NATIONAL ACADEMY OF SCIENCES
2101 CONSTITUTION AVENUE
WASHINGTON, D.C. 20418

September 19, 1974

Dr. Viktor Hamburger
Department of Biology
Washington University
St. Louis, Missouri 63130

Dear Dr. Hamburger:

Thank you for your letter of September 11. It is most welcome on two counts: First, it brings a fine bibliography of your own work; and secondly, it includes your most gracious acceptance of the authorship of the biographical memoir for Dr. Benjamin Harrison Willier.

I am forwarding copies of material sent to us by Dr. Willier, a reprint from Developmental Biology, some news clippings, and the nomination sketch used at the time of Dr. Willier's election to the Academy. In addition a copy of a recently developed booklet on the preparation of the Academy's Biographical Memoirs is being included in the hope that it may be of assistance to you. I should mention that we have an excellent photograph (1958) on file that was, according to Dr. Willier's accompanying note, one that his family and friends preferred. Unless you have another suggestion, we shall plan to use this likeness with the memoir.

Sincerely,

Victoria B. Crawford

(Mrs.) Victoria B. Crawford
Assistant to the Home Secretary

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COPY WITH ADDITIONS AND CORRECTIONS

FEATURES

News, Opinion and Letters

BENJAMIN HARRISON WILLIER: 1890-1972 [1]

HIS LIFE AS AN OUTSTANDING BIOLOGIST, EMBRYOLOGIST, AND DEVELOPMENTAL BIOLOGIST

In 1920, Dr. G. L. Streeter published a detailed description, including two beautiful wax plate reconstructions, of the Mateer embryo, a well-preserved human embryo possessing a primitive streak, an indistinct primitive node, no head-process, no neurenteric canal, and no indication of a medullary groove. Because its scientific value was recognized, this young human embryo had been presented to the Department of Embryology of the Carnegie Institution of Washington in 1916 by its owner, Dr. Horace N. Mateer of Wooster, Ohio, after it had been embedded in paraffin and cut into serial sections by his laboratory assistant, Benjamin Harrison Willier.[2]

Fifty-two years later (1968), at the age of 78, this same Benjamin Harrison Willier published a significant and comprehensive paper utilizing modern techniques of cytochemistry, radioautography and electron microscopy.[3] Saul Roseman[4] was later to say of this paper that "...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." In 1969 this same Benjamin Harrison Willier opened the Park City International Symposium on Problems in Biology: RNA in Development[5] with his introductory chapter on "Reflections on Nucleic Acids in Development." In 1971, after completing the manuscript for his biography of Charles Haskell Danforth (1883-1969) for publication in The Biographical Memoirs of the National Academy of Sciences, his thoughts again centered repeatedly on the marvels of the hen's egg and its development. These he had expressed so simply and succinctly in a letter to one of his grandchildren written in 1968: "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." He was always aware of the discrepancy of the wondrous ways of the embryo and our efforts to deal with them. In a letter to me dated January 19, 1972 he wrote, "There is so much to learn well." In his last letter to me postmarked November 8, 1972, six days after his eighty-second birthday, Willier wrote, "...I am busy with so many university affairs that I have not yet resumed my writing of 'A Cleidoic Egg: An Adventure in Embryogenesis.' This is a manuscript for Perspectives in Biology and Medicine (if it ever gets finished)."

He was still thinking actively about problems of development on November 24, the day before a fatal illness struck.[6] He died on December 3, 1972. A memorial service was held on the campus of the Johns Hopkins University on December 11, 1972 with brief comments by James D. Ebert, Jane Oppenheimer, John W. Saunders, Jr., Saul Roseman, William F. Harrington, and Stephen Roth. Possibly Insert At the end of the business meeting of the Division of Developmental Biology of ASZ in Washington, D. C., on December 27, 1972, following brief comments by Jane Oppenheimer about his great interest in developmental biology,

Some time later his daughter, Louise, and her husband made the climb to Morning Glory Lake in Canada. There, high in the Rockies, they scattered Dr. Willier's ashes. He had often said he hoped this could be done.

Willier was acknowledged as a "world-renowned colleague and inspirational leader" by a moment of silent tribute. It is appropriate that developmental biologists pause long enough to recognize and acknowledge some of the myriad ways their profession is indebted to Willier and to gain insight into some of the factors contributing to his influence.

His most enduring impact on developmental biology (and in a few instances on certain other specific fields as well) is doubtless the fact that he was the teacher and mentor of many top quality men and women interested in development.[7] Most of them have been or remain productive, versatile, and influential scholars. Many of them have occupied or now occupy key positions in major universities or other scientific institutions. Some have exhibited outstanding leadership nationally and internationally without which biology, and especially developmental biology, would not be what they are today. Some are now or have been outstanding editors and/or writers of influential books, critical review articles, articles for outstanding encyclopedias, etc. Several have exerted important influences as teachers of marine embryology at the Marine Biology Laboratory and/or other major marine stations, and one is simultaneously Director of MBL and the Department of Embryology of the Carnegie Institution of Washington. A few have already been elected to membership in the National Academy of Sciences and a few others will likely receive this signal honor in the future. Three have served as presidents of the Society for Developmental Biology, more as chairmen of the Division of Developmental Biology of ASZ. Some are the teachers and mentors of a second generation of top quality scientists who are themselves, in turn, the teachers and mentors of yet a third generation, some of whom are already rapidly proving their worth. Thus, through his doctoral students Willier's influence is being projected far into the future, a permanent and irrevocable contribution to continuing scholarship in the Willier style.

What were some of the factors responsible for Willier's remarkable record in training doctoral students? Ebert[6] wrote, "He was one of the world's keenest students of embryology." He attracted a steady stream of students of high quality and capacity. It was evident that he accepted only the best to start with. There was always the example of the high standards set in his own contributions -- clear objective thinking and precision of analysis. He was admittedly a hard taskmaster. He refused to accept anything but the best of himself and others. He was a relentless, never-satisfied critic. He always maintained exceedingly high expectations. He once stated that he wanted his students to be taught so well that they would excel their teacher in research and teaching. He compelled them to read and digest both classical and current literature and to organize and present the material with great clarity and simplicity not only in numerous seminar courses but, at least at the University of Chicago and the University of Rochester, in a fortnightly Festschrift for the discussion of interesting current papers in biology (named in honor of Hans Spemann). And, at least at the University of Rochester, his students were required to speak before the weekly departmental seminar even before their doctoral research was underway. He had a way of conveying to the student a sense of obligation to measure up to a standard that at times seemed overly strict to some, although the challenge was

almost always accepted and later, when they had gained perspective, most of his students appreciated what he had done for them. For example, one former student, now a member of the National Academy of Sciences, wrote, "I sometimes thought that the simplicity he required was overdone. Nevertheless, I am glad that I learned to state things in a way that no one could misunderstand." Similarly, another former student wrote, upon being congratulated by Willier on his election to the National Academy of Sciences, "...whatever I have done to deserve this honor was an outgrowth of that thorough training which you provided an unruly subject..." Willier provided unusually good facilities for his doctoral students, especially at the University of Rochester and at Johns Hopkins. He gave energetic students of development every opportunity to develop and a feeling that what they were doing was very important. Through the training of his doctoral students, as in other ways, Willier probably exerted a greater impact on the field of developmental biology than any other man of his generation.

