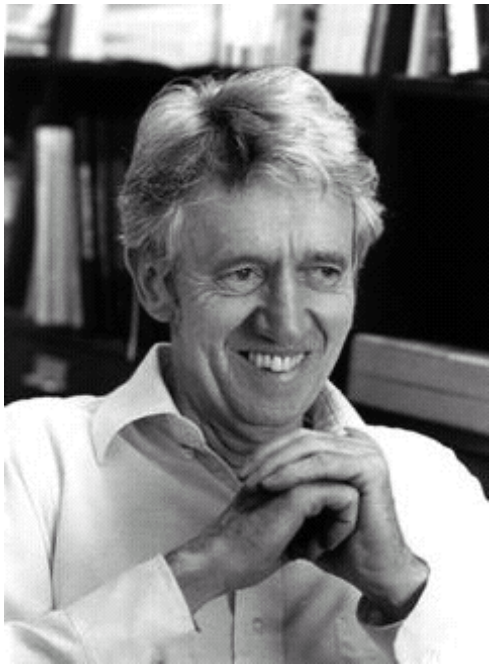

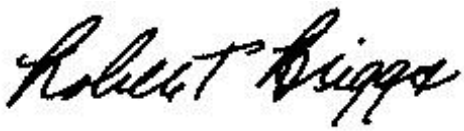

Robert W. Briggs

December 10, 1911 — March 4, 1983

By Marie A. Di Berardino

PROFESSOR ROBERT BRIGGS MADE pioneering research contributions in the developmental genetics of amphibia for over four decades. His chief embryological interest was to understand the genetic control of development. This focus led him to study, among other areas of research, two major problems: the developmental potential of nuclei during embryogenesis by means of nuclear transplantation into oocytes and the role of maternal gene products in the development of the embryo. He provided the basis for current research on cloning metazoan animals and the genetic control of pattern development.

Briggs developed with Thomas J. King a technique to transplant living frog nuclei from embryonic cells into an oocyte whose own nucleus had been removed. They found that many nuclei directed normal development of the oocytes from early embryonic stages, whereas only a few nuclei did so from advanced embryonic stages, indicating that most nuclei acquire restrictions concomitant with cell specialization. The results of these classic studies are, still today, consistent with the changing patterns of gene expression occurring during embryogenesis that are controlled by relatively stable alterations in the chromosomal proteins and DNA methylation. At least two additional results emanated from the nuclear transplantation studies: many advanced-stage nuclei undergo significant reprogramming of molecular function by the oocyte cytoplasm, and the nuclear transplantation procedure became the prototype for cloning metazoan animals.

To understand how genes control embryonic development, Briggs initiated a program on the effect of maternal gene products in the oocyte on the development of the embryo of the Mexican axolotl, a salamander. These studies were performed by analyzing the embryological, cellular, and molecular changes in embryos developing from oocytes whose mothers carried mutations. Thus, the abnormal gene products produced in the growing oocytes revealed how oocyte gene products control the initial stages of embryogenesis. This research in amphibia was one of the initial studies that revealed how maternal gene products control early pattern formation.

I should point out why I was asked to write this memoir of Bob Briggs. I knew Bob for thirty-five years, first joining his laboratory in 1948, just two years before he embarked on the nuclear transplantation experiments. By 1950 he had recruited Tom King, then a research fellow, to collaborate on the project, and in 1952 they had their first success. Later, in the 1950s and early 1960s, I had the pleasure of collaborating with Bob on some of the nuclear transfer studies and during his years at Indiana University (1956-83) I maintained contact with him. When he became research professor emeritus, he remarked that he felt like a postdoctoral fellow--he could now enjoy research with no other responsibilities. Unfortunately, he died approximately a year later.

Much of what I know of Bob stems from working with him, listening to his anecdotes at 4:00 p.m. tea breaks in Philadelphia, and the contact I had with him in later years when he was in Bloomington. Quotations that follow came from an interview conducted by Elizabeth Knight Patterson (no date) that were incorporated in her book.

