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MAMMALIAN GENETICS AND CANCER

The Jackson Laboratory Fiftieth Anniversary Symposium

EDITOR Elizabeth S. Russell

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MAMMALIAN GENETICS AND CANCER
The Jackson Laboratory Fiftieth Anniversary Symposium

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MAMMALIAN GENETICS AND CANCER
The Jackson Laboratory Fiftieth Anniversary Symposium

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Preface: A Century of Mammalian Genetics and Cancer, 1929–2029, A View at Midpassage

This volume is designed to provide (in five exciting current topics in mammalian biomedical research) a "View in Midpassage" between the status of those fields in 1929, when The Jackson Laboratory was founded, and anticipated accomplishments within the same areas achieved by that future year, 2029. The contents of this book are the proceedings of a scientific symposium held in July 1979 to celebrate the 50th birthday of The Jackson Laboratory. This anniversary came at a most propitious moment in the progress of research on mammalian genetics and cancer. Although experimental mammalian research expanded steadily and produced important results between 1929 and 1979, "center stage" was dominated by the discovery of DNA and the rise of molecular biology. In the early days of molecular genetics, critical questions could be attacked most expeditiously using microbial and viral test systems. Molecular biology focused almost exclusively on prokaryotes, while research on differentiated eukaryotes concentrated on the visible cellular and whole organism level. Now the center of excitement appears to be shifting to analysis of eukaryotic systems including control of development, differentiation, and function. By using in vitro systems, man himself has become an important experimental organism. But more and more of this new research is based on work with experimental mammals, and the five research areas discussed in this symposium are especially "hot" topics within an overall growing research field.

The five diverse topics selected for this symposium seem at first consideration somewhat unrelated: gene and chromosome organization; analysis of mammalian development; inherited diseases of mouse and man; immunogenetics; and the etiology of cancer. Actually, they tend to be mutually interdependent, so that advances in one topic lead to new possibilities in another. Also, as becomes apparent in reading papers from each session, advances in research with experimental mammals lead to advances in the understanding of human conditions; and, conversely, results of research on humans often open fruitful new avenues for experimental mammalian research.

Why was this particular set of topics selected for this symposium? None of them is brand new. Considerable attention, resulting in marked progress, has been devoted to each of these topics during the past 50 years. These topics are not old; it seems highly probable that each will continue to attract considerable interest over much of the next 50 years. It is almost a foregone conclusion that findings from basic research related to these topics (as well as to many others) will long continue to find new applications beneficial to human welfare.

Why were these five topics singled out? All have two characteristics in common. Especially rapid advances in recent years caused these to be "hot" topics in 1979; and the Jackson Laboratory feels that research at this institution has contributed materially to the long-term development of each of these fields. We wanted to celebrate! The chairman selected for each session is a long-standing friend of the Jackson Laboratory. Dr. Margaret C. Green, now Senior Staff Scientist Emeritus, has been a major force in expanding knowledge of the formal genetics of the mouse. Dr. James D. Ebert, renowned developmental biologist, was Chairman of the Board of Scientific Overseers of the Jackson Laboratory. Victor McKusick, medical geneticist from Johns Hopkins School of Medicine, has established and guided for the past 20 years an annual series of two-week Short Courses in Genetics. At first, all courses consisted of combined Johns Hopkins-Jackson Laboratory courses in Medical Genetics; later, these sessions were alternated with Jackson Laboratory Short Courses in Experimental Mammalian Genetics. Dr. Dorothea Bennett, an important mouse developmental geneticist with special interests in immunology and cell surfaces, is a member of the Jackson Laboratory Board of Scientific Overseers. Dr. Richmond Prehn, current Director of The Jackson Laboratory, did an excellent job as Chairman of Session V – The Etiology of Cancer. His introductory comments stressed the contributions of his early mentor, Dr. Howard B. Andervont, one of the organizing members of the National Cancer Institute; one of the first Jackson Laboratory summer investigators; and, for many years, a greatly valued member of the Laboratory's Board of Scientific Overseers. We regret that Dr. Andervont, originally scheduled to serve as Chairman of Session V, was unable to come to the Symposium. Dr. James F. Crow, Jackson Laboratory Overseer and a delightfully insightful geneticist whose own work centers on Drosophila, gave us an excellent overview of 50 years of developments in the whole science of genetics.

We also were very proud to have as our honored guest world-famous geneticist Sewall Wright, friend from Bussey Institute days of Clarence Cook Little, founder of The Jackson Laboratory; postdoctoral mentor of Earl L. Green, the Jackson Laboratory's second director; and doctoral sponsor of former Jackson Laboratory staff members W. L. Russell, J. P. Scott, and W. K. Silvers, and of one current staff member – myself.

In the short introduction to each session, I have attempted to orient the unfamiliar reader to the impact of each paper. Most of the papers deal with very recent advances and are presented by leading scientists in the field, four of them

currently working at the Jackson Laboratory. Eight others have a "Jackson Laboratory history." Walter Heston was an early staff member; David Baltimore and Virginia Papaioannou have been Jackson Lab "summer students"; Victor McKusick, Charles Scriver, and Philip Leder have been leading lights in Genetics Short Courses; Samuel Lux and Karl Illmensee carry on collaborative research with Jackson Laboratory investigators; and Philip Leder has recently become one of our Scientific Overseers.

