

# History of the Department of Cell Biology

Yale University School of Medicine

1813-2010

Thomas L. Lentz, M.D.

Senior Research Scientist, Professor Emeritus of Cell Biology



# History of the Department of Cell Biology

## Establishment of the Medical Institution and Anatomy at Yale

The predecessor of the Department of Cell Biology was the Department of Anatomy that has a history going back to the beginning of the School of Medicine. This history will begin with the history of anatomy and histology from which cell biology arose. The School of Medicine at Yale was established by the passage of a bill in the Connecticut General Assembly in 1810 granting a charter for "The Medical Institution of Yale College," to be conducted under the joint supervision of the College and the Connecticut State Medical Society. The institution was formally opened in 1813 with 37 students, and the first degrees were conferred the following year. In 1814, \$1,000 was spent for a library and anatomical museum. Nathan Smith, one of the founders of the school, donated his specimens to the museum. In 1839, Peter Parker, a graduate of the school and medical missionary in Canton, China, sent materials for the museum. One of the five original faculty members of the school was Jonathan Knight, M. D. (1789-1864). Knight graduated from Yale College in 1808 and received his medical license in 1811. He then attended two courses at the University of Pennsylvania, studying anatomy under Caspar Wistar under whose guidance he purchased anatomical teaching materials for use in the medical school at Yale. He was Professor of Anatomy and Physiology from 1813 to 1838 and Professor of Surgery from 1838 to 1864.



Jonathan Knight (1789-1864)

An interesting early event in the history of anatomy at Yale was the "Dissection Riots" of 1824. Cadavers were needed for instruction but at that time they were very difficult to obtain. This shortage led to grave robbing at Yale and other medical institutions. In 1824, a farmer from West Haven discovered that the body of his 19-year old daughter Bathsheba, buried two days earlier, was missing from the Grove Street cemetery. The farmer went to the medical school, then located across the street from the cemetery, and demanded to search the building. Dr. Knight knew nothing of the grave robbing and allowed the farmer to search the place. The body was found in the cellar under a large flat stone. The body was taken in a wagon to West Haven arousing the citizenry along the way. Several days of riots followed in which hundreds of citizens attacked the medical school which was defended by armed medical students. The riots were quelled when first the militia and then the

Governor's foot guard in full regalia and muskets were called out. Accused of the crime were

a medical student who fled the state and an assistant at the school who was convicted. One outcome of the riots was that the Connecticut legislature passed a law making the bodies of criminals executed or dying in prison available to professors of anatomy and physiology.



Charles Hooker (1799-1863)

were imprisoned and on trial in New Haven. Hooker was followed by Leonard J. Sanford, M. D., who was Professor of Anatomy and Physiology from 1863 to 1879 and Professor of Anatomy from 1878 to 1888.

In 1845 the Anatomical Museum was described as follows: "The Anatomical Museum, which from the efforts of the Professors, the funds of the Institution, and the liberality of friends, has been continually increasing, during more than thirty years that the Institution has been in operation, is most richly supplied with wet and dry preparations, both healthy and morbid, together with models, drawings, &c. For illustrating the course on Obstetrics, the museum is furnished with numerous wet and dried preparations, a machine for teaching the mechanism of labor and the use of instruments, together with a beautiful set of models by Auzoux of Paris. The

A thesis has been a requirement for the M. D. degree since 1837, although theses were written by some students since the opening of the school. Most of the early theses were short and little more than reviews of the limited literature or a repetition of material from lecture notes. Favorite early topics were suppuration, inflammation, burns, wounds, dislocations, and the actions of drugs and other remedies.

The Medical Institution of Yale College was located at Grove and Prospect Streets. In 1838, a new dissecting room, well supplied with subjects, was completed at the school. Charles Hooker, a descendent of one of the founders of the town of Hartford, became Professor of Anatomy and Obstetrics in 1836. He became the first dean of the school in 1845. He provided medical care for the Africans from the Amistad when they

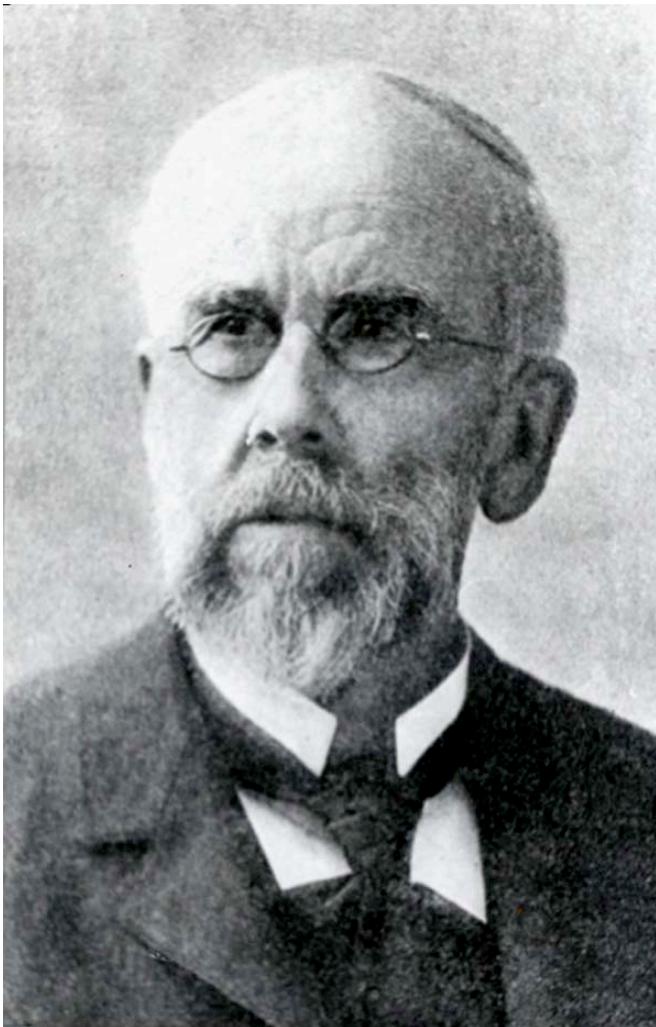


Culpeper-Loft Microscope, 1734.

Cabinet of Materia Medica contains a full collection of specimens, to illustrate the lectures in the department."

### Microscopy and Histology at Yale 1734-1891

The study of microscopy as a separate entity in the curriculum was introduced in 1860. Yale College, however, made use of the microscope long before this. Yale was the first college in America to obtain a compound microscope. In 1734, Yale purchased a Culpeper/Loft "double microscope" from Edward Scarlett in London for three pounds and three shillings. President Stiles listed in 1789 "a microscope" among the available "machines for a course in experimental philosophy," indicating the microscope was used in courses in the eighteenth century. In 1813, Benjamin Silliman, Sr., Professor of Chemistry and Natural History, gave a lecture on the microscope describing the different types of microscopes then available and what the microscope could reveal.

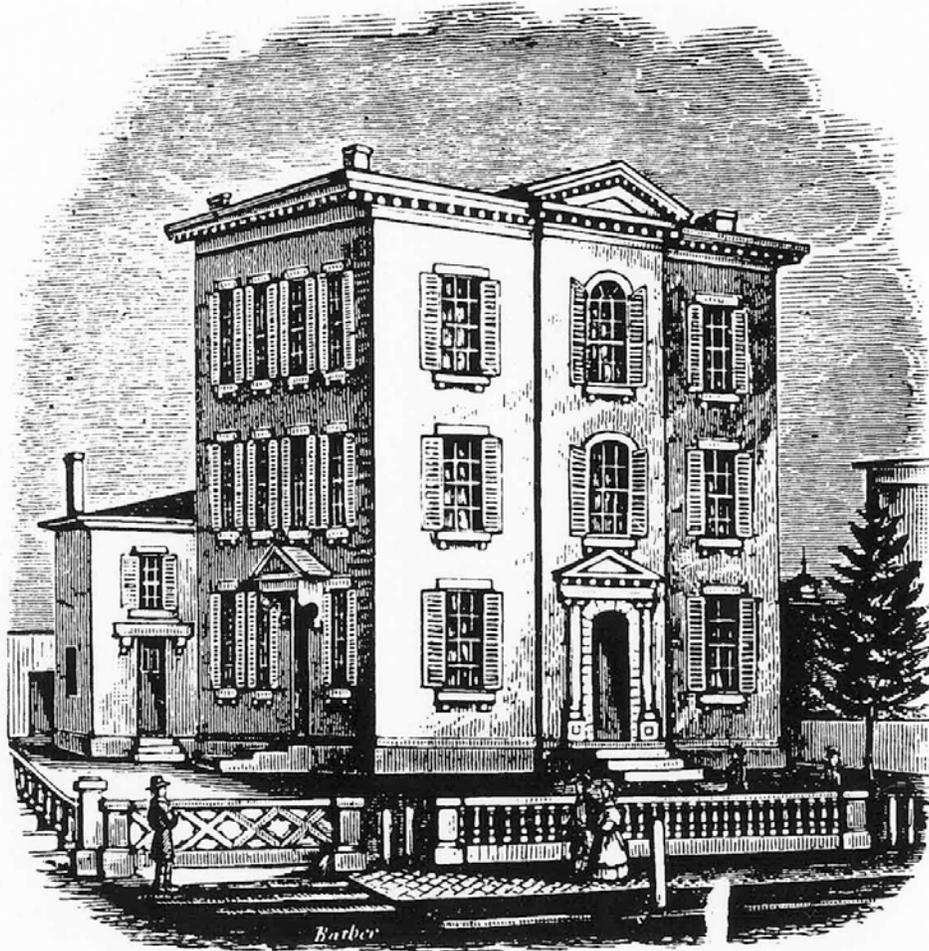


Moses Clark White (1818-1900)

Moses Clark White (1819-1900), a graduate of the Medical Institution in 1854, was appointed Instructor in Microscopy and Botany in 1862. Prior to that, he was a Methodist missionary in China. With the introduction of microscopy, the first laboratory at the medical school was established at the 150 York Street building that housed the medical school from 1860 to 1925. White was appointed Professor when the Corporation authorized a chair in Pathology and Microscopy in 1867. He was Professor of Microscopy and Pathology (1867-1868), Professor of Histology, Microscopy, and Pathology (1868-1877), Professor of Histology and Pathology (1877-1880), and Professor of Pathology (1880-1900). White served as medical examiner for New Haven from 1883 until his death in 1900. He wrote widely on microphotography and the study of blood stains.

The school went to great lengths to establish and strengthen histology and this was most likely due to the rapid advances being made in the area. In 1858, Rudolph Virchow articulated what became the accepted form of the cell theory, *omnis cellula e cellula* ("every cell is derived from a [preexisting] cell") He founded the medical discipline of cellular pathology, namely, that all diseases are basically disturbances of cells. It followed that if cells comprised the organism and could grow and divide and that diseases arose in cells, cells were extremely important subjects for research and teaching. Rapid advances were

being made at the time, especially in Europe, in describing tissues, cells, and cell constituents and it was recognized that the school needed to include the study of cells in its curriculum. Histology was a new and modern science and for a school to remain relevant and competitive, it had to have a representation in this emerging field. A comparable situation would occur a hundred years later when it became necessary to establish and strengthen the new field of cell biology at Yale.



150 York Street. The Medical School occupied this building from 1860 to 1925. Microscopy was introduced into the curriculum when this building opened.

The catalog of 1869 stated under Microscopy, "Histology and Pathology are illustrated by a sufficient number of compound microscopes and a large collection of the best preparations. It is believed that no institution in this country furnishes the student greater facilities for acquiring exact knowledge in this department." The latter statement has validity as few American schools had facilities for histology at this time. The textbooks recommended for histology were:

- Harley & Brown's Histological Demonstrations
  - Peaslee's Human Histology
  - Morell's Histology
  - Beale on the Structure of the Simple Tissues
- To this list were added:
- Strickler's Human and Comparative Histology (1875)

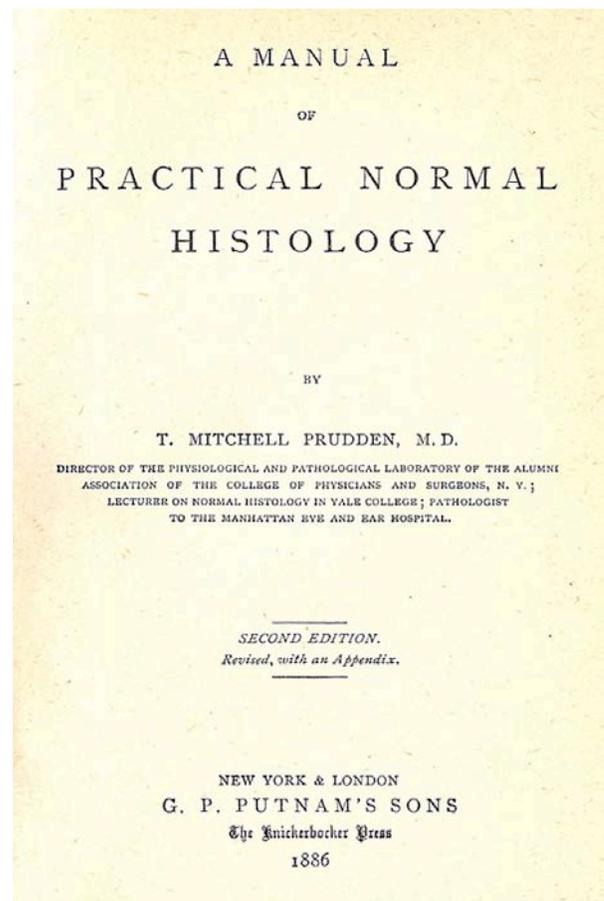
Frey's Histology and Histo-Chemistry of Man (1876)  
Prudden's Notes on Histology (1882)

In 1878, it was stated "The Lectures on Histology and Pathology are illustrated by the daily use of five or six compound achromatic microscopes, on which two sets of preparations are exhibited at every lecture. In this manner the principal microscopic structures both natural and pathologic, including urinary deposits, are exhibited to the students." This indicates that the highest quality microscopes at the time were available to the students. Some of the slides used at that time have been preserved.

