NATIONAL ACADEMY OF SCIENCES

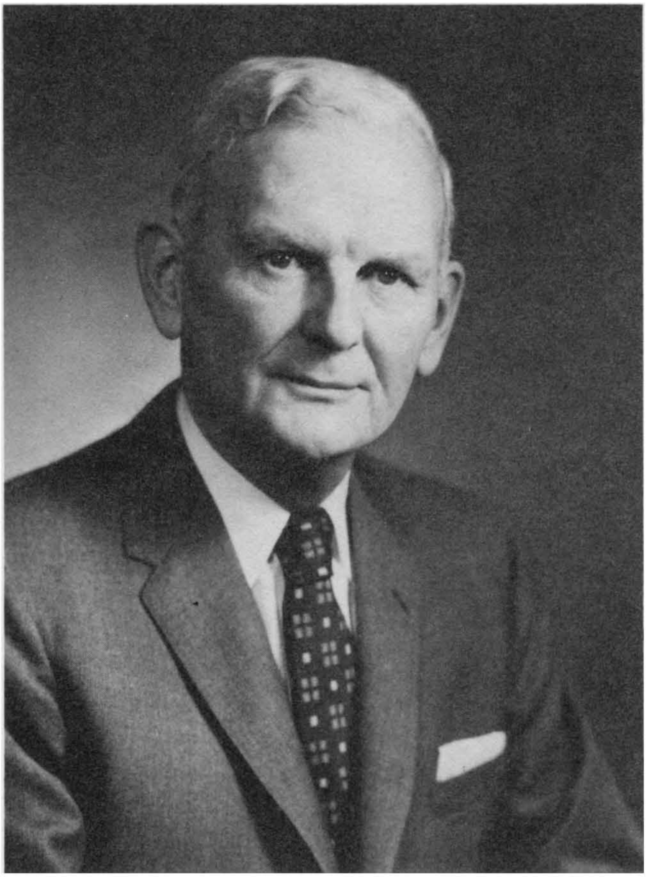
BENJAMIN HARRISON WILLIER

1890—1972

A Biographical Memoir by

RAY L. WATTERSON

Biographical Memoir



Courtesy, Ray L. Waterson

B. H. Willier

BENJAMIN HARRISON WILLIER

November 2, 1890–December 3, 1972

BY RAY L. WATTERSON

THIS MEMOIR is deliberately written as a montage, defined in *Webster's New Twentieth Century Dictionary* (1971) as "the art or process of making a composite picture by bringing together into a single composition a number of different pictures or parts of pictures and arranging these . . . so that they form a blended whole while remaining distinct." It is a montage of circumstances, experiences, reminiscences, characterizations, evaluations, anecdotes, thoughts, generalizations, and conclusions related by many people through much correspondence, by statements in publications, and in some of the subject's personal papers and 1945 autobiographical sketch on file with the home secretary of the National Academy of Sciences.

The first appearance of the name B. Harrison Willier in the scientific literature was the consequence of an unusual series of circumstances. A pregnant uterus with fibroids was removed by a prominent surgeon in Wooster, Ohio on October 19, 1915, and the implanted human embryo was carefully preserved and presented to Dr. Horace N. Mateer, an excellent teacher and head of the biology department of

NOTE: The Academy would like to express its gratitude to Dr. Gary C. Shoenwolf for his help with the preparation of this memoir after the death of Ray L. Watterson.

the College of Wooster. Willier, following his graduation from Wooster in 1915 with highest honors in biology, remained there as an instructor in biology, serving as Mateer's laboratory assistant, during the 1915–1916 academic year. During that fall Willier prepared the specimen for microscopic study by embedding it in paraffin, sectioning it serially, and mounting the sections on microscopic slides (at least those containing the embryo proper, which he also stained).[1] "When Mateer's son, a medical student at the Johns Hopkins University, bragged in a letter about the wonderful collection of human embryos he was studying there, father Mateer boxed up some of the slides Willier had made, sent them to his son saying 'Show these to your professor!' " Immediately word came back from Franklin P. Mall, professor of anatomy and director of the Department of Embryology, Carnegie Institution of Washington, "to the effect that all facilities there were at his disposal and to please send them all the slides he had so they could prepare a reconstruction and a monograph." The entire specimen was promptly deposited on temporary loan in the Department of Embryology. It proved to be a very young, well-preserved, valuable presomite embryo, and Dr. G. L. Streeter, a member of the department, prepared a detailed description and two excellent wax plate reconstructions of the embryo, which he named the Mateer embryo. His monograph, published in 1920, gave appropriate credit to Willier for his role in this chain of events. All slides were subsequently returned to Mateer at the College of Wooster where zoologist Dr. C. L. Turner prepared drawings of all sections through the em-

[1]Events described here were reconstructed from a summary of the records of the Mateer embryo graciously provided by Dr. Ronan O'Rahilly and correspondence with Dr. Lowell Coolidge of the College of Wooster and Dr. Frank R. Kille, a graduate of Wooster and a Willier doctoral student. Direct quotes are from the latter.

bryo proper and yolk sac, which he published in 1920 together with a drawing of one of his wax plate reconstructions. Drawings of one of Streeter's models, the Turner model, and one of the transverse sections through the primitive streak level of the Mateer embryo continue to illustrate Professor Leslie B. Arey's classical textbook of embryology (*Developmental Anatomy*), demonstrating the enduring significance of Willier's fortuitous, albeit minor, role early in his career in the study of this important early human embryo, whose postfertilization age has been estimated to be sixteen to seventeen days.

Many years later (1968), at the age of seventy-eight, after an unusually illustrious career as teacher, investigator, administrator, and editor, this same Benjamin Harrison Willier published a significant and comprehensive descriptive paper on development of the chick yolk sac utilizing modern techniques of cytochemistry, radioautography, and electron microscopy. What pleased him most about this contribution was that it presented new problems galore. Professor Saul Roseman of the Johns Hopkins University was to say of this paper, at the Willier memorial service, "it raised so many fundamental questions at the molecular level that I presented it at one of our biochemistry seminars and spent most of my time pointing out the diverse biochemical questions that had been asked." One year later (1969) Willier opened an international symposium entitled *Problems in Biology: RNA in Development* with a succinct, thoughtful, pertinent, and historically informative commentary entitled "Reflections on Nucleic Acids in Development" (Willier, 1970). These two publications were from a man who had often been dubbed a classical embryologist (fondly, he presumed) by his colleagues at the Johns Hopkins University! At the Willier memorial service Professor Stephen Roth of Johns Hopkins remarked "With an amazing amount of wit and charm, he linked the younger scientists to their history." Roseman stated, "He was a man who recognized the best of that which had been accomplished in the past, but at the same time perceived where and how we must go in the future. He was not only remarkable, he was almost unique."

In 1971, after completing the manuscript for his biographical memoir of Charles Haskell Danforth for the National Academy of Sciences (Willier, 1974), his thoughts again centered repeatedly on the marvels of the hen's egg and its development. These he had earlier expressed (1968) so simply in a letter to one of his granddaughters: "There is nothing so marvelous as the way an egg can make a chick or how an egg made you or how an egg made grandpapa." This was his credo throughout his scientific career. In his never-ending efforts to understand the ways of the embryo-in-the-making (one of his favorite expressions), his childlike delight in and obvious enthusiasm for what he was doing intellectually were repeatedly and increasingly manifested.

Willier died at the age of eighty-two years and one month on December 3, 1972, in Union Memorial Hospital in Baltimore, Maryland after a week's illness. He was still thinking actively about problems of development on November 24, the day before his fatal illness struck. He was survived by his wife, Helen Shipman Willier (deceased August 16, 1980), their daughters, Helen Kathryn Disser and Louise Kehoe, four grandchildren (Barbara Cathryn Disser and Leslie Louise, James Benjamin, and Lynn Louise Kehoe) and one brother, Andrew Jacob Willier, a chemist (deceased May 7, 1978). In a letter to me dated October 15, 1973, Mrs. Willier wrote that Louise and her husband had recently climbed to Morning Glory Lake high in the Canadian Rockies and there had scattered Willier's ashes as he had hoped might be done. In cards to me dated September 29 and November 8, 1972, he had characterized this area as "my favorite vacation site" and as "my favorite site for peace and rest in the mountains."

A memorial service was held at the Johns Hopkins University on December 11, 1972, with comments by Drs. James D. Ebert, William F. Harrington, Saul Roseman, Stephen Roth, John W. Saunders, Jr., and Jane M. Oppenheimer. At the end of the annual business meeting of the Division of Developmental Biology of the American Society of Zoologists in Washington, D.C. on December 27, 1972, Oppenheimer announced his death and commented briefly on his great interest in developmental biology. Members rose for a moment of silent tribute to their "world-renowned colleague and inspirational leader" (*Divisional Newsletter*, February, 1973). A comprehensive memorial article was published in 1973,[2] a brief memorial statement prepared by Ebert appeared in the March 1973 *Newsletter of the Society for Developmental Biology*, and brief memorial articles appeared in 1973[3] and 1974.[4]

ANCESTRY AND EARLY YEARS

Benjamin Harrison Willier was born on November 2, 1890, on the family farm near Weston, Wood County, Ohio.[5] During his early years his home occupations were farming and the usual barnyard chores, neither of which suited his tastes or interests. His ancestors were farmers. His mother, Mary Alice Rickard, was born in Wood County. Her father

[2]Ray L. Watterson, "Benjamin Harrison Willier: 1890–1972. His Life As An Outstanding Biologist, Embryologist, and Developmental Biologist," *Developmental Biology*, 34 (1973):f-1-f-19.

[3]Jane M. Oppenheimer, "Benjamin Harrison Willier (1890–1972)," *Year Book of the American Philosophical Society*, 1973:174–79.

[4]Jane M. Oppenheimer, "Benjamin Harrison Willier 1890–1972," *Anatomical Record*, 180 (1974):186–87.

[5]Most details included in this section are from correspondence with Mrs. Willier and their daughter, Helen Kathryn Disser, and Willier's autobiographical sketch.

(Willier's maternal grandfather), Andrew Jacob Rickard, in addition to farming, owned two sawmills, a planing mill, and later a drugstore; he also served as mayor of Milton Center, Ohio. He had planned to attend college but instead fought in the Civil War as a private in Company D of the Thirty-Fourth Regiment of Zouaves. Her mother (Willier's maternal grandmother), Emma Cole, was a well-read and self-educated woman. His maternal great-grandfather was Andrew Jackson Rickard, a carpenter as well as a farmer. Willier's father, David Willier, was born in Henry County, Ohio, near Weston. He later became a banker in Wooster, an occupation he enjoyed much less than farming. Willier's paternal grandfather, likewise named David Willier, a farmer near Weston, Ohio, was born in Switzerland, French Canton. He fought in the Civil War as a private in Company H of the Sixty-Eighth Regiment of the Ohio Infantry. His paternal grandmother, Barbara Vogel, was born in Germany and married in the United States. His paternal great-grandfather, Philip Vogel, farmer, originally settled in Chautauqua County, New York before moving to a farm in Ohio.

Willier once wrote that he was "preordained a Presbyterian prior to birth." In 1972 a former colleague at the University of Rochester, now deceased, added in a solicited communication that "He came from a narrow background family and had inherited the prejudices of a simple farmer family of fundamentalist attitudes." By contrast, Oppenheimer emphasized at the Willier memorial service that "It was his good fortune to belong to a generation closer than our own to a predominantly rural America." This circumstance profoundly influenced his life. He attended a country grammar school through the eighth grade and then a two-year high school in a small country town (Milton Center), receiving a diploma therefrom in 1909. No subject in grammar or high school really captured his imagination and interest. Of the subjects taught (science was not then in the curriculum), grammar, geography, and ancient history interested him most. At about the time of graduation from high school his sole ambition was to be a teacher in the public schools. After a year of special study, mostly in the same high school, he obtained a teacher's certificate that entitled him to teach at least the three *R*'s.

He later wrote that "A lifetime devoted to living organisms began early in life when as a boy I developed a natural interest in living things both animal and plant."[6] He took a special interest in cultivating plants and trees. He planted trees everywhere on the farm, much to the disgust of his father who wanted every inch of ground for growing crops. But his mother encouraged him, for she, too, was fond of plants. But he was most fascinated by insects and spiders, especially by the variety of insects and their behavior. One of his early experiences is best told in his own words:

> As I walked along a dusty lane leading to the back end of the family farm, my attention was suddenly drawn to an adult beetle rolling fresh cow dung into a perfect ball. Its behavior was very intriguing so I watched for hours. I had no other way of finding out about this beetle. There was no library short of thirty miles and I did not dare tell my family or ask anybody questions. Seemingly the intellectual climate was the inhibitor. What a strange boy! Not until adulthood did I find out that my beetle was akin to the *sacred beetle* of Egypt (scarab or dung beetle of the family Scarabeidae). Egyptians considered this beetle as symbolic of planetary movements and future life (often buried with mummies of great men such as kings). The ball which is rolled from sunrise to sunset represents the earth in rotation. The beetle itself (due to its head projections) personified the sun and its rays. Thirty segments of its six tarsi (tarsus = foot) represent days of the month. The beetles were thought to be all males that symbolized a race of warriors.[7]

[6] "On the Occasion of a Portrait" (unpublished pamphlet, 1968), p. 4.
[7] *Ibid.*, 4–5.

Earlier he had stated that he had observed a pair of scarab beetles working together to form the round ball of cow dung, which serves as food for the larva when it hatches, but that these observations had little or no meaning for him then because he had neither books to read nor science teachers to consult.

These comments reveal a number of personal traits that characterized Willier throughout his lifetime: an inherent curiosity about all living things; an inner urge to learn and thus fill in gaps in his knowledge and understanding; attention to detail; conciseness, simplicity, and clarity of expression; desire to know plants and animals intimately, their scientific names and taxonomy; relation of his observations of nature to other areas of knowledge; his habit of learning from authorities by questioning them; and an acute awareness of and sensitivity about the stringent limitations his childhood environment placed on his interest.

His ambition to be a public school teacher was never realized owing to a fortuitous turn of events. Through the influence of a cousin, Alice Rickard, a successful teacher in the public schools, he spent six weeks (1910) at a summer session of the State Normal College of Miami University (Oxford, Ohio). Here he was introduced to nature study; for the first time he clearly recognized his primary interest. He could no longer be a teacher of the three *R*'s.

LATER TRAINING AND THE DEVELOPMENT OF SPECIAL INTERESTS

Through the influence of his maternal grandmother (Emma Cole Rickard) and of the minister of the community church (probably Presbyterian), Willier entered Wooster Academy, then a division of the University of Wooster (later the College of Wooster), in 1910. While in the Academy he first became interested in biology as a science. Of the subjects studied, chemistry interested him, but it was natural history that thrilled him. In addition he studied botany, ecology, and physiology and was an excellent student in German and French. Upon graduation from the Academy in 1912, he entered the College of Wooster and, upon completion of the four-year program in three years, received the B.S. degree with highest honors in biology in 1915. The writer of Willier's obituary for the College of Wooster wrote "When we sat side by side in the biology lab of Dr. Mateer's introductory course in biology, Ben was already well along in his knowledge of living organisms."[8] Friendship with his future wife, Helen Beatrice Shipman, began when they worked at the same laboratory table in Dr. Mateer's biology and embryology courses. Both sang in choirs; both were very active in the Christian Endeavor Society for young people in the Presbyterian Church; and both were awarded certificates as Christian Endeavor Experts in 1913. Both were also members of a bird study group that met at 5:15 A.M. on Wednesdays and Saturdays throughout 1913. Oppenheimer later wrote, "His interest in birds was part of his life in the laboratory and out of it, and had been since he was a young child."[9] Willier was a member of the German club, a member and president of the science club, and a member and treasurer of the campus prohibition league.

In 1916, following a year as instructor in biology at his alma mater, Willier began his graduate work in the Department of Zoology of the University of Chicago. Following a brief absence during 1918 for service as a sergeant in the Army Medical Corps in the Surgeon General's Office in

[8]William Taeusch, *Wooster Alumni Magazine*, April 1973, p. 30. Information about Willier at the College of Wooster was obtained largely through the courtesy of Dr. Lowell W. Coolidge, reference associate, Andrews Library, and Mr. W. Lee Culp, registrar of that college, and from correspondence with Kathryn Willier Disser.

[9]Oppenheimer, "Benjamin Harrison Willier," p. 175.

Washington, D.C., he returned to graduate school in January 1919, married Helen Beatrice Shipman on September 11, 1919, and received his Ph.D. degree in zoology magna cum laude in 1920. He possibly went to Chicago specifically to work with Professor Frank R. Lillie, but the decision to work with Lillie may have been made after Willier arrived in Chicago. Be that as it may, Willier began to work with the right man at just the right time in the development of Lillie's research program. His graduate work started while endocrinology was in its infancy. He first encountered the term "hormone" as a student of professors Lillie and A. J. Carlson at Chicago. Willier's doctoral dissertation (1921) and many aspects of his later research stemmed directly from events transpiring in Lillie's laboratory, especially from 1914 to 1920 and thereafter. A brief digression to document these early events is pertinent to understanding Willier's lifelong research interest concerning endocrines in development and related problems, as well as the initial directions taken in development of his own research program.

Lillie had become interested in the developmental anatomy of "freemartins," that is, sterile female calves born twins of normal males. In cattle, about 87 percent of genetic females in different-sexed twin pairs are freemartins, whereas the remaining 13 percent are fertile. The existence of freemartins had long been known, as had the predominantly male character of their internal reproductive organs. Lillie once explained the reasons why his interest in freemartins had been stimulated as follows. "The writer's interest in the subject arose originally from the birth of free-martins in his own herd of cattle (from 1909 on); thus brought into immediate contact with the subject he realized its great biological significance and first took up its serious study in 1914.[10] Proximity to the Chicago stockyards from which

[10]Frank R. Lillie, "Tandler and Keller on the Free-martin," *Science*, 50 (1919):183–84.

material could be secured in abundance was another inciting cause to its study."