Benjamin H. Willier was born November 2, 1890 on a farm near Weston, Wood County, Ohio. He attended a country grammar school through the eighth grade and subsequently graduated from a two-year high school in a small country town. Although no subjects taught in these schools captured his imagination, he definitely did not enjoy farming and the usual barnyard chores. Consequently, he returned to the same high school an additional year and earned a teacher's certificate. Although he was interested in plant and animal life on the farm and was especially curious about insect behavior, he first realized where his primary interests lay during a 6-week summer session at the state Normal College at Miami University (Oxford, Ohio) where he had the opportunity to enroll in courses in nature study. His interest in biology as a science clearly emerged subsequently while a student at the Wooster Academy. He entered the College of Wooster in 1912, received his B.S. with highest honors in biology in 1915, and taught there the following year (quite possibly the year in which he embedded and serially sectioned the Mateer embryo). He then entered the University of Chicago and, as a student of Frank R. Lillie, received his Ph.D. in Zoology, magna cum laude, in 1920 after spending 1918-1919 in the Army Medical Corps. His excellent thesis entitled, "Structures and Homologies of Free-Martin Gonads," was published the following year.[8] The topic of his thesis should not be surprising since Lillie had published his epoch-making paper on the free-martin in 1917[9] and since Lillie usually suggested doctoral problems that were closely related to his own current investigations.[10] Although Willier did no other research on the free-martin per se, he thought about it and talked about it many times. He stated in a letter to me dated February 18, 1972 that he had prepared a critique on the free-martin over a year ago and added, as a postscript, "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." 10

Unfortunately there appears to be no record as to when and under what circumstances Willier decided to become an embryologist, do his graduate work at the University of Chicago, or become a doctoral student of Frank R. Lillie. It seems likely that he went to this university specifically to work with Professor Lillie since he acknowledged in his first paper on chick embryos[11] that the prob-

lem was suggested by Lillie. Moreover, he stated in a footnote to this paper that he had worked out his method of transplanting tissues to the chorio-allantoic membrane of the chick independently in the autumn of 1917 (presumably the year after entering the University of Chicago), although acknowledging that Rous and Murphy had first used the basic method in 1911 in their studies of tumors. Since Willier's investigation was designed to determine whether chorio-allantoic grafts of small pieces of thyroid glands from donor chickens varying in age from two months to two years would produce hyperthyroid conditions in host embryos, his initial interest may well have been in developmental endocrinology, i.e., in the role of hormones in embryonic development, rather than in embryology in general. This possibility is strengthened by the title of his first paper on chick embryos[11] which implied that comparable studies of the effects on host embryos of chorio-allantoic grafts of tissue from other endocrine glands might follow. Actually the only other endocrine glands similarly tested extensively for effects on host organs (and vice versa) were the ovaries and testes. Be this as it may, Willier's interest in endocrines in development repeatedly emerged in his publications and the doctoral dissertations of several students, as well as in other ways.[12] He also conducted a graduate seminar on this topic at both the University of Rochester and Johns Hopkins.

Willier was a member of the faculty of the Department of Zoology at the University of Chicago for 13 years (1920-1933) after receiving his doctorate there: instructor (4 years), assistant professor (3 years), associate professor (4 years), and professor (2 years). Since Lillie did not resign his departmental chairmanship until 1931, Willier's outstanding success as a departmental administrator elsewhere must have stemmed in part from the superb example set by Lillie, just as surely as did his research attitudes, approach to the study of the embryo, meticulousness in writing and editing, and methods of teaching graduate students.[10] During the summers of 1923-1926 he served as an instructor in the invertebrate zoology course at the Marine Biological Laboratory (he had been a member of the corporation of this laboratory since 1919). In 1924 and 1925, when his first two papers appeared utilizing transplantation to the chick chorio-allantoic membrane [11,12], Willier surprisingly coauthored two papers with Libbie H. Hyman and S.A. Rifenburgh on planarian physiology.[13] Thereafter his original research papers dealt entirely with the chick embryo with the exception of a brief summary of observations made on turtle and shark development during the summer of 1936 as a guest investigator of the Tortugas Marine Biology Station of the Carnegie Institution of Washington.[14] Moreover, the doctoral dissertations of all his students dealt exclusively with chick embryos (and/or duck embryos) with one exception in which regeneration following induced autotomy was studied in a sea cucumber (holothurian).[15]

Willier and his doctoral students repeatedly demonstrated the validity of the conviction early held by Lillie that chick embryos were excellent material for almost any type of experimental analysis (even though Lillie himself published only four brief papers involving simple operations on chick embryos in ovo).[10] It was only a few years before he left the University of Chicago that Willier was fortunate enough to be joined by Mary E. Rawles as his research assistant, as well as his

graduate student. This was the origin of one of the few outstanding research teams in experimental embryology: As early as 1931 he rated her "an unusually competent assistant and investigator" in a research grant application. Rawles remained with Willier as research assistant and subsequently as research associate until his retirement and rapidly established herself nationally and internationally as one of the most talented investigators among his doctoral students. During his last year at Chicago Viktor Hamburger came directly from Germany to Willier's laboratory as a Rockefeller Foundation Fellow and first worked there with chick embryos by learning the technique of chorio-allantoic transplantation. Hamburger likewise saw the potentialities of chick embryos for analyzing developmental problems, and thereafter seldom used any other material for his investigations. As Holtfreter[16] stated in 1968 at the twenty-seventh symposium of the Society for Developmental Biology dedicated to Professor Hamburger, "It appears that in this conversion Ben Willier played the role of godfather." The extensive correspondence between Hamburger and Willier still contained in the latter's files strongly supports this statement. According to Holtfreter[16] Hamburger once stated, "Our real teacher always has been and still is the embryo--who is incidentally the only teacher who is always right." Willier repeatedly stated this conviction in his lifetime, but in different ways. On November 25, 1970 Willier wrote to Weiss, "Like yours my life is one of exploring the embryo --there is beauty in its ways of generating itself. The embryo is my life!" And in an article dated December 17, 1968 and entitled, "On the Occasion of a Portrait," Willier wrote, "The egg's way is my life. I love it."

At Chicago C. M. Child and B. H. Willier were in the habit of taking long walking trips in Palos Park or the Indiana dunes on Saturdays. In 1926 Sewall Wright joined the zoology faculty of the University of Chicago and soon became a regular participant in these weekly trips. While observing and enjoying nature to the utmost on these walks, there was always a running discussion about those scientific areas and problems closest to their hearts. Willier's mind was constantly concerned with his intense interest in the field of development, but until Wright's tutelage he knew little about genetics. As a consequence of their continuing discussion out-of-doors both Wright and Willier became intensely interested in the relations of genetics to development, so much so that Wright started his outstanding course in physiological genetics and participated enthusiastically in Willier's seminars on problems of development. Moreover, Willier subsequently required his doctoral students, at least at the University of Rochester, to become as rigorously trained in genetics as in development. Wright may have influenced Willier and his colleagues to determine the genetic sex of chick embryos injected with sex hormones by using hybrids for a sex-linked plumage trait in which plumage of female embryos was entirely black whereas male plumage was black except for a spot of white plumage at the back of the head.[12] Wright's influence may have carried over, unconsciously, to later investigations of Willier and Rawles and some of his students devoted to analyzing the role of genes in controlling formation of specific color patterns in developing feathers. After Child's retirement Wright and Willier continued their walks with Libbie Hyman as an occasional companion. Later they were joined regularly by Professor George Link of the Department of Botany who added new

dimensions to their observations on plants of the dunes and plant pathology, and extended their discussions into the realm of philosophy. In personal correspondence dated February 8, 1973, Professor Wright stated, "I think that I enjoyed more stimulating discussion during this period 1926-1933 than at any other time." Link subsequently introduced Willier to his favorite site for peace and rest in the mountains, Lake O'Hara, the appropriate place for Willier's ashes to be scattered. Willier once wrote of Link, "Never will I forget him and pleasant memories of companionship and intellectual stimulation as we walked and talked..." These same sentiments doubtless also existed for Professor Wright.