In 1880, the faculty recommended separating pathology and histology. They wanted to make the school preeminent in histology and recommended an endowment of \$25,000 to pay the salary of a Professor of Histology. At that time in America, there were no opportunities for a faculty member to devote full-time to teaching and research. Faculty income was meager and derived from student fees for lectures and clinics paid directly to the professor. As a result, almost all faculty held other jobs, usually practicing medicine, to earn sufficient income. In 1880, the school agreed to collect the fees from students and pay the faculty \$300 a year. The faculty hoped that T. Mitchell Prudden, M. D., 1875, who had studied in Germany, would accept the position in histology. However, he had just taken a position at Columbia and decided to stay in New York. Prudden was then offered \$1,200 to come to Yale one day a week to teach histology which he did from 1880 to 1886. This caused disgruntlement on the part of some faculty members who were earning \$300 a year.



*T. Mitchell Prudden*



Prudden and his widely used manual of histology written at the time he taught histology at Yale.

In 1881, teaching of histology was described as "Practical Normal Histology is taught in the microscopical laboratory by Dr. T. Mitchell Prudden. Each student is furnished with a microscope and the requisite accessories, and is taught how to prepare and study the tissues and organs, of which he makes sketches and a typical collection of his own for future reference." It appears that Prudden introduced preparation of histological slides by students, a practice that continued for many years afterwards. In 1881, Prudden published the first edition of *A Manual of Practical Normal Histology*. Histology was taught by Thomas G. Lee, M. D., Lecturer in Histology, from 1886 to 1891.



Samuel Wendell Williston (1852-1918)

Samuel Wendell Williston was Professor of Anatomy from 1888 to 1890. He received his M. D. degree from Yale in 1880 and a Ph. D. degree in 1885. He was Assistant in Paleontology and Osteology from 1876 to 1885, Assistant Professor and Demonstrator in Anatomy from 1886 to 1888. He was a distinguished paleontologist and accompanied Othniel Charles Marsh of Yale on a fossil-hunting expedition in 1874 and led his first expedition in 1877. He was the first dean of the University of Kansas School of Medicine and then took the chair of paleontology at the University of Chicago.

The anatomy and histology courses were described in the Yale Medical School catalog for 1886-87. "The instruction in anatomy aims at thoroughness and comprehensiveness by means of lectures, recitations, and dissections. The lectures are fully illustrated, and the topics thus presented are reviewed and supplemented by the frequent recitations, accurately fixing the knowledge of the student. Practical work in the dissecting room, under the careful supervision of the Demonstrator, is required of each student. The room for this purpose is under the superintendence of the Professor and Demonstrator, and is provided with all necessary material and appliances. From the thorough methods employed in the preservation of material there is little or no danger to health from dissection wounds. During the early part of the course material for study of the bones, ligaments, and joints, is provided for the first-year students, under the direction and instruction of the Demonstrator. Practical work on the skeleton and cadaver is supplemented by a course of lectures on topographical anatomy, by the Professor, with demonstrations and examinations upon the living subject.

The course in Normal Histology was described as follows: "The course in histology consists of lectures, recitations, and practical work with the microscope in the laboratory.

"The student receives a number of specimens of each tissue and organ of the body, which are carefully prepared for him in various ways, so as fully to illustrate the different

points of structure, of which he makes drawings. In addition to this each one receives practical instruction in injecting, hardening, cutting and preserving tissues and specimens after the most approved methods.

"Lectures illustrated with the lantern are a special feature of the instruction, the transparencies being made from photographs of typical preparations and diagrams.

"A large reference collection, abundant material, and the most recent instruments and publications, afford good facilities for advanced work."

Below is the histology examination for the junior class during the session of 1888-89.

1. Describe the layers of the cerebellum.
2. Give structure of a seminiferous tubule and describe the development of spermatozoa.
3. Describe the structure of the trachea.
4. Name in order the layers of the small intestine, and describe each in detail.
5. Describe the course and structure of a uriniferous tubule.
6. From what layer of blastoderm is the spinal cord derived? What other structures originate in this same layer?
7. In what way do motor neurons terminate? Sensory nerves?
8. What kind of epithelium is found in the air vesicles of the lung? The oesophagus? the ureters? the Fallopian tube? the urethra?
9. Describe the contents of a fully developed Graafian follicle?
10. Name the varieties of connective tissue, and describe fully one form.

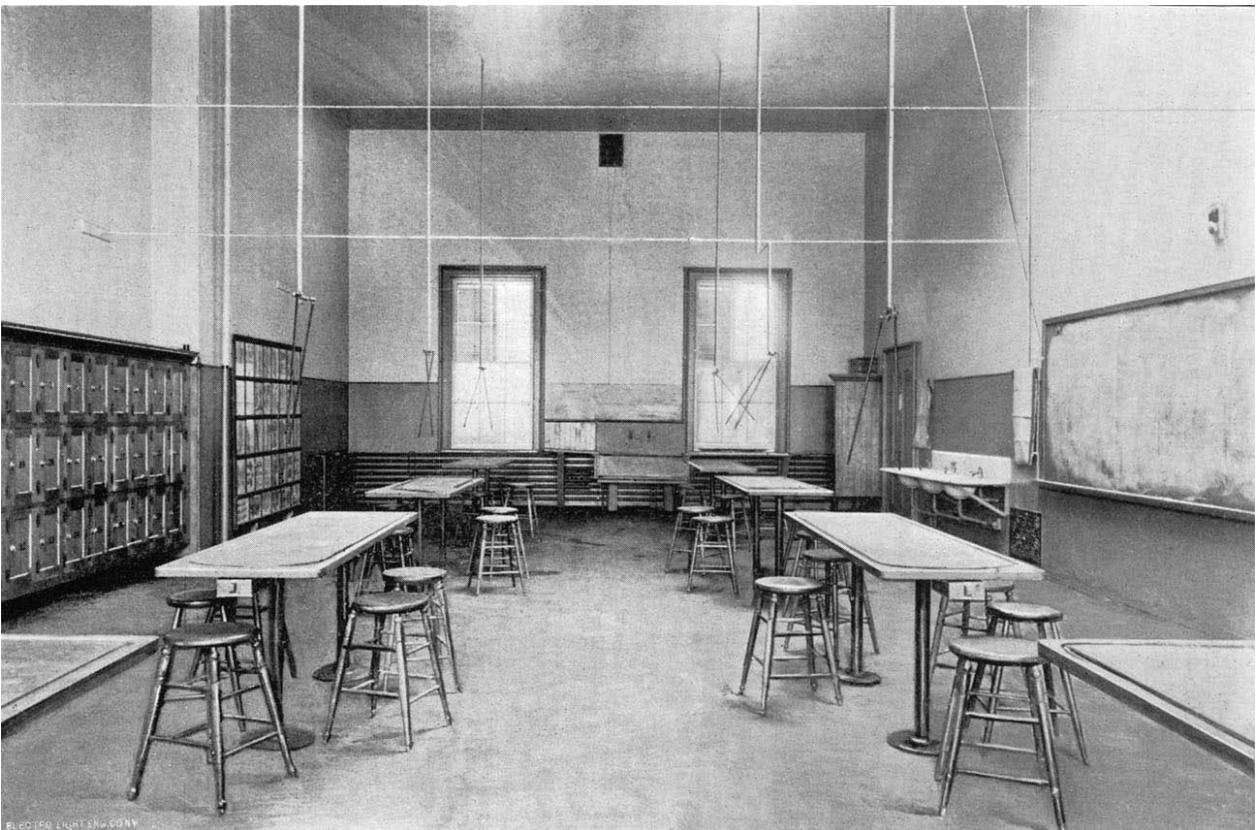
#### Department of Anatomy 1891-1974

Robert O. Moody was Instructor in Histology from 1891 to 1893 and received his M. D. degree from Yale in 1894. Harry Burr Ferris began teaching histology in 1892. The microscopical laboratory in the Medical Hall at 150 York Street was described in 1893 as "a room measuring fifty feet by twenty-five feet, is well lighted with north and west light, and thoroughly equipped with microscopes, students' lockers, work tables, and every facility for satisfactory instruction in normal and pathological histology. The microscopical laboratory is supplied with an excellent set of microscopes, and with microtomes and other laboratory requisites for the best work. Each student is provided with a locker and a set of reagents and apparatus for his own use. There is a large cabinet of sections which may be drawn upon for illustrations and for special work, and also a large collection of photographs and transparencies made from plates and photomicrographs of tissues."

The anatomical laboratory was described in 1893 as "a room measuring fifty feet by twenty-five feet, it is eighteen feet in height, well lighted by skylight and through high windows. The floor is of asphaltum, and arranged for flushing with water. The room is provided with lockers for each student, and with adequate toilet facilities. The dissecting tables are stationary slate slabs supported on two iron posts, thus affording the greatest freedom to the class working about them, and the greatest cleanliness.



Microscopical Laboratory with microscopes in Medical Hall, 150 York Street. circa 1893.



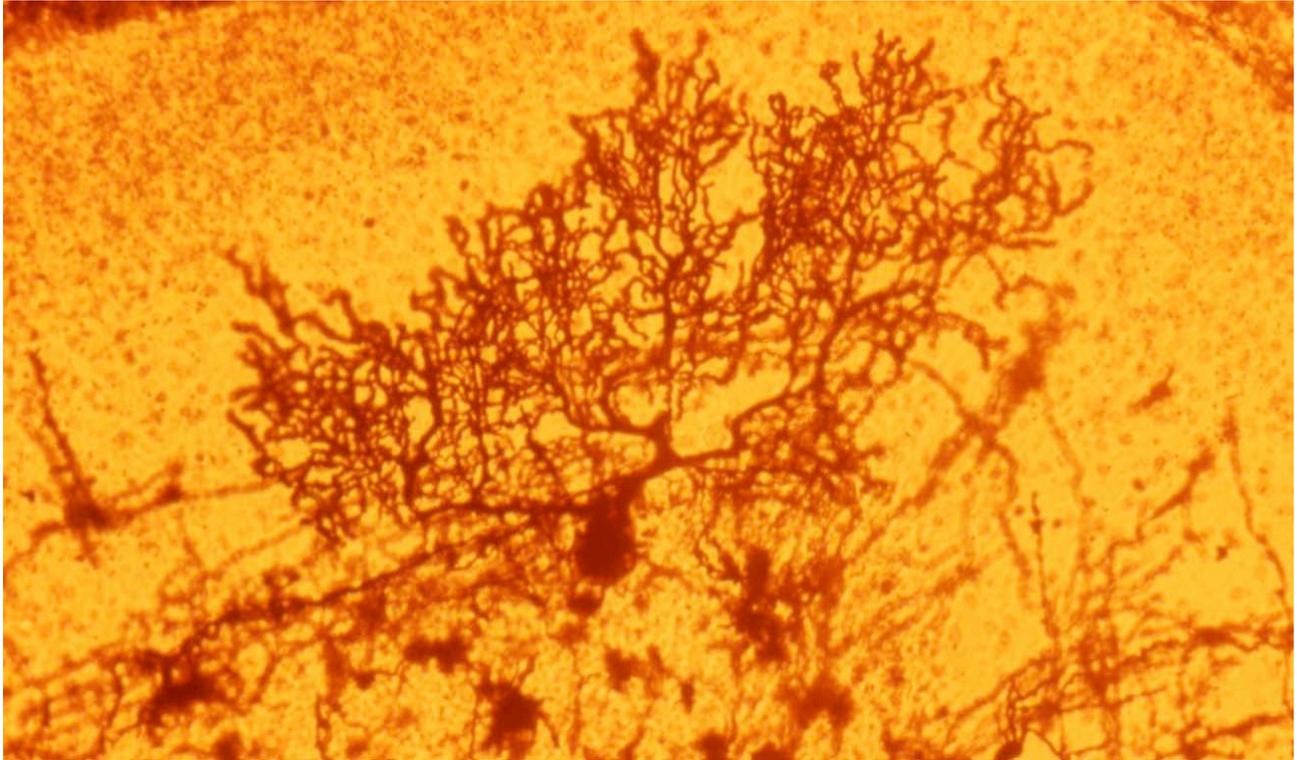
Anatomical Laboratory, circa 1893.



Anatomy class, March 1899. Harry Burr Ferris is third from left.

