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Perspectives

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One Hundred Years of Mouse Genetics: An Intellectual History. I. The Classical Period (1902–1980)

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THE year that just ended marked the 100th birthday of mouse genetics. In light of the explosion of interest in recent years in using genetics to understand mammalian physiology and development, especially human disease processes, it is worth recounting the evolution of this field over its first century and the contributions it has made.

If not for Bishop Anton Ernst Schaffgotsch of Austria, we could soon be celebrating the 150th, rather than the 100th, anniversary of mouse genetics (Henig 2000). The Augustinian monastery in Brünn (Brno) that Mendel entered as a monk was a politically liberal center of scientific thought and investigation, and its abbot was in conflict with his conservative, anti-intellectual bishop. Although the bishop was unsuccessful in his effort to close the monastery, he did succeed in forbidding Mendel from continuing his nascent efforts to study inheritance using the coat color traits of mice. Mendel, who had begun his research breeding mice in cages he kept in his two-room quarters, had to turn to his garden when his bishop insisted that it was not appropriate for a monk to share his living quarters with creatures that had sex and copulated! Fortunately for Mendel, his bishop was rather ignorant of botany, and fortunately for his brother monks, the transition must have had a rather favorable impact on the aroma of the monastery.

Although it is not likely that the history of our science would have followed a different course if Mendel had derived his laws by studying albino *vs.* pigmented, rather than smooth *vs.* wrinkled, there is a subjective warmth in knowing that the Father of Genetics could easily have been the Father of Mouse Genetics as well.

When Correns, Devries, and Tschermak independently reported their rediscoveries of Mendel's laws in 1900, each had worked with higher plants as their experimental material. The question whether Mendelism applied to animals as well as to plants immediately arose, and the answer was not long in coming. By 1902, Lucien Cuénot in France, in the first of a series of articles, demonstrated Mendelian ratios for the inheritance of coat color characters in mice (Cuénot 1902); Gregory Bateson and E. R. Saunders published their work showing that the Mendelian laws applied to the inheritance of comb characteristics in chickens; and Archibald Garrod, with Bateson's advice (Bearn 1994), was able to suggest that alcaptonuria in humans represents a rare homozygous recessive condition. Cuénot's experiments with mice went further. In 1905, he described what proved to be the first lethal mutation discovered, the A^y allele of the agouti locus, although it must be said that an understanding of Cuénot's unusual segregation ratios was not placed on solid experimental grounds until 1910, when W. E. Castle and C. C. Little (Castle and Little 1910) confirmed that crosses involving a lethal gene gave predictably aberrant Mendelian ratios in which the missing mice were replaced by dead embryos. Additionally, in his original report on A^y in 1904, Cuénot described the first case of multiple alleles at a locus, although, again, the significance of this was not appreciated until nearly a decade later when, in 1913, Alfred Sturtevant clearly stated the significance of his own finding of multiple alleles at the *white* locus in Drosophila. It was, of course, the existence of multiple alleles at a single locus that eventually served to disprove Bateson's early theory that dominant and recessive alleles represented the presence or absence of a gene. (A more in-depth description of Cuénot's efforts will appear in a forthcoming *Perspectives* by M. Hickman and J. Cairns.) Once it was understood that more than two alleles could exist at a single locus, this convenient explanation was no longer tenable, although it took another 50 years before geneticists generally came to accept the view that recessiveness and dominance are not genetic phenomena *per se*, but rather the physiological outcome of the action of gene products.

Despite these beginnings by Cuénot, mouse genetics did not start on the course it was to follow for the next half century until 1909, when two important events occurred. E. E. Tyzzer published a crucial paper (Tyzzer 1909) on the inheritance in mice of resistance to

the growth of transplanted tumors, and Little made the first matings to construct an inbred mouse strain. Indeed, Little, recognizing the importance of being able to make a reproducible genetic cross, began his matings in an effort to provide the experimental material he saw as essential to extending Tyzzer's observations. It was in these efforts that the application of mouse genetics to the analysis of mammalian physiology, biochemistry, and pathology began in the sense that we now understand it. Cuénot was a very talented scientist, and his work was quite important in the emerging science of genetics, but it was in the work of Tyzzer and Little that mouse genetics made the first of its contributions to our understanding of mammalian biology.