It is not surprising that, even though the major emphasis in this Symposium is on "Science Today," several papers (at least one per session) include historical perspectives, with gratifying reference to the role of the Jackson Laboratory. Since this occasion was the Laboratory's birthday party, I hope you will forgive me for closing with a few remarks on Jackson Laboratory history.

Some of you may recall the crash of 1929, which ushered in the Great Depression. A fine time to start a private research laboratory, particularly when there were no federal and few private foundation sources of research support! The first great accomplishment of the Jackson Laboratory was survival through its first ten years. Major research accomplishments were characterization of inbred strains of mice and demonstration of their value in research, especially through the delineation of extrachromosomal influences on the development of mouse mammary cancer. In its second decade (1939–1949), The Jackson Laboratory was still tiny and struggling, but its influence expanded because of further analysis of maternal influences on mammary cancer, demonstration of genetic influence on incidence of other types of cancer, and the beginning of advance in knowledge of the formal genetics of the mouse. To these we should add two activities whose effect was to focus attention on the research importance of genetically-controlled mice: supply of inbred and F_1 hybrid mice to outside investigators; and publication of the first edition of "The Biology of the Laboratory Mouse."

The third decade of the laboratory's history (1949–1959) was a time of rapid growth, helped greatly by the beginning of "Big Science," with support for research endeavors from the federal government and from the National Institutes of Health. The Jackson Laboratory was engaged in research on mouse immunogenetics, teratology, behavior, and genetic diseases, always utilizing genetically controlled stocks. Great advances were made in the knowledge of the formal genetics of the mouse. Studies in rabbit genetics were undertaken, and behavior-genetics research concentrated largely on dogs. During this decade Earl L. Green became the second director of The Jackson Laboratory (1956), and the 25th Anniversary was celebrated (1954) with an enthusiastic symposium. It is interesting that Sewall Wright summarized that conference, presenting "Patterns of Mammalian Gene Action." This third decade of rapid growth also was a time when the Jackson Laboratory recognized and assumed its responsibility for the genetics of the mouse by working for the Mouse News Letter and for standardized genetic nomenclature; by establishment of the breeding expansion system involving

foundation stocks, pedigreed expansion stocks, and animal resources stocks; and by attention to further characterization of a wider variety of inbred lines and organization of published information on genetically controlled mice through development of a subject-strain bibliography.

The Jackson Laboratory's accomplishments in the fourth and fifth decades are too extensive to be covered in this capsule presentation. Because our selection of five topics necessarily omitted many important facets of Jackson Laboratory contributions, it may be desirable to mention a few other highlights here. Radiation effects were studied extensively in the fourth decade, and an important start was made in biochemical genetics and the study of the genetic control of metabolism. We put forth the greatly expanded second edition of "The Biology of the Laboratory Mouse" (1966), with Earl L. Green as editor. The very large animal resources stocks were utilized for an organized study of mouse spontaneous-mutation rates. Many research advances were also made in our "five topics" in the fourth decade and, of course, even more in the past ten years. We cannot leave this capsule history without mentioning development in the fifth decade of especially valuable new genetic tools. The principles and first establishment of recombinant inbred strains and congenic and coisogenic lines stem from Jackson Laboratory geneticists, and these become more important research tools with every passing day.

It is a great pleasure to have been a part of this Symposium, celebrating research developments in mammalian genetics and cancer as well as the 50th Anniversary of The Jackson Laboratory. We are very grateful to the American Cancer Society and to the National Foundation for their generous support, which helped to make possible this joyous occasion.

Elizabeth S. Russell
The Jackson Laboratory
January 1981

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SESSION I. GENE AND CHROMOSOME ORGANIZATION

MARGARET C. GREEN, Chairman

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Introduction to Session I

During the period 1929–1979, a great deal has been learned about the genetic makeup and the cytogenetics of the 20 pairs of mouse chromosomes. This information, which has come to have elegant detail, still belongs in the breeding-experiment and light-microscope portion of a broad range of possible information about the mouse genome. A great deal has also been learned about the "mid-range" organizational level, about relations between structure and function of many of the named genes recognized in the mouse genome. Very recently, great advances have been made in understanding the *very* fine structure and regulation of function of certain favorable mouse genes. Session I deals only with the two ends of this spectrum – with what is often called formal genetics and with what is called molecular genetics. We leave the entire midspectrum for other sessions.

Session I starts by considering the history of increase in knowledge of the positions of named genes on the genetic linkage map, and its coordination with the cytogenetics map. Dr. Eva Eicher also includes fascinating predictions regarding future linkage studies. This is followed by Dr. Philip Leder's paper, molecular to the nth degree, dealing with extremely fine internal structure of mouse globin genes. The "middle range" of information about mouse genes is not at all covered in this session, where genes are either points on a linkage map or cloned DNA sequences!

So we plunge, in the first paper by Dr. Eicher, into a working cytogeneticist's excellent depiction of the growth, the present state, and the probable future course of studies of mouse formal genetics. I recommend that any nongeneticist readers who might shrink from contemplation of linkage look closely at the six successive versions of the mouse genetic linkage map, as known in 1935, 1945, 1954, 1971, 1975, and 1979, and follow in the text the evolving pattern of acquisition of new technologies and discovery of new mutants that made this rapid progress possible. The first genetic linkage in the mouse was discovered in 1915, but thereafter for a long period additions came very slowly, because the base of information to link to was so small. Prior to 1971, some acceleration resulted from simple increase in the number of recognized mutants already on the map (more "handles" available). Analysis from translocations helped somewhat in