If the descriptions of facilities and courses sound somewhat like advertisements, they were, in part, that. Yale required a college degree or examination for entrance, graded courses, and a three year course. These were high standards at the time and made it difficult for Yale to attract students. There were a large number of medical schools at the time and many were simply diploma mills with low standards and few requirements. Abraham Flexner investigated the medical schools and in his 1910 report recommended that only 31, one of which was Yale, of 155 medical schools should be retained.

In 1901, instruction in histology was described as follows: "Instruction in histology is given by recitations and lectures illustrated by charts, blackboard drawings, and lantern slides, but chiefly by laboratory work. The recitations and lectures precede and prepare for the better interpretation of the specimens in the laboratory. The laboratory is large, well-lighted and equipped, and each student is furnished a microscope and locker containing a box with all necessary apparatus and reagents. First the elementary tissues and their morphological units are studied by fresh and unstained specimens as well as by stained ones, then the various organs are systematically taken up. The student prepares, stains, and mounts the specimens so far as is practicable, making drawings of each with explanatory notes. At the beginning of each laboratory exercise, the specimens for the day are demonstrated by an excellent electric projection apparatus, experience having shown this method of instruction to be very helpful. Systematic instruction is given in the methods of fixing, embedding, and sectioning tissues, and in the structure and functions of the various parts of the microscope and accessory optical appliances... Facilities are offered and assistance given to students who are making original investigations in connection with their theses."



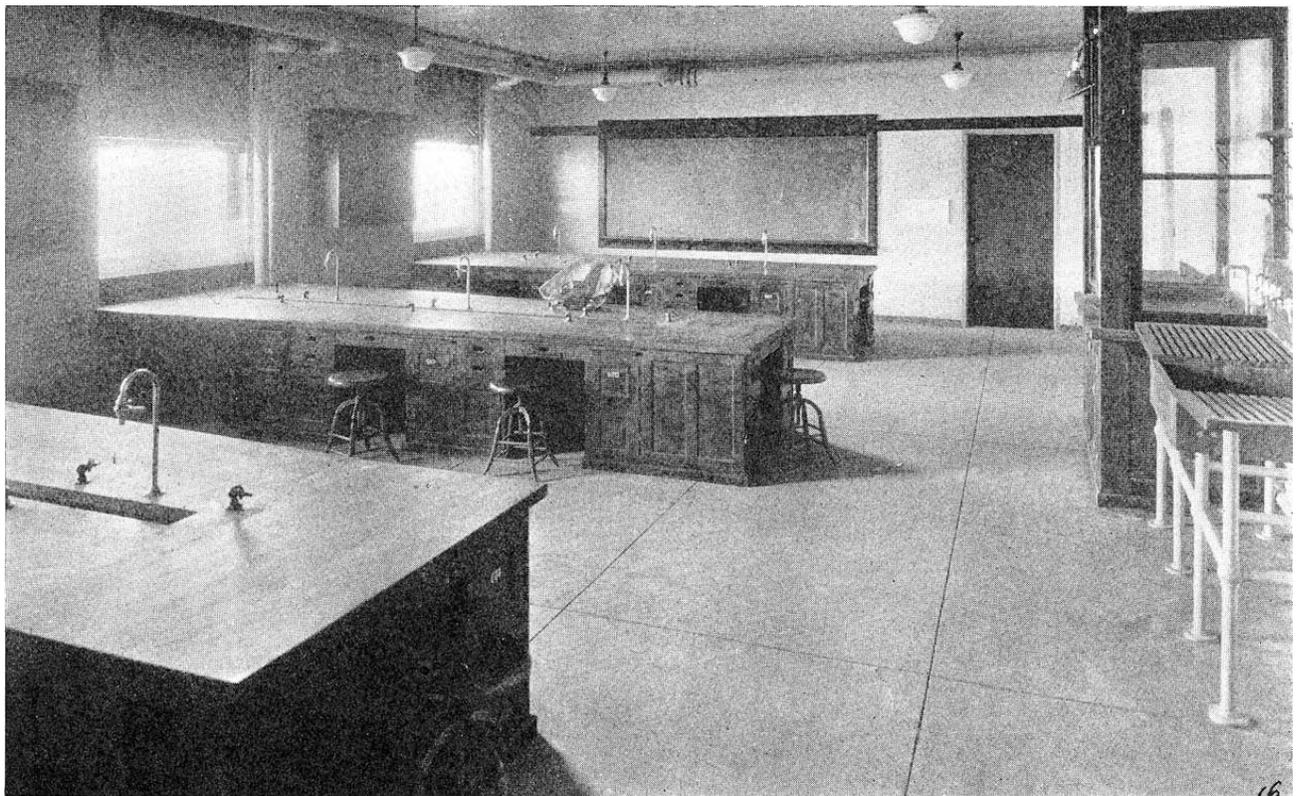
Purkinje cell, cerebellum. From a slide, possibly owned by Ross G. Harrison, in the collection of histology slides used in teaching at Yale. Golgi stain, early twentieth century.

The Sterling Hall of Medicine was dedicated in 1925 with the Department of Anatomy occupying the second, third, fourth floors of the Cedar Street wing. The full-time faculty in 1924 consisted of H. B. Ferris, M. D., Professor of Anatomy; R. G. Harrison, Ph. D., M. D., Professor of Comparative Anatomy; H. S. Burr, Ph. D., Assistant Professor of Anatomy; L. S. Stone, Ph. D., Instructor; and R. K. Burns, M. S., Assistant. The annual budget for the department was \$24,000, with \$15,000 for staff salaries, \$5,900 for janitor, technicians, and clerical help, and \$3,000 for current expenses including research. In teaching, 360 hours were devoted to anatomy, 130 hours to microscopic anatomy, 60 hours to developmental anatomy, and 60 hours to the central nervous system.

In the Department of Anatomy, there was a lecture hall on the second floor holding 73 people (the Anatomy Lecture Hall). There were also staff rooms, secretary's office, student research laboratories, museum, and museum preparation room. On the third floor, there were three large histology and neuroanatomy teaching laboratories. These three rooms remained essentially unchanged until 1970. An adjacent room served as a histological preparation room and laboratory for the research technician. There were four dissecting rooms and a topographic anatomy and study room. The fourth floor had a bone preparation room, an animal operating room, a recovery room for animals under observation, and a roof for bleaching bones and making corrosion preparations. The subbasement contained a cadaver storage room, a refrigerator capable of holding six cadavers, a large electrically driven band saw, embalming room, and storage space for skeletons and dissections.



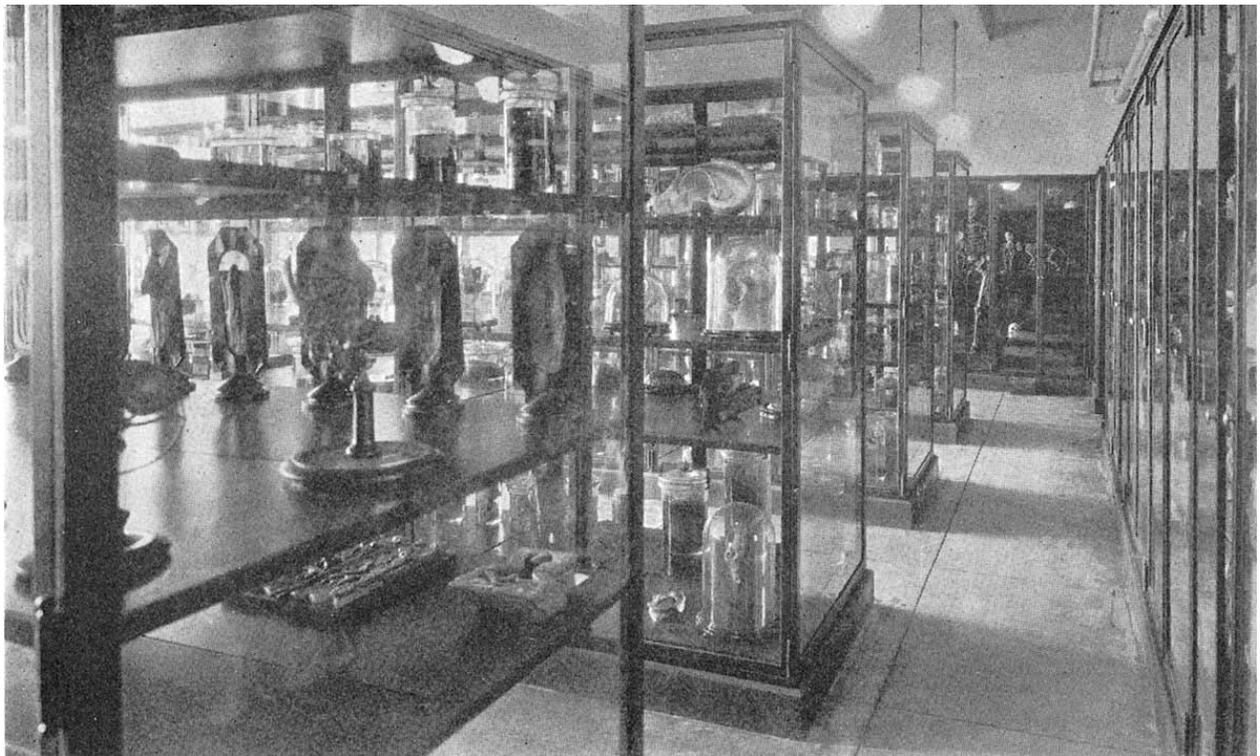
Research Laboratory, Sterling Hall of Medicine, Department of Anatomy, 1924



Histology Teaching Laboratory, Sterling Hall of Medicine, 1924

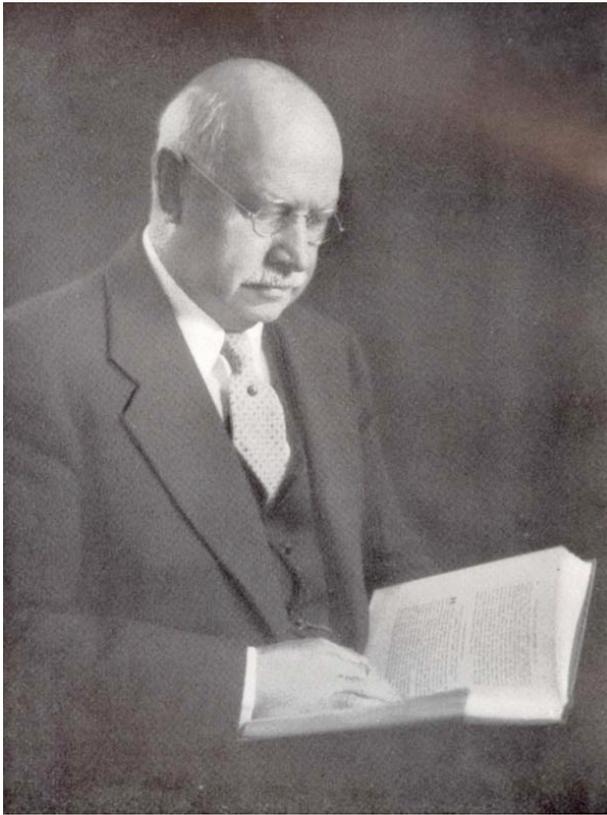


Gross Anatomy Laboratory, 1925.



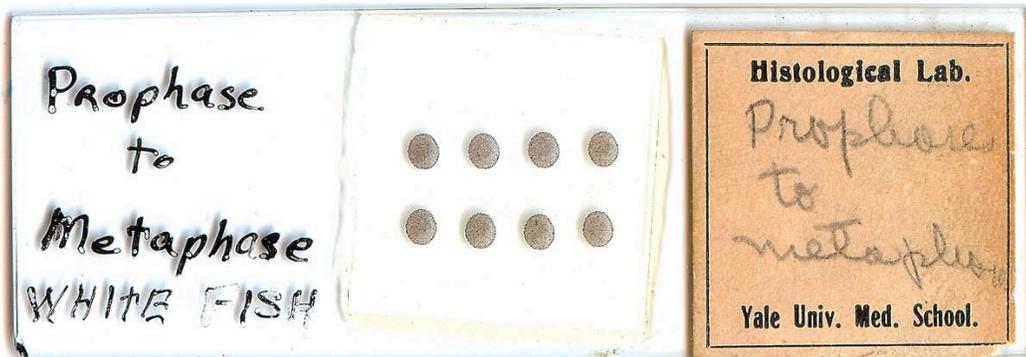
Museum, 1925

The museum had an area of 1.200 square feet. It was chiefly a teaching museum and contained a collection of Steger and other models and a complete series of wax embryological models. There were also special dissections, examples of anomalies, malformations, corrosion, and Spalteholz transparent preparations.



Harry Burr Ferris (1865-1940)

Harry Burr Ferris (1865-1940) received his B. A. degree in 1887 and his M. D. degree from Yale in 1890. He was appointed Instructor in Anatomy in 1891 and taught for 42 years until his retirement in 1933. In 1897, he was appointed E. K. Hunt Professor of Anatomy, the first named chair at the school. He was the first full-time member of the Department of Anatomy and from 1895 to 1911, the only one. He cut the histology sections and prepared demonstration slides during that time. He was extensively involved in teaching all aspects of anatomy and was considered an outstanding teacher. It is said that his knowledge of anatomy was prodigious and his memory frightening. His lectures were unforgettable. Because of his heavy teaching load, he had little time for research. However, he wrote a paper on mitotic division of cancer cells, several papers on the neuron, and later on the history of medicine.