THE CANCER PROBLEM AND THE FIRST 50 YEARS

Tyzzer's and Little's efforts originated from earlier work by J. Loeb showing that tumors arising in a particular strain of Japanese waltzing mice could be successfully transplanted to all animals of that strain, but that "common" mice were completely resistant to tumor transplantation. Tyzzer attempted to study the genetic basis for this difference by crossing the Japanese and common mice and found that, whereas all of the first generation F_1 hybrid mice were susceptible to tumor growth, none (0/54) of the second generation F_2 animals were susceptible. Reasonably enough, he concluded that tumor susceptibility was not inherited as a Mendelian trait. It was the desire to continue these experiments that led Little, who was then a graduate student, to begin the crosses leading to the construction of the first inbred strain of mice, the animals we now call DBA. He was impelled to this by the fact that, although the Japanese waltzing mice were relatively uniform genetically, being the product of many generations of limited inbreeding by mouse fanciers and hobbyists, the other stock used in the cross was rather heterogeneous. Little's goal was to create a genetically uniform stock that could be used as the second partner in making a reproducible cross with Japanese waltzing mice.

Privately, Little was driven by the belief that Tyzzer's results could be explained by Mendelian mechanisms. In 1914, the year Little received his doctorate, he published a theoretical article (Little 1914) offering his alternative explanation. In brief, Little suggested that a large number of genes were involved in determining whether a mouse would accept or reject a transplanted tumor and that for each of these genes there were two alleles, one dominant and one recessive. For a mouse to accept a tumor transplant, it had to carry at least one copy of the dominant allele at every one of the loci involved. If the mouse were homozygous for the recessive allele at even one of these loci, it would reject the tumor transplant. All of the F_1 animals were susceptible because they all received a dominant allele at every locus from the Japanese parent that provided the tumor. However, because of random assortment of the large number of genes involved, only a very rare F_2 animal would receive a dominant allele at every single one of these loci and would become susceptible to transplantation. In 1916, using the same tumor, Little and Tyzzer (1916) reported the results of a much larger experimental series in which 3 of the 183 F_2 animals were susceptible. They forwarded this as a demonstration that the ability to accept a tumor transplant was indeed a Mendelian trait and estimated that 14–15 separate genes were involved. Genetic chutzpah indeed!

The boldness of Little's efforts hardly stopped with these experiments. He went on to become a university president (twice), founded and directed The Jackson Laboratory, which over the years has served as home base for mouse geneticists, and managed in the course of all this to discover the maternal inheritance of mammary tumor susceptibility. His very colorful life has been well profiled by Jim Crow in another of these *Perspectives* (Crow 2002).

Over the next 10 years, work by Little, Leonell Strong, and John Bittner tested various tumor and strain combinations, seeking further support for the Mendelian interpretation of tumor transplantation (Little 1941). By the end of the 1920s, Strong had reported a case in which only a single gene was involved and clear Mendelian ratios were obtained and another case in which one of the genes involved showed sex linkage, and Bittner was able to explain in Mendelian terms the inheritance pattern of ability to accept transplantation of a tumor that arose in an F_1 animal. By the early 1930s, the Mendelian interpretation was generally accepted, Little's early faith in a genetic basis for tumor transplantation was vindicated, and the challenge now lay in explaining the mechanism involved.