At the memorial service for Willier, W. F. Harrington[17] said, "His knowledge of the biology of trees and flowers and of mosses and lichens was always a source of amazement to me." In view of Willier's curiosity about nature, existing since boyhood and continuously expanding as he learned more about plants and animals and their interactions from his own continued observations and his out-of-doors companions, this should not have been surprising. In a letter to me dated February 10, 1972 Willier wrote, "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!" That he was. These deep-seated interests in biology and his broad knowledge about biology must have served him well later after leaving Chicago when he was chairman of two biology departments. His compelling urge to talk about developmental problems anywhere in the great outdoors must have been an important factor in initiating the meetings of the "Sandpipers" which had much to do with the planning stage of the book, Analysis of Development, and probably with the establishment of the Society for the Study of Development and Growth (see below).

Based on investigations initiated at the University of Chicago, Willier became widely recognized as a developmental endocrinologist, especially for his studies on the role of sex hormones in differentiation of gonads and accessory reproductive structures in birds.[12] He early used the method of chorio-allantoic grafting, i.e., of transplanting bits of tissue on the highly vascular chorio-allantoic membrane of host chick embryos incubated 8 or 9 days, to determine 1) whether development of gonad-forming areas or gonad primordia, isolated from donors of one sex and transplanted to the chorio-allantoic membrane of hosts of the opposite sex, would be modified by sex hormones produced by the host gonads, and 2) whether chorio-allantoic grafts of tissue from sexually differentiated gonads, known to be capable of producing sex hormones, would modify development of host gonads and/or host accessory reproductive organs. Both approaches were negative. No signs of sex reversal were seen. [Later two of his doctoral students somewhat modified these approaches.[12] Dennis made multiple testis grafts to the chorio-allantoic membrane, hoping thereby to increase male hormone production sufficiently to modify the direction of differentiation of host gonads and reproductive ducts, but without success. He also transplanted side by side on the same chorio-allantoic membrane morphologically undifferentiated gonad tissue and differentiated gonad tissue of opposite genetic sex to determine whether contiguous or closely associated ovarian and testicular tissue could modify the direction of differentiation of undifferentiated

gonad tissue, again with negative results. Bradley transplanted donor embryonic gonad tissue into the coelom of host embryos either homoplastically (between chick embryos or between duck embryos) or heteroplastically (between duck and chick embryos). In exceptional cases he found modifications of differentiation of gonads of graft or host origin which he interpreted as due either to the action on host gonads of male or female hormones produced by the grafts, or vice versa.] With colleagues in the Department of Biochemistry at the University of Chicago Willier began injecting female or male hormones into incubating hens' eggs at certain developmental stages prior to sex differentiation.[12] In general, although there were exceptions, it was found that male and female hormones acted selectively on male or female structural components, respectively, of the bisexually organized gonads and reproductive ducts of either genetic sex. Male hormones tended to stimulate male and suppress female components of the bisexual embryo; female hormones tended to activate female and suppress male components. The degree of response depended on dosage. Whether a given sex component was activated or inhibited in its development by the action of male or female hormones was determined by its own reaction capacity. The broad range of his interests in development of endocrine glands and the effects of hormones produced by them during development is clearly indicated by the many papers, especially review articles, by Willier and the doctoral dissertations of many of his students.[12]

As an outgrowth of his early experiments with chorio-allantoic grafts designed primarily to analyze the action of sex hormones in development,[12] Willier and many of his doctoral students used the same method with phenomenal success to analyze the organization of the flat chick blastoderm [from unincubated (prestreak) stages through primitive-streak and head-process stages] by testing the developmental potencies (capacities to produce organ-specific tissues) when either whole area pellucidas or specific sectors of them were isolated on the host chorio-allantoic membrane. The organization of most organ rudiments was similarly analyzed by isolating them in whole or in part at successively older stages and allowing them to continue their development on the chorio-allantoic membrane.[18] A gradual increase with age in the developmental capacity of intact organ rudiments was interpreted as indicating a progressive change of some sort in the organization of the region tested. Only whole unincubated blastoderms or pieces containing intact the posterior quadrant (the region actively involved in primitive-streak formation) possessed the capacity to form the various tissues of the embryo. At the definitive primitive-streak stage the primitive node appeared to be the active center in development of axial parts. By the head-process stage the entire blastoderm was found to be a mosaic composed of many organ-forming areas whose boundaries were not sharply circumscribed but appeared to overlap (although particular structures, such as brain, ear, eye, heart, thyroid, mesonephros, adrenal, etc., developed only from rather definite regions of axial levels). The most concise and lucid general summary of the organization of the head-process stage and subsequent developmental events, as determined experimentally, is given by Willier (1954, p.308)[18] and is stated here almost verbatim. Each organ-forming area, such as that of the eye, heart, kidney, and thyroid, occupies a definite spatial position in relation to other areas and to the whole blastoderm. Each organ-forming area exhibits a gradient

in histogenetic potency, the intensity of which is high in the center, gradually diminishing peripherally until it completely disappears. Each area has far greater potencies for a particular organ than can possibly be the case in normal development. Areas lying across the median axis, e.g., the eye-forming area, exhibit a definite asymmetrical organization, the left portion showing a far greater histogenetic potency than the right, and the median portion the highest of all. With advance in development a progressive restriction in histogenetic capacities of the various areas takes place with the result that, just prior to the formation of a given organ primordium, the corresponding local area is limited in its potentialities to the organ-forming system in question.