EARLY PERSONAL HISTORY

Robert William ("Bob") Briggs was born in Watertown, Massachusetts, in 1911. When he was less than two years old, his mother and brother died of tuberculosis, and he was raised by his grandparents (1913-29) in Epping, New Hampshire, a small town of about 1,600 people located in the southeastern part of the state. He grew up with his uncles and aunts, one of whom was only ten years older than Bob. He had a happy childhood, as "there was an enviable stability and security in the social structure." Although his family "was rather poor like most of the other families," they did own a piano, and Bob took lessons from an aunt for several years. He recalled, "I drifted away from the piano, but the influence was a permanent one, and music has been a part of my life in one way or another ever since."

At fourteen, he began to work in the summer at the local shoe factory. In the winter, he earned money "as a banjo player in a small dance band that played two to three nights a week for dances in southeastern New Hampshire towns." Bob credits a teacher in high school for leading him into biology. "The teacher turned the students loose on projects of their own." Bob collected minnows, frogs, insects, worms, plants, etc., and studied them under magnifying glasses and a borrowed microscope. "The effect of merely looking at life at a different level was a lasting one. At the time it never occurred to me that I would become a biologist; I didn't even know that one could earn one's living this way."

After high school, Bob left home for Boston, where he "got a job working nights and attended classes by day at Boston University." Initially, he enrolled in the College of Business Administration to prepare himself to make a living. His lack of interest in those courses led him to take some science courses in the College of Liberal Arts. Still concerned about making a living, he also took courses in the School of Education. In 1934 he graduated with a B.S. and, firmly convinced that his future was in science, went to graduate school at Harvard University. Under the sponsorship of Leigh Hoadley, Bob "made a detailed analysis of changes in metabolic rate and density during the development of the frog." During graduate school he was an Austin teaching fellow in biology (1935-36), held an assistantship (1936-38), and continued his night job. In 1938 he received his Ph.D.

RESEARCH CONTRIBUTIONS

The contributions of Robert Briggs to developmental biology spanned over four decades and comprised four main periods of pioneering research in amphibian development, involving neoplasia, ploidy, nuclear transplantation, and maternal genes. After receiving his Ph.D. degree, he became a fellow in the Zoology Department at McGill University (1938-42). Here he initiated his first period, the characterization of tumor growth in the developing frog, for he recognized the importance of studying the behavior of tumors in the organization fields operative in developing systems. He was the first to induce tumors in a developing system, the larvae of *Rana pipiens*, and did so with a carcinogenic agent (1940). Also, he was the first to examine the effect of a developing organism on a malignant tumor. He transplanted fragments of the frog renal adenocarcinoma (Lucké tumor) to various sites of the larva and found that they grew well, but regressed prior to metamorphosis. He also found that good growths regressed even in tadpoles in which metamorphosis was prevented by removing the pituitary or thyroid gland (1943). He suggested that regression of this malignant tumor might be "an expression of the development of tissue specificity." Extensions of this research can be found today in studies of the development of immunocompetence, tumor immunosurveillance, and attempts to normalize cancer cells in embryonic systems.

In his second period he focused on the role of the nucleus in development. This occurred in 1942 after he joined the Lankenau Hospital Research Institute (later the Institute for Cancer Research and now the Fox Chase Cancer Center) in Philadelphia. First, he developed a method for producing anuran triploids with heat shock and analyzed the effect of ploidy on development. He found that the triploids developed normally (1947), except female gonads usually reversed to testes (1950). One practical outcome of this work was the availability of a triploid marker later to be used widely in frog embryos for various types of studies. The study on sex reversal in anuran triploids was done in collaboration with Rufus R. Humphrey and Gerhard Fankhauser. His association with Professor Humphrey later culminated in a research program in amphibian developmental genetics at Indiana University.