Prophase to Metaphase, Yale University demonstration slide, c1910.



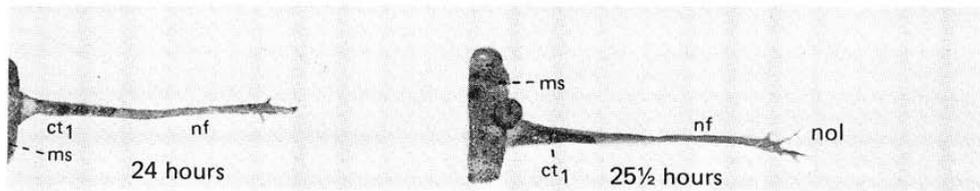
Injected Kidney, Yale University demonstration slide, c1920.

Ross Granville Harrison (1870-1959) received an A. B. degree from Johns Hopkins in 1889 and then a Ph. D. in 1894. In 1892-93 he worked with Moritz Nussbaum at the University of Bonn. After receiving his Ph. D., he returned to Bonn and received an M. D. degree in 1899. He became an instructor in the new Johns Hopkins Medical School. He taught histology and embryology from 1896-1907 and was Associate Professor of Anatomy from 1899-1907 when he came to Yale as Bronson Professor of Comparative Anatomy. In the medical school, he held the title of Professor of Embryology. After two years, he moved into the new Osborn Laboratory where he had a research laboratory and taught embryology. He was Chairman of the Department of Zoology from 1913 to 1938 and Sterling Professor of Biology from 1927 to 1938. He maintained an influential relationship to medicine on a national scale. He advised Abraham Flexner and Simon Flexner, director of the Rockefeller Institute, during the crusade to improve medical training. After retiring from Yale, he was Chairman of the National Research Council from 1938-1946. His decisions formed the basis of some of our national science policy during World War II and in the critical days of atomic development. The production of penicillin in large quantities in this country was arranged through channels that had their origin with Harrison. He was president of many scientific societies and received numerous prestigious awards.



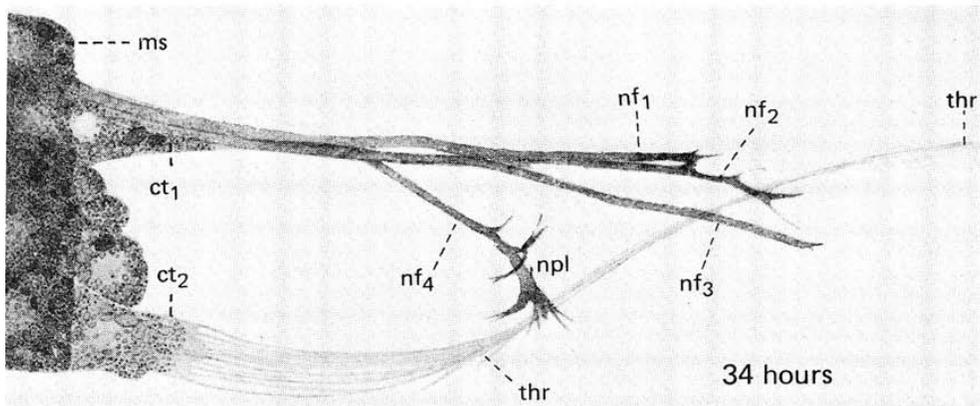
Ross Granville Harrison (1870-1959)

Harrison is best known for making one of the great scientific contributions of the century. He developed the technique of tissue culture which he used to study outgrowth of fibers from nerve cells. Harrison took cells from the spinal cord and placed them in hanging drops of lymph fluid withdrawn from the lymph heart of the frog. Processes then grew out from the nerve cell bodies. He described the growth cones at the tips of the growing fibers. This not only established tissue culture as a practical technique, but also confirmed Cajal's neuron doctrine that neurons are separate structural and functional units. It is still considered an injustice that he did not receive a Nobel Prize for this discovery. He was actually the first American zoologist to be voted the Nobel Prize. However, it was never awarded because The Caroline Institute ruled that no awards be made in Physiology and Medicine during World War I (1914-1918) and since the vote was in 1917, the award was never made. Later, he studied the problem of asymmetry in embryonic development.

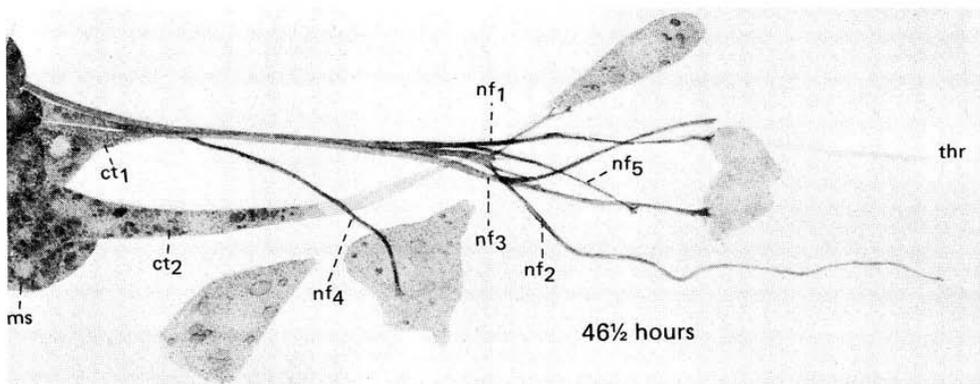


(a)

(b)



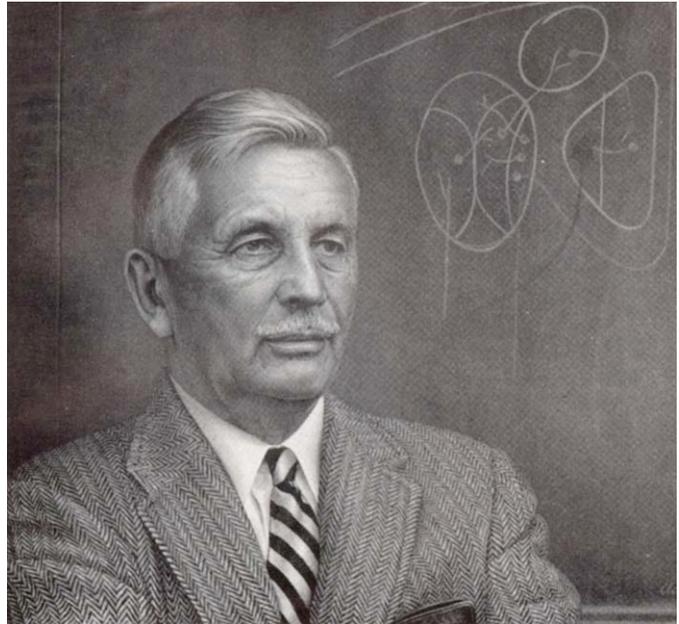
(c)



(d)

Harrison's drawings illustrating nerve fiber outgrowth from an explant of embryonic frog spinal cord. *J. Exp. Zool.*, 9:787-846 (1910).

Harold Saxon Burr (1889-1973) did his graduate work under Ross G. Harrison and was granted the Ph. D. degree from Yale in 1915. In 1914, he became Instructor in Anatomy. On the retirement of Harry Burr Ferris in 1933, he was appointed E. K. Hunt Professor of Anatomy. He was a neuroanatomist and published 93 papers on the development of peripheral nerves and the central nervous system and on bioelectric phenomena in various organisms. Leon Stansfield Stone (1893-1980) received his Ph.D. from Yale in 1921 and became an Instructor in the same year. He was Bronson Professor of Comparative Anatomy from 1940 to 1961. He performed research on regeneration of the visual system in amphibians. Edgar Allen (1892-1943), previously Dean of the University of Missouri School of Medicine, was professor and Chair of Anatomy from 1933 to 1943. He was a leading authority on the mechanism of sex hormones and discovered estrogen.



Harold Saxon Burr (1889-1973)

William U. Gardner, Ph. D., (1907-1988) became Chairman of Anatomy and Ebenezer K. Hunt Professor of Anatomy in 1943. He was a superb teacher of gross anatomy and introduced the teaching system named prosection which is used nationwide today. He was also very active in research and in later years investigated the influence of hormones on cancer. He maintained thousands of mice bearing different malignancies in a small brick building called the "mouse house" which stood between the Boyer Center and the EPH building.



Thomas R. Forbes (1911-1988)

Thomas R. Forbes, Ph. D., (1911-1988) joined the faculty in 1945 and became the Ebenezer K. Hunt Professor of Anatomy in 1977. Also a fine teacher of gross anatomy, he was a distinguished researcher in the field of reproductive endocrinology, particularly the assay and physiological action of progesterone. In later years, he turned to study of the history of medicine. He was also an Assistant and Associate Dean of Students and for 21 years was Chairman of the Admissions Committee.

In 1926, a new elective course was offered known as Advanced Microscopic Anatomy, Anatomy 117 (1926) and the name changed to Anatomy 118 (1927-1937). The title was changed again to Advanced Histology and Hematology (1938-1947). In 1938, the course taught by Dr. Gardner and Dr. Kirschbaum was described as follows. "Detailed microscopic study of connective tissues, inflammation, blood, normal and pathologic hemopoiesis, the endocrine organs, and tissues affected by the secretions of the latter. Morphological variations resulting from different physiological states will be considered in the case of other tissues. Instruction in histochemical procedures, and the making of microscopic preparations will be given. Lectures, demonstration, and laboratory." This course represented a significant advance over histological observation of tissues in that it included correlation of histology and pathology, consideration of the physiological function of tissues, and identification of chemical constituents of tissues through histochemistry. It formed the basis for subsequent teaching in histology.

Edmund S. Crelin (1923-2004), Professor of Anatomy, was another outstanding teacher of gross anatomy and performed research on bone and connective tissues. He published a widely used book on the anatomy of the newborn in 1969. With Allen, Gardner, and Forbes, the department was especially strong in the emerging field of endocrinology in the mid twentieth century. The long and distinguished existence of the Department of Anatomy ended in 1974.

### Beginnings of Cell Biology 1949-1973

Anatomy departments in the first part of the twentieth century traditionally had four sections or parts organized around their teaching missions. These were gross anatomy, microscopic anatomy, neuroanatomy, and embryology. In the 1960s, the research activities of faculty in microscopic anatomy became increasingly devoted to cell biology; those in neuroanatomy to neurobiology; and those in embryology to developmental biology. As faculty became increasingly subcellular and molecular in their approaches, "anatomy" was



Russell J. Barnett 1971

no longer an appropriate description for the departments. Anatomy departments were modified, combined with other disciplines, or abolished at many medical schools. In their place, departments or sections of molecular biology, cell biology, structural biology, neurobiology, genetics, and developmental biology were created. The newly emerging sciences were incorporated into the medical school curriculum, although it still remained necessary to teach medical students the original four basic disciplines.

Although the Department of Anatomy was composed mostly of classical anatomists, it was recognized that to remain current and relevant, the department needed greater representation in the newly emerging field of cell biology. Sanford L. Palay, who took some of the earliest electron

micrographs of the nervous system, had joined the faculty in 1949 but left in 1956. Russell J. Barnett was recruited to Yale from Harvard in 1959 in order to build up the department's strength in cell biology. Thomas L. Lentz was a cell biologist and joined the faculty in 1964. Walter J. Gehring, a developmental biologist, was an Associate Professor from 1969 to 1972. Barnett's laboratory had an RCA EMU 3F electron microscope. A Hitachi HU 11E electron microscope was added in 1975.

Russell J. Barnett (1920-1989) received his M. D. degree from Yale in 1948 and joined the Department of Anatomy in 1959. He was Chairman from 1967 to 1974. From 1974 to 1979, he was Chairman of the Section of Cytology. His area of expertise was the development and use of cytochemical techniques for the localization of enzymes and other substances in tissues and cells. With David Sabatini and Klaus Bensch, he discovered the use of glutaraldehyde as a fixative for electron microscopy. He was extremely enthusiastic about science and was supportive of young investigators. His lab was an exciting and dynamic place and attracted people such as David Sabatini, Floyd Bloom, George Aghajanian, Jack McMahan, Tom Lentz and many others who became productive scientists.