Lillie wrote (p. 371): "No one has hitherto attempted to explain how the association of male and female *in utero* could lead to sterility of the female with a more or less pronounced male organization of the internal organs of reproduction, nor why certain females should escape the defect, nor why the phenomenon should be peculiar to cattle."[11] In order to initiate investigations of these problems, in the autumn of 1914 Lillie began, with the cooperation of a major meat packing company in Chicago, to collect uteri (ideally with both ovaries attached) containing twins from freshly slaughtered pregnant cows. Willier later remarked at the Lillie memorial meeting at the Marine Biological Laboratory at Woods Hole, Massachusetts (Willier, 1948, p. 153): "As a student, I remember seeing him garbed immaculately in a white gown and wearing rubber gloves, examining and dissecting pregnant uteri containing young twins which the collector had rushed to his laboratory table in a breathless manner."

Theoretically, half the developing twin pairs should consist of one genetic male and one genetic female. In such heterosexual twin pairs, the developing male should in most cases somehow suppress the female-type development of the female's internal reproductive organs and favor their development in the male direction. Careful examination of available heterosexual twin pairs within the uteri (thereby revealing the exact relationships of their encircling chorions, with emphasis on whether or not they were fused), careful study of their vascularizations, preferably injected (with emphasis on whether or not they were anastomosed), detailed anatomical and histological studies of developing reproductive organs of the genetic female member of each twin pair, and,

[11]Frank R. Lillie, "The Free-martin; A Study of the Action of Sex Hormones in the Foetal Life of Cattle," *Journal of Experimental Zoology*, 23 (1917):371–452.

finally, point-by-point comparisons with their development in normal male and female embryos of comparable stages should demonstrate how, why, and to what extent these striking transformations occurred, as well as why they sometimes failed to occur.

The results of this broadly conceived investigation, their interpretations and derived principles, published in 1916 and 1917, are classics that can best be summarized succinctly in Lillie's own words: "The conclusion was reached that the sterile free-martin is zygotically a female modified by the sex hormones of the male twin, which circulate in both individuals during foetal life owing to secondary fusion of the chorions and anastomosis of the foetal circulation of the two individuals."[12] In short, Lillie concluded that "the deviations of the sterile free-martin from the female type are due to the action of the male sex-hormones."[13] This epoch-making statement came at a time when very little was known about the nature, origin, and action of sex hormones! He recognized and stated explicitly, however, that "we are unable to assert definitely in just what positive ways the male hormones act on the female zygote, because the earliest determinable result of such action is the suppression of the ovarian cortex, which must be regarded as practically equivalent to castration."[14] And he added further that in freemartin development "we cannot study separately the effect of early embryonic castration of the female, but only as it is modified by the simultaneous presence of male hormones."[15]

Nevertheless, the broad implications of his investigation were clearly enunciated by Lillie on the same page. "The

[12]*Ibid.*, p. 371.

[13]*Ibid.*, p. 405.

[14]*Ibid.*, p. 418; Frank R. Lillie, "Sex-determination and Sex-differentiation in Mammals," *Proceedings of the National Academy of Sciences of the United States of America*, 3 (1917), p. 469.

[15]Lillie, "The Free-martin," p. 415.

free-martin gives us additional evidence of considerable value concerning the problem of sex-determination and sex-differentiation in mammals, especially in its suggestion that the course of embryonic sex-differentiation is largely determined by sex-hormones circulating in the blood." He pointed out that "On the male side there is complete absence of information as to the effects of early embryonic castration and the possible effect of the presence of female hormones in the absence of male hormones."[16] He also emphasized the need to know the effects of "treatment of the male zygote from the beginning of sex-differentiation with female hormones," as well as the need "to regulate time and dosage of hormones better than is done in this experiment of nature,"[17] which development of the freemartin represents. Thus Lillie clearly delineated most of the essential experimental approaches that would be critical to achieving real understanding of the roles of sex hormones in sex differentiation in mammals and other vertebrates. These approaches were initially followed assiduously by Willier (in birds) and Professor Carl R. Moore (in mammals) at the University of Chicago, and subsequently by Willier at the University of Rochester and by many other investigators at Chicago and elsewhere.

Lillie's pioneering studies of the reproductive systems of prenatal freemartins were restricted to gross anatomical features. Published back-to-back with his major 1917 paper was a study of the microscopic anatomy of the internal reproductive organs of seven fetal freemartins and one twenty-one-day-old specimen from Lillie's collection, the doctoral dissertion of his Ph.D. student, Catharine L. Chapin.[18] She reported that gonads of the youngest available

[16]*Ibid.*, p. 415–16.

[17]Lillie, "Sex-determination and Sex-differentiation in Mammals," p. 470.

[18]Catharine L. Chapin, "A Microscopic Study of the Reproductive System of Foetal Free-martins," *Journal of Experimental Zoology*, 23(1917):453–82.

freemartin fetus (7.5 cm long) were already modified in the male direction. Most significant was the complete absence of secondary sex cords (rudiments of the ovarian cortex of the female), although in a normal female 7.3 cm in length these cords were in an early stage of development and had already formed a narrow ovarian cortex. She also noted two other male modifications in the gonads of the youngest freemartin: the presence of a distinct connective tissue capsule (the tunica albuginea) and of a thin external layer of peritoneum. Thus masculine development of ovaries is initiated very early in the prenatal life of those genetic females in cattle destined to become freemartins. These and other specific male-type modifications described by Chapin in freemartins—especially, but not necessarily, in older specimens—developed as a consequence of "suppression of the cortex and over development of the medullary cords and urinogenital union under the influence of male sex-hormones."[19] She also noted the presence of a few germ cells within some medullary cords in gonads of the five youngest freemartins, but their absence in gonads of the postnatal specimen she examined, the oldest fetal freemartin (28 cm long), and one of three prenatal specimens (approximately 20 cm in length). Interstitial cells, presumed sources of male hormone(s) in testes, were not observed by Chapin.

GRADUATE STUDENT DAYS

Because of the difficulty of obtaining late fetal stages in cattle, no heterosexual twin pairs with body lengths greater than 28 cm were available for study of male-type modifications of freemartin gonads during the remainder of pregnancy. Gonads of nine postnatal freemartins ranging in age

[19]Summarized in Lillie, "Sex-determination and Sex-differentiation in Mammals," p. 468.

from five days to three years were available, however, provided by three postnatal freemartins in the Lillie collection (including the twenty-one-day-old specimen whose gonads were described by Chapin), and six other freemartins made available through the courtesy of Professor Leon J. Cole of the University of Wisconsin. The microscopic anatomy of these gonads was very carefully studied by Willier and was described in detail in his beautifully organized and illustrated doctoral dissertation, his first scientific publication (1921). It was completed in a remarkably short time, considering the year spent in the service and other demands on his time as a graduate student. In this investigation Willier also reexamined the histology of the prenatal freemartins described by Chapin.

Willier's publication lucidly interpreted the microscopic anatomy of postnatal gonads on the basis of their prenatal development. It provided irrefutable evidence that ovaries of zygotic females in cattle can be completely transformed into testes that are morphologically complete, including development of interstitial cells. Germ cells were almost invariably absent in gonads of postnatal freemartins in agreement with Chapin, who noted that although a few were still present in some medullary cords of prenatal freemartin gonads in two of three approximately 20 cm specimens in the Lillie collection, they were not present thereafter. The bisexual organization of the indifferent gonads of mammalian genetic females was strikingly demonstrated by this research. It inaugurated an extensive series of investigations by Willier on the role of sex hormones in development of the reproductive systems of chick embryos and related studies that established his early reputation as an authority on development of the components of the reproductive system. It marked the beginning of Willier's lifelong interest in developmental endocrinology, including his subsequent interest in feather morphogenesis, with emphasis on genetic, and later on hormonal, control of production of certain colors and color patterns in plumage resulting from the synthesis and subsequent deposition of pigment granules in feather-forming cells by pigment cells (melanocytes).

Willier never forgot the early investigations on freemartin development, up to and including his own. In a letter to me dated February 10, 1972, ten months before his death, he mentioned that more than a year earlier he had prepared a critique on the freemartin, subsequently mislaid. He added a postscript that read as follows.

> I want to add a note on the work of Catharine Chapin. I read it critically recently. The gonad material shows evidence of bad fixation—probably put into fixation after several hours in getting back to Lillie's office from the stockyards. I wish you could get normal calf embryos and make some excellent, well-stained sections and check for a bisexual organization (male and female components) that is so important for Lillie's theory.

Yet there is anecdotal evidence provided in a letter dated January 28, 1982, from Professor Howard L. Hamilton, one of Willier's former doctoral students, that the freemartin investigation was probably not the research problem Lillie initially had in mind for Willier:

> When he first reported to Dr. Lillie to be assigned a research problem, Dr. Lillie told him that he wished to isolate the gonads of an embryo from the body but to have them still in communication by way of the blood stream. He asked Willier to look into the possibility of grafting them to a vascular membrane such as the chorio-allantois, and then dismissed him, and told him to come back when he had some results. There was no further guidance, and Willier was left to his own devices in trying to solve the problem. Shortly before Thanksgiving, he obtained his first graft. Greatly excited, he ran in to Dr. Lillie's office and showed him the empty shell with the vascular C.-A. membrane and graft clinging to it. Dr. Lillie turned the shell and, carefully inspecting it from all angles, then said just two words: "Very interesting."

These events must have made a lasting impression on Willier since the following statement appeared verbatim in three of his Lillie biographies, two in 1948 and the major biographical memoir (p. 187) in 1957.

> The young student when he began research was to a large extent thrown upon his own resources. He found out for himself whether he was fitted to be an independent investigator. Once the problem was suggested and the way of approach briefly sketched, the student knew that results were expected. Only when a preliminary result was obtained did the student report to Dr. Lillie, and even then only when he was prepared to make a possible interpretation.

Apparently in many instances Willier introduced his own graduate students to their research problems in much the same way. In my own experience the introduction was even more terse.

Some of Willier's statements about Lillie as a teacher in his biographical memoir (1957, pp. 185–87) not only provide an excellent summary of Willier's formal training under Lillie and reveal his reactions to it, but serve remarkably well to characterize many basic features of Willier's own subsequent style of teaching.

> His lectures were invariably characterized by a masterful plan of organization of factual information and conciseness of statement. . . . The student was trained to think by one who directs without seeming to do so, and was attracted first of all to the organization of the seminar and graduate courses in which the results of research, interpretations, and theories were ingeniously knit together around a central theme. . . . Candidates for the doctorate were trained by the seminar method in which the student was challenged in his report of original literature to exercise judgment in the selection of pertinent data and in making significant interpretations and generalizations. The seminars covered a variety of topics such as Physiology of Development, Problems of Fertilization, and Biology of Sex.

Elsewhere Willier wrote (pp. 408–9 of his memorial resolution for the American Society of Zoologists) that "He guided the development of the student as a scientist by 'precept and example' and rarely by direct criticism or suggestion." Those who were later his graduate students at Rochester and Baltimore will recognize that Willier obviously developed much of his teaching style very early in his career. Moreover, as stated by Oppenheimer "Lillie himself held tightly in his time to the highest possible standards of scientific workmanship, and he passed them on to his students."[20] Willier later wrote at an unknown time and on an unknown occasion: "Like Socrates I *learn* and *teach* by asking questions . . . strive to have students so well taught that they would excel their teacher in research and teaching."

THE UNIVERSITY OF CHICAGO

Willier was associate in zoology at the University of Chicago (1919–1920), instructor (1920–1924), assistant professor (1924–1927), associate professor (1927–1931) and professor (1931–1933). Professor David Bodian, one of his undergraduate students at Chicago, later a colleague at Johns Hopkins and a member of the National Academy of Sciences, wrote in a letter to me on October 19, 1973, "I took an invertebrate course and two advanced embryology courses under Ben," and added, "the courses are still memorable." Professor Dorothea Rudnick, another of his students, first as an undergraduate, then as a doctoral candidate, commented in a letter to me written on February 17, 1973, that "He was not popular with the pre-medics (those 'discussions' were bitterly resented); students with more intellectual orientation found him refreshing—probably it was the contrast between his sparsely worded, highly organized lectures, his Socratic lab and discussion tactics, and his obvious innate pleasure in the material and ideas with which he dealt."

[20] Oppenheimer, "Benjamin Harrison Willier," p. 176.

Another of his doctoral students at Chicago, Frank R. Kille, wrote in 1982, "I was impressed with the care in which he presented his lectures in embryology. He was meticulous and hard working himself, and expected his students to be the same. He was also a perfectionist. And he could be very domineering and demanding." The latter traits were still evident occasionally later on at the University of Rochester and in his early years at Johns Hopkins, along with a few others that made him less than endearing to some of his graduate students at times. In 1973 one of his colleagues at Rochester (now deceased) wrote that "He was a hard task-master and many students suffered under it while they had their predoctoral training with him."

Following publication of his doctoral dissertation (1921), Willier next reported (1923, 1924) results of his first experiments utilizing the technique of transplantation to the highly vascular chorioallantoic membrane of chick embryos—the striking effects of grafts of small pieces of thyroid glands from chickens on development of host embryos (reduction in size and emaciation of the body in particular). These modifications were interpreted as hyperthyroid symptoms, and they clearly demonstrated that the thyroid tissue secretes a hormone into the host circulation in amounts capable of affecting host metabolism and development. The way was seemingly open for subsequent investigations of the effects, if any, of gonadal hormones of *host* origin on grafts of embryonic gonads (the original thesis problem suggested by Lillie) or, alternatively, the effects, if any, on host gonads of hormones of *donor* origin from gonad grafts from posthatching chicks and related problems (1925–1927; 1928 with E. C. Yuh; 1931–1934; 1936 with Mary E. Rawles; and 1937).

Finding no effects of gonadal hormones on or from such grafts, he analyzed, by chorioallantoic grafting, the changing differentiation capacities of gonad-forming areas and gonad rudiments and possible factors essential for attainment of these capacities. Discoveries from this period of experimentation of special interest to him, and that he regarded as most important, include demonstrations that a sterile gonad, at least a testis, can form and differentiate in grafts to the chorioallantoic membrane (CAM) in the absence of primordial germ cells; that undifferentiated germ cells can only differentiate within male sex cords or female cortical cords; and that primordial germ cells of a given genetic sex can differentiate into oogonia in the ovarian part, or into spermatogonia in the testicular parts, of an ovotestis formed by a CAM graft of the gonad-forming area of a 31-somite chick embryo, probably a genetic male, thus revealing the bisexual potentialities of the germ cells. His superb chapter entitled "The Embryological Foundations of Sex in Vertebrates," in the first edition of *Sex and Internal Secretions* (1932), reviewed these and other significant findings from his research program at the University of Chicago, as did his 1934 paper in the *Collecting Net.*

In a letter to me dated February 12, 1982, Rudnick commented (solicited correspondence) that "Mary (Rawles) appeared in the fall of 1928, simply registering as a graduate student, for a master's degree. It didn't take very long for her to become fascinated by the chorioallantoic graft work, nor did it take long for Benjie to recognize her technical skill and perfectionist devotion to elegant experimentation." Willier was fortunate enough to be able to offer her a research assistantship in 1929; she was to continue to work as his assistant, then his research associate, at the University of Rochester and the Johns Hopkins University until 1957. Rudnick also noted that "By 1928 Lillie was not taking any new graduate students; probably all the new people (interested in embryology) took Benjie's embryology courses, so he was the obvious person to work with and very welcoming. He worked together . . . with all of his beginning graduate students. He also believed strongly in students helping one another; there was always an elder graduate student about to consult if the Boss wasn't available." Kille, who first arrived in Chicago at this time to work for a master's degree, wrote in 1982: "I will always remember his personal demonstration of the whole procedure of making the grafts of embryonic material and his pleasure with what success I had when I made my try."

Because Willier's research while a faculty member of the University of Chicago, as well as the research work of twelve of his fifteen doctoral students (two in 1929, one in 1930, three each in 1931 and 1932, four in 1934, and one each in 1935 and 1937), involved grafting of tissues to the chorioallantoic membrane (CAM) of chick embryos, it seems appropriate to comment briefly about the nature, the developmental history, and the early utilization of this technique. This seems all the more pertinent since Professor Viktor Hamburger later noted that when he came to the University of Chicago as a Rockefeller Fellow in 1932, it was "the only experimental method then available for the analysis of problems of embryonic determination . . ." in the chick and added that "important results were obtained through its application by Willier and his school and by others."[21] Moreover, Rawles wrote "The technique of grafting isolated portions of embryos to the chorio-allantoic membrane has offered opportunity for an attack upon widely varied types of embryological problems and has been used more extensively than any other in vivo method."[22] Subsequently Oppenheimer wrote "His exploitation of the membranes as a method of study had wide effects on embryology; because of

[21] Personal communication, Viktor Hamburger, 1977.

[22] Mary E. Rawles, "Transplantation of Normal Embryonic Tissues," *Annals of the New York Academy of Sciences*, 55 (1952):302.

his insight and precision of technique others soon became aware that such experiments could elicit straight answers, and chorio-allantoic grafting remains today one of the most important devices of the chick embryologist."[23] In relation to this last statement, it should be noted that use of this technique led directly through Willier (1924 and related unpublished results) to the doctoral dissertation of James D. Ebert, a Willier doctoral student.[24] This led, in turn, to the very important role of Ebert and collaborators[25] in demonstrating the existence of graft versus host reaction and related phenomena when grafts of adult chicken spleens were grown on the CAM of host chick embryos.

