NATIONAL ACADEMY OF SCIENCES

# CARROLL MILTON WILLIAMS

*1916—1991*

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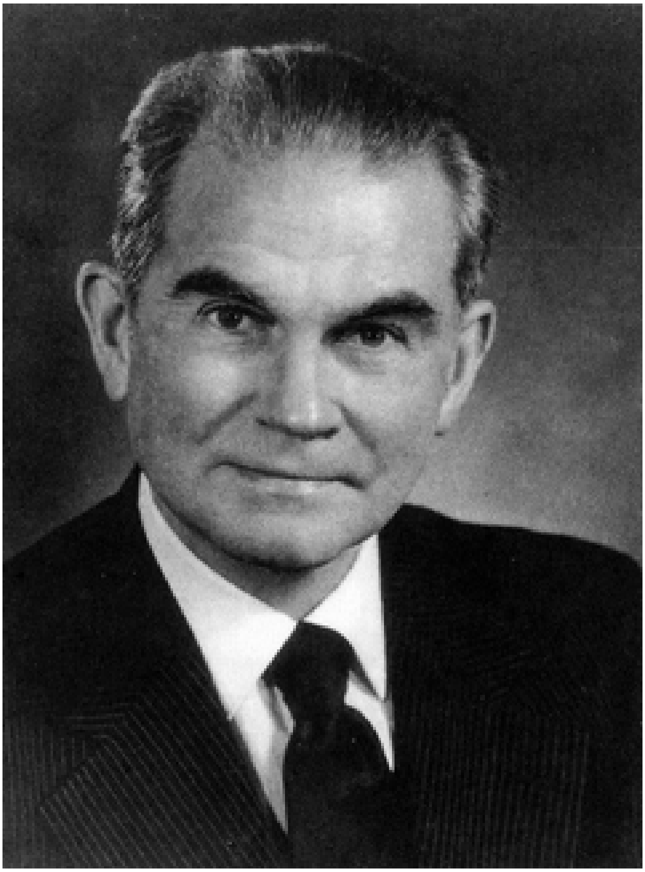
*A Biographical Memoir by*
A.M. PAPPENHEIMER, JR.



*Biographical Memoir*



Carroll M. Williams

# CARROLL MILTON WILLIAMS

*December 2, 1916–October 11, 1991*

BY A. M. PAPPENHEIMER, JR.

CARROLL MILTON WILLIAMS was born in Richmond, Virginia, on December 2, 1916. Even in his early school days he showed great interest in science and soon after entering the University of Richmond at the age of sixteen began collecting and studying lepidoptera. Upon graduation, he gave his outstanding collection to the university.

Carroll published his first paper on butterflies in 1937, when he was twenty, just before graduating from college. In the fall of that year he became a graduate student at Harvard University, where he was to remain for the rest of his life. His thesis adviser was Professor Charles Brues, a well-known entomologist. Carroll's remarkable and brilliant thesis was titled "A Morphological and Physiological Analysis of the Flight of *Drosophila,* with Special Reference to Factors Controlling Wing Beat" and was written in what was to become Williams's characteristic and unique style with its humorous overtones. In collaboration with Leigh Chadwick and with advice from Professor Edgerton of MIT, Carroll designed a small apparatus that measured accurately and reproducibly, by a stroboscopic method, the wing beat frequency of both wild-type and mutant strains of tiny fruit flies in flight under a wide variety of conditions, such as temperature, atmospheric pressure, $O_2$ tension, etc. Individual flies from various inbred strains varied between 12,000 and 14,000 beats per minute of sustained flight until exhaustion set in after as much as three hours, or more than 2 million double wing beats. He measured the glycogen content of the thoraces of the blowfly (a slightly larger insect) during flight to exhaustion and determined the energy expended in terms of glucose consumption. Finally, he succeeded in demonstrating, where others had failed, the neuromuscular network in the thorax that controls the wing beat.

In 1941, after receiving his Ph. D., Carroll was appointed a junior fellow of the Harvard Society of Fellows. It was clear from his thesis that he needed a larger experimental animal than *Drosophila* to pursue the studies he contemplated on insect development and morphogenesis. He therefore selected the giant silkworm, *Hyalophra* (formerly *Platysamia*) *cecropia*, as his experimental animal and soon made the important and useful observation that insects can be anesthetized for long periods of time, under continuous flow of carbon dioxide in a Buchner funnel, thus permitting surgical manipulations without loss of blood or damage. While still a junior fellow, he decided to obtain a medical degree and in 1946 received his M.D. summa cum laude from the Harvard Medical School.