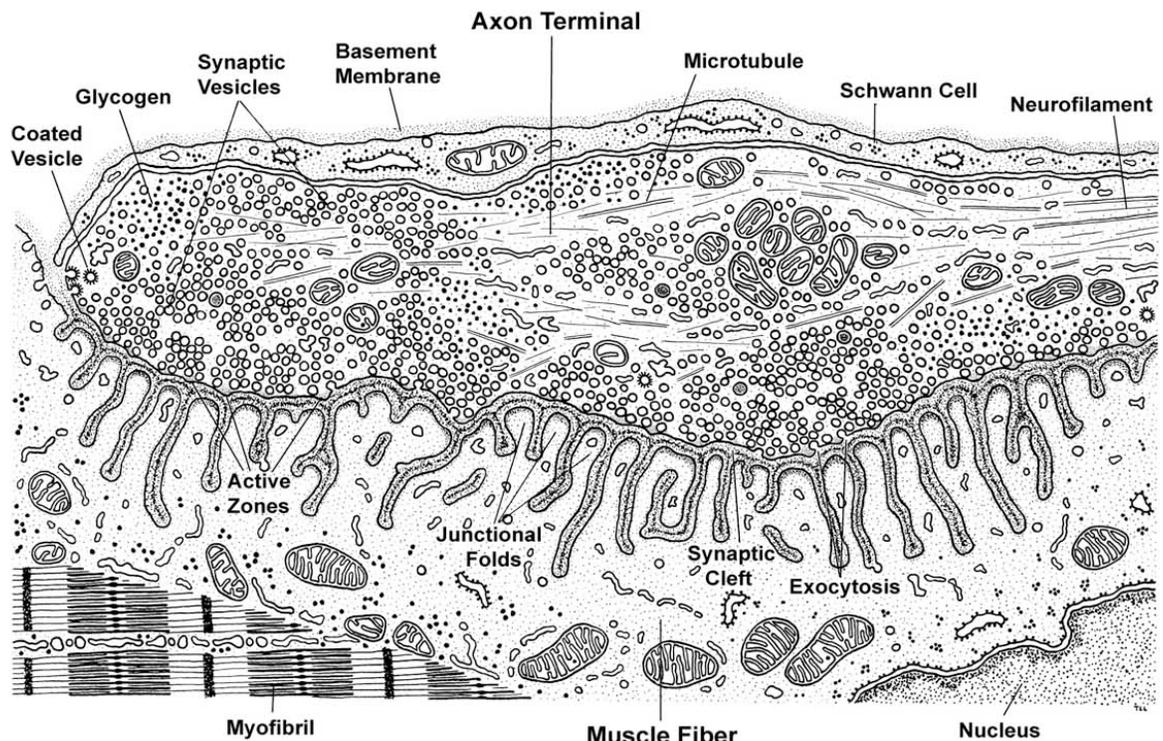
Laboratory, second floor, C-wing, Sterling Hall of Medicine c1969. Thomas L. Lentz at Porter-Blum ultramicrotome used for making thin sections for electron microscopy. This was the state of laboratories at the time, prior to the renovations for the new Section of Cell Biology.



Thomas L. Lentz 1995

Thomas L. Lentz (1939- ) came to Yale as a medical student in 1960 and worked in Russell J. Barnett's laboratory. He received his M. D. degree in 1964 and was hired as an Instructor in Anatomy to teach and set up a laboratory in cell biology. His research interests during his career included study of primitive nervous systems, trophic regulation by the nervous system, development of the neuromuscular junction, identification of the neurotoxin-binding site on the nicotinic acetylcholine receptor, structure-function relationships of the acetylcholine receptor, and cellular receptors and intracellular trafficking in neurons of the neurotropic rabies virus. He authored a book *Cell Fine Structure* widely used in teaching cell biology. He was appointed Professor of Cell Biology in 1985. In 1972, he became chair of the Committee on Admissions for the School of Medicine. He was appointed Assistant Dean in 1976 and Associate Dean in 2000. He was Vice-

Chairman of the department from 1992 to 2006. He retired in 2006 and currently directs the microscopic anatomy laboratory as Senior Research Scientist and Professor Emeritus of Cell Biology.



### NEUROMUSCULAR JUNCTION

Neuromuscular Junction, modified from Lentz, T. L., *Cell Fine Structure*, 1971.

The Department of Anatomy in 1974, the last year of its existence, consisted of Russell J. Barnett, Professor and Chairman; Edmund S. Crelin, William U. Gardner, and Thomas R. Forbes, (Professors); M. David Egger, O'Dell W. Henson, Joan A. Higgins, and Thomas L. Lentz (Associate Professors); and J. M. Gilliam (Assistant Professor).

### Section of Cell Biology 1973-1983

Although the Department of Anatomy had taken steps to introduce cell biology, it was recognized that a major expansion of cell biology was necessary if Yale was to be competitive in this field. In 1973, Yale became preeminent in cell biology when George Palade, along with Marilyn Farquhar and James Jamieson, came to Yale from the Rockefeller Institute and formed the Section of Cell Biology. George Palade is considered the founder of the science of modern cell biology and received the Nobel Prize in Physiology or Medicine in 1974, which he shared with Albert Claude and Christian DeDuve.

The second floor of the C-wing was extensively renovated to provide laboratory space for the Section of Cell Biology. The Department of Anatomy was abolished in 1974 with gross anatomy becoming a Section in the Department of Surgery and microscopic anatomy becoming the Section of Cytology with Russell Barnett as head. Neuroanatomy was taught by outside instructors until 1978 when Pasko Rakic was recruited by George Palade to head a Section of Neuroanatomy, now the Department of Neurobiology.

George Palade was dedicated to teaching and made the cell biology course for medical students the outstanding course in the basic sciences at the medical school and probably in the country. Beginning in 1973, Cell Biology 102 was taught by the faculty of the Department of Anatomy, later Section of Cytology, and Cell Biology. Experts from other departments participated. It was an advanced cell biology course for first year medical students and included microscopic anatomy. The schedule of the first part of the course is shown below.

In 1976, Cell Biology 102 was described as follows. "This course focuses on the structural basis of cell and tissue functions in mammals. The lectures are grouped in two main series. The first series surveys the structural basis of the following cellular functions: replication, transcription, and translation of the genome (nucleus, chromosomes, nucleolus, ribosomes); interactions and exchanges with the environment (plasmalemma); energetics (mitochondria); protein synthesis for secretion (endoplasmic reticulum and Golgi complex); lipid synthesis; intracellular digestion (lysosomes); translocation and motility (microtubules and microfilaments); and excitability, conduction, and impulse transmission (plasmalemma, synapses). Tissues are presented as structural expressions of the functional differentiation of their cells. In the second series, the structural basis of organ function is examined starting from the cell and tissue levels. Emphasis is put on cell differentiation and interactions among differentiated cells. Examples taken from all major systems (digestive, excretory, circulatory, integument, reproductive, and endocrine) are discussed in terms of integrated functions of their constituent cell populations. The laboratory section of the course is concerned with microscopic anatomy. The structure and organization of cells are analyzed at the subcellular, cellular, tissue, and organ levels using the light microscope and electron micrographs. Twelve weeks, with 3 hours of lecture and 4 hours of laboratory a week."

CELL BIOLOGY

Anatomy 102a - 1973

		<u>Lecture</u>	<u>Laboratory</u>
Sept. 6	8:30 AM	Introduction (Dr. Thomas L. Lentz)	Histology of the cell
	1 PM	Cytochemical reactions (Dr. Russell J. Barnett)	
11	11 AM	Specializations of the cell surface (Dr. George E. Palade)	Epithelium
	1 PM	Adipose cells - Lipid synthesis and mobilization (Dr. Russell J. Barnett)	
13	11 AM	Collagen synthesis and extracellular matrices (Dr. James M. Gilliam)	Connective tissue, adipose tissue, cartilage
	1 PM	Cilia and flagella (Dr. Joel L. Rosenbaum)	
18	11 AM	Microtubules and microfilaments (Dr. Joel L. Rosenbaum)	Bone
	1 PM	Mitochondria (Dr. Leonard A. Sauer)	
20	11 AM	Granulocytes and lysosomes (Dr. Marilyn G. Farquhar)	Peripheral blood
	1 PM	Cell differentiation (Dr. Frank H. Ruddle)	
25	11 AM	Ribosomes (Dr. George E. Palade)	Bone marrow-hematopoiesis
	1 PM	Endoplasmic reticulum and Golgi apparatus (Dr. George E. Palade)	
27	11 AM	Antibody formation (Dr. Byron H. Waksman)	Lymphatic tissues and organs
	1 PM	Membrane structure and biogenesis (Dr. Russell J. Barnett)	
Oct. 2	11 AM	Nervous system I (Dr. Floyd E. Bloom)	Nervous system
	1 PM	Nervous system II (Dr. Floyd E. Bloom)	
	4 11 AM	Muscle (Dr. Thomas L. Lentz)	Muscle, blood vessels
	1 PM	Capillaries (Dr. George E. Palade)	
	9 11 AM	Functional organization of the cell (Dr. George E. Palade)	Review
	1 PM	Skin (Dr. Joseph S. McGuire, Jr.)	

The Sections of Cell Biology and Cytology were merged in 1979 to form the Section of Cell Biology with George Palade as chairman. The primary faculty at that time consisted of George Palade, Marilyn Farquhar, James D. Jamieson, and Russell J. Barnett (Professors); Thomas L. Lentz (Associate Professor); and Anne Hubbard, Richard Galardy, and J. David Castle (Assistant Professors). Each year in the 1970s and 1980s, Nicolai and Maya Simionescu came to Yale from Romania as Visiting Professors for a semester to teach histology and do research. George often had to intervene with the President of Romania in

order for the Simionescus to obtain permission to leave, as the Communist regime feared they would not return.



George E. Palade 1970

George E. Palade (1912-2008) received his M. D. from the School of Medicine of the University of Bucharest, Romania. He was a member of the faculty of that school until 1945 when he came to the United States for postdoctoral studies. He joined A. Claude at the Rockefeller Institute for Medical Research in 1946 and was appointed Assistant Professor at the Rockefeller in 1948. He progressed from Assistant Professor to full Professor and head of the Laboratory of Cell Biology until 1973 when he moved to Yale as Professor and chair of the Section of Cell Biology. He was Sterling Professor of Cell Biology from 1975 to 1983. He became a Senior Research Scientist, Professor Emeritus of Cell Biology and Special Advisor to the Dean in 1983. In 1990, he moved to the University of California San Diego as Professor of Medicine in Residence, and Dean for Scientific Affairs. He was a member of the National Academy of Sciences and of the American Academy of Arts and Sciences. He received a number of honorary degrees and prizes, which include a Nobel Prize in 1974 (shared with Albert Claude and Christian DeDuke), and the National Medal of Science, USA in 1986.

## THE ENDOPLASMIC RETICULUM\*

BY GEORGE E. PALADE, M.D.

(From The Rockefeller Institute for Medical Research)

PLATES 31 TO 38

### History

*Original Findings on Cultured Material.*—The relatively short history of the endoplasmic reticulum started 10 years ago, in 1945, when Porter, Claude, and Fullam (1), noted the presence of a “lace-like” reticulum in the ground substance of cells grown in tissue culture and examined *in toto* in the electron microscope. In describing their findings, these authors mentioned that “at higher magnifications vesicle-like bodies, that is elements presenting a center of less density and ranging in size from 100 to 150  $m\mu$ , appear arranged along the strands of the reticulum.” In retrospect, it can be said that two of the main features of this new cytoplasmic system, namely (a) its reticular disposition and (b) the vesicular character of its component elements, were already clearly noted in its first description. In subsequent papers, Porter and his collaborators described the preferential concentration of the vesicular elements of the reticulum in the endoplasm, and their scarcity or absence in the supposedly exoplasmic periphery of the cytoplasm (2, 3), a finding which eventually led to the selection of “endoplasmic reticulum” as a name for the system. The term was first cautiously tried in a caption in 1948 (3) and finally used in an article published by Porter and Kallman in 1952 (4). It appears that, at that time, our group was not yet engaged in large scale production of new cytological terms with a heavy Latin flavor, and was still proceeding with cautious restraint in matters of nomenclature. Besides the reticular disposition and the endoplasmic location implied in the name, Porter’s studies established a number of other important features for the new cytoplasmic component, namely the usual continuity of the system throughout the endoplasm of normal cells, the remarkable polymorphism of its component elements, and the breaking down of the entire system in cytolysis into a collection of isolated vesicles.

*The Shift from Spread to Sectioned Cytological Specimens.*—The information obtained from the study of cultured cells was presented by Porter in a final article in 1953 (5), at a time when new embedding and microtomy procedures

\*This presentation is based on the observations made, and the interpretations advanced, by Dr. S. L. Palay, Dr. K. R. Porter, Dr. P. Siekevitz, Dr. M. L. Watson, and the author working together at various times in the Department of Cytology at The Rockefeller Institute in New York.