The CAM technique, without specific details, involves incubating host eggs for seven to ten days, candling them (placing them above a bright shielded light to illuminate the interior of the shell), locating the junction of two or more large blood vessels of the chorioallantoic membrane, marking a rectangular area of the shell above this junction, removing that shell area, slitting the underlying shell membranes (thus exposing the vascular chorioallantoic membrane and, in particular, the blood vessel junction), placing a bit of donor tissue upon the membrane in the angle formed by the intersection of blood vessels where it could become vascularized by capillary sprouts from the latter, closing the opening in the shell by sealing back in place with melted paraffin the piece of shell initially removed, and continuing incubation of the operated host egg as desired. In 1924 Willier reported in a footnote (p. 70): "The technique as

[23] Oppenheimer, "Benjamin Harrison Willier," p. 177.

[24] James D. Ebert, "Ontogenetic Change in the Antigenic Specificity of the Chick Spleen," *Physiological Zoology*, 24 (1951):20–41.

[25] L. E. DeLanney and J. D. Ebert in collaboration with C. M. Coffman and A. M. Mun, "On the Chick Spleen: Origin; Patterns of Normal Development and Their Experimental Modification," *Carnegie Institution of Washington, Contributions to Embryology*, 37 (1962):57–85.

above described was independently worked out during the autumn of 1917. After several interruptions these experiments were resumed in the summer of 1920. This method of transplanting tissues to the chorio-allantoic membrane of the chick was first employed, so far as the writer is aware, by Rous and Murphy ('11) in studying tumors."

Actually this method originated quite by accident when Rous and Murphy attempted to inoculate the newly discovered Rous chicken transmissible sarcoma into the chick embryo. They ended up making most of their observations on tumors (sharply defined and easily accessible) that were located in the fused chorion and allantois, since the chorioallantoic membrane was necessarily pierced in inoculating the embryo. Its inoculation could scarcely be avoided in withdrawing the needle. The Rous sarcoma was later successfully inoculated into the CAM of pigeon and duck embryos by Murphy and Rous.[26] Interestingly, in view of the stated independent development of this technique at the University of Chicago, their Figure 3, showing the location of the growths on the CAM (and other extraembryonic membranes) of a chick embryo during the twelfth day of incubation, was adapted from the first edition of Professor Lillie's classical textbook, *Development of the Chick. An Introduction to Embryology* (1908)! In 1913, in addition to successful inoculations of the chick CAM with the Jensen rat sarcoma, Murphy wrote "Other tissues grown in the chick embryo (on the CAM) are various embryonic cells from the chicken, mouse, and rat, the Ehrlich sarcoma and chondroma of the mouse, a mammary carcinoma of the mouse, the Flexner-Jobling adenocarcinoma of the rat, and a human sarcoma."[27] In

[26] James B. Murphy and Peyton Rous, "The Behavior of Chicken Sarcoma Implanted in the Developing Embryo," *Journal of Experimental Medicine*, 15 (1912):119–32.

[27] James B. Murphy, "Transplantability of Tissues to the Embryo of Foreign Species. Its Bearing on Questions of Tissue Specificity and Tumor Immunity," *Journal of Experimental Medicine*, 17 (1913):492.

1916 Murphy[28] deposited on the CAM of host chick embryos incubated seven days, small amounts of finely divided adult chicken organs (spleen, liver, kidney, bone marrow, bone, and muscle). On the eighteenth day he examined the CAM of each surviving host embryo. If a living CAM "graft" was present, he examined the body of each host embryo externally and internally. He was the first to observe and to emphasize that his grafts of the first four organs listed above caused enlargement of the host spleen and that "In the extreme cases the spleen was greatly enlarged and many times the size of that seen in the normal animal (Fig. 4)" (p. 2). This 1916 paper, and two publications by Vera Danchakoff[29] in the same year, constitute an early prelude to the discovery of the graft versus host reaction and related interactions in avian embryos. Vera Danchakoff wrote that "The method of transplantating isolated chick primordial structures and parts of blastoderms into the allantois of another developing chick embryo has been used by me since 1916."[30] Earlier she had expressed her indebtedness to Murphy for demonstrating the method of grafting she utilized extensively. Thus the CAM technique had been developed, described, and utilized for a variety of purposes elsewhere before Willier worked out the method independently in the autumn of 1917. Initially used for studying the growth of abnormal tissues, it was soon taken over almost entirely for studying embryonic differentiation.

Surprisingly, in papers published by three students at the

[28] James B. Murphy, "The Effect of Adult Chicken Organ Grafts on the Chick Embryo," *Journal of Experimental Medicine*, 24 (1916):1–6.

[29] Vera Danchakoff, "Equivalence of Different Hematopoietic Anlages (by Method of Stimulation of Their Stem Cells). I. Spleen." *American Journal of Anatomy*, 20 (1916):255–328; "The Differentiation of Cells as a Criterion for Cell Identification, Considered in Relation to the Small Cortical Cells of the Thymus," *Journal of Experimental Medicine*, 24 (1916):87–105.

[30] Vera Danchakoff, "Lens Ectoderm and Optic Vesicles in Allantois Grafts," *Carnegie Institution of Washington, Contributions to Embryology*, 18 (1926):66.

University of Chicago, credit for developing the technique there was inconsistently or vaguely stated. Thus Hiraiwa (a nondoctoral student with Willier) wrote "The method of grafting upon chick membranes . . . was independently worked out in this laboratory by Minoura ('21) and Willier ('24)."[31] But Minoura (a Lillie student) wrote only (except for a footnote crediting three earlier references, two erroneously) that "Experiments of a similar kind have also been performed in this laboratory by Mr. B. H. Willier, and I had the privilege of examining Mr. Willier's material."[32] Hoadley (another Lillie student) simply stated that "The methods of grafting employed are similar to those used by Murphy and Danchakoff with certain modifications developed at this laboratory."[33]

A general statement by Rawles clearly specifies the uses to which the CAM was put at the University of Chicago, not only by Willier (in papers appearing annually from 1925 through 1934 and later at the University of Rochester in 1936 and 1937), but also by almost all of his fifteen doctoral students at Chicago. "The method of transplanting tissues to the chorio-allantoic membrane has been used successfully, not only to elucidate problems of early embryonic organization of the chick blastoderm, but also to study the development of virtually all of its individual organs and organ systems."[34] Early embryonic organization was unveiled by testing on the CAM the developmental potencies or differential capacities of specific isolated blastodermal areas from

[31] Y. K. Hiraiwa, "Studies on Grafts of Embryonic Tissues of the Rat on the Chorio-allantoic Membrane of the Chick. I. Differentiation of Ectodermal Derivatives," *Journal of Experimental Zoology*, 49 (1927):444.

[32] T. Minoura, "A Study of Testis and Ovary Grafts on the Hen's Egg and Their Effects on the Embryo," *Journal of Experimental Zoology*, 33 (1921):32–33.

[33] Leigh Hoadley, "The Independent Differentiation of Isolated Chick Primordia in Chorio-allantoic Grafts. I. The Eye, Nasal Region, Otic Region, and Mesencephalon," Biological Bulletin, 46 (1924):281–315.

[34] Rawles, "Transplantation of Normal Embryonic Tissues," p. 303.

stages ranging from the unincubated blastoderm through the formation of somites. As stated by Rudnick, "Such studies were carried to their logical end by Rawles (1936), who transplanted separately eighteen different pieces of the head-process blastoderm, and clearly established, in one coherent set of experiments, the regions or levels of specific potency for such tissues as central nervous system, heart, liver, thyroid, mesonephros, gonad and intestine."[35] It was the 1936 publication by Rawles, more than any other single factor, that attracted me to Willier's laboratory at the University of Rochester for my doctoral study.

In order to illustrate the technical intricacies and the incredible amount of labor involved in investigations of this type, information from Rawles' investigation (her doctoral dissertation) cited by Rudnick can be used as an admittedly extreme example. The area, subdivided into eighteen pieces, averaged 1.9 mm in width and 2.8 mm in length. The pieces were separated by five transverse and two longitudinal cuts. Transverse cuts were made through or at measured distances anterior or posterior to the primitive pit, the two longitudinal cuts at measured distances on either side of the pit. In carrying out this study on the developmental potencies of the various sectors, she obtained more than 500 grafts, 388 of which she sectioned serially, mounted, stained, and examined histologically throughout all sections. She then used the information gleaned from 216 of the latter grafts to construct her classical maps, showing separately the localizations of developmental potencies of ectodermal, mesodermal, and endodermal structures. It must be added that, as stated by Rudnick, "These results indicate a pattern either of intrinsic potencies, or of localized correlative factors, but do not offer direct evidence in favor of either

[35] Dorothea Rudnick, "Early History and Mechanics of the Chick Blastoderm. A Review," *Quarterly Review of Biology*, 19 (1944):203.

alternatives."[36] This is true since, although these are designated as maps of developmental potencies, sectors of the individual germ layers could not be tested separately on the CAM for technical reasons. Willier (in his autobiographical sketch for the National Academy of Sciences) regarded the findings from this and numerous other related systematic investigations carried out by himself and in cooperation with his students at the University of Chicago as among his most important discoveries: "The disclosure that the pre-somite chick blastoderm is made up of organ-specific areas, orderly and spatially arranged with respect to each other, and that each area possesses a specific quality (for tissue differentiation), a gradient in developmental potency (or intensity), and axial (direction) properties."

Willier (1928, 1929, 1930) also used grafts to the CAM to advantage in the experimental analysis of the development of the suprarenal (adrenal) glands of chick embryos, whose cortical rudiments are more or less continuous with the gonad rudiments (germinal epithelia). He also used grafts to the CAM to investigate the relation of Hensen's node to the formation of axial parts of chick embryos (Willier and Rawles, 1929, 1931) and the correlation in development of the heart and liver (Willier, 1930; Willier and Rawles, 1930, 1931). The method was also used for his work at the University of Rochester, concerning other problems in organ-forming areas (Rawles and Willier, 1934; Willier and Rawles, 1935). All these Willier-inspired investigations helped to bring the very young chick embryo into the forefront, where it remains as very favorable material for experimentation.

It should be noted that, beginning with his first doctoral student, Willier adopted the policy of never publishing

[36] *Ibid.*, p. 203.

doctoral dissertations jointly with his students. He consistently adhered to this policy throughout his career. Another policy he adopted at Chicago was that his doctoral students must work with the chick embryo. Earl A. Dennis wrote to me in 1973 about his experience with this requirement upon his arrival at Chicago: "At that time I was quite enthusiastic about doing some experimental work on Cryptobranchus (the hell-bender, a tailed amphibian about a foot and a half long) eggs and had an almost complete developmental series preserved from the one cell stage through cleavage, blastula, gastrula, tailbud, and early larval stages. Dr. Willier discussed this with me and told me quite frankly that if I wanted to work on amphibians I should have gone to Yale under Ross Harrison." Willier adhered to this policy with but one exception.

Frank R. Kille wrote on October 21, 1982 that he returned to Chicago in 1931 as a doctoral student with some 145 stages of regeneration in Thyone (a sea cucumber) following induced evisceration (autotomy), which he had obtained at Woods Hole and hoped to use as the basis for a doctoral dissertation. Since he had no faculty sponsor at Chicago for such a project, he considered asking Willier to serve in that capacity. "One old timer among the Willier students threw cold water on that idea with the remark 'Forget it! If Willier sponsors your doctoral work, you will soon be down in the basement sawing eggs with the rest of us!' " Instead, to his surprise and delight, Willier agreed to sponsor his work on Thyone, "but with one very important reservation, namely, that since he was not familiar with the literature in this subject, that would have to be my responsibility. If I learned I was repeating work already done, even in a late stage of my research, the thesis would not be accepted and I had only myself to blame. Several years later, I asked him why all his students worked on the chick embryo and his immediate reply was, 'This is the field I know best and am able to suggest several subjects for their attack. No one has ever come to me with a problem in development that he wanted to work on.' " He added "I am not sure that Willier would have sponsored my work on Thyone if I had not already showed him that I could do satisfactory research and writing in chick embryology." The latter project was a thesis for his master's degree with Willier based on grafts of the early adrenal gland to the chorioallantoic membrane of the chick embryo.

As an indication of Willier's liberal nature early in his career, it should be noted that he identified and worked closely with splendid women scientists long before it was fashionable to do so, including Libbie Hyman, Dorothea Rudnick, Mary Rawles, and Jane Oppenheimer, to name but four. Moreover, seven of his fifteen successful doctoral students at the University of Chicago were women, including Rudnick and Rawles. It is also pertinent to note that the first graduate student to receive his Ph.D. with Willier at the University of Rochester was a black student, and that he also encouraged one of the very first black graduate students at the Johns Hopkins University. In both these respects he was strikingly similar to his preceptor, Professor Frank R. Lillie.

As Ebert wrote in 1972 in a news release at the time of Willier's death, "These were the formative years of his career, years that helped shape the field of experimental embryology as well." During his last year at the University of Chicago (1932–1933) Willier exerted a very positive effect on the field of experimental embryology in another way. As stated earlier, Hamburger arrived at the department of zoology in 1932 on a one-year fellowship from the Rockefeller Foundation. According to Professor Johannes Holtfreter, only after Hamburger arrived in this country did he make his "first acquaintance with the chick embryo."[37] Until that time his research material was the developing frog. Thereafter almost all of his research utilized chick embryos. Appropriately Holtfreter wrote "It appears that in this conversion Ben Willier played the role of a godfather." It was during that year that Hamburger succeeded in performing his first extirpations of chick limb buds and transplantations of supernumerary limb buds to the flanks of chick embryos. He commented on these technical advances as follows:

> Thus a broad new field of intraembryonic experimentation on chick embryos was opened up which lent itself to the study of a great variety of problems in chick embryology; and the chick embryo thereby achieved equal rank with the amphibian embryo in experimental embryology. My accomplishments were made possible by the generosity of Dr. Willier and his very able associate, Dr. Mary Rawles, whose expertise in handling chick embryos was unsurpassed, and placed at my disposal.[38]

Moreover, a close friendship developed between Willier and Hamburger. The latter wrote on January 9, 1982, in a solicited letter, that a few weeks after he arrived in Chicago in September, 1932, he "then moved to Willier's house and stayed there for several months, perhaps even to the following summer," and that "As the years went by, the friendship became warmer, and I would count him among my best friends."

Willier and Professor C. M. Child, of the zoology department of the University of Chicago, had for years been in the habit of taking long walking trips in Palos Park or the Indiana dunes on Saturdays. Professor Sewall Wright joined

[37] Johannes Holtfreter, "Address in Honor of Viktor Hamburger," *The Emergence of Order in Developing Systems,* ed. Michael Locke (New York: Academic Press, 1968), p. xiv.

[38] V. Hamburger, personal communication, 1977.

the department in 1926, overlapped Willier there through 1933, and was invited to go along on these outings soon after he came to Chicago. The nature of this pursuit, which continued at the University of Rochester and at the Johns Hopkins University, as well as the traits it revealed, is best revealed simply and beautifully in Wright's own words in a solicited letter to me dated February 8, 1973.

> I remember that we often discussed the validity of developments in genetics. Benjie did not know much about genetics at first but soon both of us were intensely interested in its relation to development. I started a course in Physiological Genetics and greatly enjoyed taking part in Benjie's evening seminar on Problems of Development. We continued going out together on Saturdays after Dr. Child retired to Stanford. Benjie took up collecting dragon flies and I spiders as hobbies appropriate to such trips. Libbie Hyman went with us several times. Later we were regularly joined by George Link of Botany who added new dimensions to our interests: the plants of the dunes, plant pathology, the philosophy of Santayana, etc. I think that I enjoyed more stimulating conversation during this period 1926–33 than at any other time. Benjie was an ideal companion, always considerate, with a good sense of humor, capable of discussing interestingly the most diverse subjects.

These remarks were reinforced by others. At the Willier memorial service Professor Harrington stated "He was a delightful companion on walking tours with a vast store of anecdotes. His knowledge of the biology of trees and flowers and of mosses and lichens was always a source of amazement to me. His explanations were invariably given with humor and with childlike enthusiasm which was infectious." Oppenheimer wrote, "he never broke his strong affinities with nature, with the lakes and the seas, the rocks and the mountains, the flowers and the birds. His bonds with nature-as-a-whole remained always an integral part of his highly integrated life and thought. His excursions, into the wilderness when possible, or at least into the countryside, were shared with his teachers, his students, his colleagues, his friends, and his family."[39] For all his guests these walks were invariably learning experiences, albeit on different levels. Recollections of his daughter Kathryn make this especially clear: "Scientific discussions were the norm. We were introduced to many aspects of nature from the plants, leaves, small creatures underfoot to the surrounding terrain and the birds in the sky. Much of my early knowledge of science came from these walks and the questions I asked and the things I observed. Dad taught me to be observant."[40] As Ebert commented in 1972 in his news release at the time of Willier's death, "A remarkable naturalist, Willier was equally at home on the shores of Cape Cod, the dunes of Lake Michigan, and the mountains of the West. He knew the trails, the animals and plants and their interactions. He was a practical ecologist long before the word became popular. On February 10, 1972, Willier wrote to me "What a nice trip on a research cruise on the Gulf to and from Galveston! Wish I could have been a companion. I am a good ecologist!" The exclamation marks are his.

