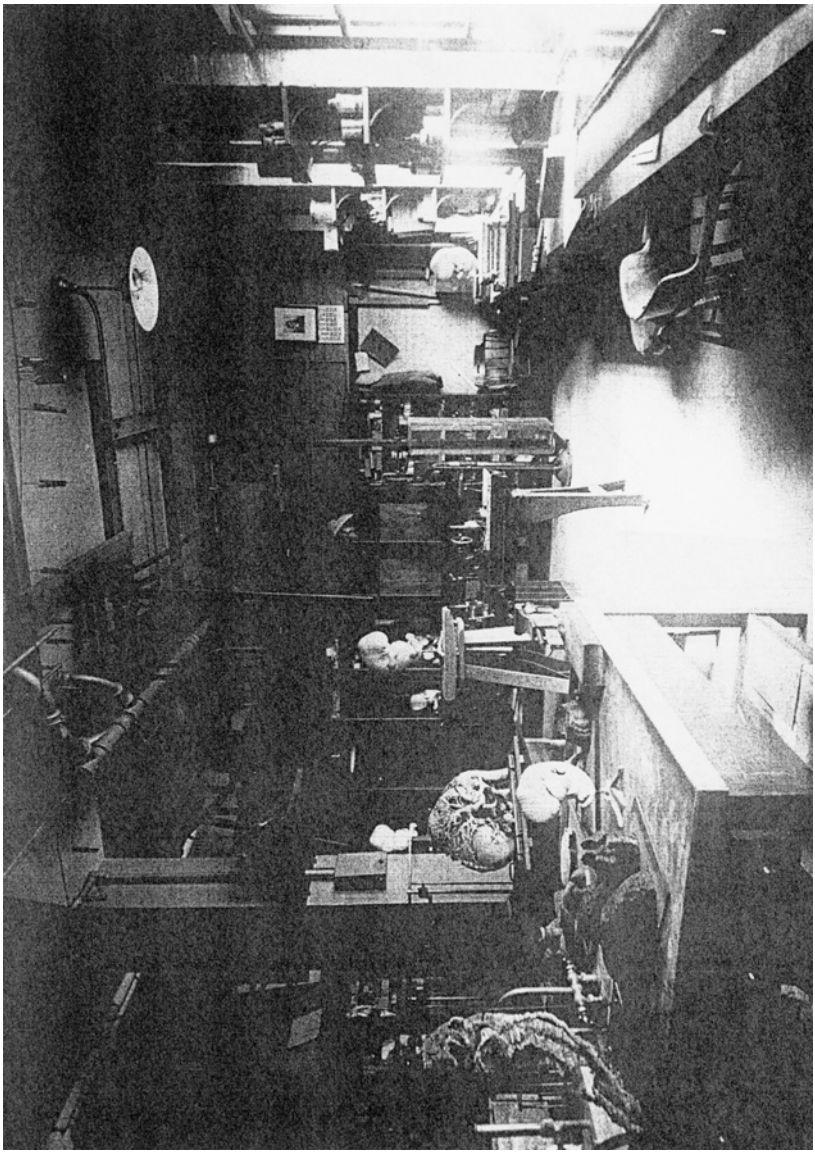

Figure 1.3 Carnegie Laboratory of Embryology, Modeling Department, 1921.

In supporting the project, the Carnegie Institution soon officially opened the Department of Embryology on the Johns Hopkins Medical School campus, with Mall as Director. Within a few years, they were expanding the facilities, adding square footage and facilities for photography, machinery to support making the models, and expanded storage for the collection and the records. By 1915, Mall had formally transferred ownership of his collection of over 2000 specimens to the Carnegie.

Over the next decades, researchers sectioned the specimens, recorded the sections with photographs and drawings, and preserved the materials themselves in fireproof vaults with considerable attention to the acknowledged irreplacability of the collection. In many cases, to augment the specimens themselves and the detailed records about their collection and their analysis, the researchers had models constructed. As His had in Germany to develop his collection, Mall's group hired sculptors to ensure quality and accuracy (Fig. 1.3). By 1914, Mall had hired His's former student and collaborator Franz Keibel from Germany. Keibel had considerable experience in preparing the embryos, so this was a major advance that moved what had initially been a collection of embryos to a major and long-term project of considerable embryological and medical significance. Mall also attracted George Streeter from the University of Michigan, whose work focused on development of the nervous system. And cytologists such as research associate Edmund Cowdry assisted with histological studies while Warren and Margaret Lewis contributed other cell studies.