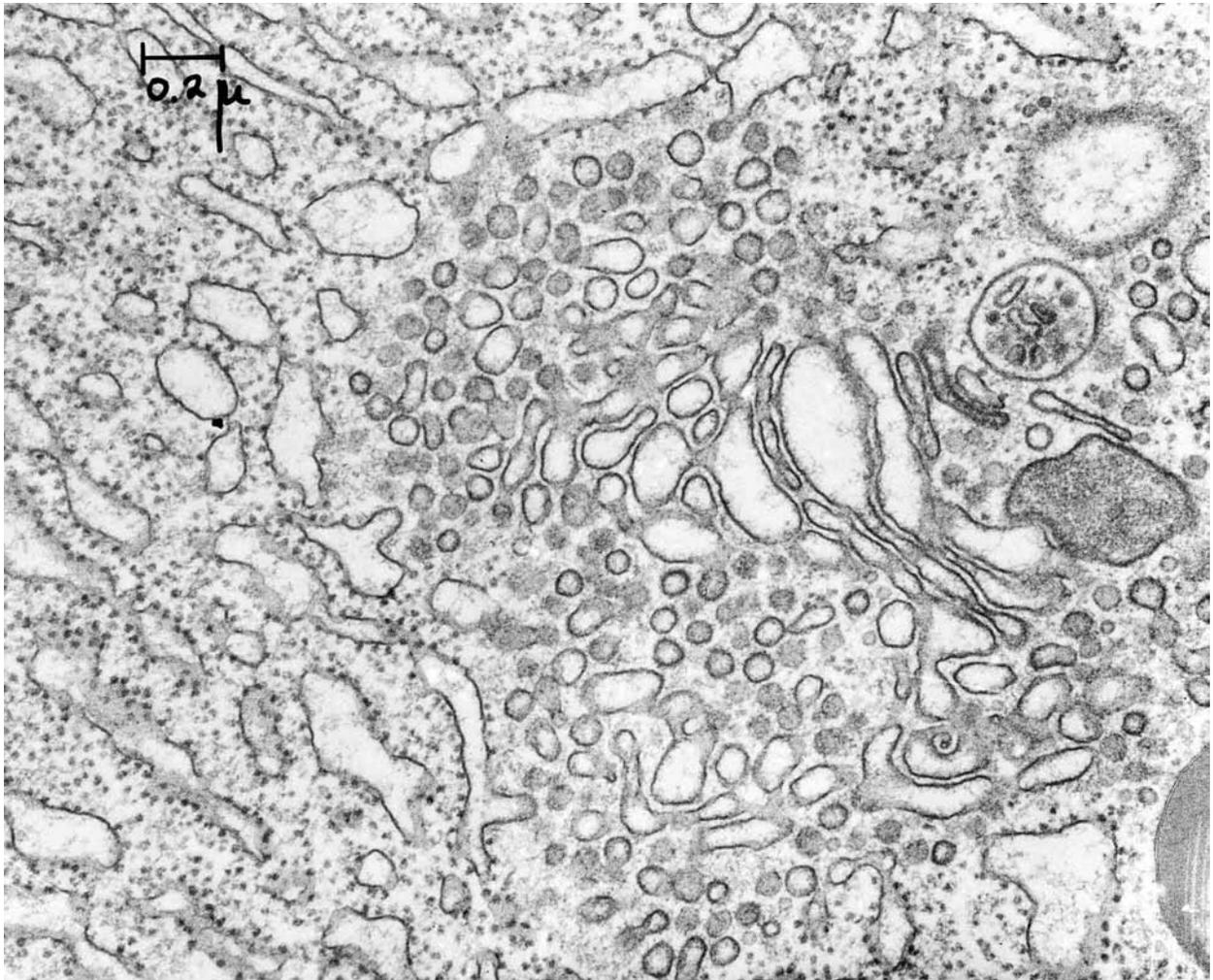
85

J. BIOPHYSIC. AND BIOCHEM. CYTOL., 1956, Vol. 2, No. 4, Suppl.

J. Biophys. Biochem. Cytol., Suppl. 2:85-298 (1956)

The Palade laboratory was actively involved in integrated morphological and biochemical studies of subcellular components already known to exist or discovered in the early 1950's as the result of the introduction of electron microscopy in cell research. The work relied heavily on the development of progressively refined cell fractionation procedures of which the last one is immunoisolation using specific antibody/antigen interactions. These integrated studies, supplemented by autoradiography at the electron microscope level and by immunocytochemical procedures, have led to the identification of the compartments of the secretory (exocytic) pathway; vesicular carriers at important relays along the pathway; the energy requiring steps; and isolation and partial characterization of different classes of vesicular carriers. This body of knowledge has been extended by other laboratories to the endocytic pathway and to the processing of membrane proteins along

these different pathways. General principles underlying the process of membrane biogenesis have also been developed during this work. In recent years the work of his laboratory was concentrated on the vascular endothelium, especially the continuous type of endothelium found in the microvasculature of muscles, myocardium and lungs. It led to the identification of plasmalemmal vesicles or caveolae of this type of endothelium as the transcytotic carriers for macromolecules, especially proteins larger than 20Å diameter.



Electron micrograph taken by George Palade of a pancreatic acinar cell showing the rough endoplasmic reticulum, transitional vesicles, and Golgi apparatus.

In announcing the 1974 prize, the Nobel committee said of Palade: "He added important methodological improvements both to the differential centrifugation and to the electron microscopy. In particular he became instrumental in combining two techniques, often in combination, in order to obtain biologically basic information. His early work, largely in collaboration with K. Porter was mainly descriptive, morphological and was devoted to components in the area of the cell outside its nucleus, the cytoplasm. In particular they studied a network of submicroscopic membranes, called the endoplasmic reticulum, originally discovered by Claude and Porter. They showed that the reticulum can be described as a multiply folded, more or less deflated sack occupying most of the cytoplasm. Palade discovered and described small granular components now known under the name of ribosomes covering the outside of the membranes, and he showed, with other groups, that the ribosomes carry out the protein synthesis in the cell. In a series of

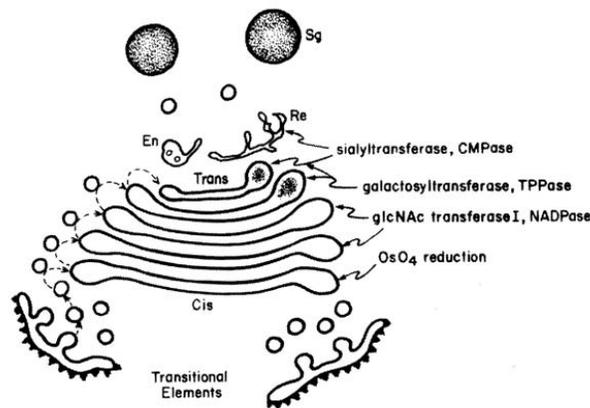
extremely elegant papers he and his coworkers showed how in secretory cells the secretory proteins, produced by the ribosomes on the outside of the reticulum enter the space between its membranes, migrate to a special organelle, the Golgi complex, where they are changed to a form suitable for secretion. Many fascinating details of the secretory process were demonstrated. The work of Palade includes many other important structural-functional analyses of different cellular components."



Marilyn G. Farquhar 1988

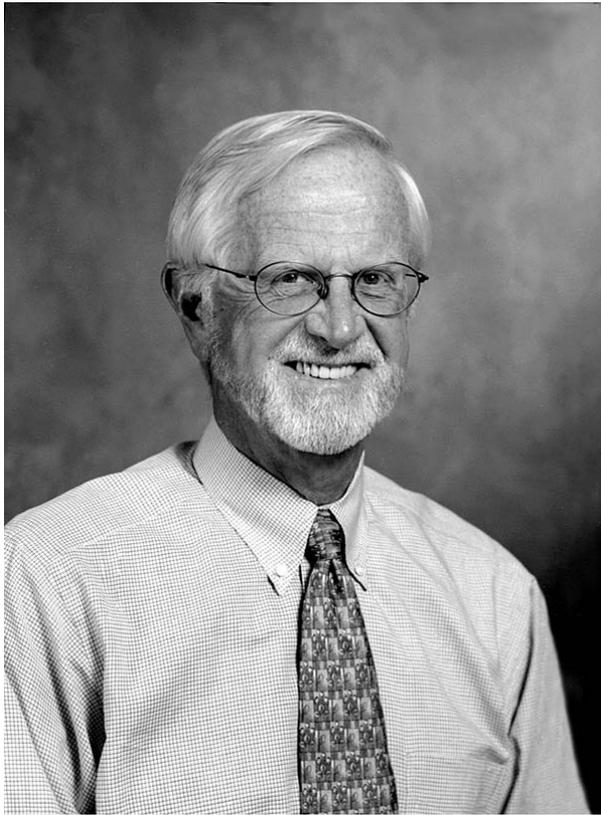
Marilyn Gist Farquhar (1928- ) received her A. B. degree in Zoology, and her Ph. D. in Experimental Pathology from the University of California, Berkeley. Dr. Farquhar's academic appointments are Professor of Pathology at the UCSF School of Medicine, Professor of Cell Biology at Rockefeller University, and Sterling Professor of Cell Biology and Pathology at Yale University School of Medicine. She was on the faculty at Yale from 1973 to 1990. Currently she is a Professor of Pathology, and Chair, Department of Cellular & Molecular Medicine at the UCSD School of Medicine. Her distinctions include the Wilson Medal of the American Society of Cell Biologists and membership in the National Academy of Sciences and the American Academy of Arts and Sciences. Dr. Farquhar's early

studies helped elucidate the function and structure of the anterior pituitary gland including mechanisms of exocytosis and hormone packaging. She was also instrumental, along with Dr. George Palade, in elucidating, by electron microscopy, the components of the junctional complex. A long-standing interest of her laboratory is in understanding the cellular and molecular basis of diseases of the kidney glomerulus, especially autoimmune diseases and the function of the basement membrane.



Golgi apparatus, Marilyn G. Farquhar, 1988

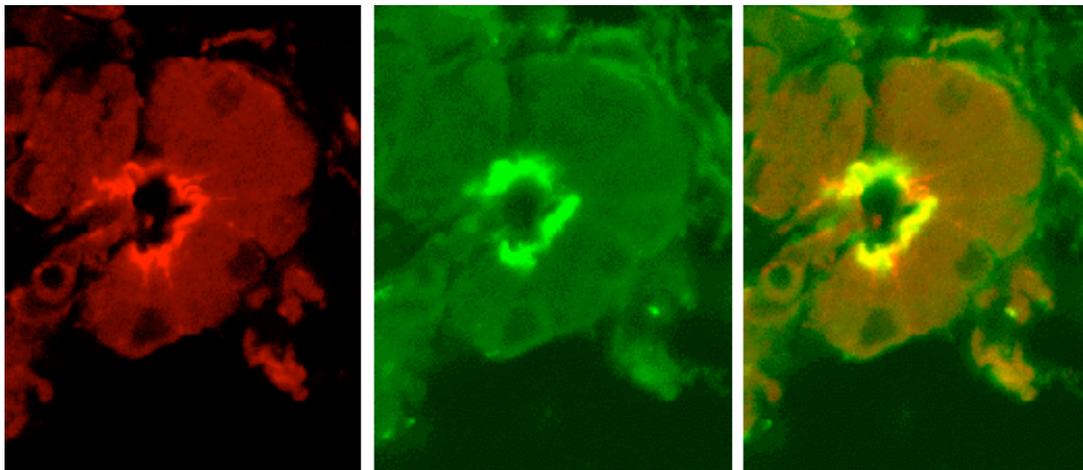
James D. Jamieson (1934- ) received his M. D. from the University of British Columbia, Canada, in 1960 where he worked with Sydney Friedman, M. D., Ph. D. Following medical school, he moved to the Rockefeller University where he worked with George Palade on his Ph. D. (1966) which concerned the "Intracellular Transport of Secretory Protein: Role of the Golgi Complex". He stayed on at the Rockefeller first as a post doctoral fellow with Dr.



James D. Jamieson 1999

Palade then joined the faculty as Assistant Professor progressing to the rank of Associate Professor. In 1973, Dr. Jamieson left the Rockefeller to join Drs. Palade and Farquhar at Yale University School of Medicine as Associate Professor where they formed the Section of Cell Biology. He was promoted to Professor of Cell Biology in 1975 and was the first chair of the Department of Cell Biology when the Section of Cell Biology became a Department in 1983. He is currently Director of the M. D.-Ph. D. Program at Yale University. His distinctions include president American Society for Cell Biology (1983) and Distinguished Achievement Award, American Gastroenterological Association (1993). Dr. Jamieson's research interests have mainly focused on identification of components of the intracellular transport pathway in the pancreatic acinar cell as a model of a regulated secretory system. He used techniques of electron microscopic autoradiography, cell fractionation and electron microscopic immunocytochemistry to define the central role of the Golgi complex in the

processing and packaging of secretory proteins into zymogen granules. His more recent studies were directed at an understanding of the role of low molecular weight GTP binding proteins and the actin cytoskeleton in the process of membrane fusion and membrane retrieval during regulated exocytosis.



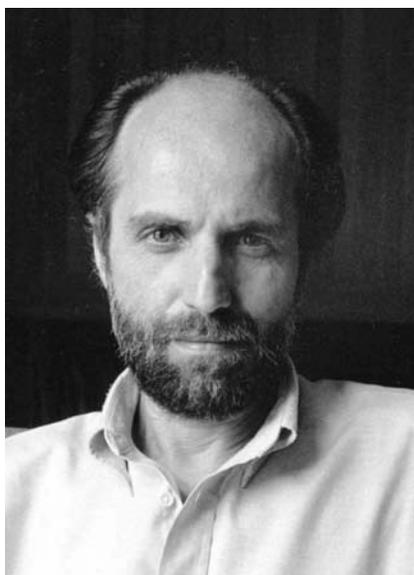
Localization by confocal microscopy of actin (red) and rab4 (green) showing colocalization (yellow) in pancreatic acinar cells. James Jamieson.