Following Lillie's demonstration in cattle of the role of male hormone(s) in development of a sterile freemartin from a genetic female born twin to a genetic male and his formulation, essentially in its present outlines, of the hormonal theory of sex differentiation (that is, that the course of embryonic sex differentiation is largely determined by sex hormones circulating in the blood), Lillie (in Willier's words, 1957, p. 220) had "immediately initiated among his colleagues and students a broad and intensive program of research on the isolation and purification of sex hormones and on their role in regulating the expression of sex characters." The rapid advances of this project from 1922 to 1932 were made possible primarily by the combined efforts of Carl

[39] Oppenheimer, "Benjamin Harrison Willier," p. 175.
[40] Solicited communications dated March 18 and 25, 1982.

R. Moore, L. V. Domm, Mary Juhn, and Dorothy Price (endocrinologists-zoologists) and F. C. Koch, T. F. Gallagher, and R. F. Gustavson (biochemists). Lillie himself was primarily involved, in cooperation with colleagues, in demonstrating and analyzing the effects of hormones on regenerating feathers, chiefly in Brown Leghorn fowl. Lillie wrote "For the interpretation of the results knowledge of the *mechanics* of development of the feather is necessary. As this was substantially unknown, a detailed study of the development of the feather was necessary."[41] The first of his series of seven magnificent publications concerning the physiology of development of regenerating feathers under normal and experimental conditions (two coauthored with Mary Juhn and four with Hsi Wang) was published in 1932.

Willier's research program at the University of Chicago was of an entirely different nature and was entirely independent, even though it coexisted very effectively with the zealous research activity engendered there by the programs summarized above, part of a decade of great and brilliant advances in endocrinology. But later Willier cooperated with Koch and Gallagher of the biochemistry department in a very significant project on effects of sex hormone preparations on development of chick embryos. Later still he drew extensively on the results and interpretations of the feather-hormone work of Lillie and coworkers in interpreting the findings of his own entirely new research program, especially at the Johns Hopkins University.

In counseling me wisely on several occasions about whether or not it would be better for me to remain at Chicago rather than to go elsewhere, he commented in a letter dated August 3, 1947, "I would weigh heavily the advantages of being associated with distinguished colleagues

[41] Frank R. Lillie, "The Physiology of Feather Pattern," *Wilson Bulletin*, 44 (1932):195.

at Chicago (three are members of the National Academy)." And on April 11, 1949, he wrote "As you know, I have had a keen interest in your work at the University of Chicago, where I spent thirteen very happy years on the staff."

THE UNIVERSITY OF ROCHESTER

In 1933, the third year after his advancement to a full professorship in zoology at the University of Chicago, Willier accepted an appointment at the University of Rochester as professor of zoology and chairman of the Division of Biological Sciences. This move provided a superb opportunity for him to develop and test his administrative skills. He was accompanied by four of his doctoral students who had not yet completed their dissertations at Chicago. Under his leadership the biological sciences grew in stature, but not without difficulty. Inflexible incumbents on his faculty created problems, and space, sorely needed for development of his faculty and the training of graduate students, was yielded reluctantly by members of another department. Moreover, it was necessary to give some undergraduate instruction on the downtown Prince Street Campus for women, although most of it, and all graduate instruction, was provided on the River Campus (the men's campus). This separation of campuses was inconvenient; it necessitated assigning some faculty members to the women's campus and requiring other faculty and graduate teaching assistants to commute from the River Campus. Willier developed and staffed a rigorous and up-to-date introductory course in general biology with teaching laboratories on both campuses. His criteria in identifying faculty for participation in this course were the ability to organize factual material so that students could grasp the main points and generalizations, a sensitivity to student reactions, an infectious enthusiasm for the subject, and the desire to discourage pure memory work and to help students learn to think.

At Rochester Willier progressively brought together a carefully selected, very competent group of promising young people and seemed to hold their devoted allegiance. Two of them later became members of the National Academy of Sciences. Curt Stern (genetics) first came there as a research associate (1933–1935); he was later appointed to an assistant professorship. In succession Willier appointed as instructors: Adrian Buyse (anatomy) and Robert W. Ramsey (physiology) in 1934, David R. Goddard (botany and plant physiology) in 1935, Donald R. Charles (statistical genetics) in 1937, Kenneth W. Cooper (cytology) and Richard H. Goodwin (botany and plant anatomy) in 1938, and John B. Buck (cytology) in 1939 to replace Cooper. In addition, Willier attracted as research fellows in embryology Dorothea Rudnick (1934–1937, who set up the first tissue culture apparatus in Willier's laboratory and used it to good advantage), Ernst Hadorn (1936–1937), Jane Oppenheimer (1937–1938), and Peter Gray and Hans Ris (during 1938–1939). Six students received their doctorates with Willier at Rochester, one in 1936, two in 1938, two in 1940, and one in 1941; two others began their work with Willier at Rochester but received their doctorates with him at the Johns Hopkins University.

Three of these students (Hermann Rahn, Howard L. Hamilton, and Ray L. Watterson), together with Harvard Professor G. H. Parker, gave one of the Tuesday evening seminars at the Marine Biological Laboratory at Woods Hole on July 22, 1941, on their studies on vertebrate pigment cells (melanophores) and/or hormones affecting the latter. Years later Willier recalled that evening with evident satisfaction when he wrote to me about "the great days we had together at Woods Hole—especially the big night when my students excelled in speaking in a well-organized language." And he wrote further, in response to favorable comments about that evening from members of the audience and questions about his teaching methods that made this evening the success that it was, "How did I do it? I told them that it was the seminar method of teaching."

Willier's files contained an undated information sheet that listed the objectives of his seminar method of graduate teaching and gave specific directions for preparation of student abstracts and presentation of their reports. I quote the objectives verbatim.

1. First-hand acquaintance with significant literature in a given field of knowledge.
2. Practice in exercising *judgment* in selection of pertinent data, significant interpretations and conclusions. Distinguish important from less important.
3. Practice in clarity of exposition—logical organization of talk—logical sequence of presentation—clear thinking—before an audience.
4. To acquaint the student with the present status of knowledge on a given problem. To present new problems for analysis and ultimate solution.

This information ended appropriately with three brief exhortations quoted from Robert de Sorbon's advice to the students in the college he founded in 1252: "Concentrate on what you read. Never read superficially, skimmingly." "Extract from the reading one salient thought and etch it deeply on your mind." "Also write a digest of it. Thoughts not set down and so chained in words fly like chaff before the wind." I do not recall ever having seen this information sheet before.

At Rochester all of Willier's and Stern's doctoral students participated actively each year in Willier's embryology seminar during one semester and Stern's genetics seminar during the next until they had completed the entire sequence of topics covered in each discipline. James G. Foulks, one of Willier's doctoral students, wrote on February 19, 1982 (solicited communication):

> The responsibility to carry their share of the load in these seminars was thrust on graduate students from the very beginning of their sojourn in the department. I have vivid recollections of sweating over the translation of lengthy papers by Roux and Driesch during my first month at Rochester. I believe that these exercises contributed greatly to the development of trainees as teachers as well as investigators. In these sessions the historical emphasis, based on the review and analysis of classical as well as current work, not only gave students an overall perspective but helped to evoke that sense of adventure which is associated with working at the growing frontier of knowledge.

Another of his doctoral students, Alfred J. Coulombre, commented on August 4, 1982 (solicited communication), about these seminar experiences he participated in at Johns Hopkins as follows: "There each utterance by a presenter or from a listener at the table was subject to immediate incisive feedback from the professor. Almost any declarative statement drew from him a quiet 'How do you know that?' or 'What is the evidence for that?' Those forums gave us each an arsenal of excellent weapons for a career in science." Foulks also wrote as follows: "He was demanding with respect to evidence and logical criteria, and he instilled this attitude in others. But this trait also was reflected in his ability to recognize what was valid and important in new as well as in old ideas. For example, his marriage of embryology and genetics as the foundation for training in developmental biology when you and I were graduate students, he later extended to include the relevant areas of biochemistry as this aspect of the field emerged and matured."

In addition to their active participation in demanding graduate seminars, Willier's and Stern's doctoral students were required to review and formally discuss interesting and meaningful current papers in biology at fortnightly evening sessions of faculty and graduate students. This was a custom initiated by Willier at the University of Chicago and continued at Rochester. The name "Festschrift" was given to these meetings as a tribute to Professor Hans Spemann, awarded the Nobel Prize in Medicine and Physiology in 1935 for his demonstration of the action of the "primary organizer" in amphibian development. Beyond that we were required to speak before the excellent weekly departmental seminar, either to present the results of our own research or, if in our first year, the published results of investigators elsewhere related to our emerging research interests. With this kind of "upbringing" it is small wonder that Saunders remarked at the Willier memorial service about Willier Ph.D. students: "The majority of these are known to be unusually effective speakers." Professor Robert K. Burns, Jr., a colleague at Rochester, wrote in 1973 (solicited communication), in commenting about Willier's training of his graduate students, "he had a way of conveying to students a sense of obligation to measure up to a standard which may at times have seemed overly strict to some. And yet the challenge was almost always accepted."

Within five years of Willier's arrival at Rochester, he had provided remarkably good facilities for the experimental work of graduate students and faculty, primarily through the acquisition of considerable space, formerly used as a museum, on an upper floor of the Dewey Building. Along each side were a number of relatively large rooms separated by glass partitions beginning a few feet above the floor. One room was equipped as a general operating room, one housed the departmental artist, another provided office and research space for a faculty member, and still another was equipped as a tissue culture laboratory. Except for the latter, which housed two doctoral students, each doctoral student had a room to himself! Opposite the main entrance another room provided office and research space for a second faculty member. In the center was a large unpartitioned area (with an alcove to one side equipped with a sink, refrigerator, etc.), occupied primarily by a very large round table where faculty and students could prepare and eat their lunches or snacks and spend time together informally. I shudder to think how many times we ate watery scrambled eggs prepared from fertile eggs, unincubated or incubated, from which blastoderms had been removed that morning to provide material for an investigation of oxygen consumption of early chick embryos at various stages! The entire complex was designated, appropriately, as "Himmel." Foulks also commented in his letter previously mentioned that "I only spent one year in 'Himmel' but I would surmise that it was fairly unique as a social as well as a scientific environment. All of these factors worked together to furnish a lively and stimulating atmosphere." And to these must be added the intellectual ferment provided by most of Willier's young faculty, his research associate, and research fellows. Also provided were a first-rate photographer very familiar with optical equipment (who served primarily as storekeeper), excellent photographic equipment, and a productive departmental technician and laboratory for preparation of specimens for microscopic study in teaching laboratories. Rudnick put it nicely in her letter dated February 17, 1973, in which she wrote: "I always felt that he had a strong sense of what a good lab and teaching department should be, and refused to accept anything but the best, of himself and others, while at the same time his gentle, social personality-self hated fighting, making a fuss, telling people off. Colleagues and his elders certainly trusted his balance, his judgment and his standards."

At the University of Chicago Willier had devised experiments with chick embryos designed to bring about vascular relationships between host gonads grafted to the chorioallantoic membrane that stimulated those found during uterine life between a developing freemartin (a modified genetic female) and its male twin. These resulted in a singular lack of sex modifications in host embryos or grafted gonads; contrary to expectation, no information was forthcoming about possible roles of sex hormones in differentiation of avian reproductive systems. If host gonads of chick embryos or grafted gonads were synthesizing and releasing sex hormones into the circulation, perhaps they were too diluted in the blood reaching distant CAM grafts or host gonads to modify their development or, if not, failed to reach receptor tissues early enough to exert their effects.

By 1934 sex hormones were available in relatively pure form. These included female hormones (crystalline theelin [oestrone, estrone] and crystalline theelol [oestriol, estriol]), male hormone preparations (bull testis extracts and a variety of male human urine preparations), and later several synthetic male hormones (androsterone, dehydroandrosterone, and testosterone propionate). Willier, together with the biochemists T. F. Gallagher and F. C. Koch of the University of Chicago, began a systematic investigation of the effects on development of gonads and gonoducts of genetic male and female chick embryos of injections of various concentrations of these hormones into the albumen of incubating eggs well before the onset of sex differentiation. Three abstracts and one paper by Willier, Gallagher, and Koch appeared in 1935, and one comprehensive paper was published in 1937. Willier (1937) published an abstract on effects of injecting synthetic male hormones, and in 1938 he coauthored a paper on this subject with Rawles and Koch. These investigations in relation to his earlier experiments and those of others were lucidly reviewed in Willier's 1939 revised chapter entitled "The Embryonic Development of Sex" in the second edition of *Sex and Internal Secretions.*

Most striking were the effects of female sex hormones on gonad development in genetic males. In a few extreme cases, the *left* testis enlarged and flattened. Its transient germinal epithelium (an incipient cortex) was stimulated to proliferate an ovarian cortex, and its testicular cords were modified into medullary cords, both characteristic features of normal *left* ovaries. In these same extreme cases, the *right* testis was modified in size and shape until it resembled a normal *right* ovary. It lacked an ovarian cortex (the right testis usually lacks any trace of an incipient cortex in normal genetic males), and its testicular cords were largely transformed into medullary cords, both characteristic features of a normal *right* ovary. Thus in size, shape, and histological structure, the normal *left* testis of a genetic male was transformed into a typical *left* ovary, and the normal *right* testis into a typical *right* ovary, under the influence of injected female sex hormones. It is especially noteworthy that the asymmetry in size, shape, and histological structure characteristic of left and right ovaries of normal genetic females in embryonic and post-hatching stages was faithfully reconstructed during the transformation of embryonic testes developing under the influence of injected female sex hormones. Moreover, the transient oviducts (Müllerian ducts) of genetic males persisted following injection of female hormones, whereas they normally degenerate. By contrast, the Wolffian (mesonephric) ducts developed as in normal males, that is, their development was unaffected by injected female hormones. Except for the latter feature, genetic male reproductive systems were almost completely transformed into female-type reproductive systems by these hormones.

Although injections of bull testis extracts, known to contain testosterone, exerted little action on development of the sexual apparatus of genetic females, they did cause hypertrophy of their rudiments of Wolffian (male-type) ducts. Injections of synthetic male hormones (testosterone propionate, androsterone, and dehydroandrosterone) into genetic females caused variable degrees of degeneration of the cortex of the *left* ovary, hypertrophy of its medulla, and transformation of its medullary cords into testicular cords, as well as assumption of a testis-like form. The *right* ovary (normally lacking ovarian cortex) enlarged, assumed a testis-like form, and many of its medullary cords were modified into testicular cords. Moreover, under the influence of synthetic male hormones, the *left* oviduct (normally the only functional oviduct in most avian genetic females) remained rudimentary; its development was inhibited by synthetic male hormones, and the latter stimulated hypertrophy of the Wolffian (male-type) ducts of genetic females as did bull testis extracts. Thus, although the transformations of the reproductive systems of genetic female chick embryos caused by injected synthetic male hormones were not as spectacular as those in genetic males injected with female sex hormones, genetic female reproductive systems were almost completely transformed into male-type reproductive systems by the male hormones used.

These experiments, excluding certain unexplained feminizing actions of human male urine preparations and of synthetic androsterone and dehydroandrosterone (hormones known to be present in the urine preparations), conclusively demonstrated that sex reversal in chick embryos, as in amphibians, can go either in the male or female direction. Moreover, the data demonstrated that sex reversal in chick embryos proceeds more readily in the male to female direction, because a smaller quantity of sex hormone is required for feminization of genetic males than for masculinization of genetic females. Careful examination of large numbers of untreated chick embryos and comparison of their development with those of embryos treated with sex hormones clearly demonstrated, with emphasis on the existence of a transient ovarian cortex on the left testis and its very rare occurrence on the right testis (and then only in reduced amounts and in restricted areas), that "sex hormones do not originate any morphological component but merely activate or alter the development of those already laid down in normal development" (Willier et al., 1937, p. 116). This is remindful of a statement made by Lillie: "In the case of the free-martin we do not find that male hormones (from the genetic male twin) cause the development of any structure (in the genetic female twin) which is not represented embryologically in the normal female; the hormones act in this case merely by inhibition or stimulation of normal embryonic rudiments."[42] Lillie's statement, if modified slightly, also expresses extremely well the nature of the action of exogenous sex hormones in chick embryos, especially of female sex hormones in genetic males.

The results of these investigations and the consequent significant generalizations reinforced Willier's already established reputation as an authority on embryonic development of vertebrate reproductive systems and the hormonal mechanisms involved. This mastery was demonstrated by his superb invitational review papers on this topic in 1939 (with N. T. Spratt, Jr.), 1942, 1950, and 1952 and his excellent summaries of the ontogeny of endocrine correlations in vertebrates in 1954 and 1955. Willier's files revealed that on November 21, 1950, Professor Viktor Hamburger, president of the Society for the Study of Development and Growth (now the Society for Developmental Biology) wrote to Wil-

[42] Lillie, "The Free-martin," p. 419.

lier, inviting him to speak at the tenth symposium of the society: "You have been one of the most active members of the society since its birth, but you have never had the opportunity to speak before this group. All the members of the executive committee are in agreement that no one could do this topic (comprehensive review of the present status of the problem of the control of sex hormones) better justice than you would." Willier declined this invitation on the grounds that he was too busy editing the magnum opus, *Analysis of Development.* He followed his declination with a surprisingly discouraged comment: "Very few people working in the field have paid much attention to what I have already said." This is the only remark of this nature I have ever known him to make about his own work, although his files revealed that he did, on occasion, express keen disappointment that some vigorous scientists are more interested in factual knowledge than in integration and synthesis, that some are too often concerned with minutiae, overlooking the general principles involved, and that only a few know what a concept means. But, in marked contrast, he characterized one of his former doctoral students as "a master of generalization and in the synthesis of knowledge."