The years that followed were exciting and fruitful ones. Carroll was appointed assistant professor of biology in 1946, promoted to associate professor two years later, and became professor of zoology in 1953 at the age of thirty-six. Finally, in 1965, he was appointed the first Bussy Professor of Biology. As one of his graduate students during the earlier period wrote:

When I think of Carroll's achievements, I am overwhelmed by memories of hilarious events and merry times. And I am sure this was one of the reasons for Carroll's success in attracting students and bringing out the best in them: life in his lab was usually such fun and we all shared so many laughs.

*Cecropia* moths lay their eggs in early summer. After hatching, the tiny caterpillars grow rapidly and after four molts attain a length of more than three inches. They then spin a cocoon inside of which they metamorphose and enter a prolonged period of pupal diapause over the winter. If pupae that have entered diapause are placed at 3° to 5°C for a few weeks, adult development may be initiated promptly by removing them to warm temperatures. Without this period of chilling, adult development will not begin for many months, if indeed at all. Carroll began his studies on adult development by placing diapausing pupae in different orientations under temperature gradients with one end kept at 3° to 5°C and the other at 25° to 30°C. He observed that although development began in the *chilled anterior* end, once started, the heated end developed faster. It was these initial observations that led Carroll to publish a long series of remarkable and highly original papers in the *Biological Bulletin* on the physiology, biochemistry, and hormonal control of insect diapause and adult development. Many of these and his subsequent papers and lectures were illustrated by the excellent photographs and slides made by his wife Muriel.

Carroll's experiments were often amusing as well as ingenious and revealing. He began with parabiotic experiments in which he joined together by their heads diapausing pupae and *chilled* diapausing pupae. Almost simultaneously, both began to develop into adult moths. He soon found that removal of the brain from a pupa leads to permanent diapause but that adult development took place promptly if the brain from a *chilled* pupa was dropped into a brainless diapausing pupa at 25°C, even if the latter was of a different species, such as *Antheraea* (formerly *Telea*) *polyphemus* or *Samia cynthia.* By means of plastic windows placed in either the face or the tip of the abdomen, development could be followed day by day from its onset until emergence of the adult moth twenty-one days later. Although it was evident that the *chilled* brain secreted a hormone necessary for initiation of adult development, it was soon shown that this was not a sufficient condition. When brainless pupae were cut in half and chilled brains were dropped into each half-pupa, only the anterior half went on to develop into *half* an adult moth! However, if both a *chilled* brain and a bit of prothoracic "gland" tissue, dissected from a normal pupal thorax, were dropped into the posterior end, an adult abdomen developed (see Figure 1). Further work showed that a tropic hormone was synthesized by a set of eleven neurosecretory cells in the anterior part of the chilled brain that activated the prothoracic glands to produce a growth and development factor. In 1954 Peter Karlson, working in Butenant's laboratory in Germany, isolated 25 mg of the crystalline growth factor from 500 kg of *Bombyx mori* pupae. He named it *ecdysone* and determined its steroid structure.

It was obvious that each morphological change from larva to diapausing pupa and finally to an adult moth must be accompanied by dramatic changes in metabolism. During the next few years these changes were studied by Carroll and his students—R. C. Sanborn, H. A. Schneiderman, D. G. Shappirio, and W. R. Harvey. It came as no surprise to find that oxygen consumption dropped precipitously upon entering diapause and rose again during adult development. Nor was the fact that, upon entering diapause, most components of the cytochrome system were broken down and, with the exception of the intersegmental muscles of the pupal abdomen, tissue respiration, including that of the heart, which continued to beat slowly, became insensitive