Worthy of special comment is the fact that Willier found that sterile gonads occasionally developed among a variety of types of chorio-allantoic grafts. They were small, testis-like structures whose sex cords were typically male in every respect except for the complete absence of germ cells (sterile cortical cords characteristic of left ovaries never formed). Whether these sterile gonads formed in the absence of germ cells originated from genetic male or genetic female donors is unknown, although efforts were made to determine this by studying chromosomes in mitotic figures. He also found that the primordial germ cells remain undifferentiated unless they enter testicular or cortical sex cords. In the former they differentiate towards spermatogonia, in the latter towards oögonia. In one graft which formed an ovotestis, the differentiation of the primordial germ cells, even though of the same genetic sex, was clearly in the female direction in the ovarian part of the gonad and in the male direction in the testicular part. Thus in birds the germ cells are dependent upon the specific tissue environment of the sexual cords both for onset and direction of their differentiation. Transplantation to the chorio-allantoic membrane has also been used to advantage by Willier and his doctoral students to investigate a variety of other interesting problems.[18]

In 1933 Willier was named Professor of Zoology and Head of the Biology Department at the University of Rochester, a post he held until 1940. Accompanying him from Chicago were Mary E. Rawles and ~~all~~ most of his other graduate students who had not yet completed their doctorates at Chicago. This was obviously very important to Willier since he noted in his superb biography of Frank R. Lillie[19] that when C. O. Whitman moved from Clark University to become Chairman of the Department of Zoology of the newly founded University of Chicago, "In affectionate admiration and loyalty...every student went with Whitman." His former doctoral student, Dorothea Rudnick, joined his research group as a research fellow from 1934-1937 and introduced the tissue culture technique to his laboratory, much to the advantage of Nelson T. Spratt, Jr., one of Willier's doctoral students during her last year there. In 1938 Rudnick published three papers using this technique, rather than the earlier method of transplantation to the chorio-allantoic membrane, to test the developmental capacities of parts of early chick blastoderms, and in 1940 Spratt published his doctoral thesis on an *in vitro* analysis of the eye-forming area of early chick embryos,[20] initiating a lifetime of research utilizing tissue culture techniques. Moreover, when Howard L. Hamilton arrived in 1938 to begin his doctoral work, he found excellent tissue culture facilities awaiting him. During 1937-1938 Jane Oppenheimer was a

research fellow there. She valued her experience in Willier's laboratory very highly. The mutual respect established between these two scholars grew over the years and culminated much later in their joint editorship of Foundations of Experimental Embryology[21], reproducing with brief editorial comments a group of published articles carefully selected for their unusual excellence, pioneering and enduring quality, and influence on the rise of experimental embryology.

Willier believed a departmental administrator should be a scientist of outstanding achievement and that he should be a leader in determining the plans for and the policy of the department and in dealing with the administrative officers of the university. He exercised this leadership very effectively at the University of Rochester. He had a strong sense of what a good research laboratory and teaching department should be. As Ebert[6] stated, "He had an uncanny knack of selecting future leaders and of providing an environment in which they could develop." Thus Curt Stern joined the department as a research associate in 1933 and became a faculty member in 1935. David Goddard joined his faculty in 1935, Donald R. Charles (deceased) in 1936, Kenneth Cooper and Richard H. Goodwin in 1938, and John Buck in 1939.

During his years at Rochester (1933-1940) Willier spent his summers at the Marine Biological Laboratory. He served as a trustee of MBL from 1933 to 1950, as chairman of the committee on lectures from 1938 to 1943, and as a member of the executive committee from 1941 to 1943. From 1933-1940, he was an active and enthusiastic member of the "Sandpipers," a small group of embryologists who gathered periodically in the sand dunes along the north coast of Cape Cod near Barnstable to discuss informally the problems of development and possible mechanisms of embryogenesis, much as he had done earlier on his Saturday walks at the University of Chicago. One direct consequence of these discussions was the decision that their essence should be incorporated into a book addressed to active or potential investigators particularly in the experimental branches of embryology, pathology, histology, endocrinology, and developmental genetics. Its goal would be to provide a basis of departure for the new minds of the future. This book, Analysis of Development, a collaborative work edited by Willier, Weiss, and Hamburger, was published in 1955[22]. Each editor was author or coauthor of a major chapter in this book. Quite a few chapters are classics, a few are literary masterpieces, some are of mediocre quality, but in general this book provides present-day developmental biologists with a very useful analysis of the state of our knowledge of the principles and mechanisms of development prior to their application of quite different methods to old problems and to a much wider range of developmental problems than those investigated by embryologists. Willier bore the major brunt of this demanding project and was primarily responsible for seeing it through to completion, even though he was disappointed that parts of it were far from meeting his rigorous standards.

It is interesting to note that "The Developmental Biology Conference Series of 1953," held just one year after publication of this book, brought together experts from diverse fields of biology, many of them young, to focus on developmental problems much more broadly conceived. Paul Weiss served as organizer,

insert closing quotes

fund raiser, and general chairman for an initial workshop, followed by a series of 10 conferences[23] entitled: "Embryonic Nutrition," "Regeneration in Vertebrates," "Cytodifferentiation," "Environmental Influences in Prenatal Development," "Immunology and Development," "Physiology of Insect Development," "Dynamics of Proliferating Tissues," "Endocrines in Development," "Mitogenesis," and "Wound Healing and Tissue Repair." Willier was an important factor in the success of the workshop, served as chairman of the conference on "Endocrines in Development," and was a participant in the conferences on "Cytodifferentiation" and "Mitogenesis." It is also interesting to note that the first informal meeting of developmental biologists interested in improving their organizational stature occurred in 1956 at the AIBS meeting at the University of Connecticut and that in 1958 at the AIBS meeting at Indiana University, following a second informal meeting of the group at the AIBS meeting at Stanford in 1957, the Division of Developmental Biology of ASZ was formally organized and its first officers elected. In April, 1958, when Willier presented me with three autographed volumes containing reprints of all the papers from his research laboratories published up to that time, he wrote on the flyleaf of one volume, "Zealous research so changed the shape of embryology that it will never be the same." This statement certainly characterizes the period since publication of Analysis of Development!

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It seems probable because of the timing, some of the people involved, the general format of the growth symposia, their informal atmosphere, and the attractive surroundings where they were held, that the meetings of the "Sandpipers" from 1933-1940 may have been responsible, in part, for the establishment of the Society for the Study of Development and Growth (since 1964 called the Society for Developmental Biology). In 1937 appeared a new journal, "Growth," established largely through the efforts of Frederick S. Hammett. After two years of publication the editors of "Growth" sponsored a symposium on "Development and Growth" in August, 1939, at North Truro, Mass. and published it as a first supplement to their journal under the title, "First Symposium on Development and Growth." Because this symposium was so successful, the Society for the Study of Development and Growth was organized by those present to call together similar meetings in future years.[24] Although Willier was a member of the editorial board of "Growth" from 1939-1949 and his membership in the Society dates from 1939, he apparently was not present at the first symposium nor was he a member of the organizing committee for the society. Yet Ebert[6] stated that Willier "regarded as especially significant his role in establishing the Society for the Study of Development and Growth and... his presidency in it (1943-1945)...." In 1950 Viktor Hamburger invited Willier to speak about sex differentiation at the growth symposium in 1951, stating in his letter, "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." But Willier declined, no doubt in part because he was then active in an entirely different research area, but also because he was already feeling the editorial burden of Analysis of Development, although he gave different reasons. On July 13, 1966 Jerome A. Schiff, Secretary of the Society for Developmental Biology, wrote to Willier, "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."