FEATHER PIGMENTATION RESEARCH AT ROCHESTER AND THE JOHNS HOPKINS UNIVERSITY

During 1936 and 1937, while investigations of sex hormone effects on development of the sexual apparatus of avian embryos were still under way, Professor Ernst Hadorn was a research fellow in embryology at the University of Rochester. During that year Willier, Rawles, and Hadorn (1937) initiated a very fortunate series of experiments, best described in the words of Willier and Rawles (1940, p. 177): "By grafting a piece of skin ectoderm (between embryos of genetically different breeds of fowl) from the head to the wing—regions differing greatly in the arrangement, size, and shape of feathers—it was hoped that some light might be thrown upon the problem of the distribution of feather germs (that is, their arrangement and spacing in tracts) and the localization and nature of the factors controlling their rate of growth, shape of feather produced, etc. The effects of the mesodermal substratum and humoral agents of the host on such developmental processes could thus be tested." Moreover, any effects of the operations on the pigmentation of feathers developing in and around the transplantation site could be analyzed. Their single brief cooperative effort in 1937 initiated a fascinating and fundamental research program of superior quality concerned in many ways with different aspects and basic mechanisms of cellular differentiation. It resulted in publication of six research papers (1937, two each in 1938 and 1940, 1944), five abstracts (1938, 1939, two in 1940, 1944), and eight review papers written at Johns Hopkins (1941, two in 1942, 1944, 1948, 1950, 1952, 1953), most coauthored with Rawles, seven doctoral dissertations, and an excellent paper by Hans Ris (1941), based on his research in Willier's laboratory in 1938 and 1939 as a research fellow in embryology. Furthermore, during her tenure as Willier's research associate, Rawles published independently seven superb research papers, three abstracts, and four excellent review papers on pigmentation problems in birds and mammals.

Fortunately Rudnick could recall some of the circumstances resulting in the Willier-Rawles-Hadorn collaboration and wrote about them in her letter dated February 12, 1982, as follows: "I'm quite certain that the feather-pigment *ideas* were floating about much earlier than Hadorn's advent. But definitely, Hadorn was the immediate instigator. You recall, he had previously been working with inter-species transplants in amphibia. On the way to Rochester, he spent some time with Walter Landauer in Storrs, talking over color- and other varieties in chickens. I don't know how much he worked with Mary (Rawles); Benjie and they certainly talked together. I imagine Mary took over the experimental work with chick skin . . . with delight." That she did!

The basic experimental technique utilized in 1937, which served as the point of departure for all subsequent investigations (a slight modification of the technique of limb-bud transplantation developed by Hamburger while at the University of Chicago), was the insertion of a minute piece of skin ectoderm from a donor embryo of one breed of fowl, through an incision in the skin ectoderm of an embryo of another breed, and into the underlying host mesoderm deeply enough to anchor it in position. In most combinations this procedure developed in the host embryo an area of donor-colored down feathers, usually replaced later with donor-colored juvenile feathers, at and around the transplantation site. It was soon demonstrated histologically that the implanted skin ectoderm replaced little, if any, of the host epidermis of the affected area and this, as well as several other lines of evidence, proved conclusively that the feathers of donor-colored areas originated exclusively from host epidermis. Therefore the major goal of the initial investigation was never attained. It had been expected that the transplantation of embryonic skin ectoderm from one area of a donor embryo to a host embryo of a different breed would enable Willier et al. to ascertain the role of position in the body in determining the distribution of feather germs (their arrangement and spacing in tracts) and the localization and nature of factors controlling the growth rates, shapes, and other specific properties of individual feathers both in different positions within different feather tracts and within the same tracts. (Convincing solutions to these and related problems were provided over two decades later in a symposium volume honoring Willier in a synthesizing paper by Professor John W. Saunders, Jr., a former Willier doctoral student.[43] This paper was based to a considerable extent on clever experiments initiated by Saunders as a graduate student in Willier's laboratory, and originally conducted under his direction. They were a logical extension of his doctoral dissertation, which stimulated many significant investigations in his laboratory and elsewhere on the role of epithelial-mesenchymal interactions in limb-bud development in birds and mammals.)

It soon became apparent that the transplanted epidermis simply served as a vehicle to transfer any contained melanoblasts (embryonic pigment cells) of donor origin that, if present, rapidly proliferated, invaded host skin ectoderm, and, in host feathers developing therefrom, differentiated into mature pigment cells (melanophores) that contributed the pigment granules (melanosomes) they synthesized to developing ectodermal components of host feathers. The resulting donor-colored feathers were thus nonliving chimeras composed of pigment granules produced by melanophores with the *donor* genotype and keratinized ectodermal feather cells with the *host* genotype. Donor melanosomes of one breed in host keratinized feather cells of another were remarkably donor-specific in size, shape, and color at the light microscope level, strongly suggesting a precise genetic control of the synthesis of the components of, and their assembly into, these very small complex morphological entities.

Embryonic Source of Melanoblasts. It was then noted that in potentially pigmented donors incubated less than 79–80 hours, skin ectoderm isolated from wing buds failed to

[43] John W. Saunders, Jr., "Inductive Specificity in the Origin of Integumentary Derivatives in the Fowl," in *The Chemical Basis of Development*, ed. William D. McElroy and Bently Glass (Baltimore: The Johns Hopkins Press, 1958), pp. 239–53.

produce any donor-colored feathers in host embryos around the transplantation sites, whereas skin ectoderm from over the somites (adjacent to a well-formed neural tube) did so. Earlier still, as folding of the neural plate into a tube and somite formation occurred, all isolated portions of the neural tube wall itself could, when grafted, produce melanophores, whereas grafted somites could not. Subsequently it was demonstrated in Willier's laboratory by Ris that with the appearance of discrete dorsolateral neural crests (a relatively small transitory aggregation of neural cells situated between skin ectoderm and closing neural tube on each side of the embryo), pigment-forming capacity became restricted to the dorsal half of the neural tube and finally to the neural crests themselves. Thereafter only when neural crest cells disengaged from the neural crests and migrated into adjacent regions (as demonstrated histologically) could the latter produce melanophores when transplanted from potentially pigmented donor embryos to host embryos. Thus these systematic investigations demonstrated experimentally for avian embryos, as had previously been done for amphibian embryos, that melanoblasts that differentiate into melanophores are exclusively neural crest derivatives.

Initial Blockage of Migration of Host Melanoblasts by Donor Melanoblasts and Eventual Disappearance of This Blockage. Does the presence of a normal complement of donor melanoblasts in the skin ectoderm of host embryos or the proliferating zone (collar) of developing host juvenile feather germs somehow block the entrance of host melanoblasts? Yes. Even melanoblasts from donor embryos of white breeds, which are peculiar in that they die prematurely before depositing the few pigment granules they synthesize, can prevent invasion of melanoblasts furnished by embryos of host breeds with pigmented plumage *provided they get there first*, thus producing areas of colorless (white) host feathers. It is as if the donor melanoblasts, arriving first in areas of host skin ectoderm around the transplantation site, occupy all available places in the latter (and later in the collar of the host juvenile feather germs) with no places left for host melanoblasts to invade. Such a static morphological visualization of the phenomenon would seem to be unacceptable today in view of the current emphasis on the variety of cell-cell interactions in populations of cells in developing organisms.

Are areas of juvenile host feathers with donor coloration replaced by regenerated host feathers with host coloration following molting of juvenile feathers? Yes. The proliferation of donor melanoblasts provided by embryonic transplantation techniques does not continue indefinitely through successive feather generations. It usually becomes inadequate after formation of juvenile host feathers is completed or even before, enabling host melanoblasts to invade the epidermal component of regenerating host feather germs and produces in them the host color or color patterns. This striking change can occur quite suddenly along the apicobasal axis of a developing host feather, and once it has occurred it is almost always irreversible.

Precise Genetic Control within Donor Melanophores of Their Capacity to Produce Donor Color or Color Patterns in Developing Host Feathers. Is the genotype of donor melanophores of one breed of fowl, insofar as the genes known to control color or color pattern are concerned, the primary factor in controlling production of *donor* color or color patterns in developing host feathers of a different breed whose feathers are normally of a different color or color pattern? Yes. This has been the most consistent and by far the most striking discovery of these investigations. As Willier wrote in his 1942 paper in *Annals of Surgery* (p. 599), "This was found to be true for all donor breeds and species tested such as Barred Plymouth Rock, New Hampshire Red, Black Minorca, Brown Leghorn, White Wyandotte, White Silkie and White Plymouth Rock, crow, robin, ringed-neck pheasant." And other donor breeds or species were later added to this list, including Red and Buff Minorca and the Guinea Fowl. Probably the most memorable experience of my graduate school days occurred on the stage of Strong Auditorium at the University of Rochester in late October 1937, during a live demonstration before the meeting there of the National Academy of Sciences. I was trying to retain my decorum while helping Mary Rawles shepherd a dozen or more chicks loose on the stage, each bearing an area of host plumage with the specific color or color pattern produced by melanophores from an embryo of one of several different breeds of fowl, and each attempting to run in a different direction!

There is a distinct sexual dimorphism of barred patterns (alternate black and white transverse bars) in feathers of Barred Plymouth Rock chickens. In genetic males (whose melanophores contain two dominant sex-linked barring genes), a narrow gray-black bar alternates with a wide and almost pure white bar. In genetic females (whose melanophores contain only one dominant sex-linked barring gene), a wide black bar alternates with a narrow gray-white bar. Thus the barring gene appears to exert dosage effects in the sense that the two barring genes in genetic males restrict the width of their black bars and the intensity of their pigmentation more than one barring gene in genetic females, which form wider, more intensely pigmented black bars.

The mechanism of gene action in forming such precise barring patterns is truly remarkable. As a given feather germ forms a feather, one population of melanophores actively synthesizes and deposits pigment granules as one transverse level of the feather is being formed and a black bar results. A different population of melanophores (but with the same genotype) fails to synthesize and deposit melanosomes as the subjacent (more proximal) level is formed, resulting in a transverse, pigment-free region or white bar. Experiments by Mark Nickerson in Willier's laboratory in 1944 demonstrated conclusively that incompletely differentiated melanophores or melanoblasts were present in that level of a Barred Plymouth Rock or Silver Campine feather germ during formation of a white bar. Upon transplantation of small sectors of the white-forming level into the coelom (body cavity) of a White Leghorn host embryo, a considerable number of fully differentiated melanophores appeared in the graft. Moreover, equivalent sectors transplanted instead to the flanks of White Leghorn host embryos produced donor-colored areas of host down feathers around the transplantation sites. These results indicated that complete differentiation of melanophores in situ in a developing white bar region of a developing feather that is forming a barring pattern is inhibited in some way, possibly by proximal diffusion of some inhibitory substance formed distally by the metabolic activities of melanophores as they formed a transverse black bar. The results demonstrated that under normal circumstances the genotypes of the melanophores themselves brought about the rhythmic inhibition of the pigmentation process essential for development of barred patterns in plumage, a completely new interpretation of gene action in formation of barred color patterns.

This presumably was also true of the genetic mechanism involved when melanoblasts from Barred Plymouth Rock embryos of known genetic sex, transplanted to embryos of different breeds that lack the barring gene, faithfully reproduced the sexually dimorphic barring patterns characteristic of each sex in developing host feathers, and did so irrespective of the genetic sex of the hosts, that is, irrespective of the host sex hormonal milieu.

Role of Specific Host Feather Germs in Modifying Complex Color Patterns Controlled Primarily by Genotypes of Donor Melan-

ophores. Do different developing feather germs within different feather tracts or within a given feather tract of a host of one breed of fowl modify complex color patterns produced by donor melanophores of another breed? The answer is emphatically yes, as explained in one example in Willier's words (1952, p. 118):

> In the Barred Plymouth Rock, melanoblasts from either male or female, when introduced into host White Leghorn chicks produce a variety of black and white patterns depending upon the position of the feather on the body of the host. No two feathers have identical barred patterns. Although the patterns are similar in feathers adjacent to one another in the same tract, they are not exactly alike. Feathers farther apart topographically tend to show a wider difference in the quality of the patterns. It is clear, therefore, that the individual feather papilla influences in a more or less specific manner the expression of melanoblasts of the Barred Rock. Each feather papilla appears to have its own kind of influence. Nevertheless, every variation hangs together in that the underlying barred pattern is discernible.

These results, along with detailed analyses of several other donor-host combinations, clearly revealed specific differences in the ability of individual developing host feathers to produce modifications of several complex color patterns whose formation is primarily controlled by the genotypes of donor melanophores. Analyses thereafter attempted to demonstrate specific physiological differences in different developing host feathers, such as growth rate, that might be factors in modifying the basic donor color patterns.

After 1944 Willier's publications on feather pigmentation were review papers (1948, 1950, 1952, 1953) that stressed primarily hormonal regulation of feather pigmentation in the fowl and integrated skillfully the results of investigators at the University of Chicago with those from his own laboratory. Oppenheimer wrote "For him, what followed analysis was synthesis, and he was a master at synthesis, too."[44] In her overall evaluation of this research program she also wrote "the exploitation of the feather as an element in a complex whole was most productive, and the explanation of feather pattern development as controlled by genes and hormones was a magnificent accomplishment."[45] These beautiful experiments in Willier's laboratory point up problems not yet resolvable in molecular terms—supracellular problems—and may well be considered classics in developmental genetics when "discovered" by future developmental biologists.

THE JOHNS HOPKINS UNIVERSITY

At the University of Rochester, as stated by Ebert in his 1972 news release at the time of Willier's death, Willier's "capacity for scientific leadership came to the fore, especially his critical judgment and ability to assess scientific talent. It was these traits, along with his own impeccable standards in research, that led to his joining the Johns Hopkins University in 1940 as Chairman of the Department of Biology and Henry Walters Professor of Zoology."

Administrative Activities. During 1940 and 1941 Willier and his associates (Mary E. Rawles and Nelson T. Spratt, Jr.) and three graduate students, all from Rochester, occupied the greenhouse separated from the university faculty club by a formal garden. Here his research program on differentiation of pigment cells continued, with emphasis on the roles of genes and hormones in the mechanisms of feather coloration. During that academic year, a major responsibility was the construction of the Mergenthaler Laboratory for Biology, completed in 1941, to provide for the creation of a single department from the previously separate departments of

[44] Oppenheimer, "Benjamin Harrison Willier," p. 175.
[45] *Ibid.*, p. 178.

botany, zoology, and physiology. At the formal dedication of this building on February 23, 1942, the honorary degree of Doctor of Laws was bestowed upon professors Ross G. Harrison of Yale and Frank R. Lillie for their outstanding contributions to the field of embryology. A second major responsibility was the unification and consolidation of these departments into one and the establishment of a program of teaching and research at the level of fundamental biology. In addition, decisions had to be made concerning the areas of biology that should be emphasized in the future development of the new department. Physiology, genetics, and embryology were wisely selected initially for emphasis. As Ebert remarked, again in his 1972 news release at the time of Willier's death, "he developed what was widely regarded as a model modern department of biology. He had an uncanny knack of selecting future leaders and of providing an environment in which they could develop." As Roseman later stated at the Willier memorial service, he created "a new type of biology department, a department of molecular biology, in spite of the fact that his own training and expertise were in the area of classical biology." In making his new appointments, Willier was always out for quality. He recognized the need to select investigators with insight and imagination who would be able to change methods and aims as knowledge advanced. In this he was eminently successful.

On December 5, 1950, at a ceremony commemorating the unveiling of a bronze tablet in memory of Ottmar Mergenthaler, whose name graced the new biology building, it was stated "From the beginning the policy has been to select staff members who are research-minded, who have an infectious enthusiasm for their subject, and who can arouse the intellectual curiosity of the student. The quality of a staff is gauged by its productivity in research and by its students who carry its objectives and ideals into other universities and walks of life." This research emphasis was a pattern set by Willier, which was considerably expanded by his administrative successor, Professor William D. McElroy. Consequently the Department of Biology and the McCollum-Pratt Institute at Johns Hopkins deservedly became recognized as among the leading research centers in the country in the field of molecular biology. On December 17, 1968, a letter was written to Willier by William Bevan, vice president and provost at Johns Hopkins, stating "The University has been honored by your distinguished career as a scientist and has benefited from the important contribution you have made in building the Biology Department into one of the finest in the country." In view of the original decision that genetics and embryology would be two cornerstones for development of the new Department of Biology, it was highly appropriate that a Symposium on the Chemical Basis of Heredity, held at Johns Hopkins under the sponsorship of the McCollum-Pratt Institute in 1956, was followed in 1958 by a Symposium on the Chemical Basis of Development, the latter dedicated to Willier.

Willier once expressed his views very specifically (letter in his personal files) about what he believed the role of a departmental head or chairman should be and about the disadvantages of a rotating chairmanship.

> [He] should be, in my opinion, a scientist of outstanding achievement in some branch of zoology. The head should be a leader in determining the plans for and policy of the department and in dealing with the administrative officers of the university concerning promotions, appointments, etc. Also the head should see that the program of study and research of the department conforms to the overall policy of the university at large. Rotation of chairmen in some universities has not proved to be very effective in seeking funds or in maintaining strength over a period of years. A chairman of vision combined with high standards of productive scholarship can bring about appointment of staff members of such high quality as to attract financial support. In sum, as a department builds in

strength and reputation through effective leadership, it stands a better chance to obtain funds from various agencies for its individual staff members or the staff as a whole.