The result was an impressive group of researchers, established with Carnegie funding and cooperation with Johns Hopkins, at a time when German hegemony in the fields of anatomy and embryology was being considerably undercut by the onset of the First World War. This period of research led to the set of what the group codified as twenty-three distinct stages from fertilization to the eight-week, or fetal, stage. The Carnegie stages, solidified by Streeter, became the standard worldwide for human embryos, and the staff provided a public service for physicians by comparing with the normal stages the abnormal, spontaneously aborted specimens acquired from autopsies sent in by physicians.

Streeter described in the 1918 *Year Book* report the research that Mall had been pursuing at the time of his death in November 1917, including calculations that for every twenty spontaneous abortions, there are eighty full-term births; and that an additional thirty "monsters" are born to every 5,000 pregnancies. In addition, the Carnegie group had made further progress in detailing the timing and sequence of steps in human fertilization and embryo implantation. Streeter was enlisted to serve as Acting Director of the Department for one year after Mall died, and then served as Director until he retired in 1940. As with all the other departments, Carnegie researchers do not receive tenure, and many leave after establishing a research record in this

rich and supportive environment. Fortunately, a few of the leading scientists have remained and have taken on important leadership and administrative positions and stayed with the Carnegie throughout their careers.

By the next year, after his first full year as director, Streeter had had time to reflect on the directions of the Department. He reported that they remained focused on human embryology as their primary problem, including microscopic study of cell structure and gross anatomy of organ systems to understand the body as a whole. They were discovering the value of comparing not only the standard normal, but also pathological specimens to appreciate the factors involved in producing abnormalities. This was obviously of medical importance though not involving clinical research directly and once again reflects the practical aspects of the Carnegie mission. Already there were plans for a new building to provide more space. Warren Lewis had been made a research associate to the Department and had, with his wife Margaret, developed valuable tissue culturing techniques that had already proved innovative for culturing embryonic tissues and expanding cytological studies. Under Streeter, the embryological work continued, but Streeter's own contributions soon brought that line of research to a natural end that pointed in new directions.

By 1973, the emphasis of the Department had changed so much that the collections were really no longer used. They were moved to the University of California at Davis, and then again in 1990 to the National Museum of Health and Medicine of the Armed Forces Institute of Pathology, where they reside today. The collection has recently been digitized and is available through the internet as a resource for the medical and research community and for historians.[8] Adrianne Noe discusses this phase in the history of the Department both in this volume and in her other work cited there.

Primate and comparative studies

Following the emphasis on anatomy with the human embryos came comparative studies with other animals such as chicks, pigs, cows, and then primates, with a focus on physiology. Elizabeth Hanson's chapter in this volume, chapter 3, describes and explains the importance of the primate colony for the CIW study of embryology. It was during Streeter's chairmanship of the Department that the monkeys arrived. One of Mall's students, George Corner, studied anatomy and had become particularly interested in the cycle of reproduction in mammals. He began his studies of rhesus monkeys in a laboratory at the Johns Hopkins, and continued that work through the CIW. He then moved to head the Department of Anatomy at the University of Rochester Medical School from 1923 to 1940.

The initial small group of monkeys became a large colony of rhesus macaques, and the Carnegie researchers' continuing studies achieved such success that the Department recruited Corner to return and follow Streeter

as Director of the Department from 1941 to 1955. Corner's role as Director indicates the direction of research during this period. As Hanson shows in chapter 3, Corner's rhesus monkey colony made possible detailed study of this mammal thought to be closely related to humans and with a menstrual cycle like that in humans. The studies played an important role in focusing serious biological attention on reproductive biology. Adele Clarke's chapter in this volume, chapter 4, demonstrates the nature and importance of that reproductive study, which shaped and even substantially helped to create a disciplinary field of study. Hanson shows that the decision to establish and sustain such a monkey colony required considerable continued investment. As Clarke demonstrates, that investment paid off well in both basic and practical knowledge, in this case to benefit women as part of the Carnegie objective of seeking "improvement of mankind." Although the primate colony was eventually transferred, as Hanson explains in chapter 3, the reports of the 1930s and 1940s are full of discoveries about endocrinology, physiology, and neurology (related to primate) and gynecology (related to human).