The groundwork for that explanation came in 1936, when Peter Gorer established the immunological basis of tumor resistance, which had been postulated by J. B. S. Haldane (1933) 3 years previously. Despite earlier failures by others, Gorer succeeded in demonstrating the existence of red cell antigens in mice similar to those already known in humans. Obtaining antisera against two immunologically distinct red cell antigens, he found these present in some mouse strains and absent from others (Gorer 1937a,b). Gorer went on to show that a single gene determined the presence of one of these antigens (erythrocyte antigen 2) and that this gene cosegregated with one of the genes determining resistance to tumor transplantation. Moreover, animals rejecting tumors developed antibodies recognizing the same red cell antigen. Gorer had succeeded in demonstrating two crucial points: that a gene determining resistance to tumor transplantation acts by determining the presence of a cellular antigen and that tumor rejection is associated with formation of antibodies against that

antigen. The major histocompatibility complex, *H2*, had been discovered.

It was now possible to explain the early experiments on tumor transplantation. If a tumor carrying a particular antigen is transplanted into a mouse lacking that antigen, the recipient will mount an immunological reaction against the antigen and reject the tumor. If the recipient carries the antigen, it will be tolerant to that antigen and unable to reject the tumor. In the original experiments of Tyzzer and Little, many such antigens and their genes were involved, and an F_2 animal had to receive an allele for the presence of every one of these antigens to accept a tumor transplant. If even a single one of the antigens was missing in an F_2 animal, the animal would be capable of mounting an immune response against that antigen and thus become capable of rejecting the transplant.

One additional step had to come before it was possible to unravel the intricacies of *H2*; this was George Snell's introduction in 1948 (Snell 1948) of co-isogenic or, as they came to be later called, congenic strains as a means of eliminating the complexities introduced by the presence of so many other histocompatibility loci. In essence, Snell's idea was to make an F_1 hybrid between two strains, backcross these hybrids to one of the parents (the recipient), and choose progeny retaining the *H2* type coming from the other parent (the donor). By repeating this process for many generations, the eventual result would be a mouse whose genome came almost entirely from the recipient strain except for a small segment of chromosome containing the *H2* locus derived from the donor strain. In practice it was not so simple, because Snell had to alternate each backcross generation with an intercross generation to produce mice that were homozygous for the donor *H2* allele to select a mouse that would transmit the allele in the next backcross. Nevertheless, using a common recipient strain and various donors, he was able to construct a series of strains carrying different alleles of *H2* and other histocompatibility loci on a common genetic background. The construction and study of these strains proved crucial in the analysis of *H2*, and that, in turn, led to the finding of the human major histocompatibility locus, *HLA*. For his pioneering work in this endeavor, Snell later received a Nobel Prize in 1980. J. Klein (2001) has provided an essay in this series on Snell's early work.

From 1916 onward, while studies of the genetic basis of tumor transplantation were proceeding apace, many of the same group of geneticists were concerned with the other side of the problem, the genetic factors underlying spontaneous neoplasia. A number of the inbred mouse strains in common use today were developed during that period, either as strains exhibiting a very high incidence of spontaneous neoplasia or as strains that provided necessary low-incidence controls. The A strain with a high incidence of lung adenomas and the C3H strain with a high mammary tumor incidence were bred by Strong; the high leukemia strains AKR and C58 were bred by Jacob Furth and Carleton MacDowell, respectively.

A key finding in the genetic analysis of spontaneous tumor incidence came in 1933 when, under C. C. Little's leadership, the entire staff of the nascent Roscoe B. Jackson Memorial Laboratory (as The Jackson Laboratory was then called) published a note in *Science* (Roscoe B. Jackson Memorial Laboratory Staff 1933) reporting that the propensity to form mammary tumors in mice is maternally inherited; the genetic origin of the fathers was irrelevant. These facts were independently established by Korteweg in the Netherlands (Korteweg 1936), and the explanation for maternal inheritance came 3 years later when Bittner foster-nursed newborn mice on susceptible and resistant mothers and discovered that the factor being transmitted was in the mother's milk (Bittner 1936), not in the genome. By 1942 the milk factor was recognized as a virus (Bryan *et al.* 1942; Visscher *et al.* 1942); by 1968 the mouse mammary tumor virus (MMTV) was an established entity, and the concept of germ-line transmission of provirus was understood (Mühlbock and Bentvelzen 1968; Varmus *et al.* 1972). Conceptually similar experiments led to an understanding of the viral etiology of murine leukemia, except that here the virus was transmitted by experimental inoculation of newborn mice, rather than spontaneously through the milk. From those experiments came our understanding of mammalian retroviruses and an understanding of their ability to induce tumors by attaching an active viral promoter of gene transcription to an adjacent chromosomal proto-oncogene.