## Department of Cell Biology 1983-2007

The Section became the Department of Cell Biology in 1983 with James D. Jamieson as Chairman. George Palade and Marilyn Farquhar left Yale to go to the University of California San Diego School of Medicine in 1990. Ari Helenius became Chairman in 1992 followed by Pietro De Camilli in 1997 and Ira Mellman in 2000. Ari Helenius capitalized on the ability of viruses to utilize the membrane traffic machinery to enter and exit cells to learn about fundamental mechanisms in membrane traffic. Ira Mellman advanced knowledge in the field of endocytosis, antigen presentation, and dendritic cell function. He was named Sterling Professor of Cell Biology in 2002. A Center for Cell Imaging (CCI), first formed in 1989 and maintained by the department and medical school, has state of the art facilities for electron and confocal microscopy. A fourth floor containing research labs, library, and seminar room for cell biology was added to the end of the C-wing. In 2001, the second floor was renovated to create modern research laboratories. Teaching laboratories in the new Anlyan Center for Medical Research and Education (TAC Building) accommodate microscopic anatomy and small group teaching beginning in 2003.



Ari Helenius, 1992-1997



Pietro De Camilli, 1997-2000



Ira Mellman, 2000-2007

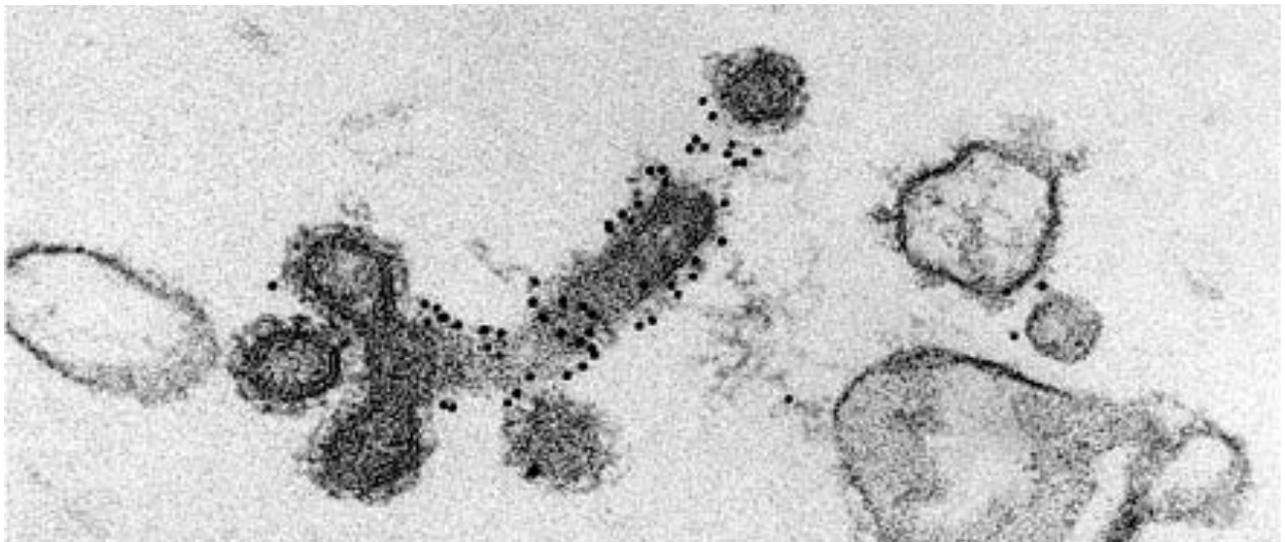
### Chairs of the Department of Cell Biology

Pietro De Camilli received his M.D. degree in 1972 from the University of Milan. He worked at the University of Milan with Jacopo Meldolesi, who had studied with George Palade and James Jamieson at the Rockefeller University. He then did post-doctoral work at Yale with Paul Greengard, who later won the Nobel Prize for Physiology or Medicine in 2000. He then joined the Section of Cell Biology as Assistant Professor in 1980. After two years, he returned to the University of Milan for six years and returned again to Yale as Associate Professor of Cell Biology in 1988. He was promoted to full Professor and appointed as a Howard Hughes Medical Institute Investigator in 1992. He chaired the department from 1997 to 2000. He was elected to the National Academy of Sciences and to the American Academy of Arts and Sciences in 2001 and the Institute of Medicine in 2005. In 2003, he was named Eugene Higgins Professor of Cell Biology. His research has involved study of the molecular mechanisms involved in the fusion of synaptic vesicles with the presynaptic membrane, with release of neurotransmitters by exocytosis, and the recycling

of vesicle membrane. He has identified and/or characterized many of the proteins including synapsin, dynamin, synaptojanin, and endophilin that participate in this process. More recently, he has demonstrated the crucial role of protein-lipid interactions and phosphoinositide metabolism in the control of membrane traffic at the synapse. He has applied his research to diseases and found that patients with stiff man syndrome and insulin-dependent diabetes mellitus have auto-antibodies against a neuronal antigen, glutamic acid decarboxylase.



Pietro De Camilli 1997



Immunogold labeling for PIP kinase on membranes from which clathrin-coated pits originate. Pietro De Camilli.

Since 1979, many new faculty have joined the department and some have left. The third floor of the C-wing was renovated to accommodate some of the new faculty and the Section of Neuroanatomy. New appointments were Ira Mellman and Ari Helenius (1981), Robert Levenson (1983), Susan Ferro-Novick and Peter Novick (1985), Pietro De Camilli (1988, also earlier Assistant Professor and Visiting Professor), Spyridon Artivanis-Tsakonis, Carl Hashimoto, and Sandra Wolin (1990), Norma Andrews (1993), Michael Tiemeyer (1994), Graham Warren (1999), Karin Reinisch and Peter Takizawa (2001), Gero

Miesenböck (2004), Derek K. Toomre (2005), Haifan Lin (2006), Daniel Colon-Ramos, Thomas Melia, and Fred Gorelick (2009), and Joerg Bewersdorf, Shawn Ferguson, Megan King, C. Patrick Lusk, Tobias Walther, and Yongli Zhang (2010).

Beginning in the late 1970s, department retreats were held annually. These were held at the Marine Biological Laboratory at Woods Hole, Massachusetts until 1991. They ran from Friday evening through Sunday morning. At the retreats, faculty members gave brief talks on the research being conducted in their laboratories. There was a poster session. There were also social activities including a reception, trip to Martha's Vineyard, and visits to Captain Kidd's Tavern. In recent years, the retreats have been held at locations in Connecticut and last one day. The department also held an annual picnic and holiday party. In the 1980s and 90s, the department had a softball team named the "Palade Bodies." During the year, there are weekly Progress Reports where graduate students and postdoctoral fellows give talks on their research. There is an active seminar program in which distinguished scientists are invited to Yale to present their research.

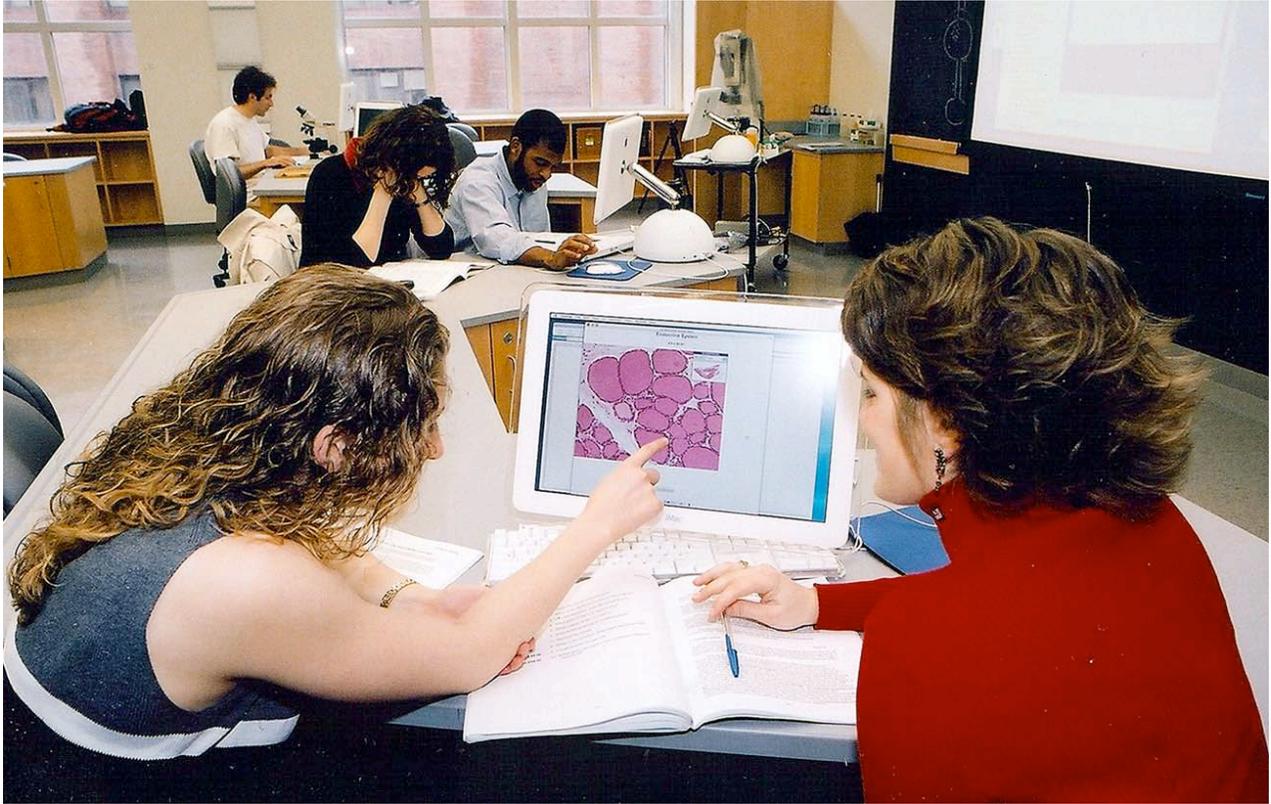
In 2001, the major course taught by the department for the class of 100 medical students was described as follows. "Cell Biology 502, The Cellular Basis of Human Biology. This full-year course is designed to provide medical students with a current and comprehensive review of biologic structure and function at the cellular, tissue, and organ system levels. Areas covered include replication and transcription of the genome; regulation of the cell cycle and mitosis; protein biosynthesis and membrane targeting; cell motility and the cytoskeleton; signal transduction; nerve and muscle function; and endocrine and reproductive cell biology. Clinical correlation sessions, which illustrate the contributions of cell biology to specific medical problems, are interspersed in the lecture schedule. Histophysiology laboratories provide practical experience with the light microscope for exploring cell and tissue structure. J. Jamieson, T. Lentz, F. Gorelick, and staff." Teaching of microscopic anatomy was greatly enhanced by the introduction of virtual microscopy of histological sections in 2003. The virtual microscope consists of high-resolution scans of histological sections that can be viewed on a computer screen. As with microscopes, students can scan through the section and change magnification.

An important course, directed by Frederick Gorelick, M. D., Professor of Medicine (Digestive Diseases) and Cell Biology, is Cell Biology 601a/b, Molecular and Cellular Basis of Human Disease. This course emphasizes the connections between diseases and basic science using a lecture and seminar format. It is designed for students who are committed to a career in medical research, those who are considering such a career, or students who wish to explore scientific topics in depth. The course is organized in four- to five-week blocks that topically parallel CBIO 502a,b. Examples of blocks from past years include "Diseases of protein folding" and "Diseases of ion channels." Each topic is introduced with a lecture given by the faculty. The lecture is followed by sessions in which students review relevant manuscripts under the supervision of a faculty mentor. Several special sessions are dedicated to technologic advances. In addition, three sessions are devoted to academic careers and cover subjects such as obtaining an academic position, promotions, and grant writing. The course is open to M.D. and M. D./Ph. D. students who are taking or have taken Cell Biology 502a,b. Student evaluations are based on attendance, participation in group discussions, formal presentations, and a written review of an NIH proposal.



Teaching Laboratory, The Anlyan Center, 2003

A graduate program in cell biology was instituted in 1973 when the Section of Cell Biology was formed. Since then, over a hundred students have received their Ph. D. degrees in the department. In addition, many medical students and M. D./Ph. D. students have done their thesis work in the department. The cell biology department in 2003 is part of the Combined Program in the Biological and Biomedical Sciences (BBS) and is in the Molecular Cell Biology, Genetics, and Development track. Fields of study available to graduate students in the department include membrane biology of eukaryotic cells (molecular mechanisms of membrane biogenesis, traffic, and fusion; organelle biogenesis), intracellular transport of membrane and secretory proteins, receptor-mediated endocytosis, generation of trans-membrane signals, epithelial cell polarity and the extracellular matrix, protein folding, membrane function in the nervous system (synapse formation and function), developmental genetics, cell biology of protozoan parasites and of pathogen/host interactions, cell biology of the immune response, mRNA and protein localization, cell biology of bone remodeling and of the cytoskeleton. Approaches to these topics include biochemistry, molecular biology, and macromolecular crystallography; yeast and *Drosophila* genetics; immunocytochemistry and electron microscopy; cell fractionation; and live cell imaging.



Histology class, 2003. Students are using the virtual microscope.