In a letter to me dated August 3, 1947, Willier stated that at Johns Hopkins he took the position that promotions should be based on merit or achievement in research and that salary adjustments should be made in accordance with advances in living costs. He noted that this was not the procedure of many institutions at that time. While he was on the faculty of the University of Chicago, he decided that he should consider only appointments at private universities. He felt that policies concerning research and financial support could be radically changed by state legislatures and that he could never feel secure about a research program at a state university because he believed that its business was primarily teaching.

Willier's views were widely sought by other institutions to help them determine directions departments of zoology or biology should take; promising young scientists in fields that should be represented; biologists who should be appointed, promoted, named chairmen or departmental heads and awarded fellowships; traits that characterize the most effective teachers and what quality teaching programs should be; and the like.

Papers Published and Books Edited Prior to Retirement. Prior to his retirement at Johns Hopkins, Willier published only two original papers and one abstract, all in 1944, from his research program on pigmentation of host feathers by donor melanophores. These papers exemplified to perfection one of Willier's basic scientific traits as identified by Oppenheimer: "Analyzing very particular processes in a very particular way was his greatest pleasure in the laboratory."[46] These

[46] *Ibid.*, p. 174.

were extremely thorough and time consuming analyses of the minute details of specific color patterns, especially as controlled primarily by sex-linked genes for barring in melanophores from male and female F_1 hybrid embryos from a cross between a Barred Plymouth Rock female and a Rhode Island Red male and from male and female Barred Plymouth Rock embryos. In these papers full advantage was taken of the fact that the specific behavior of the donor melanophores in developing host feathers is recorded permanently and in detail as color or color patterns in the mature feathers. Direct comparisons were made of the individual patterns produced by donor melanophores of known genotype in feathers collected from given feather follicles of hosts of various breeds with those produced in homologous feather follicles not only of control chicks of the same donor breeds, but in some cases even from the homologous follicles of the donors themselves, which sometimes survived through hatching and developed normally. It was therefore possible to determine to what extent the genotypes of the donor melanophores controlled the feather color patterns they formed in each developing host feather and to what extent physiological properties of individual host feather follicles, and in some combinations the sex hormone milieu of the host as well, modified the basic donor patterns.

Thus, for the first time, it became possible to understand some of the factors involved in development of a few of the complex color patterns so characteristic of the plumage of many breeds of fowl and species of birds. Dissertations of six of Willier's doctoral students at Johns Hopkins (one each in 1941, 1943, 1944, two in 1948, and one in 1956) also contributed to this understanding. Dissertations of his seven other doctoral students at Hopkins dealt experimentally with diverse—but always significant—aspects of the development of chick embryos (one each in 1948, 1950, 1951, 1952, 1953, and two in 1954). Three of the latter concerned different problems in developmental endocrinology (James F. Case, 1951; Irwin R. Konigsberg, 1952; W. E. Dossel, 1954), a field of great interest to Willier throughout his scientific career. Three others led the students directly into most of the research problems they investigated so successfully throughout their careers (J. W. Saunders, Jr., 1948; James D. Ebert, 1950; Alfred J. Coulombre, 1953).

Most of Willier's papers published from Johns Hopkins prior to his retirement were invitational papers based on presentations at national and international meetings. All were closely related to his own investigations. Most of them carefully integrated more recent discoveries in his own and other laboratories. These articles dealt exclusively or primarily with pigmentation problems in plumage development (1941, two in 1942, 1948, 1950, 1952, and 1953); a few (1942, 1948, and 1950) were concerned in part with hormonal regulation of feather pigmentation in fowl. One dealt in part with sex inversion in chick embryos following treatments with sex hormones (1942), another with the production of sterile gonads in chick embryos and the problem of germ cell origin in embryonic development (1950), and still another (1952) with the evidence for the development of sex hormone activity in the avian gonad. In addition, a major paper (1955) provided the first comprehensive, timely, and useful survey of the course of differentiation of the functional activity of the endocrine glands of amphibians, birds, and mammals, the extent to which their initial activity arises independently of other hormones, and the time of onset of the functional interactions between them.

A major sustained effort during these years was devoted to planning the contents and logical sequence of topics; allotting the number of pages for each section and its chapters, if any; selecting the authors; editing the manuscripts; proofreading; and the like for a book entitled

Analysis of Development, published in 1955 under the combined editorship of Willier, Paul A. Weiss, and Viktor Hamburger. The origin of this book goes back to Willier's years at Rochester (1933–1940), when a small group of embryologists (self-designated the "Sandpipers") met informally during several summers at the Marine Biological Laboratory in the sand dunes of Cape Cod near Barnstable to discuss the problems of development and the mechanisms of embryogenesis. The need for a formal, balanced account of these matters became evident. The primary goal of such a book was to provide an overview of the current status of the field of development that would serve as the basis of departure for new minds of the future. By August 8, 1945, a list of topics to be included was drawn up, resulting in 1947 in a comprehensive plan for a collaborative work. Once this blueprint and some general suggestions for authors were in hand, twenty-eight authors agreed to write individual sections or chapters. Eleven of these (including all three editors) were, or subsequently became, members of the National Academy of Sciences.

Initially it was hoped that the contents of the book could somehow be integrated. In the original plans the book was to end with an evaluation of the developmental process, some general conclusions, and a few statements about future prospects in the field of development. Instead each author's contributions were prepared quite independently of the others. Nevertheless, Oppenheimer later characterized this book as "a towering landmark in the literature of what Willier used to like to call analytical embryology, with analysis culminating in synthesis."[47] Chronologically, the appearance of this book essentially marked the end of the major impact of classical experimental embryology and the begin-

[47] *Ibid.*, p. 178.

ning of the rapid emergence of the much broader field of developmental biology, and in this sense it constituted an "old testament." Willier was directly involved in this changing emphasis as he and many others participated in the organizational meeting for the Developmental Biology Conference Series of 1956 (with Paul Weiss as organizer and chairman) and in three of the ten subsequent conferences devoted to specific topics, but his most active participation was as chairman of the Conference on Endocrines in Development on September 24–26, 1956.[48] That same summer, at the meeting of the American Society of Zoologists at Storrs, Connecticut, a group of developmental biologists initiated discussions that resulted two years later in the formal organization of the Division of Developmental Biology of the American Society of Zoologists. And in 1959 a new journal, *Developmental Biology*, began publication. Willier was not directly involved in the latter two events.

Another major effort was the exceedingly meticulous writing of his superb biographical memoir of Professor Frank R. Lillie (1957), which followed publication of his two brief memorial articles in 1948. When asked to write the memoir of another member of the National Academy of Sciences, he declined in a letter in his files dated December 16, 1955, which contained the following remarks: "It took me nearly 8 years of careful search and study to prepare the biography of my professor, Frank R. Lillie. During that time I was unable to conduct any original research. I am too much of a perfectionist—I could not prepare a biography in a perfunctory manner. I must check every detail in his scientific career and make as sound an appraisal of his contributions to science as my ability permits and check my appraisal with that of others who work in the same special field."

[48] Ray L. Watterson, ed., *Endocrines in Development* (Chicago: University of Chicago Press, 1959), pp. i–xi, 1–142.

In 1945 Willier was elected to membership in the National Academy of Sciences, and in 1955 to membership in the American Philosophical Society. Also in 1955 Willier retired as chairman of the Biology Department at the Johns Hopkins University. In recognition of his fifteen years of devoted and enlightened administrative service to the department and university, as well as his many contributions as investigator, teacher, and editor and his tremendous accomplishment in training doctoral students of high calibre, a Willier Doctorate Program was held on the afternoon of April 6, 1956, as one of the scheduled sessions of the American Association of Anatomists meeting in Milwaukee, Wisconsin. On this special occasion thirteen of his thirty-four doctoral students presented twelve exciting papers in the following sequence: J. P. Trinkaus, James Case, Clement L. Markert, Nelson T. Spratt, Jr., Casimer T. Grabowski, Ray L. Watterson, James D. Ebert, Irwin R. Konigsberg, Alfred Coulombre, Dorothea Rudnick, John W. Saunders, Jr., and Thomas E. and Eleanor A. Hunt. Eighteen of his students gathered afterwards for a reception and banquet.

Scientific Activities and Recognition Following Retirement. In 1958 Willier retired as Emeritus Professor of Biology at Johns Hopkins University. He retained his campus office, and laboratory facilities were available to him. In many ways it was "business as usual" until his fatal illness struck on November 25, 1972. His philosophy about retirement was simply stated: "Leisure time is just as busy as working time is a way to make retirement a happy period in life."[49] Fortunately his good health enabled him to fulfill this creed. Moreover, as stated by Stephen Roth at his memorial service "his interest in embryology was more profound and more

[49] Brief autobiographical sketch received April 21, 1965, by the Alumni Office, the College of Wooster.

enthusiastic after a half a century of work than has been the interest of most other scientists of any age."

Willier immediately turned his attention to fundamental research problems different from those of all his previous studies and those of his students. On September 9, 1958, he wrote to me as follows: "Officially retired, I am, however, engaged in research on a grant from the Atomic Energy Commission—in cooperation with a biochemist here—on 'Pathways of Metabolism in the Chick Embryo.' My particular aspect of the investigation involves a cytological and histochemical analysis of the yolk sac membrane, a living way station between the yolk and the developing embryo." This is a two-layered extraembryonic membrane composed of a layer of parenchymal (endodermal) cells adjacent to the yolk and an adjacent layer of splanchnic mesoderm in which capillaries of the yolk sac (vitelline) circulation develop. These layers elaborated by the incubating egg eventually enclose the yolk within the yolk sac, whose vitelline vessels are continuous abdominally through the umbilicus of the developing chick embryo with the intraembryonic vessels of the latter. It is the cells of these layers that make possible the transfer of yolk substances, certain of their metabolic products, and/or substances synthesized from them to the blood, which transports them to the embryo for utilization.

Willier (1966) presented a preliminary paper, by title and abstract only, based on this research to the summer meeting of the American Society of Zoologists. In 1968 his full paper appeared, replete with superb radioautographs of the yolk sac membrane showing with excellent clarity the size, shape, and localization of H^3-glycogen granules within parenchymal cells following injection of H^3-glucose into the yolk, superb photomicrographs of these cells stained cytochemically for glycogen and certain other chemical components, and excellent transmission electron micrographs for ultrastructural details. Armed with this information, obtained during the middle third of embryonic life, he constructed a remarkably complete diagrammatic representation of the yolk sac membrane that provided the basis for a comprehensive, clear, and characteristically cautious interpretation of the cytological structure of the yolk sac membrane relative to some of its major functions. This publication emphasized: 1) the presence and possible roles of cup-shaped folds and of pinocytic invaginations at the apical ends of parenchymal cells in the uptake of whole yolk spheres or soluble yolk substances respectively; 2) apical-basal changes in intracellular yolk spheres indicative of their degradation; 3) three types of intimate specialized spatial relationships observed between cytoplasmic matrix containing glycogen particles and limiting membranes of yolk spheres suggestive of transfer of glycogen precursors from the yolk spheres to the cytoplasm; 4) observations indicating synthesis of glycogen in the apical halves of parenchymal cells, intracellular transport of glycogen basally as more yolk is engulfed apically, accumulation of glycogen basally where glycogenolysis occurs releasing glucose; and finally 5) the presence of pinocytic indentations and vesicles formed by the plasma membranes of the basal ends of the parenchymal cells and at the outer and luminal surfaces of capillary wall (endothelial) cells, suggesting possible mechanisms for the exchange of substances between parenchymal cells and blood in vitelline capillaries. In 1971 Willier published a brief article on the yolk sac in the *McGraw-Hill Encyclopedia of Science and Technology*, for which he served as consulting editor in the field of growth and morphogenesis from 1960 to 1963.

In the fall of 1958 Willier had already assumed new and different responsibilities.[50] He was named director of an

[50] *Food Field Reporter*, November 10, 1958, provided courtesy of Julia B. Morgan, the Ferdinand Hamburger, Jr., Archives of the Johns Hopkins University.

oyster research program dealing with Chesapeake Bay oysters undertaken jointly by the Food and Drug Administration, Field and Wildlife Service, and the Oyster Institute of America, and financed equally by each group. This was a two-year project involving a review of all available literature and data on oysters by Willier, based in Baltimore, and the laboratory work of three technicians (two chemists and a marine engineer) working under Willier's supervision at the Virginia Fisheries Laboratory, Gloucester Point, Virginia. The goal was to devise legally enforceable standards for shipping raw oysters, in part to enable FDA to support food adulteration charges, including oyster watering. Earlier, while still chairman of the Department of Biology, Willier had been involved with Chesapeake Bay research in a more limited way.[51] In 1947 Commander Roger Revelle had proposed the establishment of a Chesapeake Bay Institute on the campus of the Johns Hopkins University, and this proposal had been conveyed to President Bowman by Willier. The institute was established in 1948, and in 1981 was moved to excellent new facilities in the town of Shady Side, Maryland on the West River south of Annapolis. Physical oceanography had always been the institute's forte. Post-expansion plans included the addition of studies in microbiology, fish genetics, and toxicology. On October 23, 1970, Willier transferred his academic correspondence related to the creation of this institute to the Eisenhower Library of Johns Hopkins, where it was designated as "The Willier Collection."

During 1937 and 1938 Jane Oppenheimer was a research fellow in embryology at the University of Rochester. She valued her experiences in Willier's laboratory very highly,

[51] *Johns Hopkins Journal,* winter, 1982, p. 2. Also memorandum from Steven Muller, President, the Johns Hopkins University, to alumni, parents, and friends of September 30, 1981.

and in a letter to him dated March 30, 1958, she wrote "I am not officially classed as your student, yet I have benefited so much from the time in your laboratory at Rochester and Hopkins, I count myself lucky to have had it." Willier always felt himself a part of ongoing history, and in 1970 acknowledged this sentiment explicitly in an article in which he recalled some of the ways past scientific developments and the scientists responsible for them had engendered his intellectual development. Oppenheimer became widely recognized as a superb writer and historian in the fields of biology and development. The mutual respect between these two scholars grew over the years, and culminated in 1964 in their joint editorship of *Foundations of Experimental Embryology*, reproducing chronologically, each with excellent brief editorial introductions, eleven articles published between 1888 and 1939. Each of these was carefully selected for its excellence, pioneering and enduring quality, and influence on the rise of experimental embryology. Five of these were exceedingly careful translations from the originals published in German. In 1974 a second edition appeared with a most useful twelve-page introduction written in Oppenheimer's inimitable style, adding greater perspective for the readers. She also added three additional significant articles published in 1954, 1969, and 1973, again with effective introductions to each.

In the summer of 1939 Willier had been a guest investigator in the laboratory of Professor Charles H. Danforth in the Department of Anatomy, School of Medicine, Stanford University. From 1927 through 1939 Danforth had published thirty-two papers dealing with many aspects of feather development, growth, and pigmentation and the effects of genetic and hormonal factors on these processes in a variety of birds. In these investigations the method of skin transplantation in *posthatching* stages was a major tool. His discussions with Danforth and his first-hand acquaintance with his experiments must have had a marked influence on Willier's thinking and writing, and also on Willier's research associate, Mary Rawles. She spent four months in Danforth's laboratory in 1940 and learned from him the basic technique she later used so successfully in Willier's laboratory to transplant embryonic skin to newly hatched chicks to investigate pigmentation problems, experiments which doubtless encouraged her to initiate equally successful skin transplants from rat fetuses to newborn rats and to exchange skin sectors of newborn rats for similar purposes. A logical consequence of these earlier associations with Danforth was the writing of Danforth's excellent biographical memoir by Willier. He mentioned in an undated card written some time during 1971 that he had "Just finished a 60 pp. memoir of Charles Danforth for the Academy." Because Willier's death occurred before the processing of this manuscript had been completed, Leslie C. Dunn, Ronan O'Rahilly, Sewall Wright, and Curt Stern assumed this responsibility. The memoir was published in 1974. In Danforth's life prior to graduate school, as recorded in his 1948 autobiographical sketch prepared for the National Academy of Sciences, which was quoted extensively in this memoir, Willier had found a "soulmate" with the love of nature foremost in his life, but with the considerable difference that Danforth had available to him in his early years great books and distinguished naturalists.

During Willier's active retirement, there were special events honoring him in a variety of ways. On May 22, 1963, a letter was written by Professor Alfred S. Romer, President of the XVI International Congress of Zoology, the first of these congresses to be held in the United States since 1907, inviting Willier to serve as one of the vice presidents of the Congress, but he declined, recommending another. Professor Jerome

A. Schiff, Secretary of the Society for Developmental Biology (earlier the Society for the Study of Development and Growth) wrote to Willier on July 13, 1966, as follows:

> It is a great pleasure for me to inform you that the Society for Developmental Biology, on the occasion of its 25th Symposium at Haverford College, voted enthusiastically and by acclamation to express to you its thanks for all you have done to further the cause of developmental biology. On this happy occasion it was noted that you had made extraordinary contributions to the field as an investigator, as an educator, as an administrator, and above all, as the mentor of a large number of excellent embryologists. Your contributions to the field and to the Society leave all of us in your debt.

Although Willier was unable to attend the first symposium of the original society in the summer of 1939 because he was at Stanford University with Danforth at the time, and was thus unable to be directly involved in the steps taken there to establish the original society, he had been instrumental, nevertheless, in its establishment, had participated actively in its annual meetings, and had served as its president from 1943 to 1945.