Two themes, then, dominated the first 50 years of mouse genetics. One was the study of genetic factors determining susceptibility to transplanted tumors, which eventually led to the discovery and analysis of the major histocompatibility complex. The other was the effort to analyze the genetic basis for differences in the incidence of spontaneous neoplasms, which eventually led to the discovery of retroviruses and their role in neoplastic transformation. Related by the cancer problem, these two lines of research provided the original motivation for establishing inbred mouse strains and later stimulated several of the other technical developments of the mouse as a genetic system. The conceptual goal, one that intensely motivated many of the early workers on a personal level, was an understanding of cancer, and, as always, methodology was developed in response to experimental needs. Cancer was the driving force that carried mouse genetics through its first 5 decades and greatly influenced the development of the mouse as a genetic system. The pressure to solve an important medical problem resulted in the creation of a new experimental system that was to have far wider application in the years to come. For the cancer problem itself, the eventual outcome proved to be one of those

recurrent ironies of scientific history. While the study of spontaneous neoplasms led to the discovery of retroviruses and oncogenes and has brought us to the brink of a deep understanding of the biological basis of cancer at a molecular level, the studies of tumor transplantation, which started it all, had no significant impact on our understanding of cancer. Rather, in leading to the discovery of the major histocompatibility complex, these studies inadvertently initiated the description of a molecular complex central to the operation of cellular immunity.

THE EXTENSION OF MOUSE GENETICS TO MAMMALIAN BIOLOGY AT LARGE

Beginning about 1960, a series of quite different subjects began to appear in the mouse genetics literature with increasing frequency. The genetic systems that had been developed for the analysis of the cancer problem were proving powerful enough to be turned to new uses, and these soon moved to the forefront.

Sex determination and dosage compensation: One of these uses was in providing an explanation of how mammals cope with having two X chromosomes in females and only one in males. In 1961, Mary Lyon proposed the now widely accepted inactive X mechanism to resolve the X chromosome dosage dilemma (Lyon 1961). Her hypothesis derived from observation of the expression of X chromosome mutations with visible phenotypes and suggested that the problem of having two copies of the X chromosome in females and only one copy in males is solved in mammals by having one of the two female X chromosomes randomly inactivated for the life of the organism in each cell of early embryos. This is in contrast to flies, in which both X chromosomes are active in all cells, but at a reduced level compared with the single X present in males.

Almost simultaneously, studies of human and mouse chromosome abnormalities made it clear that the Y chromosome determines sex. It rapidly became apparent that in mammals sex determination and dosage compensation of the X chromosome occur by mechanisms fundamentally different from the classic explanations originally derived from Drosophila studies. Mammalian sex is determined by the presence or absence of a Y chromosome and not by the relative numbers of X chromosomes and autosomes, as occurs in flies. The crucial observation was that among mammals, XO individuals are females, whereas among flies they are males (albeit sterile). We now understand that the driving factor on the Y chromosome is the *Sry* gene, coding for a DNA-binding protein.