During 1936-37 Ernst Hadorn was a Rockefeller Foundation Fellow in the laboratories of Willier and Stern at the University of Rochester. In 1937 Willier, Rawles, and Hadorn published a brief paper on experiments originally designed to analyze factors responsible for the location of specific feather tracts, the arrangement and spacing of feather germs within given feather tracts, the rate of growth and shape of the feathers produced, etc. Instead this paper initiated a new and highly productive line of research concerning factors involved in the development of specific colors or color patterns in plumage, the ramifications of which were later pursued vigorously by Willier and Rawles and most of his doctoral students until his retirement[25] and increasingly independently by Rawles. Minute pieces of skin ectoderm from the dorso-lateral surface of the head anterior to the otocyst, largely freed of mesoderm, were isolated from 75-hour donor embryos, either from a cross producing chicks with black down plumage (except for a patch of white plumage on top of the heads of males) or from a breed producing chicks with red plumage. These were inserted into an incision in the skin ectoderm at the base of wing or leg buds of 75-hour host embryos of a white breed (White Leghorns), or vice versa. When potentially pigmented donors were used an area of donor-color down feathers, sometimes quite extensive, subsequently surrounded the transplantation site, but not when White Leghorn donors were used. The pigmented feathers formed on White Leghorn hosts resembled <u>host</u> feathers in all respects other than their donor coloration. (This became especially evident in later experiments extending into posthatching stages when donor-colored down feathers were gradually replaced by donor-colored juvenile plumage. In later experiments using donor embryos from different pigmented and white breeds, it was found that skin ectoderm from embryos of certain <u>white</u> breeds other than White Leghorns, transplanted to embryos of pigmented breeds, likewise produced an area of donor-colored (white) plumage around the transplantation site and that when embryos from certain pigmented breeds (Black or Buff Minorcas) served as hosts, even skin ectoderm from White Leghorn embryos can have this consequence.)

It was soon realized that feathers of donor-colored areas originated from <u>host</u> ectodermal cells and that the donor skin ectoderm simply acts as a "carrier" for donor melanoblasts which later escape from the graft, invade host ectoderm, differentiate therein into melanocytes which synthesize donor-specific pigment granules (melanosomes) and contribute them to the host ectodermal cells actually forming the feathers. Skin ectoderm from embryos of white breeds likewise contains melanoblasts which likewise escape from the graft and invade host ectoderm (somehow preventing <u>host</u> melanoblasts from doing so), and likewise differentiate therein into melanocytes capable of synthesizing only a few pigment granules before they die, thus leaving around the transplantation site an area of

unpigmented (white) host feathers. This explantation was based on Hamilton's studies of the differentiation capacities of melanoblasts from white breeds in vitro and of the synthetic capacities and survival times relative to onset of synthesis of pigment granules of the resulting melanocytes. Hans Ris, a fellow in Willier's laboratory during 1938-39, provided conclusive evidence of the neural crest origin of melanoblasts in birds by carefully correlating presence or absence of melanocytes formed by grafts isolated from one side of the donor body with presence or absence of neural crest cells in each graft as demonstrated histologically in sections through the corresponding region of the other side of the body. He then went to Columbia University for his doctorate in cytology. The ability to combine at will melanocytes from any donor breed with developing feather germs of any host breed made it possible to analyze the extent to which formation of any complex feather color pattern was due to the genotype of the melanocytes, the growth rates of the particular host feathers containing donor melanocytes, the sex hormones of the host, etc. The generalization from their many studies on pigmentation problems[12, 25] regarded by Willier as having the most significant implications was that the genotypic constitution of the pigment cells governs the kind of response which they are able to give in the feather germ in the production of color or color patterns in feathers of the domestic fowl.

In 1940 Willier moved to Baltimore, again accompanied by Mary E. Rawles, all his graduate students who had not yet completed their doctorates at the University of Rochester, and Nelson T. Spratt, Jr. From 1940-1955 he served as Chairman of the Department of Biology at Johns Hopkins University, from 1940-1958 he was Henry Walters Professor of Zoology, and from 1958-1972 Professor of Biology Emeritus. During the winter term of 1964 he was a visiting professor in the Department of Anatomy of the College of Medicine of the University of Florida. On the basis of his splendid record at the University of Rochester, Willier was brought to Johns Hopkins to revitalize the role of this institution in the field of biology. He planned the construction of the Mergenthaler Laboratory for Biology, dedicated on Feburary 23, 1942. At these ceremonies honorary LLD's were appropriately conferred on two outstanding biologists and students of the embryo, Ross G. Harrison and Frank R. Lillie. In statements made on December 5, 1950, commemorating the unveiling of a bronze tablet in memory of Ottmar Mergenthaler, the basis for selection of new faculty members was concisely 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." Willier 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.[4] He recognized that he must select investigators with insight and imagination who can change methods and aims as knowledge advances. This was done so successfully by Willier and especially by Willier's successor, William D. McElroy, appointed to the faculty as an instructor in 1945, that the Biology Department and the McCollum-Pratt Institute at Johns Hopkins are considered among the leading research centers in the country in the field of molecular biology, frequently

called the "new biology."

At the University of Chicago and the University of Rochester with only two exceptions[15,26], topics of doctoral dissertations of Willier's students were quite closely related to his current research interests. At Johns Hopkins this was true of six of his thirteen students who worked on pigmentation problems, some involving the use of specific hormones.[12,25] Three others worked on problems in developmental endocrinology.[12] The other four worked on problems quite different from Willier's current interests and those of each other. One extended much earlier experiments on flat blastoderm stages by studying the effects on subsequent development in ovo of excising Hensen's node.[27] One, intending originally to analyze factors that control the orderly spatial distribution, orientation, and tract specificity of feather germs in the wing (the same goal as the investigation that opened up for exploration many plumage pigmentation problems) [25], analyzed instead the sequence in which the tissues for the future wing parts originate in the wing bud and the role of the apical ectodermal ridge in this process[28], thus initiating a lifetime of research in this general area. Another explored the factors involved in enlargement of the host spleen following transplantation of adult spleen to the chorio-allantoic membrane, an effect long known, and in the course of his analysis introduced immunological methods into Willier's laboratory.[29] Still another worked on the temporal correlations of histogenesis, growth, and chemistry of the developing retina[30] and has continued to work on problems of eye development since that time.

In 1956, at the meeting of the American Association of Anatomists in Milwaukee, one session of papers contributed entirely by his former students was designated as the "Willier Doctorate Program," and was followed by a dinner, both events in honor of Willier's retirement as Chairman of the Biology Department at Johns Hopkins. Papers were presented by Case, Coulombre, Ebert, Grabowski, Thomas and Eleanor Hunt, Konigsberg, Markert, Rudnick, Saunders, Spratt, Trinkaus, and Watterson. In 1958 a symposium on The Chemical Basis of Development[31] was sponsored by the McCollum-Pratt Institute in honor of Professor Willier "for his distinguished contributions as teacher and investigator in developmental biology." On November 7, 1972, only a short time before his death, Willier wrote in a letter to J. G. Goellner, Editorial Director of the 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." On the other hand he wrote to Paul Weiss on November 25, 1970, "I like to tease any biochemist who expects to find answers to morphological complexity."

Willier was associate editor of the Journal of Morphology (1932-34); a member of the editorial boards of Physiological Zoology (1937-63), Growth (1939-49), and Bios (1952-72); editor of the Quarterly Review of Biology (1941-57) and a member of the advisory board (1958-1972); advisory editor of the Survey of Biological Progress (1946-72) and for the third edition of Lillie's Development of the Chick by H. L. Hamilton (1952). He also served for several years prior to 1964 as a consultant for the McGraw-Hill Encylopedia of Science and Technology in

the areas of growth and development.