A portrait of Willier was presented in his honor to President Lincoln Gordon of Johns Hopkins by the Department of Biology on December 17, 1968. It hangs in the main hallway of Mergenthaler Hall, the biology building. A major event in Willier's life occurred on May 27, 1970, when the Johns Hopkins University conferred on him the Doctor of Laws Degree. He was presented for this degree by Professor James D. Ebert as "my teacher . . . pioneering and gifted experimentalist, rigorous yet fairest of critics, warm friend and inspiring teacher of embryologists . . . and devoted student of the embryo." On November 2, 1970, on the occasion of his eightieth birthday, Willier received from his good friend Professor Paul Weiss a remarkable handwritten letter not simply congratulating him, but reminding him of all that he had done for embryology, not only "by steadfastly setting an inimitable model of the virtue of scholarship and working discipline" but also for providing "a new generation in vigorous self-reproduction which is steeped in the knowledge of true embryology." A typewritten copy of this letter was placed by the departmental chairman in a locked case with a glass door to the left of Willier's portrait, so that all who passed by could see it. In May 1972 another treasured event took place: his election to membership in the American Academy of Arts and Sciences.

The memory of Benjamin and Helen Willier has been honored posthumously in a most appropriate way. Two seats in the renovated Lillie Auditorium at the Marine Biological Laboratory now bear permanent plaques with their names inscribed thereon. Funds contributed for this purpose reflect the esteem in which they were held by Willier's students and colleagues, and by the Marine Biological Laboratory. The front cover of the fine new book *Developmental Biology, Patterns/Problems/Principles*, published in 1982 by John W. Saunders, Jr., is emblazoned with a striking full-color photograph of a four-day experimental chick embryo, a veritable "coat of arms" for the Willier doctoral students. And on page iv the following words appear in distinctive type: "To the memory of Benjamin Harrison Willier, Teacher, Scholar."

SOME REVEALING STATEMENTS ABOUT HIMSELF

Some notion of Willier's thoughts and activities toward the end of his career, and especially in the last year of his life, emerges from brief quotations from letters to me and others and from memoranda he wrote. *April 30, 1968*: "When I am not working in my garden, I am planning the content of a paper dealing with discoveries not looked for." *November 4, 1969*: "I am not one who has to force myself to work. It is as much my recreation as my vocation." *November 25, 1970* (to

Paul Weiss): "Like you my life is one of exploring the embryo—there is beauty in its ways of generating itself. The embryo is my life." *July 9, 1971* (on reflections following a visit to the Marine Biological Laboratory, where he had spent many happy times as a member of the teaching staff, the corporation, and the board of trustees, contributed quite a few of the evening lectures and devoted much time to reading and writing): "Moreover, all of the great at the M.B.L. in the early twenties (E. B. Wilson, F. R. Lillie, Ralph S. Lillie, T. H. Morgan, J. Loeb, Ross Harrison) I thought of as having a strong influence—each in his own way—on the maturation of the ways of my intellectual life. Momentarily, M.B.L. became a mecca to me." *January 19, 1972*: "I have a title which is 'Adaptive Correlations between the Chick Embryo and Its Yolk Sac Membrane in Development.' There is so much to learn well." *February 10, 1972*: "Over a year ago I prepared a critique of the Free Martin—so valuable (so I thought) that I cannot find it." *March 8, 1972*: "I have been thinking on the question of why the chick embryo stores glycogen—especially why no one seems to have a fruitful idea as to the function of the glycogen body. I am now writing under the heading 'The Embryo's Need for an Extra-Essential Organ'—the latter is the yolk sac membrane at phase II. It then attains its greatest structural complexity and greatest functional activity. Is the glycogen body something *extra*?" *May 17, 1972* (to the President of Johns Hopkins University): "I am deeply indebted to the Johns Hopkins University for giving me the opportunity and the privilege of laying down a few foundation stones on which the life sciences has been well built." *May 25, 1972* (letter to Tri Beta, biology honorary fraternity, on the occasion of its 50th anniversary): "I see myself as an investigator sharing the excitement of discovery with fellow members of the Society, and as a teacher who shares with students the excitement of learning diversified patterns of organisms and their modes of living." *September 29, 1972*: "I am happy only when I can play with ideas—if I can have them at my age eighty-two." *November 7, 1972* (letter to Mr. J. G. Goeller, editorial director, Johns Hopkins University Press): "I note with keen interest a rapidly growing number of young scientists who are currently active in research on the chemistry of gene action in the differentiation of cells and in the mechanism of shaping of the embryo and its organs." *November 8, 1972*: "I am so busy with so many university affairs that I have not yet resumed my writing on 'A Cleidoic Egg: An Adventure in Embryogenesis'. This is a manuscript for 'Perspectives in Biology and Medicine' (if it ever gets finished). At the present I am trying to get the Hopkins Press to publish a paperback edition of *Foundations of Experimental Embryology* by the photo offset process. I am also trying to get started for the centennial in 1976 a program honoring Ross G. Harrison for his discovery of tissue culture and the neuron as a single cell and not a chain of cells." As Professor Clement L. Markert, a Willier doctoral student, wrote on February 2, 1973 (solicited communication), "it was obvious . . . that interest in scientific exploration was the central concern of his intellectual life and gave him enormous satisfaction. He was fortunate to be able to proceed to the end of his life with his interests and satisfactions undiminished."

A MAJOR CONTRIBUTION TO THE FUTURE: WILLIER'S LEGACY

Professor Robert K. Burns, Jr., one of Willier's colleagues, wrote of him in 1973 (solicited communication) "I would stress another contribution of possibly even greater value in the long run (than his great contributions to embryology in the form of his personal research)—the unusual number of students trained under his close guidance and already to be found in many important academic posts about the country. His influence thus affected not only his own generation but is being projected far into the future. He attracted to his laboratory a steady stream of students of high quality and capacity. It was evident that he accepted only the best." Rudnick wrote in 1973 "Obviously Benjie's departments gave energetic students of development ample space to develop, and this became known." Markert remarked in the same year "Objectively there is no doubt that he produced a great many very successful students and consequently had a greater impact on the field of developmental biology than, perhaps, any other man of his generation, not because of his own research, but because of his students." A letter to Willier from Oppenheimer dated March 30, 1958, stated "You have taught your students to appreciate high standards—made your students a unique group (very important for the present and future of embryology)." In her memorial article on Willier for the American Association of Anatomists Oppenheimer wrote "Good young people found their way into his laboratories, and then became even better young people and first-rate scientists. Many of them have themselves become embryologists of singular distinction. He set the same high standards for his students as for himself; but no matter how tough the young people found the going during their training, once they were ultimately on their own they appreciated profoundly what had been given them."[52]

Professor J. Philip Trinkaus, one of Willier's doctoral students, wrote on May 16, 1982 (solicited communication): "We had a lot of independence and we knew we had to do it on our own, and we knew that he had high standards and we had to measure up." He also emphasized that he was "the best person to work with at the time," and that all his fellow

[52] Oppenheimer, "Benjamin Harrison Willier," p. 187.

Willier graduate students at Hopkins "were bright, independent, driving types." In a letter dated August 4, 1982, Coulombre stated "Dr. Willier simply did not 'direct' the research of his graduate students. He rarely came to the laboratory (the . . . large, communal room which housed his students' bench space) and waited for each of us to approach him about progress (or lack of it) in our work. It was an optimal stance for fostering independence, allowed for the emergence of any creative talent the student might have and allowed each of us to tap his experience and advice when and to the extent we felt the need for them." He also wrote that on a particular occasion Willier later acknowledged to some of his former doctoral students that "It was my policy to allow my graduate students to stand on their own feet." A letter from Foulks dated February 19, 1982, stated "I drew more in the way of intellectual ferment from some of Willier's associates . . . at Rochester . . . (and) at Hopkins, as well as from other graduate students and fellows, than from the Chief himself. *But he deserves full credit for the design and implementation of these programmes, and for bringing the components together*" [italics mine]. My overall evaluation of this aspect of his scientific life is that he provided for his students very special opportunities and exceedingly high expectations. In an undated card Willier once wrote to me "Many of my students just wanted to learn. I am lucky to have so many students who liked the egg's way to make a new individual."

Ebert wrote in his news release at the time of Willier's death, "Over the years he trained thirty-four Ph.D. students; included in this number are many of the nation's current leaders in several fields. He took great pride in the accomplishments of his scientific 'family,' 'children,' 'grandchildren,' and in recent years even 'great-grandchildren,' and in their new directions of research, *which he strove to understand*" [italics mine].

Saunders commented at the Willier memorial service about Willier's former doctoral students as follows. "The majority of these have, themselves, enjoyed distinguished careers as teachers and investigators and have achieved international recognition. Many have served as advisors to federal agencies, have exercised significant editorial responsibilities for major journals and have written significant textbooks. Several have been departmental chairmen in major institutions and some have been named to the National Academy of Sciences." Quite a few have been active participants in numerous major symposia and have contributed excellent chapters to books based on the symposia or upon invitation. Several have been presidents of one or more major professional societies (The American Institute of Biological Sciences, The American Society of Zoologists, The Society for Developmental Biology [earlier The Society for the Study of Development and Growth], The American Physiological Society, The American Society for Pharmacology and Experimental Therapeutics and The Pharmacological Society of Canada). One has also been director of the Department of Embryology of the Carnegie Institution of Washington, president of the Marine Biological Laboratory, and is currently president of the Carnegie Institution of Washington and vice president of the National Academy of Sciences. In April 1977 a symposium entitled "Molecular Biology and Genetics of Development" was held in honor of another at North Carolina State University, covering research areas in which he had already initiated investigations while still a graduate student. Still another, a research scientist and administrator in the National Institutes of Health, had dedicated to him in July, 1982, the first part of Volume 92(1) (pages 1–134) of the journal *Developmental Biology* "as a tribute to his importance to the field of developmental biology" and in recognition of his "nearly thirty years as a distinguished investigator of ocular morphogenesis." Several have been chairmen of the Division of Developmental Biology of the American Society of Zoologists, and others have been faculty members and one a director of the marine embryology course of the Marine Biological Laboratory; yet another has also taught marine embryology courses at the marine laboratories of Stanford University (Hopkins Marine Station) and the University of Washington (Friday Harbor Laboratories). Several have edited various books in the field of development, others have served as editors for various publishing companies, and still others have been invited contributors of embryological articles to a number of major encyclopedias, including the *Encyclopaedia Britannica, Encyclopedia Americana, McGraw-Hill Encyclopedia of Science and Technology, Encyclopedia of the Biological Sciences*, and other encyclopedic publications such as the *Dictionary of Scientific Biography*. Collectively the impact of quite a few of the former Willier doctoral students has been remarkable, as has the quality of the training of excellent predoctoral and postdoctoral students by some of them. The careers of others took quite different directions. One, after an academic career, a deanship, and very active roles in a variety of national, regional, and state committees and commissions concerned with education, joined the New York State Education Department and advanced to Associate Commissioner for Science, Technology, and the Professions. His involvement in education was worldwide. The other soon became a foreign service officer and served as officer-in-charge of our cultural information and educational exchange programs in our U.S. embassies in Wellington, New Zealand; Copenhagen; and Stockholm.

When Willier was about to retire at Johns Hopkins, he assembled, in the spring of 1958 and at no small expense to himself, the published works of his laboratory into three large volumes, one representing his scientific output and that of his students and collaborators at each of his major university posts: Chicago, Rochester, and Hopkins. He presented autographed sets of these volumes to quite a few of us as a unique and precious gift, and on the fly leaf of the volume containing the publications from the university that awarded each of us his Ph.D. degree he wrote in his distinctive handwriting a special comment, a few examples of which follow. "Exploring with my students how embryos are made has been a great joy and intellectual satisfaction. Zealous research so changed the shape of embryology that it will never be again the same." "May you long continue to be successful in exploring the ways of an embryo-in-the-making from the egg and have much fun at it—as much as I have had in working with my doctoral students." "We observe and record the ways of the embryo. Then conclude as best we can, for quoting Hippocrates, 'life is short, the art long, opportunity fugitive, experience deceptive, judgment difficult.' " And on a reprint of his 1968 paper on the yolk sac membrane he wrote simply to a colleague, "The end justifies the work."

WILLIER AND HIS FAMILY

Mrs. Willier majored in Latin and Greek at the College of Wooster. From 1914 to 1915 she was school principal at Melvern, Ohio, then a teacher at Ford City, Pennsylvania until the summer before her marriage to Willier on September 11, 1919. Their first home was in Chicago, where she continued for several years to take a number of courses not available to her at Wooster, including one with Professor Frank R. Lillie in whose class she "always felt a bit scared." But she also stated that both Dr. and Mrs. Lillie were very gracious to the students, and that "we enjoyed their hospitality often both in Chicago and Woods Hole." Both daughters were born in Chicago. In Baltimore Mrs. Willier participated in many local activities such as the Women's Club of Johns Hopkins University, the Three Arts Club of Homeland, the American Association of University Women, and several garden clubs.

Oppenheimer, in her comments at the memorial service, very sagaciously expressed her gratitude to Mrs. Willier and the family "for all they did that enabled Willier to do so much for us and for embryologists of the future." Regrettably not too many of Willier's own students fully appreciated the ways in which Mrs. Willier aided and abetted his career or the warmth of their feelings towards his students. Their daughter, Helen Kathryn Disser, certainly did when she wrote as follows in 1981 about her mother and life in the Willier home:

> Mother was always very supportive of Dad's career. She enjoyed entertaining and keeping a good home. As I recall, she made home life easy and pleasant for Dad. Mother was general handyman, cook, nurse, letter writer, bill payer, record keeper and disciplinarian when needed. Dad just didn't have time for such things. He spent lots of time reading, mostly technical papers and journals. Mother was the one who helped us with our home work and encouraged us to do well. Mother was a whiz at math. She loved tending her indoor plants. She was an excellent cook and enjoyed watching the graduate students appreciate her efforts. She and Dad just thought of the students as 'their boys' and as part of our family. I know I often felt as if I had many older brothers.

Oppenheimer also noted that the Williers were wonderfully hospitable at home. On October 4, 1974, Mrs. Willier wrote to me "It always made me glad that I had a very small part in making life a bit more pleasant for the wonderful men and women who worked with my husband. They have all proved that they were worthy of all the efforts he expended during those years." And on September 6, 1977, she wrote "It was my pleasure to have students as guests in our home. We began to do it in Chicago and Rochester."

Helen Kathryn also wrote in 1981 and 1982 "Mother and Dad were gardeners and nature lovers. Dad always worked on his yard making it a showplace. Mother had her rose garden and Dad specialized in azaleas, chrysanthemums, the lawn, trees, and shrubs. During World War II we had an extensive victory garden." There was music in the home. "Dad enjoyed music and played the piano for many years. He bought the piano, a baby grand Steinway, a couple of years before he bought his first car. We listened to the radio operas and Sunday philharmonic concerts. We attended concerts and had the opportunity to see and hear many famous artists in Rochester particularly." According to Kathryn her father started taking many beautiful nature shots even before she was born, and over the years enclosed with letters to her were many of these photographs, with notes on the backs about the places concerned. Showing his slides of favorite places was often part of small gatherings in the Willier home, a special treat for those who had not yet been able to travel. She also wrote "Our summers were usually spent at Woods Hole, Massachusetts. Dad always seemed to be writing or reading in his office at M.B.L. (the Marine Biological Laboratory). Every afternoon Dad, Louise and I went swimming. Sundays we would drive around the Cape. We often picnicked in the Barnstable sand dunes or at some of the beaches."

The Williers loved to travel. The two daughters were always included in these trips and other family activities. In Chicago days their trips were to the sand dunes in Indiana or Michigan and a summer cabin north of Chicago on a lake. In Rochester days Easter vacations were spent along the Atlantic Coast, on Okracoke Island or near Charleston, South

Carolina, or on the offshore islands. They visited many lovely gardens, plantations, and historic places. In 1939 there was a trip to Stanford University with sight-seeing along the way. Thus the daughters saw much of the United States before they were married. Later, after their marriages, "Mother and Dad always included a visit with each of us every summer." Moreover, each daughter continued to share some trips with her parents. On August 29, 1958, Willier wrote "Helen, Louise and I have been traveling by automobile in northwestern U.S. and Canada. Our main goal was Lake O'Hara in the Canadian Rockies where Louise and I climbed the mountains almost daily for two weeks. After this we went by train from Winnepeg to Churchill on the Hudson Bay. Seeing the muskeg along the way was a most thrilling experience. At long last I was able to realize my lifelong desire to see the North Country." In the summer of 1971 Willier thoroughly enjoyed a 7500-mile trip with his wife, daughter Louise, and a three and one-half-year-old granddaughter, which included a day at the Marine Biological Laboratory, a tour of part of the Cape landscape, a trip to Newfoundland, and then on to Louise's home on the Flathead River in a mountain valley just west of Glacier National Park. Kathryn's trips with them included other places her parents had never visited, such as Hawaii and the Natural Bridge National Monument and King's Canyon-Sequoia National Parks.

As Kathryn wrote, "Life with Mom and Dad was almost never boring."

CODA

Willier once wrote in answer to a questionnaire about his life and career "Recognitions came as a result of systematic and diligent effort. Livelihood was solely through work in the laboratory." Saunders stated at the Willier memorial service "He examined his own scientific work, that of his students and others with meticulous attention . . . in long hours alone at his desk confronting a manuscript or a stack of reprints or journals." A distinguished colleague once emphasized that "His research was not due to pressures of publish or perish, but stemmed from personal motivation." On February 8, 1973, Willier's colleague at Chicago and a close friend of long duration, Professor Sewall Wright, wrote "I would say that his success in his field was due primarily to his intense interest which kept it continually in his mind and also to his capacity for rigorous objective thought and his skill and patience in carrying through critical experiments." Oppenheimer stated that "The most salient features of his life as a biologist were his maintenance, throughout his career, of his childhood love of nature; his refusal, even during the years when many of his contemporaries became fiercely competitive, to hurry his work; and his continual reflectiveness."[53] Rudnick characterized him as follows in a letter dated February 17, 1973. "He certainly gave the impression of a person who was doing exactly what he wanted to do, meeting daily tasks in a calm, well-balanced manner, and thinking enigmatic thoughts about enigmatic problems. Also, he really was happy in the old-fashioned academic life, where there was time and appreciation for scholarship and leisure for one's friends." At the Willier memorial service Harrington remarked "He had an inner serenity which was unusual and he seemed to have resolved in some remarkable way the problem of adapting to new thoughts and new ideas which always confront the older teacher in a university environment." To this Roth added on the same occasion "It would be difficult to ask for a richer life."