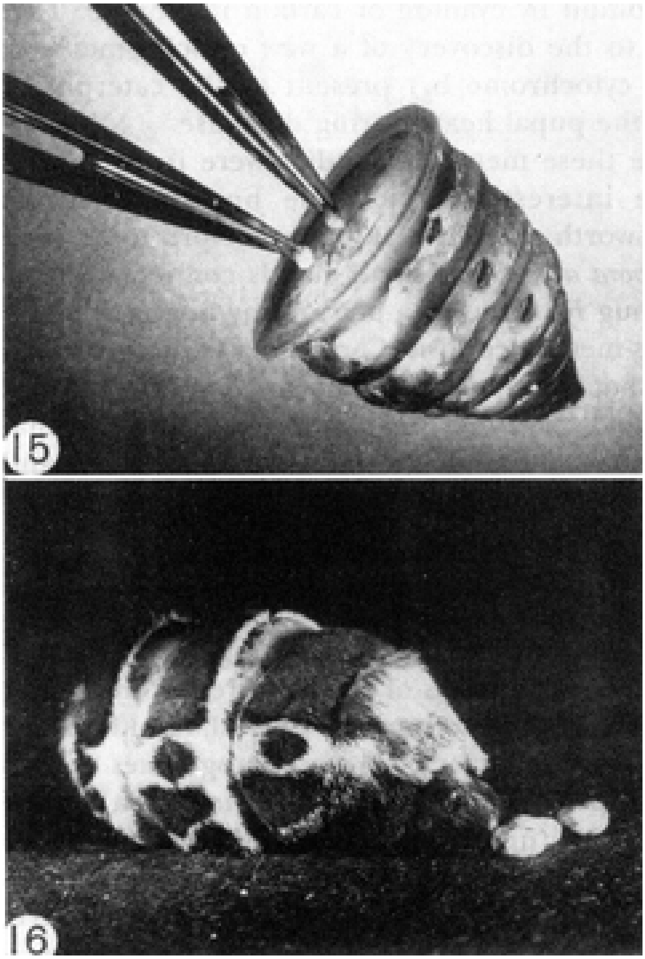



FIGURE 1 Upper: Brain and prothoracic glands obtained from previously chilled pupae being implanted into an isolated pupal abdomen. Lower: Implanted endocrine organs have caused adult development of the abdomen, which is shown laying eggs.

to inhibition by cyanide or carbon monoxide. These studies led to the discovery of a new cytochrome X (later renamed cytochrome $b_5$) present in the caterpillar midgut and in the pupal heart during diapause.

While these metabolic studies were in progress, Carroll became interested in juvenile hormones, which V. B. Wigglesworth showed many years before to be secreted by the *corpora allata*, two small glands connected to the brain of the bug *Rhodnius* by a pair of tiny nerves. This hormone opposes metamorphosis. Carroll made the surprising observation that excision of the *corpora allata* from *chilled cecropia* pupae had no effect on development into normal fertile adult moths, although when removed from adults and tested, they proved to be more active than at any stage of its life history. However, during the very early stages of adult development, addition of the hormone caused transformation into a second pupa with mere traces of adult characteristics. Finally, the most surprising finding was that the highest concentrations of all were present in the abdomens of adult *male cecropia* moths. Carroll found that the hormone could be extracted from homogenates of male abdomens by petroleum ether, which yielded a potent water-insoluble oil upon evaporation. Even after 50,000-fold purification, the active component still contained impurities, but the purest preparations had the properties of a terpenoid acid, and certain synthetic derivatives of farnesoic acid had potent juvenile hormone activity.

In 1964 Dr. Karel Slama came from Czechoslovakia to work in Carroll's laboratory, bringing with him fertile eggs from the bug *Pyrrhocoris* that he had been rearing in Petri dishes without difficulty in his Prague laboratory for ten years. In the Harvard laboratory, however, all larvae continued to experience additional larval molts and died without becoming adults. The difficulty was finally traced to Scott paper toweling that had been placed in the rearing jars. When replaced by Whatman filter paper, all larvae developed normally into adult bugs. The following is a quotation from a paper by Slama and Williams published in the *Proceedings of the National Academy of Sciences* in 1965:

> Indeed, pieces of American newspapers and journals (*New York Times, Wall Street Journal, Boston Globe, Science,* and *Scientific American*) showed extremely high juvenile hormone activity when placed in contact with *Pyrrhocoris* larvae. The *London Times* and *Nature* were inactive.

The active factor could be extracted from Scott paper towels with organic solvents and was found to be a petroleum ether-soluble oil that was highly active as a juvenile hormone when tested on *Pyrrhocoris* but that had no effect on metamorphosis of *Cecropia.* The factor could easily be extracted from American balsa fir, but only traces were present in European paper pulp. Even in his first paper on juvenile hormone, which appeared in 1956 as a letter to *Nature,* Carroll realized its potentiality as a pesticide and wrote as follows:

> In addition to the theoretical interest of the juvenile hormone, it seems likely that the hormone, when identified and synthesized, will prove to be an effective insecticide. This prospect is worthy of attention because insects can scarcely evolve a resistance to their own hormone.

By the mid-1970s this prediction had been verified. Three closely related juvenile hormones had been synthesized, and several substances that derail development of certain insect species by turning off secretion of juvenile hormone by the *corpora allata* had been isolated from plants in other laboratories. The chemical industry was engaged in synthesizing hundreds of cheaper and more stable analogs of these compounds. In a number of cases, these analogs have shown highly *specific* activity for certain insect species. For example, the juvenile hormone analog Methoprene is now in use in controlling the floodwater mosquito *Aedes nigromaculus*, a species that had become resistant to conventional pesticides. Less than 5 g spread per acre gives good control.

About this time, Carroll found that he was unable to mate *polyphemus* moths in the laboratory. The larva of this moth feed on oak. With Lynn Riddiford, he soon found that, after adding a few oak leaves to the cages, the females secreted a pheromone that attracted males and stimulated mating. (I cannot resist quoting here from a short note published in *Science* by Riddiford and Williams: "The action of oak factor on the female can be masked by other volatile agents including Chanel No. 5."