He became a member of Sigma Xi (1919), AAAS (member, 1921; fellow, 1921; council member, 1938-40); ASZ (member, 1922; executive committee, 1934-35); American Association of Anatomists (1924); American Microscopical Society (1924); Society forExperimental Biology and Medicine (1927); American Society of Naturalists (1930); Phi Beta Kappa (1930); Genetics Society of America (1937); Society for the Study of Growth and Development (member, 1939; president, 1942-1945); Association for Study of Internal Secretions (1942); Institut International d'Embryologie (1945); National Academy of Sciences (member, 1945; elected chairman of the section of zoology and anatomy in 1949 and again in 1952); International Society of Cell Biology (1950); The American Philosophical Society (1955); life membership in the Corporation of the Marine Biological Laboratory and trustee emeritus (1969), and the American Academy of Arts and Sciences (1972). He served as commissioner, Department of Research and Education, State of Maryland (1941-61); member, Board of Directors, Long Island Biological Association, Cold Spring Harbor (1942-60); director, Government-Industry Cooperative Oyster Research Program (1958-60); and member, Board of Trustees, Science Service (1959-65).

lower case?

On December 17, 1968 a portrait of Willier was presented to Johns Hopkins University. It is located in the main hallway of the Mergenthaler Laboratory of Biology. To the left of the portrait in an alcove behind locked glass doors is a typewritten copy of a letter from Paul Weiss written in longhand to Dr. Willier on the occasion of his eightieth birthday. Much of this letter was quoted verbatim at the memorial service by Saul Roseman.[4] It reads in part, "You have single-handedly salvaged the tradition of true embryology. You have done it not only by consistently advancing the field by your own persistently perfectionist work, but above all, by steadfastly setting an inimitable model of the virtue of scholarship and working discipline...." Another close colleague evaluated Willier's life very simply: "I think he represented the best of American science."

Professor of Genetics and Development; Professor of Basic Medical Sciences

Ray L. Watterson
~~Professor Zoology and Basic Medical Sciences~~
University of Illinois, Urbana

Notes and references: [1] I wish to acknowledge my indebtedness to the following: Mrs. Benjamin H. Willier and Dr. James D. Ebert for permission to examine Dr. Willier's personal files and their kindly hospitality while doing so, and to the latter for providing additional resources; to Dr. Alan V. Astin, Home Secretary, National Academy of Sciences, for breaking precedent and sending me the autobiographical material provided by Dr. Willier prior to publication of his biography by the National Academy; to Drs. James D. Ebert, William Harrington, Jane Oppenheimer, Saul Roseman, Stephen Roth, and John W. Saunders, Jr., for the opportunity to see copies of their remarks made at the Willier memorial service; to the following colleagues who graciously provided extremely helpful comments and evaluations from their vantage: Drs. Robert K. Burns, George W. Corner, Viktor Hamburger, Clement L. Markert, Dorothea Rudnick, Nelson T.

Spratt, Jr., Curt Stern, Paul Weiss, and Sewall Wright; and to Dr. Mary Rawles Spurbeck for her willingness to edit the manuscript critically and to check the accuracy of comments made and events described. [2] Streeter, G. L. (1920). A human embryo (Mateer) of the presomite period. Contrib. Embryol. Carnegie Inst. Wash. 9, 384-424. (It is an interesting coincidence that many of the early investigations of Willier and his doctoral students were devoted to analyzing the organization of the chick blastoderm in primitive-streak and head-process stages.) [3] Willier, B. H. (1968). Glycogen synthesis, storage and transport mechanisms in the yolk-sac membrane of the chick embryo. Wilhelm Roux' Arch. 161, 89-117. (Drs. James D. Ebert, Heinrich Ursprung, and perhaps others were essential catalysts in the completion of this project for publication.) [4] Roseman, Saul (1972). Remarks at the memorial service for Dr. Willier. [5] Willier, B. H. (1970). Reflections on nucleic acids in development. In "Problems in Biology: RNA in Development" (E. W. Hanly, ed.), pp. 1-9. University of Utah Press, Salt Lake City. [6] Ebert, James D. (1972). Article prepared for the Baltimore Sun. [7] The 34 individuals receiving their doctorates under Dr. Willier's tutelage are listed alphabetically following the name of the university conferring their degrees. University of Chicago: Alfred Brauer, Elizabeth Butler, L. Floyd Clarke, Earl A. Dennis, Eleanor A. Hunt, Thomas E. Hunt, Frank R. Kille, Mary E. Rawles, Dorothea Rudnick, Carl J. Sandstrom, Ruth H. Sandstrom, Charles H. Seevers, Kathryn F. Stein, Sybil F. Street, and B. K. Chen. University of Rochester: Lloyd E. Alexander, E. Morton Bradley, Frederick S. Philips, Hermann Rahn, Nelson T. Spratt, Jr., and Ray L. Watterson. Johns Hopkins University: James F. Case, Alfred J. Coulombre, William E. Dossel, James D. Ebert, James G. Foulks, Casimer T. Grabowski, Howard L. Hamilton, Irwin R. Konigsberg, Clement L. Markert, Mark Nickerson, Willie M. Reams, Jr., John W. Saunders, Jr., and J. Philip Trinkaus. [8] Willier, B. H. (1921). Structures and homologies of free-martin gonads. J. Exp. Zool. 33, 63-127. [9] Lillie, F. R. (1917). The free-martin; a study of the action of sex hormones in the foetal life of cattle. J. Exp. Zool. 23, 371-452. [10] Watterson, R. L. (1973). Frank R. Lillie (1870-1947). In "Dictionary of Scientific Biography" (Charles C. Gillispie, ed.), vol. VIII, in press. Charles Scribner's Sons, New York City. [11] Willier, B. H. (1924). The endocrine glands and the development of the chick. I. The effects of thyroid grafts. Amer. J. Anat. 33, 67-103. (In subsequent investigations by Willier and those of his doctoral students using the method of chorio-allantoic grafting, this paper was usually referred to for details of the method). [12] Willier, B. H. (1925). The behavior of embryonic chick gonads when transplanted to embryonic chick hosts. Proc. Soc. Exp. Biol. Med. 22, 26-30. Willier, B. H. (1927). The specificity of sex, of organization, and of differentiation of embryonic chick gonads as shown by grafting experiments. J. Exp. Zool. 46, 409-465. Willier, B. H., and Yuh, E. C. (1928). 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. Willier, B. H. (1932). The embryological foundations of sex in vertebrates. In "Sex and Internal Secretions" (Edgar Allen, ed.), pp. 94-159. Williams and Wilkins Co., Baltimore. Brauer, A. (1932). A topographical and