I AM GREATLY INDEBTED to many individuals for their splendid cooperation in preparation of this memoir: Mrs. B. H. Willier and

[53] Oppenheimer, "Benjamin Harrison Willier," p. 175.

especially Helen Kathryn Willier Disser for details of Willier's ancestry, early life and family life; Mrs. Willier and Professor James D. Ebert for access to Willier's files and for their hospitality while perusing them and, above all, to Ebert for making time in his demanding schedule to read critically my penultimate draft, to bring to my attention some unintentional omissions and a number of changes which would strengthen the manuscript and later for reviewing the revisions I had made; Professors James D. Ebert, William F. Harrington, Jane M. Oppenheimer, Saul Roseman, Stephen Roth, and John W. Saunders, Jr., for providing transcripts of their remarks at the Willier memorial service; Professors David Bodian, Robert K. Burns, Jr., George W. Corner, Viktor Hamburger, Jane M. Oppenheimer, Curt Stern, Paul A. Weiss, and Sewall Wright, all closely associated Willier colleagues, and Professors Alfred J. Coulombre, Earl A. Dennis, William E. Dossel, James G. Foulks, Howard L. Hamilton, Thomas E. Hunt, Frank R. Kille, Clement L. Markert, Mark Nickerson, Dorothea Rudnick, Nelson T. Spratt, Jr., and J. Philip Trinkaus, all former Willier doctoral students, for their insight and most helpful solicited commentaries.

WILLIER'S DOCTORAL STUDENTS

UNIVERSITY OF CHICAGO

1929	Thomas E. Hunt
	Carl J. Sandstrom
1930	Eleanor Abrams Hunt
1931	Ben Kang Chen
	Dorothea Rudnick
	Kathryn F. Stein
1932	Alfred Brauer
	Ruth Holton Sandstrom
	Charles H. Seevers
1934	Elizabeth Butler
	Earl A. Dennis
	Frank R. Kille
	Mary E. Rawles
1935	L. Floyd Clarke
1937	Sibyl F. Street

UNIVERSITY OF ROCHESTER

1936	Lloyd E. Alexander
1938	Encil Morton Bradley
	Hermann Rahn
1940	Frederick S. Philips
	Nelson T. Spratt, Jr.
1941	Ray L. Watterson

JOHNS HOPKINS UNIVERSITY

1941	Howard L. Hamilton
1943	James G. Foulks
1944	Mark Nickerson
1948	Clement L. Markert
	John W. Saunders, Jr.
	J. Philip Trinkaus
1950	James D. Ebert
1951	James F. Case
1952	Irwin R. Konigsberg
1953	Alfred J. Coulombre
1954	W. E. Dossel
	Casimer T. Grabowski
1956	Willie M. Reams, Jr.

HONORS AND DISTINCTIONS

HONORS

Sigma Xi, 1919
Fellow, American Association for the Advancement of Science, 1925
Phi Beta Kappa, 1930
Honorary D. Sc. degree, College of Wooster, 1941
Member, National Academy of Sciences, 1945 (Chairman, Section of Zoology and Anatomy, 1949–1955)
Member, American Philosophical Society, 1955
Willier Doctoral Program, American Association of Anatomists, 1956
Symposium, the Chemical Basis of Development, Johns Hopkins University, in Willier's honor, 1958
Honorary LL. D. degree, Johns Hopkins University, 1970
Member, American Academy of Arts and Sciences, 1972

ANCILLARY APPOINTMENTS

Member, Zoology Staff, Marine Biological Laboratory, 1923–1925
Guest Investigator, Marine Biological Station at Tortugas, Carnegie Institution of Washington, summer 1936
Guest Investigator, Department of Anatomy, School of Medicine, Stanford University, summer 1939
Visiting Professor, Department of Anatomy, College of Medicine, University of Florida, winter term 1964

ADVISORY BOARD MEMBERSHIPS

Marine Biological Laboratory: Trustee, 1933; Executive Committee, 1941–1943; Trustee Emeritus, 1969
Commissioner of Research and Education, State of Maryland, 1941
Long Island Biological Association, Board of Directors, 1942
Oyster Research Program, Director, 1958
Science Service, Board of Trustees, 1959
Maryland Society for Medical Research, Board of Directors

EDITORIAL ACTIVITIES

Associate Editor, *Journal of Morphology*, 1932–1934
Associate Editor, *Physiological Zoology*, 1937–1963

Editorial Board, *Growth*, 1939–1949
Editor, *Quarterly Review of Biology*, 1942–1957; Emeritus Editor, 1958–1972
Editorial Committee, *Johns Hopkins Magazine*, 1942–1954
Advisory Board, *Survey of Biological Progress*, 1946–1962
Advisory Editor, *Lillie's Development of the Chick*, 3d ed., 1952
Editorial Board, *Bios*, 1953–1955
Senior Editor (with Paul A. Weiss and Viktor Hamburger), *Analysis of Development*, 1955.
Consulting Editor, Growth and Morphogenesis, *McGraw-Hill Encyclopedia of Science and Technology* and *Yearbooks*, 1960–1963
Senior Editor (with Jane M. Oppenheimer), *Foundations of Experimental Embryology*, 1964 (Expanded 2d ed., 1974)

PROFESSIONAL SOCIETIES OR ORGANIZATIONS

Corporation, Marine Biological Laboratory, 1919; life membership, 1969
American Association for the Advancement of Science, 1921 (Council, 1938–1940)
American Society of Zoologists, 1922 (Executive Committee, 1934–1935)
American Association of Anatomists, 1924
American Microscopical Society, 1924
Genetics Society of America, 1927
Society for Experimental Biology and Medicine, 1927
Society for the Study of Development and Growth, 1939 (President, 1942–1945)
Endocrine Society, 1942
Institut International d'Embryologie (Utrecht, Holland), 1945
Society of Cell Biology (London), 1950

BIBLIOGRAPHY

1921

Structures and homologies of free-martin gonads. J. Exp. Zool., 33:63–127.

1923

The effects of thyroid grafts on the development of the chick. Anat. Rec., 26:339–40.

With Libbie H. Hyman. The physiology of protein digestion in triclad flatworms. Anat. Rec., 26:368.

1924

The endocrine glands and the development of the chick. I. The effects of thyroid grafts. Am. J. Anat., 33:67–103.

With L. H. Hyman and S. A. Rifenburgh. Physiological studies on planaria. VI. A respiratory and histochemical investigation of the source of the increased metabolism after feeding. J. Exp. Zool., 40:473–94.

1925

With Libbie Henrietta Hyman and Sumner Adam Rifenburgh. A histochemical study of intracellular digestion in triclad flatworms. J. Morphol. Physiol., 40:299–340.

The behavior of embryonic chick gonads when transplanted to embryonic chick hosts. Proc. Soc. Exp. Biol. Med., 22:26–30.

The specificity of sex, of organization, and of differentiation of embryonic chick gonads as shown by grafting experiments. Anat. Rec., 31:298.

1926

The development of implanted chick embryos following the removal of the 'primordial germ cells.' Anat. Rec., 34:158.

1927

The specificity of sex, of organization, and of differentiation of embryonic chick gonads as shown by grafting experiments. J. Exp. Zool., 46:409–65.

With Y. K. Hiraiwa. The differentiation of isolated parts of rat embryos when transplanted to chick embryos. Anat. Rec., 35:40.

Is embryonic sex differentiation in the chick modifiable by sex hormones of engrafted gonads? Anat. Rec., 37:163.

1928

An experimental study of the origin of the adrenal gland in the chick embryo. Anat. Rec., 41:73.

With Eliot C. Yuh. The problem of sex differentiation in the chick embryo with reference to the effects of gonad and non-gonad grafts. J. Exp. Zool., 52:65–125.

1929

Origin of the adrenal gland, with reference to its sympathetic nerve components in the chick embryo as shown by chorio-allantoic grafts. Anat. Rec., 42:42.

With Mary E. Rawles. The relation of Hensen's node to the formation of axial parts of the chick embryo as studied by chorio-allantoic grafts of whole blastoderms. Anat. Rec., 44:254–55.

1930

A study of the origin and differentiation of the suprarenal gland in the chick embryo by chorio-allantoic grafting. Physiol. Zool., 3:201–25.

With Mary E. Rawles. Correlation in development of the heart and liver in chorio-allantoic grafts of whole chick blastoderms. Anat. Rec., 45:248–49.

The developmental relations of the heart and liver in chorio-allantoic grafts of whole chick blastoderms. Collecting Net, 5:147.

1931

With Mary E. Rawles. Developmental relations of the heart and liver in chorio-allantoic grafts of whole chick blastoderms. Anat. Rec., 48:277–301.

Potencies of the gonad-forming area in the chick as tested in chorio-allantoic grafts. Anat. Rec., 51(suppl.):60–61.

With Mary E. Rawles. The relation of Hensen's node to the differentiating capacity of whole chick blastoderms as studied in chorio-allantoic grafts. J. Exp. Zool., 59:429–65.

1932

Germ cells in relation to the differentiation of the sex gland. Collecting Net, 7:221, 225.

The embryological foundations of sex in vertebrates. In: *Sex and Internal Secretions*, ed. Edgar Allen, pp. 94–159. Baltimore: The Williams & Wilkins Company.

1933

On the origin and differentiation of the sexual gland. Am. Nat., 67:1–8.

Potencies of the gonad-forming area in the chick as tested in chorio-allantoic grafts. Wilhelm Roux Arch. Entwicklungsmech. Org., 130:616–48.

1934

With Mary E. Rawles. A study in the localization of organ-forming areas in the chick blastoderm of the head-process stage. Anat. Rec., 58(suppl.):34.

Experimental study of sex-differentiation in the chick embryo. Collecting Net, 9:81, 85–88.

1935

With T. F. Gallagher and F. C. Koch. Sex-modification in the chick embryo resulting from injections of male and female hormones. Collecting Net, 9:295.

With T. F. Gallagher and F. C. Koch. The action of male and female sex hormones upon the reproductive glands and ducts of the chick embryo. Anat. Rec., 61(suppl.):50.

With T. F. Gallagher and F. C. Koch. The action of male and female hormones upon the reproductive glands and ducts of the chick embryo. J. Biol. Chem., 109:xcix-c.

With T. F. Gallagher and F. C. Koch. Sex-modifications in the chick embryo resulting from injections of male and female hormones. Proc. Natl. Acad. Sci. USA, 21:625–31.

With Mary E. Rawles. Organ-forming areas in the early chick blastoderm. Proc. Soc. Exp. Biol. Med., 32:1293–96.

1936

With Mary E. Rawles. The distribution of the so-called primordial germ cells in early chick blastoderms and their relationship to sterile gonad formation in chorio-allantoic grafts. Anat. Rec., 64(suppl.):77.

Studies on turtle and shark development. Ann. Rep. Tortugas Lab., Carnegie Inst. Wash., 92–93.

1937

With T. F. Gallagher and F. C. Koch. The modification of sex development in the chick embryo by male and female sex hormones. Physiol. Zool., 10:101–22.

Reversal of sex in the chick embryo by the action of male and female sex hormones. Am. J. Obstet. Gynecol., 33:529.

The action of synthetic male hormones upon the differentiation of sex in the chick embryo. Science, 86:409.

Experimentally produced sterile gonads and the problem of the origin of germ cells in the chick embryo. Anat. Rec., 70:89–112.

With Mary E. Rawles and E. Hadorn. Skin transplants between embryos of different breeds of fowl. Proc. Natl. Acad. Sci. USA, 23:542–46.

1938

With Mary E. Rawles and F. C. Koch. Biological differences in the action of synthetic male hormones on the differentiation of sex in the chick embryo. Proc. Natl. Acad. Sci. USA, 24:176–82.

With Mary E. Rawles. Factors controlling feather development of skin grafts made between chick embryos of different breeds. Anat. Rec., 70 (suppl. No. 3):81–82.

With Mary E. Rawles. Feather characterization as studied in host-graft combinations between chick embryos of different breeds. Proc. Natl. Acad. Sci. USA, 24:446–52.

With Mary E. Rawles. Skin transplants between embryos of different breeds of fowl. Biol. Bull., 75:340.

With Mary E. Rawles. Skin transplants between embryos of different breeds of fowl. Collecting Net, 13:53, 60–61.

1939

The embryonic development of sex. In: *Sex and Internal Secretions*, 2d ed., ed. Edgar Allen, Charles H. Danforth, and Edward A. Doisy, pp. 64–144. Baltimore: The Williams & Wilkins Company.

With N. T. Spratt, Jr. Embryonic sex differentiation. Tabulae Biol., 17:1–23.

With Mary E. Rawles. The localization of pigment-producing potency in presomite chick blastoderms. Anat. Rec., 73(suppl.):43.

1940

With Mary E. Rawles. The control of feather color pattern by melanophores grafted from one embryo to another of a different breed of fowl. Physiol. Zool., 13:177–99.

Feather color pattern produced by grafting melanophores during embryonic development. Collecting Net, 15:125, 138–39.

With Mary E. Rawles. Control of specific feather color pattern in fowl hosts by grafted melanophores from donor embryos of various groups of birds. Anat. Rec., 76(suppl.):46.

With Mary E. Rawles. A study of feather color patterns produced by grafting melanophores during embryonic development. Biol. Bull., 79:345.

1941

An analysis of feather color pattern produced by grafting melanophores during embryonic development. Am. Nat., 75:136–46.

1942

Hormonal control of embryonic differentiation in birds. Cold Spring Harbor Symp. Quant. Biol., 10:135–44.

The control of hair and feather pigmentation as revealed by grafting melanophores in the embryo. Ann. Surg., 116:598–603.

With Howard L. Hamilton. Developmental physiology. Ann. Rev. Physiol., 4:67–88.

1944

With Mary E. Rawles. Genotypic control of feather color pattern as demonstrated by the effects of a sex-linked gene upon the melanophores. Genetics, 29:309–30.

With Mary E. Rawles. Melanophore control of the sexual dimorphism of feather pigmentation pattern in the Barred Plymouth Rock fowl. Yale J. Biol. Med., 17:319–40.

Melanophore control of the sexual dimorphism of feather pigmentation in the Barred Plymouth Rock. Biol. Bull., 87:153.

1948

Hormonal regulation of feather pigmentation in the fowl. Spec. Publ. N.Y. Acad. Sci., 4:321–40.

Frank Rattray Lillie. Memorial resolution. Anat. Rec., 100:407–9.

With R. G. Harrison, H. B. Bigelow, and E. G. Conklin (Addresses at the Lillie memorial meeting Woods Hole, August 11, 1948), Frank Rattray Lillie 1870–1947. Biol. Bull., 95:151–62.

1950

Sterile gonads and the problem of the origin of germ cells in the chick embryo. Arch. Anat. Micros. Morphol. Exp., 39:269–73.

Specializations in the response of pigment cells to sex hormones as exemplified in the fowl. Arch. Anat. Micros. Morphol. Exp., 39:451–66.

1952

Development of sex-hormone activity of the avian gonad. Ann. N.Y. Acad. Sci., 55:159–71.

Cells, feathers and colors. Bios, 23:109–25.

1953

Basic mechanisms in the differentiation of pigment cells. J. Embryol. Exp. Morphol., 1:297–99.

1954

Phases in embryonic development. J. Cell. Comp. Physiol., 43:307–17.

1955

Ontogeny of endocrine correlation. In: *Analysis of Development*, ed. B. H. Willier, Paul A. Weiss, and Viktor Hamburger, pp. 574–619. Philadelphia: W. B. Saunders Company.

With Paul A. Weiss and Viktor Hamburger, eds. *Analysis of Development*, Philadelphia: W. B. Saunders Company, i–xii + 1–735.

1957

Frank Rattray Lillie, 1870–1947. In: *Biographical Memoirs of the National Academy of Sciences*, 30:179–236. New York: Columbia University Press.

1960

Lillie, Frank Rattray (1870–1947), *Encyclopaedia Britannica*, 14:123.

1964

With Jane M. Oppenheimer, eds. *Foundations of Experimental Embryology*, Englewood Cliffs, N.J.: Prentice-Hall, Inc., i–xi + 1–225.

1966

Glycogen synthesis, storage and transportation in the yolk-sac membrane of the chick embryo. Am. Zool., 6:357.

1968

Glycogen synthesis, storage and transport mechanisms in the yolk-sac membrane of the chick embryo. Wilhelm Roux Arch. Entwicklungsmech. Org., 161:89–117.

1970

Reflections on nucleic acids in development. In: *Problems in Biology: RNA in Development*, ed. E. W. Hanly, pp. 1–9, Salt Lake City: University of Utah Press.

1971

Yolk sac. In: *McGraw-Hill Encyclopedia of Science and Technology*, 14:690. New York: McGraw-Hill, Inc.

1974

With Jane M. Oppenheimer, eds. *Foundations of Experimental Embryology*, 2d ed., New York: Hafner Press, i–xxiv + 1–277.

Charles Haskell Danforth, 1883–1969. In: *Biographical Memoirs of the National Academy of Sciences*, 44:1–56. Washington D.C.: The National Academy of Sciences.