His investigation of the haploid syndrome showed that reduction of egg cytoplasm decreased the severity of the haploid syndrome, but it did not overcome the abnormalities (1949). This work showed that the nucleocytoplasmic ratio played a role in the haploid syndrome, but it suggested that deleterious genes were mainly responsible for the haploid abnormalities. Next, the production and analysis of embryos lacking functional chromosomes showed that anuran embryos lacking a functional nucleus but containing a normal cleavage center can develop into partially cleaved blastulae (1951). This study, predating the explosion of the molecular biology of embryos, indicated that gene products formed during amphibian oogenesis are sufficient to support cleavage, but post-blastula development requires new gene products. In addition, this study laid the foundation for the interpretation of nuclear transplantation experiments that occupied his third period of research.

In 1952 in collaboration with Thomas J. King, Briggs pioneered the development of the technique of amphibian nuclear transplantation in determining whether somatic nuclei remain equivalent to the zygote nucleus in developmental potential during embryogenesis, a question posed previously by H. Spemann and others. Briggs and King initially focused on cell nuclei from undetermined regions of the embryo and showed that, after transplantation singly into enucleated frog eggs (*R. pipiens*), many of these nuclei directed the eggs to develop into normal tadpoles (1952) and in a later study into normal metamorphosed frogs (1960). This was the first time successful nuclear transplantation had been accomplished in metazoans. Subsequently, they tested nuclei up to tailbud stages and found that simultaneously with cell differentiation there is a progressive decrease in the percentage of nuclei capable of supporting normal development (1977). The importance of this technique was immediately recognized, and Bob generously hosted in his laboratory numerous scientists to help them learn the procedure. Soon various laboratories around the world applied this technique to different amphibian species and confirmed the decreased developmental potential of most nuclei concurrently with advancing embryogenesis.

The conservative conclusion in the classic 1952 paper was that "although the method of nuclear transplantation should be valuable principally for the study of nuclear differentiation, it may also have other uses." Some of its applications have been the analysis of haploidy, hybrid incompatibility, cancer, immunobiology, and cellular aging. It provided insight into the cytoplasmic control of nuclear and gene function, including reprogramming of nuclear and gene function. Most importantly, nuclear transfer became the prototype for cloning metazoan organisms and was extended to insects, fish, and mammals. In 1997 the first metazoan animal (a lamb, Dolly) was cloned from an adult cell, and this was followed in 1998 by the cloning of mice and calves from adult cells. During this period, the first transgenic lambs carrying the human gene (clotting factor IX) were cloned from fetal cells and the first transgenic calves were cloned also from fetal cells. The fundamental research begun in 1952 will now be translated into important biomedical and agricultural applications.

In 1956 Bob Briggs resigned from his post as head of the Embryology Department at the Institute for Cancer Research and became professor of zoology at Indiana University. He then embarked on his fourth and final period of research, the establishment of amphibian developmental genetics. He had been convinced for some time that the gap between embryology and genetics needed to be bridged in order to understand how the nucleus interacts with the cytoplasm in directing embryonic development. Recognizing the importance of the genetic lines of Mexican axolotl (*Ambystoma mexicanum*) that Professor Rufus Humphrey had developed, Bob recruited Humphrey to Indiana University soon after Humphrey retired from his post at the University of Buffalo Medical School (now the State University of New York at Buffalo). Humphrey became research scholar in the Department of Zoology, and together they built the research program in the developmental genetics of axolotl.

Briggs realized that the developmental genetics of early development would be revealed best by mutations showing a maternal effect (i.e., those that were expressed in the embryo regardless of the normal genes contributed by the sperm). Previous experimental embryologists had shown that the pattern of early development is controlled by morphogenetic substances produced during oogenesis and present in the egg cytoplasm at fertilization. Genes that exerted maternal effects through modifications of the egg cytoplasm were therefore of special interest, as they provided a means to study how the egg cytoplasm acts to control early embryonic development. Several such genes and others that act later were found by Humphrey. For example, four mutations cause early arrest. One in particular, the o^+ gene, produced a substance during oogenesis that is required for development beyond gastrulation. Injections of cytoplasm or nucleoplasm of germinal vesicles from normal oocytes into mutant eggs corrected the deficiency, resulting in normal development (1966). Eight other genes exerted specific effects on embryonic organs, whereas four caused alterations in pigment cells and four did so in nucleoli (1973).