cytological study of the sympathetic nervous components of the suprarenal of the chick embryo. J. Morphol. 53, 277-325. Willier, B. H., Gallagher, T. F., and Koch, F. C. (1935). Sex-modification in the chick embryo resulting from injections of male and female hormones. Proc. Nat. Acad. Sci. U.S. 21, 625-631. Willier, B. H., Gallagher, T. F., and Koch, F. C. (1937). The modification of sex development in the chick embryo by male and female sex hormones. Physiol. Zool. 10, 101-122. Willier, B. H., Rawles, Mary E., and Koch, F. C. (1939). Biological differences in the action of synthetic male hormones on the differentiation of sex in the chick embryo. Proc. Nat. Acad. Sci. U.S. 24, 176-182. Willier, B. H. (1939). The embryonic development of sex. In "Sex and Internal Secretions," 2nd ed. (Edgar Allen, Charles H. Danforth, and Edward A. Doisy, eds.), pp. 64-144. Williams and Wilkins Co., Baltimore. Spratt, N. T., Jr., and Willier, B. H. (1939). Embryonic sex differentiation. Tabulae Biologicae 17, 1-23. Rahn, H. (1939). The development of the chick pituitary with special reference to the cellular differentiation of the pars buccalis. J. Morphol. 64, 483-517. Hamilton, H. L. (1940). Influence of sex hormones and desoxycorticosterone on melanophore differentiation in birds. Proc. Soc. Exp. Biol. Med. 45, 571-573. Hamilton, H. L. (1941). Influence of adrenal and sex hormones on the differentiation of melanophores in the chick. J. Exp. Zool. 88, 275-305. Bradley, E. Morton (1941). Sex differentiation of chick and duck gonads as studied in homoplastic and heteroplastic host-graft combinations. Anat. Rec. 79, 507-529. Willier, B. H. (1942). Hormonal control of embryonic differentiation in birds. Cold Spring Harbor Symp. Quant. Biol. 10, 135-144. Willier, B. H. (1948). Hormonal regulation of feather pigmentation in the fowl. Spec. Publ. N.Y. Acad. Sci. 4, 321-340. Markert, C. L. (1948). The effects of thyroxine and antithyroid compounds on the synthesis of pigment granules in chick melanoblasts cultured in vitro. Physiol. Zool. 21, 309-327. Trinkaus, J. P. (1948). Factors concerned in the response of melanoblasts to estrogen in the Brown Leghorn fowl. J. Exp. Zool. 109, 135-169. Willier, B. H. (1950). Specializations in the response of pigment cells to sex hormones as exemplified in the fowl. Arch. Anat. micros. Morphol. exp. 39, 451-466. Willier, B. H. (1952). Development of sex-hormone activity of the avian gonad. Annals N. Y. Acad. Sci. 55, 159-171. Willier, B. H. (1952). Cells, feathers and colors. Bios 23, 109-125. Case, J. F. (1952). Adrenal cortical-anterior pituitary relationships during embryonic life. Annals N.Y. Acad. Sci. 55, 147-158. Konigsberg, I. R. (1954). The effects of early pituitary removal by "decapitation" on carbohydrate metabolism in the chick embryo. J. Exp. Zool. 125, 151-170. Dossel, W. E. (1954). An experimental study of the structural and functional development of the thyroid of the chick embryo. Doctoral dissertation, Johns Hopkins University. Willier, B. H. (1955). Ontogeny of endocrine correlation. In "Analysis of Development" ~~B. H.~~ (Willier, B.H., Weiss, P. A., and Hamburger, V., eds.), pp. 574-619. W. B. Saunders Company, Philadelphia. Willier, B. H. (1956). Conference Chairman, "Endocrines in Development" (R. L. Watterson, ed.). University of Chicago Press, Chicago (1959). [13] Hyman, L. H., Willier, B. H., and Rifenburgh, S.A. (1924). Physiological studies on Planaria. VI. A respiratory and histochemical investigation

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Dennis, E. A. (1936) Gonad differentiation in the chick embryo as studied in heterosexual graft and host-graft combinations. Physiol. Zool. 9, 204-230.

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of the source of the increased metabolism after feeding. J. Exp. Zool. 40, 473-494. Willier, B. H., Hyman, L. H., and Rifenburgh, S. A. (1925). A histochemical study of intracellular digestion in triclad flatworms. J. Morphol. Physiol. 40, 299-340. [14] Willier, B. H. (1936). Studies on turtle and shark development. Ann. Rep. Tortugas Lab., Carnegie Institution of Wash., pp. 92-93. [15] Kille, F. R. (1935). Regeneration in Thyone briareus Lesueur following induced autotomy. Biol. Bull., 69, 82-108. [16] Holtfreter, Johannes (1968). Address in honor of Viktor Hamburger. In "The Emergence of Order in Developing Systems" (M. Locke, ed.), pp. ix-xx. Academic Press, Inc., New York City. [17] Harrington, W. F. (1972). Remarks at the memorial service for Dr. Willier. [18] Willier, B. H. (1930). A study of the origin and differentiation of the suprarenal gland in the chick embryo by chorio-allantoic grafting. Physiol. Zool. 3, 201-225. Rudnick, Dorothea (1930). Bilateral localization of prospective thyroid in the early chick blastoderm, studied in chorio-allantoic grafts. Proc. Soc. Exp. Biol. Med. 28, 132-134. Hunt, T. E. (1931). An experimental study of the independent differentiation of the isolated Hensen's node and its relation to the formation of axial and non-axial parts in the chick embryo. J. Exp. Zool. 59, 395-427. Willier, B. H., and Rawles, Mary E. (1931). Developmental relations of the heart and liver in chorio-allantoic grafts of whole chick blastoderms. Anat. Rec. 48, 277-301. Willier, B. H., and Rawles, Mary E. (1931). The relation of Hensen's node to the differentiating capacity of whole chick blastoderms as studied in chorio-allantoic grafts. J. Exp. Zool. 59, 429-465. Hunt, Eleanor A. (1932). The differentiation of chick limb buds in chorio-allantoic grafts, with special reference to the muscles. J. Exp. Zool. 62, 57-91. Rudnick, Dorothea (1932). Thyroid-forming potencies of the early chick blastoderm. J. Exp. Zool. 62, 287-317. Sandstrom, Carl J. (1932). Heteroplastic transplants of duck kidney tissue on the chorio-allantoic membrane of the chick in conjunction with adult chick spleen graft. Anat. Rec. 52, 69-81. Sandstrom, Carl J. (1932). The growth and differentiation of duck kidney tissue on the chorio-allantoic membrane of the chick and duck. Physiol. Zool. 5, 354-374. Seevers, C. H. (1932). Potencies of the end bud and other caudal levels of the early chick embryo, with special reference to the origin of the metanephros. Anat. Rec. 54, 217-246. Willier, B. H. (1933). Potencies of the gonad-forming area in the chick as tested in chorio-allantoic grafts. Wilhelm Roux' Arch. 130, 616-649. Stein, Kathyrn F. (1933). The location and differentiation of the presumptive ectoderm of the forebrain and hypophysis as shown by chorio-allantoic grafts. Physiol. Zool. 6, 205-235. Sandstrom, Ruth H. (1934). The differentiation of hepatic and pancreatic tissues of the chick embryo in chorio-allantoic grafts. Physiol. Zool. 7, 226-246. Willier, B. H., and Rawles, Mary E. (1935). Organ-forming areas in the early chick blastoderm. Proc. Soc. Exp. Biol. Med. 32, 1293-1296. Butler, Elizabeth (1935). The developmental capacity of regions of the unincubated chick blastoderm as tested in chorio-allantoic grafts. J. Exp. Zool. 70, 357-395. Clarke, L. F. (1936). Regional differences in eye-forming capacity of the early chick blastoderm as studied in chorio-allantoic grafts. Physiol. Zool. 9, 102-128. Rawles, Mary E. (1936). A study in the localization of organ-forming areas in the chick blastoderm of the head-