The cell is the fundamental unit of all life on earth. Cell Biology therefore defines the very center of all efforts to understand all aspects of biology and human disease. Cell Biology seeks to understand a continuum that starts with elucidating the molecular basis of how cells are constructed, how the thousands of cell types accomplish their individual tasks, and finally how these different cells cooperate to form tissues, systems, and organisms. Cell biology utilizes many approaches to achieve this goal and, as a result, forms a bridge between biochemistry, structural biology, development, physiology, neurobiology, genetics, immunobiology, microbiology, informatics, and disease processes. Today, the major research interests of the faculty in the department cover a diverse range of topics in the field of cell biology. The research budget for the department in 2002/03 was \$4,500,000. The research areas of the primary faculty in 2004 are listed below.

1. Biogenesis and traffic of synaptic vesicles; autoimmunity to nerve terminal proteins (Pietro DeCamilli, M. D., Eugene Higgins Professor of Cell Biology).
2. Membrane traffic and organelle biogenesis (Susan Ferro-Novick, Ph. D., Professor of Cell Biology).
3. Biological regulatory mechanisms involving serine proteases and serpins (Carl Hashimoto, Ph. D., Associate Professor of Cell Biology).
4. Secretion and membrane polarity in epithelial cells (James D. Jamieson, M. D., Ph. D., Professor of Cell Biology and Biology).

5. Rabies virus entry and trafficking in neurons; functional domains on the acetylcholine receptor (Thomas L. Lentz, M. D., Vice-Chairman, Professor of Cell Biology).
6. Endocytosis mechanisms; intracellular transport and function of MHC class II molecules; antigen processing and presentation; dendritic cell function and development (Ira S. Mellman, Ph. D. Chairman, Sterling Professor of Cell Biology and Immunobiology).
7. The function of biological neural networks; neural ensemble codes in *Drosophila* olfaction (Gero Miesenböck, M. D., Associate Professor of Cell Biology).
8. Mechanism of plasma membrane assembly and cell surface organization in yeast; interaction between cytoskeleton and secretory machinery (Peter J. Novick, Ph. D., Professor of Cell Biology).
9. Structural biology of mammalian viruses and other macromolecular assemblies (Karin Reinish, Ph. D., Assistant Professor of Cell Biology).
10. Biochemical and cellular analysis of the processes of mRNA and protein localization in yeast and neurons (Peter Takizawa, Ph. D., Assistant Professor of Cell Biology).
11. Membrane sorting, traffic, and fusion as explored in living cells with advanced imaging techniques (Derek K. Toomre, Ph. D., Assistant Professor of Cell Biology).
12. Growth and division of the Golgi apparatus (Graham Warren, Ph. D., Professor of Cell Biology).
13. Biogenesis of polymerase-III-transcribed small RNAs; RNA binding proteins (Sandra Wolin, M. D., Ph. D., Associate Professor of Cell Biology and Molecular Biophysics and Biochemistry).

In addition to the primary faculty, a large number of faculty with joint appointments contribute greatly to the research and teaching activities of the department. Their research interests are as follows:

1. Invasion, survival, and signaling mechanisms of intracellular pathogens (Norma W. Andrews, Ph. D., Professor of Microbial Pathogenesis).
2. Molecular mechanisms in bone resorption during growth, development, and skeletal homeostasis (Roland Baron, D. D. S., Ph. D., Professor of Orthopaedics and Rehabilitation).
3. Molecular signals and cellular machinery involved in generating the polarity of the cell surface membranes of epithelial cells and neurons (Michael J. Caplan, M. D., Ph. D., Professor of Cellular and Molecular Physiology).
4. Molecular genetics of *Drosophila* oogenesis; actin cytoskeleton regulation (Lynn Cooley, Ph. D., Associate Professor of Genetics).

5. Molecular mechanisms of antigen processing; assembly and intracellular transport of class I and class II MHC molecules; functions of interferon  $\gamma$ -inducible GTPases (Peter Cresswell, Ph. D., Professor of Immunobiology and Dermatology).
6. Cellular mechanisms of the pathogenesis of *Salmonella typhimurium* (Jorge Galán, Ph. D., D. V. M., Chairman, Professor of Microbial Pathogenesis)
7. Protein kinases and membrane transport (Frederick S. Gorelick, M. D., Professor of Medicine, Digestive Diseases).
8. Structure and function of membrane-associated cytoskeleton (Vincent T. Marchesi, M. D., Ph. D., Professor of Pathology).
9. Studies of the brush border cytoskeleton; cytoskeletal structure, motility, and assembly (Mark Mooseker, Ph. D., Ross Granville Harrison Professor of Molecular, Cellular, and Developmental Biology and Pathology).
10. Second messengers and regulated secretion in polarized epithelia (Michael H. Nathanson, M. D., Ph. D., Professor of Medicine, Digestive Diseases).
11. Testing hypotheses about molecular mechanisms of actin-based cellular movements using a combination of biochemical, biophysical, cellular, and genetic experiments (Thomas D. Pollard, M. D., Higgins Professor of Molecular, Cellular, and Developmental Biology).
12. The molecular mechanism that underlies neuronal growth cone guidance (Elke Stein, Ph. D., Assistant Professor of Molecular, Cellular, and Developmental Biology).
13. Transcription and RNA processing in trypanosomes (Elizabetta Ullu, Ph. D., Professor of Medicine).



Haifan Lin 2006

Haifan Lin joined the faculty in 2006 as Professor of Cell Biology and Genetics. He received his Ph. D. in 1990 from Cornell University. After a postdoctoral fellowship with Allan Spradling at the Carnegie Institution in Washington, he was Professor of Cell Biology at Duke University Medical Center. His laboratory studies molecular mechanisms underlying the self-renewing division of stem cells. Currently, he focuses on small RNA-mediated epigenetic programming and translational regulation that are required for the self-renewal of germline and embryonic stem cells. He uses *Drosophila* as a pilot model to explore molecular mechanisms underlying stem cell division, and the mouse as an advanced model to expand what is learned from *Drosophila* to mammalian and human systems. Dr. Lin is also Director of the Yale Stem Cell Center.

## Expansion of Cell Biology 2008-present

In 2007, Ira Mellman resigned to take a position at Genentech, Inc., in California. James D. Jamieson resumed the chair as Interim Chair. In 2008, President Richard Levin and Dean Robert Alpern made a major commitment to strengthen Cell Biology at Yale University. James E. Rothman, Ph.D., was recruited and named the Fergus F. Wallace Professor of Biomedical Sciences and the next Chairman of Cell Biology. In addition to existing space in Sterling Hall of Medicine, one floor of a building at the West Campus in West Haven and Orange, formerly the Bayer Company facility, was devoted to Cell Biology. There, James Rothman has launched a Center for High-Throughput Cell Biology. Tools and techniques have been developed to determine the cellular functions of the 25,000 known protein-coding genes in the human genome. This research should provide a basis for the development of new molecular targets for therapy of many diseases.

Dr. Fred Gorelick received a primary appointment as Professor of Cell Biology in 2009. He has been a Professor of Medicine (Digestive Diseases) since 1994. After completing medical school at the University of Missouri in 1973 and internal medicine training at the University, Dr. Fred Gorelick came to Yale for a fellowship in gastroenterology in 1976. He began basic science training with Dr. James Jamieson at Yale in 1978. During that period, he described calcium-calmodulin dependent protein kinase II. He subsequently worked with Dr. Paul Greengard at Rockefeller University to demonstrate how this enzyme could become calcium-independent and function in memory. His later work has focused on the mechanisms of acute pancreatitis and how digestive enzymes, such as trypsin, are activated within the pancreas during this disease. Dr. Gorelick directs a course, Cell Biology 601, the *Molecular and Cellular Basis of Human Disease* that helps educate physician scientists.



Fred Gorelick 2009

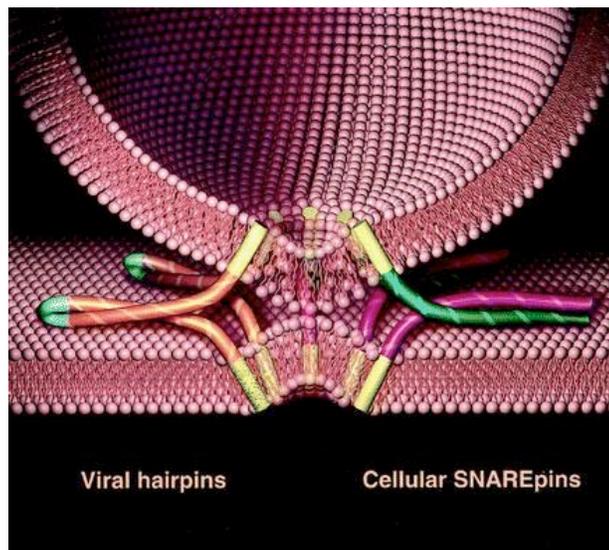
James Rothman graduated *summa cum laude* from Yale College in 1971 with a degree in physics. He attended Harvard Medical School, but before completing his medical degree, decided he wanted to pursue research in basic science. He earned a Ph. D. in biological chemistry from Harvard in 1976. He then spent two years as a postdoctoral associate with Harvey F. Lodish at the Massachusetts Institute of Technology. In 1978, he took a position as an assistant professor at the Stanford School of Medicine. He was at Princeton University from 1988 to 1991. In 1991, he became the first chair of the Department of Cellular Biochemistry and Biophysics at Memorial Sloan-Kettering Cancer Center in New York and vice-chair of the Sloan-Kettering Institute. He was Professor of Physiology and Cellular Biophysics at the College of Physicians and Surgeons of Columbia University and the Clyde and Helen Wu Professor of Chemical Biology. He is a member of the National Academy of Sciences and the Institute of Medicine, a fellow of the American Academy of Arts and Science, and a foreign associate of the European Molecular Biology

Association. He has received many honors including the Louisa Gross Horwitz Prize and the Albert Lasker Award for Basic Medical Research in 2002. In 2010, he was awarded the Kavli Prize in Neuroscience.



James Rothman 2008

James Rothman's research involves study of the molecular mechanisms and regulation of vesicular traffic and membrane fusion in cells. He employs diverse biophysical, biochemical, and cell biological approaches to characterize the fundamental participants in intracellular transport processes. He formulated the "SNARE hypothesis" by which distinctive, complementary proteins known as SNAREs, expressed on both vesicles and target membranes, ensure that different classes of vesicles bind to the appropriate target membranes and then initiate the biochemical changes leading to fusion of vesicles with the target membrane and delivery of the vesicles' cargo to their proper destinations.



Vesicle-plasma membrane interaction, James Rothman, 2008

In 2010, the Department of Cell Biology at Yale comprises a dynamic and interactive group of 34 faculty members and their research laboratories that span every major area of investigation central to the field. There are also 111 postdoctoral fellows and 73 graduate students. The external grant funding is \$7,700,000. The primary facilities are located at the School of Medicine and at Yale's new West Campus. Cell Biology is developing rapidly at areas of interface between conventional molecular cell biology of single cells and more complex cellular systems at one extreme, and at the interface with protein structure and molecular mechanisms at the other. Therefore, the Department operates Yale's Center for High Throughput Cell Biology which carries out genome-wide screening to establish patterns of gene function in cellular systems. The Department has become a center of excellence in biophysical methodologies related to molecular mechanisms, such as X-ray crystallography, super-resolution optical imaging, and optical tweezers force analysis. Cell imaging in particular is the vital core of Cell Biology. The Department maintains a high level of capability in electron microscopy, including immunocytochemistry and tomography; in conventional optical microscopy at the Center for Cell & Molecular Imaging (CCMI) which performs state of the art electron microscopy and immunocytochemistry, as well as routine single and multi-photon confocal microscopy; and the CINEMA Lab, a world leader in the development of new optical techniques for live cell imaging and quantitative analysis.

## References

Bulletin of Yale University, School of Medicine.

Burrow, Gerard N. 2002 A History of Yale's School of Medicine: Passing Torches to Others, Yale University Press, New Haven, 368pp.

[Catalog] Yale University, Department of Medicine (Yale Medical School).

Catalogue of the Faculty and Students of the Medical Institution of Yale College.

Catalogue of the Officers and Students of the Medical Institution of Yale College.

Catalog of Yale University, 1813-1972.

Falvey, K. L. 2010 Medicine at Yale The First 200 Years. Yale University Press, New Haven, 256pp.

Ferris, H. B. 1924 Yale University School of Medicine Department of Anatomy, Methods and Problems of Medical Education, First Series, The Rockefeller Foundation, New York, 1-16.

Flexner, S. 1924 T. Mitchell Prudden, 1849-1924. Science 60:415-9.

Jamieson, J. D. 2008 A tribute to George E. Palade. J. Clin. Invest. 118:3517-8.

Lentz, T. L. 2011 History of the Department of Cell Biology at Yale School of Medicine, 1813-2010. Yale. J. Biol. Med. 84:69-82.

Nicholas, J. S. 1960 Ross Granville Harrison 1870-1959. Yale J. Biol. Med. 32:407-12.

Smith, Herbert E. [c1893] The Yale Medical School, Tuttle, Morehouse & Taylor, New Haven, 30pp.