Biochemical genetics: The contemporary study of biochemical genetics in mice developed out of work in K. Paigen's laboratory on the β-glucuronidase gene (Paigen 1961a,b; Swank *et al.* 1973) establishing that there are genetic determinants closely linked to the structural gene for this enzyme deciding its tissue-specific pattern of expression, intracellular location, and responsiveness to hormonal regulation, thereby demonstrating for the first time the existence of mammalian genetic regulatory systems at the molecular level. During the 1960s and '70s a number of laboratories analyzed increasing numbers of genetic variants with altered enzyme activity, until a fairly comprehensive picture of the kinds of genetic variation likely to lead to changes in enzyme activity emerged. Two salient features were noted. One was the independent (so-called codominant) expression of the two alleles of a gene, a finding that was important in clarifying the physiological basis of recessive *vs.* dominant inheritance. The other was that, almost without exception, regulatory differences were *cis*-acting, mapping to the structural genes themselves. No regulatory systems akin to those discovered in *E. coli* were found. It will be interesting to see how our rapidly evolving abilities to study mammalian regulation at the molecular level modify these insights.

Mammalian physiology: The last 25 years have also seen the steady accumulation of physiologically and biochemically interesting mutants of the mouse, mutants that allowed mammalian geneticists to enter entirely new areas of research. Many came from The Jackson Laboratory, where mouse handlers in the production department were trained to recognize and save any mouse showing exceptional appearance or behavior; from the MRC Radiobiology Unit (now the Molecular Genetics Unit) at Harwell; and from the observations of numerous investigators elsewhere. There ensued a steady flow of useful new mutants with immune deficiencies, endocrinological defects, blocks in specific differentiation pathways such as hematopoiesis, and neurological and behavioral abnormalities of all kinds. All of this was in addition to a variety of mutants whose physiological bases at that time could only be guessed (Green 1981). The early analysis of mutants provided important genetic as well as physiological insights. One with far-reaching implications was the demonstration by Douglas Coleman and Katrina Hummel of the importance of the genetic background and the modifier genes it may contain on the expression of a single major locus determining a pathological trait (Hummel *et al.* 1972). They found that the *obese* and *diabetic* mutations, which produced quite different phenotypes in the two inbred strains in which they arose, actually produced the same phenotype if they were present in the same genetic background. This observation, the importance of strain background and modifier genes, has been observed repeatedly and, indeed, has become a major theme in contemporary experimentation. Coleman (1978) went on to show by parabiosis experiments that, although the two mutations gave the same phenotype, they were physiologically quite distinct. *Obese* determines a circulating satiety factor (later identified as leptin) and *dia-*

betic determines its site of action (later identified as the leptin receptor).

THE MOUSE AS A GENETIC SYSTEM

The development of the mouse as a genetic system for the analysis of mammalian biology was driven by research requirements.

Inbred strains: The first major development and the one that determined the course of mouse genetic research more than any other was, of course, the development of inbred strains of mice. Beginning with Little's first crosses in 1909, workers had been continuously developing new inbred strains, until by 1980 over 300 such strains existed (Staats 1980). Many of the most commonly used strains originated in the 20 years following Little's initial breeding efforts as a response to the need for genetically uniform stocks in the study of the cancer problem. In no other eukaryote have such a variety of genetically uniform stocks been available as the starting point for genetic work. The genotypic and phenotypic diversity across these strains is quite remarkable, often exceeding that of the entire human population and serving as a starting point for the identification of the underlying genetic elements. The sources of this variation are likely twofold. The common laboratory mouse is not, strictly speaking, a species in the Linnaean sense, but rather a mixture of genomes from at least four species and subspecies, if not more. It is likely that, in the course of laboratory-directed brother-sister matings, sets of once compatible alleles at multiple genes were disrupted and arbitrary new sets were created. And all of the buffering effects of heterozygosity were removed when strains were made completely homozygous. Although this variation was not created intentionally, it is now of great utility, and a phenome project has developed to characterize and record this diversity for its scientific utility (http://www.jax.org/phenome).

Genetic maps: Every genetic system ultimately rests on the availability of a useful set of "markers," genes or DNA sequences whose alleles can be conveniently typed in crosses to track the inheritance of chromosomal regions. The map, describing the linear arrangement of these sites along with estimates of the distances between them, is an essential genetic tool. Together, the markers and map allow us to locate new genes and manipulate them in experimentally useful ways. To the outsider, the geneticist's obsession with markers and maps may appear amusing, even pedantic, but the insider knows that we live by our markers and maps. The more complete and detailed these are, the more precise and elegant our efforts.