In 1970 or 1971 Carroll abandoned his favorite experimental animal, *cecropia*, and switched to *Manduca sexta* (the tobacco hornworm). The great advantage of *Manduca* is that it can be raised, even during the winter, on a simple artificial diet, making possible the study of the larval stages all year round.

*Manduca* larvae during their final fifth instar increase their weight within four to five days from about 1 g to as much as 10 g, after which they stop feeding and purge their gut, reducing their weight to 5 g. After the purge the larvae enter a "wandering stage" that soon ends in an abrupt onset of negative phototaxis. In the wild, larvae would then dig into the ground before pupation. The experiments at the Harvard laboratory, however, were carried out on a twelve-hour light/dark cycle. Most of the experiments on hormonal control of *Manduca* development were carried out by postdoctoral fellows and students during the decade before Carroll's retirement to emeritus status. *Manduca* has now become one of the most important model systems for the study of insect physiology, development, neurobiology, and molecular biology.

During the last few years before his final illness, Carroll did very little at the bench himself. Nevertheless, he kept up with current literature and realized that many of the questions raised by his experiments on insect development and the regulation of insect hormone expression could be answered by the techniques of present-day molecular biology. After departmental colloquia he often rose to ask visiting lecturers important and penetrating questions relating to the biological significance of their molecular findings, even though the subject might be quite remote from his own field.

Carroll enjoyed teaching and was not only an entertaining and popular lecturer but also stimulated many students to become interested permanently in biology and often to seek to do graduate study under his guidance. But he never directed a large team of graduate students and postdoctoral fellows as is so often the case in molecular biology today. Almost all of his students came to his laboratory because they fell under his spell while listening to his lectures or because they were fascinated by his published experimental work. Carroll's five o'clock laboratory teas were legendary and were attended by everyone, from undergraduates to visiting professors. The following are direct quotations from letters written to me by three of his former graduate students, now tenured professors of biology at the State University of New York at Stonybrook, the University of Washington, and the University of Michigan, respectively:

> Carroll was also exceptional—certainly by the standards of today—in his willingness to point students to problems that were quite remote from the work he did himself. He did not hesitate to launch students on projects that required techniques he had never used and which were founded on principles about which he had little knowledge. Carroll would learn along with the student and seemed always to contribute the needed experimental trick or flash of insight.

Carroll was always full of ideas and tried to instill into his graduate students and postdoctoral associates the importance of doing experiments to test ideas particularly those that seemed far-fetched. He had little patience with students who would find various theoretical reasons why something might not work and would not go to the lab to test an idea. He also, though, was a hard task master in ensuring that experimental results were repeatable and that further experiments necessary to explain the results were done before they were published. Hence, many of his papers talk about work done over years.

In the years I was a graduate student, we had tea each afternoon. Undergraduates, graduate students, postdoctoral fellows and visitors regularly attended. Of all the insect hormones then known (and perhaps now known), juvenile hormone was the most mysterious and fascinating. At the tea-table I heard what I think were his first statements about using it and perhaps other insect hormones as insecticides of the future or third generation pesticides.

It will come as no surprise to learn that Carroll was in much demand as a gifted lecturer. He was invited to deliver more than forty named lectures, among which, to mention only a few, were the Lowell lectures in Boston (1948); the Harvey Lecture in New York (1952); the AAAS Holiday Lecture, University of Chicago (1970); and the CSIRO Lectures in Australia (1973).

Carroll was elected a fellow of the American Academy of Arts and Sciences in 1951 and served on its council from 1952 to 1955 and again from 1974 to 1977. He was elected to the National Academy of Sciences in 1960 and was a member of its council from 1973 to 1976 and again from 1985 to 1988. He was chairman of the Section on Biological Sciences from 1981 to 1984. He also became a member of the Philosophical Society in 1969 and was a member of numerous other learned societies, including the Pontifical Academy of Rome.

I AM GREATLY INDEBTED to Professors Lynn M. Riddiford, William G. Van der Kloot, and David G. Shappirio for sending me their reminiscences of Carroll and to Daniel Branton and Fotis Kafatos for critical reading of the manuscript.

## HONORS AND DISTINCTIONS

Borden Research Award, Harvard Medical School, 1946
AAAS-Newcomb Cleveland Prize, 1950
Guggenheim Fellowship (Cambridge University), 1955-56
Founders Memorial Award, Entomological Society of America, 1958
Boylston Medalist, Harvard Medical School, 1961
Trustee of Radcliffe College, 1961-64
George Leslie Award, Harvard University, 1967
Howard Taylor Ricketts Award, University of Chicago, 1969
Chief scientist to *Alpha Helix* expedition to the upper Amazon

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