Streeter noted in his report for 1936 that there were differences of opinion about just how far the researchers ought to be pressed to develop the medical applications of their work, and about how to organize that work. "The question is raised as to how much freedom should be given to the independent investigator." Should there be dedicated institutes just for the study of cancer, for example? This approach would be too regimented, Streeter concluded. He noted that in pursuing other studies the Department of Embryology had made important discoveries about the nature of tumor development, for example, and the Department of Genetics had added knowledge about tumor heredity even though cancer research was not their primary mission. This argued against single-mission medical laboratories and called for the importance of supporting research into "the fundamental facts upon which an understanding of the nature of cancer must eventually rest," or a call for basic research.

Furthermore, different groups, working quite independently of each other, were making discoveries that complemented each other and added up to significantly advanced knowledge. Therefore, "It is obvious that intercommunication between the groups should be frequent and full, in so far as this can be brought about without infringement upon the backgrounds and approaches of the respective groups. Such an intergroup awareness is facilitated by our administrative organization as a division."[9] Distances between the individual labs, such as Embryology at Johns Hopkins and Genetics at Cold Spring Harbor, should not be allowed to become a barrier to exchange of ideas and free and open cooperation. Any university today would be happy with that emphasis on collaboration, which is something they all seek – or at least say they do.

The CIW sought to realize those hopes by coordinating the Department of Embryology and the Department of Genetics, plus the Nutrition Laboratory

in Boston and the Tortugas Marine Laboratory in the Florida Keys, into a Division of Animal Biology starting in 1934. Streeter served as Chairman and explained that the separate biological studies had been "in each case located where it seemed they could be best conducted." The tendency to overlap and to relate to one another had become sufficiently strong, however, that by 1934 formal coordination had seemed desirable.[10] Yet, as Garland Allen explains in chapter 6, this volume, this spirit of cooperation at times remained more rhetorical than real across the areas of embryology and genetics. By 1941, reports once again came from the separate departments.

Recording cell and tissue development

Hannah Landecker explains the contributions of Warren Harmon and Margaret Reed Lewis in chapter 5, this volume. Rather than theoretical originality, they brought technical skills to the study of cells and tissues. In particular, the techniques to culture tissue and cells outside the body afforded the opportunity to record what happens in the culture. Ross Harrison had developed the very first tissue culture techniques, using hanging drops to culture nerve fibers and demonstrate that they experience protoplasmic outgrowth that appears to be just like that in normal development.[11] Harrison first pursued this work at Johns Hopkins, before moving to Yale, and he worked with the Lewises. While Harrison gave up the technique as not central to the problems he wished to pursue, the Lewises carried development of the technique further. Landecker's account of their work focuses on the intriguing decisions to record the steps of development on film.

Clearly, embryonic development is a process, and it takes place through time. The fascination with capturing the movement is obvious. The idea that following cells and tissue changes during every step of the process rather than just at defined "stages" must have been compelling. Furthermore, the attraction is enhanced by the possibilities for speeding up and slowing down the film to observe details even better. As Landecker explains, the Lewises contributed to a significant shift in anatomical and embryological studies, toward seeing the cell as a dynamic contributor rather than passive respondent in the developmental process. This work began while Streeter was Director, during the 1920s, and continued under Corner's direction into the 1940s.

What the Lewises contributed, as Landecker shows so nicely, was techniques. They helped to develop infrastructure that allowed the research to succeed. The embryo collection, the primate colony, and the tissue culturing and video recording all provided considerable support for investigations by others, both within and beyond the CIW. The Lewises therefore provide a beautiful example of the wisdom of the Carnegie philosophy. Investing in people and supporting their innovations and encouraging them to work together produced a lively intellectual community. The case of the Lewises