The first genetic markers of the mouse go back to antiquity. The term for a spotted mouse appears in the earliest Chinese lexicon dating back to 1100 BC, and waltzing mice have been known since 80 BC. For 1300 years, beginning in the fourth century AD, the Chinese government kept records of the finding of wild albino mice. In Japan, the mouse was admired as the symbol and messenger of the God of Wealth, Daíkoku, and old Japanese woodcuts clearly show such familiar mouse mutations as albino, non-agouti, dominant and recessive spotting, and pink-eyed dilution. These ancient mutations, preserved by mouse fanciers, provided the earliest markers of mouse genetics.

In 1915, Haldane, Sprunt, and Haldane described the first genetic linkage in the mouse, between albino and pink-eyed dilution (Haldane *et al.* 1915), to create linkage group I, which in later years was located to mouse chromosome 7. Initially, progress was slow; it was 12 years to the next linkage, and by 1935 only 11 markers had been collected into five linkage groups. But mapping efforts continued to accelerate, and for a long time the map grew exponentially with a doubling time of about 8 years. Mary Lyon (1990) has provided an illuminating description of these efforts. Initially, the maps were assembled by Margaret Dickie, but for many years the cartographer of this effort was Margaret C. Green, who patiently collated the accumulating data and annually revised the map.

The genetic markers came in three waves. Initially, there were morphological mutants whose changes in coat color or skeletal characteristics were obvious to the naked eye. Then came the biochemical variants, primarily alternate electrophoretic forms of enzymes that could easily be stained in gels. Finally, we saw the introduction of DNA sequence polymorphisms that can be detected with molecular technologies, which in the post-1980 period took us to a doubling time of 2–3 years. The first molecular markers were restriction fragment length polymorphisms (RFLPs), then simple sequence length polymorphisms (SSLPs), and finally single nucleotide polymorphisms (SNPs). Several million SNPs are present in the mouse (and human) genomes, providing an inexhaustible supply of densely spaced markers. Now, with the mouse genome sequence virtually complete, we can know their physical as well as genetic location.

Assigning genetic linkage groups to physical chromosomes occurred very rapidly once the requisite technical advances had occurred. In essence, making these assignments involved three experimental steps. First, cytogenetic techniques, especially quinacrine staining, were developed, enabling each chromosome to be recognized by its unique banding pattern. Then a series of chromosome rearrangements were obtained. These were either translocations that produced new physical connections between parts of chromosomes or chromosome fusions that attached two previously separate chromosomes. Finally, genetic crosses were carried out to determine which linkage groups were affected in each case. Outstanding among the laboratories involved in the tedious work of finding and characterizing rearrangements were the groups of T. C. Carter, Mary Lyon, and A. G. (Tony) Searle at Harwell, England. Much of

the work of correlating linkage groups with physical chromosomes (Francke and Nesbitt 1971; Nesbitt and Francke 1971; Miller and Miller 1972) was done in the laboratories of D. A. and O. J. Miller. Eva Eicher, who provided the first such attachment, has provided an intriguing history of the multiple efforts (Eicher 1981). The process of assigning all 20 linkage groups to chromosomes was completed by 1980.

Congenic strains: As already mentioned, Snell, in 1948, had introduced the concept of congenic strains into his studies of histocompatibility genes as a way of examining one gene at a time. Nowadays, so-called "speed congenics" can be constructed in about four generations by using genome-wide marker scans to take advantage of chance variation among backcross offspring to minimize the transmission of unwanted donor strain genes.