process stage. J. Exp. Zool. 72, 271-315. Street, Sybil F. (1937). The differentiation of the nasal area of the chick embryo in grafts. J. Exp. Zool. 77, 49-85. Willier, B. H. (1937). Experimentally produced sterile gonads and the problem of the origin of the germ cells in the chick embryo. Anat. Rec. 70, 89-112. Alexander, L. E. (1937). An experimental study of the role of optic cup and overlying ectoderm in lens formation in the chick embryo. J. Exp. Zool. 75, 41-73. Willier, B. H. (1950). Sterile gonads and the problem of the origin of germ cells in the chick embryo. Arch. Anat. micros. Morphol. exp. 39, 269-273. Willier, B. H. (1954). Phases in embryonic development. J. Cell. Comp. Physiol. 43 (suppl. 1), 307-317. INSERT [19] Willier, B. H. (1957). Frank Rattray Lillie 1870-1947. Biographical Memoirs of the National Academy of Sciences 30, 179-236. (In a letter dated Dec. 16, 1955, Willier stated, "...it took me nearly 8 years of careful search and study to prepare the biography of my professor, Frank R. Lillie. 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...)" [20] Spratt, N. T., Jr. (1940). An in vitro analysis of the organization of the eye-forming area in the early chick blastoderm. J. Exp. Zool. 85, 171-209. [21] Willier, B. H., and Oppenheimer, Jane, eds. (1964). "Foundations of Experimental Embryology." Prentice-Hall, Inc., Englewood Cliffs, N. J. [22] Willier, B. H., Weiss, P. A., and Hamburger, V., eds. (1955). "Analysis of Development." W. B. Saunders Co., Philadelphia. INSERT [23] Each conference formed the basis of a small book published by the University of Chicago Press, Chicago, in 1958 or 1959. [24] Berrill, N. J. (1939). First Symposium on Development and Growth. Growth Suppl., Foreword. Hoadley, L. (1950). Founding of the Society for the Study of Development and Growth. Growth 14, 261. Oppenheimer, Jane M. (1966). The growth and development of developmental biology. In "Major Problems in Development" (M. Locke, ed.), pp. 1-27. Academic Press, Inc., New York City. [25] Willier, B. H., Rawles, Mary E., and Hadorn, E. (1937). Skin transplants between embryos of different breeds of fowl. Proc. Nat. Acad. Sci. U.S. 23, 542-546. Willier, B. H., and Rawles, Mary E. (1938). Feather characterization as studied in host-graft combinations between chick embryos of different breeds. Proc. Nat. Acad. Sci. U.S. 24, 446-452. Willier, B. H., and Rawles, Mary E. (1940). The control of feather color pattern by melanophores grafted from one embryo to another of a different breed of fowl. Physiol. Zool. 13, 177-199. Hamilton, H. L. (1940). A study of the physiological properties of melanophores with special reference to their role in feather coloration. Anat. Rec. 78, 525-547. Ris, Hans (1941). An experimental study on the origin of melanophores in birds. Physiol. Zool. 14, 48-66; not a doctoral dissertation. Willier, B. H. (1941). An analysis of feather color pattern produced by grafting melanophores during embryonic development. Amer. Nat. 75, 136-146. Willier, B. H. (1942). The control of hair and feather pigmentation as revealed by grafting melanophores in the embryo. Annals Surg. 116, 598-603. Watterson, Ray L. (1942). The morphogenesis of down feathers with special reference to the developmental history of melanophores. Physiol.

Closely related to early investigations listed in footnote 18 was the only doctoral dissertation not published by a Willier student: Chen, B. K. (1931). The early development of the duck's egg with special reference to axial relations and the origin of the primitive streak. The University of Chicago.

(Reprinted by Hafner Publ. Co., Inc., New York City).

Zool. 15, 234-259. Foulks, J. G. (1943). An analysis of the source of melanophores in regenerating feathers. Physiol. Zool. 16, 351-380. Willier, B. H., and Rawles, Mary E. (1944). Genotypic control of feather color pattern as demonstrated by the effects of a sex-linked gene upon the melanophores. Genetics 29, 309-330. Willier, B. H. and Rawles, Mary E. (1944). Melanophore control of the sexual dimorphism of feather pigmentation pattern in the Barred Plymouth Rock fowl. Yale J. Biol. Med. 17, 319-340. Nickerson, Mark (1944). An experimental analysis of barred pattern formation in feathers. J. Exp. Zool. 95, 361-397. Willier, B. H. (1952). Cells, feathers and colors. Bios 23, 109-125. Willier, B. H. (1953). Basic mechanisms in the differentiation of pigment cells. J. Embryol. Exp. Morphol. 1, 297-299. Reams, W. M., Jr. (1956). An experimental study of the development of pigment cells in the coelomic lining of the chick embryo. J. Morphol. 99, 513-548. [26] Philips, F. S. (1941). The oxygen consumption of the early chick embryo at various stages of development. J. Exp. Zool. 86, 257-289. [27] Grabowski, C. T. (1956). The effects of the excision of Hensen's node on the early development of the chick embryo. J. Exp. Zool. 133, 301-342. [28] Saunders, John W., Jr. (1948). The proximo-distal sequence of origin of the parts of the chick wing and the role of the ectoderm. J. Exp. Zool. 108, 363-403. [29] Ebert, James D. (1950). An analysis of the effects of anti-organ sera on the development, in vitro, of the early chick blastoderm. J. Exp. Zool. 115, 351-378. Ebert, James D. (1951). Ontogenetic change in the antigenic specificity of the chick spleen. Physiol. Zool. 24, 20-41. [30] Coulombre, A. J. (1955). Correlations of structural and biochemical changes in the developing retina of the chick. Amer. J. Anat. 96, 153-190. [31] McElroy, W. D., and Glass, B., eds. (1958). "The Chemical Basis of Development." The Johns Hopkins Press, Baltimore.

A THEORY OF ASYMMETRIC CELL DIVISION (DIFFERENTIATION)

The progeny of the division of a parent cell of type A may be classified as follows: 2A, undifferentiated division; 2B, symmetric differentiation; A and B, or C and B, asymmetric differentiation. For the last process, a number of different mechanisms may be proposed:

(1) The parent cell may have inherent architectural asymmetry (for instance, the grasshopper neuroblast)[2]; (2) A gradient of temperature, chemical composition, etc., is required and must be significant over cellular dimensions (as may be of importance in epimorphic regeneration which takes place in the presence of gradients and mitosis[3]; (3) The process is initiated on one of a set of sites within the cell or in the membrane by an external agent on a time scale such that the time between initiations on two separate sites is long compared to the time an inhibition signal takes to propagate from an initiated site to the remaining uninitiated sites to irreversibly prevent their activation[4]; (4) The process may be of genetic origin, such as inexact replication which yields daughters of different genotypes, or as in chromatin diminution (for instance bifurcations of the germ cell from the somatic cell lines.[5]