The action of these mutant genes on development was elucidated by various methods (cytological, biochemical, embryological, molecular, and physiological) by Briggs, Humphrey, students, and others. In his 1973 review, Briggs credits especially the pre- and postdoctoral students, who in many cases published their findings independently. This was the policy of Bob, who gladly counseled students, but encouraged them to develop on their own. Various axolotl mutants and others to be discovered were supplied to other investigators for their research projects, and this continues today at the axolotl colony of Indiana University. The studies on maternal genes initiated in the 1950s provided a background and direction for the elegant molecular genetic experiments of others to follow in *Drosophila, Xenopus*, zebrafish, chordates, and invertebrates, in which many genes contributing to pattern formation have been identified and, in the best cases, several genes acting in a specific biochemical pathway have been recognized and elucidated.

Bob retired in 1982 and became research professor emeritus at Indiana University. He continued his research at this time on a newly discovered temperature-sensitive mutant in the axolotl. One of the projects was completed before his death from kidney cancer on March 4, 1983, and was published posthumously (1984). He died in the Krannert Pavilion of the Indiana University School of Medicine in Indianapolis, and was survived by his second wife Francoise and two sons and a daughter: Evan of Bloomington, Indiana; Alexander of Hillsdale, New York; and Meredith Briggs Skeah of Green Village, New Jersey. His former wife, Janet Bloch Briggs of Hillsdale, and mother of his children also survived him.

HONORS AND OTHER CONTRIBUTIONS

Bob Briggs was the recipient of various honors, including election to the American Academy of Arts and Sciences (1960) and the National Academy of Sciences (1962). He was named research professor of zoology at Indiana University (1963) and fellow of the International Institute of Embryology. He was awarded honorary doctorate degrees by the Medical College of Pennsylvania (1971) and Indiana University (1983). In 1973 the French Academy of Sciences awarded him and Thomas J. King the Charles-Leopold Mayer Prize for their pioneering studies in amphibian nuclear transplantation. During his career he participated in many major symposia, served on editorial boards of important journals, and provided intellectual leadership as chair of zoology (1969-72) at Indiana University.

CODA

Bob Briggs will be remembered both as an outstanding scientist and a generous and cordial human being. He left a legacy not only of pioneering research but also a legacy of numerous problems for other investigators to pursue. He enjoyed life and had numerous hobbies, including listener and performer of classical music, as well as golfer, bowler, and sports car and motorcycle enthusiast. His earlier interest in playing classical music on the piano was followed by playing the recorder. As early as the 1950s, he owned an Austin-Healy, later a Corvette, and finally a top-of-the-line BMW motorcycle. He frequently shared these pastimes with students and colleagues, including his weekly Sunday morning golf.

REFERENCES

Etkin, L. D. 1998. Personal communication.

Justus, J. 1998. Personal communication.

Malacinski, G. M. 1998. Personal communication.

Patterson, E. K. No date. *Growth--The Early History of a Cancer Research Institute (1927-1957)*. Philadelphia: Talbot Research Library of the Fox Chase Cancer Center and American Philosophical Society.

SELECTED BIBLIOGRAPHY

1940

Tumour induction in *Rana pipiens* tadpoles. *Nature* 146:29.

1942

Transplantation of kidney carcinoma from adult frogs to tadpoles. *Cancer Res.* 2:309-23.

1943

With R. Grant. Growth and regression of frog kidney carcinoma transplanted into the tails of permanent and normal tadpoles. *Cancer Res.* 3:613-20.

1947

The experimental production and development of triploid frog embryos. *J. Exp. Zool.* 106:237-66.