Recombinant-inbred lines: Constraints of generation time and population size originally limited genetic mapping efforts in the mouse. Later, the development of recombinant-inbred (RI) lines drastically increased these capabilities. The first use of such lines was reported by Bailey in 1971 (Bailey 1971), following up on a theoretical suggestion published 40 years earlier by J. B. S. Haldane and C. H. Waddington. The basic principle is straightforward. Two mouse strains are crossed, and from the F_2 generation, mating pairs are used to establish a new set of inbred lines by repeated generations of brother-sister matings. Within a line, each pair of chromosomes is homozygous for a mosaic of alternating DNA stretches derived from the two parents, and each of the new lines has a randomly different mosaic arrangement. In any set, the number of recombinant-inbred lines that are concordant for the segregation of two genes will be greatest when the two genes are very close to each other, and the degree of discordance is a measure of the distance between them. On average, closely linked markers show a fourfold increase in the apparent genetic distance between them because of the multiple opportunities for recombination over the course of inbreeding.

The elegance of the RI strain approach to mapping becomes apparent when we realize that each of these new inbred lines can be maintained indefinitely as the equivalent of an "immortal" segregant in a cross; a new gene tested for its segregation pattern now can be compared for genetic linkage with every gene that was ever scored by any laboratory in the same set of strains, and it can eventually be compared for linkage with any gene that is tested in the future. Initially, this approach was carried forward extensively by Ben Taylor (1978) and since then has been widely adopted. Over time, approximately 20 sets of recombinant-inbred lines arising from various pairs of progenitor strains were constructed and mapped for hundreds of markers (http://www.informatics.jax.org), making it quite probable that, when a new gene is tested for its segregation pattern, a genetic linkage and map position will be forthcoming.

Today, although any DNA sequence can be mapped instantly by reference to the mouse genomic sequence, RI resources still have a powerful utility in mapping the genes underlying phenotypes whose molecular basis is still unknown and are especially useful for complex phenotypes, such as developmental processes, regulatory phenomena, or disease progression, that cannot be determined on a single mouse. Such phenotypes can be determined across multiple animals within each member of a set of RI lines, searching for concordant distribution with previously typed molecular markers. For a single-gene effect, typing 14 or more lines is enough to provide a defined map location with a resolution of a few centimorgans.

Variations on the recombinant-inbred lines: Peter Demant, in an effort to reduce genetic complexity when multiple genes underlie a phenotypic difference, in his case tumor susceptibility, extended the basic concept of RI lines by constructing RI lines he called recombinant congenics, in which one parent contributes 1/8 and the other 7/8 of the composite genome (Demant and Hart 1986). In yet another variation, Ariel Darvasi has suggested construction of "advanced intercross lines," in which multiple generations of random mating precede interbreeding as a means of increasing recombination and hence the resolving power of genetic crosses (Darvasi and Soller 1995).

Chromosomally engineered lines: Several additional approaches have been developed to provide a more orderly, less random means of assigning genetic determinants to phenotypes. Although developed post-1980, it is appropriate to mention them here. One is chromosome substitution lines (called consomics), in which one chromosome at a time in a recipient strain is replaced by its homolog from a donor strain, a strategy first carried out by Jean-Louis Guénet, who introduced chromosomes from *Mus spretus* into a *M. musculus* laboratory mouse strain. Another, which reduces the size of introgressed DNA even further, is the construction of a set of congenic strains carrying pieces that systematically cover the entire genome, each about one-fourth of a chromosome in size.

THE WINTER OF 1980–1981

Numerous historical accounts describe various aspects of this classical period of mouse genetics to which the interested reader is directed for further insight (Little 1941; Heston 1949; Staats 1966; Potter and Lieberman 1967; Keeler 1973; Klein 1975; Morse 1978). Then, at the end of 1980, in a period of a few months, an entirely new era in mouse genetics began, with the creation of the first transgenic mice, initiated by the abrupt and then continuing entry of molecular biological techniques into what had, until then, been a

classical genetic system. What ensued was an explosion of knowledge when a myriad of new biological and molecular insights appeared over the following years. Although certainly built on the past, the new science quickly developed a life of its own and deserves its own chapter.

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