1949

The influence of egg volume on the development of haploid and diploid embryos of the frog, *Rana pipiens*. *J. Exp. Zool.* 111:255-94.

1950

With R. R. Humphrey and G. Fankhauser. Sex differentiation in triploid *Rana pipiens* larvae and the subsequent reversal of females to males. *J. Exp. Zool.* 115:399-428.

1951

With E. U. Green and T. J. King. An investigation of the capacity for cleavage and differentiation in *Rana pipiens* eggs lacking "functional" chromosomes. *J. Exp. Zool.* 116:455-99.

1952

With T. J. King. Transplantation of living nuclei from blastula cells into enucleated frogs' eggs. *Proc. Natl. Acad. Sci. U. S. A.* 38:455-63.

1954

With T. J. King. Transplantation of living nuclei of late gastrulae into enucleated eggs of *Rana pipiens*. *J. Embryol. Exp. Morphol.* 2:73-80.

1955

With T. J. King. Changes in the nuclei of differentiating gastrula cells, as demonstrated by nuclear transplantation. *Proc. Natl. Acad. Sci. U. S. A.* 41:321-25.

With T. J. King. Specificity of nuclear function in embryonic development. In *Biological Specificity and Growth*, ed. E. G. Butler, pp. 207-28. Princeton, N.J.: Princeton University Press.

1956

With T. J. King. Serial transplantation of embryonic nuclei. *Cold Spring Harb.Symp. Quant. Biol.* 21:271-90.

1957

With T. J. King. Changes in the nuclei of differentiating endoderm cells as revealed by nuclear transplantation. *J. Morphol.* 100:269-312.

1959

With T. J. King. Nucleocytoplasmic interactions in eggs and embryos. In *The Cell*, vol. 1, eds. J. Brachet and A. E. Mirsky, pp. 537-617. New York: Academic Press.

1960

With T. J. King. Nuclear transplantation studies on the early gastrula (*Rana pipiens*). I. Nuclei of presumptive endoderm. *Dev. Biol.* 2:252-70.

1961

With T. J. King and M. A. Di Berardino. Development of nuclear-transplant embryos of known chromosome complement following parabiosis with normal embryos. In *Symposium on Germ Cells and Earliest Stages of Development*, ed. S. Ranzi, pp. 441-77. Milan: Fondazione A. Baselli, Istituto Lombardo.

1962

With J. Signoret and R. R. Humphrey. Nuclear transplantation in the axolotl. *Dev. Biol.* 134-64.

1966

With G. Cassens. Accumulation in the oocyte nucleus of a gene product essential for embryonic development beyond gastrulation. *Proc. Natl. Acad. Sci. U. S. A.* 55:1103-09.

1968

With J. T. Justus. Partial characterization of the component from normal eggs which corrects the maternal effect of gene *o* in the Mexican axolotl (*Ambystoma mexicanum*). *J. Exp. Zool.* 167:105-15.

1969

Genetic control of early embryonic development in the Mexican axolotl, *Ambystoma mexicanum*. *Ann. Embryol. Morphog.* 1(suppl.):105-13.

1972

Further studies on the maternal effect of the *o* gene in the Mexican axolotl. *J. Exp. Zool.* 181:271-80.

1973

Developmental genetics of the axolotl. In *Genetic Mechanisms of Development*, ed. F. H. Ruddle, pp. 169-99. New York: Academic Press.

1975

With H.-M. Chung. Experimental studies on a lethal gene (*l*) in the Mexican axolotl, *Ambystoma mexicanum*. *J. Exp. Zool.* 191:33-47.

1977

Genetics of cell type determination. In *Cell Interactions in Differentiation*, eds. M. Saxen and L. Weiss, pp. 23-43. New York: Academic Press.

1984

With F. Briggs. Discovery and initial characterization of a new conditional (temperature-sensitive) maternal effect mutation in the axolotl. *Differentiation* 26:176-81.