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9

Genetic Studies with *Arabidopsis:* A Historical View

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In recent years, *Arabidopsis* has become a most popular tool for plant biological studies. Although it is well suited for a wide range of research areas, we focus primarily on its use for genetic analyses. It is often heard: *Arabidopsis genetics*, but we should rather say *genetics with Arabidopsis*. The interest is not in the specificities of this plant but, rather, in what it can reveal about basic biology. The primary advantages of *Arabidopsis* for studying basic biological phenomena (Rédei 1970, 1975a, 1992; Meyerowitz 1987, 1989; Somerville 1986, 1989; Rédei and Koncz 1992) were first summarized by Laibach (1943).

In comparison, Mendel's peas were very advantageous in the 19th century because spontaneous recessive variants were available in this autogamous plant, and the second generation could be classified within the pods of the F_1 plants. *Drosophila* has a 2-week life cycle and can be raised in large numbers in small milk bottles, and the polytene chromosomes of the salivary glands display 5000 landmarks. Genetic segregation in maize can be followed by the large number of individual kernels immobile on a single cob. In addition, at the pachytene stage, the extended chromosomes display discrete chromomeres. Crossing is easy because about 50 million pollen grains may be released by a single monoecious plant. Some principal advantages of *Neurospora* are the linear arrangement of the meiotic products in the asci and the less than 2-week life cycle, with vegetative cultures requiring only 4–5 days. Yeast (*Saccharomyces cerevisiae*) can be manipulated similarly to prokaryotes because the size of individual cells is only a little larger than that of bacteria; both haploid and diploid phases are available, and its life cycle is barely longer than 1 hour under most favorable conditions. The approximate genome size of these organisms varies greatly: maize 7×10^9 bp, *Drosophila* 1.6×10^8 bp, *Arabidopsis* 9×10^7 bp, *Neurospora* 4.2×10^7

bp, yeast 1.4 x 10^7 bp, *Escherichia coli* 4.5 x 10^6 bp.

Sturtevant (1971) was wise in pointing out that the right choice of a genetic organism depends on the nature of the problem, the historical time, and the experimenter's skill. We believe that *Arabidopsis* may be the best choice for many at the end of our century and beyond.

ARABIDOPSIS: A LATE-COMER TO FORMAL GENETICS

Botanical description of *Arabidopsis* began with the Saxonian physician Johannes Thal, who identified this species before Linnaeus (1753) listed it as *Pilosella siliquosa minor*. During the centuries that followed, several other names were given to this monotypic genus (Rédei 1970). The taxonomic status of *Arabidopsis* is somewhat controversial (Berger 1968). *Arabidopsis suecica* had been renamed to *Hylandra suecica* by Löve (1961) because Hylander (1957) suggested that this species is an amphiploid of *Cardaminopsis arenosa* and *Arabidopsis thaliana*. All early efforts to produce an actual hybrid failed because *C. arenosa* (2*n*=32) is probably an autotetraploid and the *Arabidopsis* (2*n*=10) parent used was diploid. Měsíček (1967) successfully crossed *C. petraea* (2*n*=16) with *Arabidopsis* and obtained a sterile hybrid. Rédei (1974a) obtained fertile (2*n*=26) hybrids of *C. arenosa* (2*n*=32) and tetraploid *Arabidopsis*. Thus, a synthetic *H. suecica* was obtained. However, the problem remained, because the fertile hybrid did not resemble *H. suecica*, as expected. Rédei also obtained trigeneric (and other complex) hybrids with variable fertility. Yet, the evolutionary relationships remained unresolved; perhaps future molecular studies will shed more light on the origin of these species.

The first Mendelian segregation studies with *Arabidopsis* were conducted during World War II by Reinholz (1945). Mapping of genes started belatedly in *Arabidopsis*. The first linkage information, involving 21 loci, was obtained by Rédei and Hirono (1964). As expected, the number of linkage groups exceeded the chromosome number because syntenic gene clusters, far apart, recombined freely. To overcome this problem, trisomics were developed (Lee-Chen and Bürger 1967; Lee-Chen and Steinitz-Sears 1967). These permitted in *Arabidopsis* a correlation between genetic maps and chromosomes and facilitated the chromosomal assignment of genes (see Rédei et al. 1988). On the basis of double reduction frequencies, the relation of some genes and centromeres could be deduced (Lee-Chen and Steinitz-Sears 1967; Sears and Lee-Chen 1970). McKelvie (1965) reported a linkage group of about 150 map units, and later Koornneef et al. (1983) developed mapping information for all five chromosomes with a total length of about 500 map units. Hirono (1964) developed mathematical procedures based on the relationship between marker transmission, distorted segregation ratios, and map distances, thereby localizing deletions within the genetic map. Li (1968) simplified the procedure by considering the reduction of transmission through only one of the sexes and still obtained good estimates on the relative position of deficiencies. For several years, *Arabidopsis* geneticists relied on the product ratio method for calculating linkage intensities (Fisher and Balmakund 1928; Stevens 1939). The product method is fully efficient and gives estimates similar to those obtained by the maximum likelihood method even if the transmission of both recessive markers is reduced, but not when only one is afflicted (Bailey 1961). Both methods were developed by Fisher, but the so-called maximum likelihood procedure is considered superior. Linkage intensities were then converted to map units by either Haldane's (1919) or Kosambi's (1944) mapping functions; the former was more aesthetic, the latter perhaps more practical. In higher plants, mapping functions were first generally used in *Arabidopsis*. To estimate linkage, including restriction fragment length polymorphisms (RFLPs), the MAPMAKER and the JoinMap computer programs are used today (Stam 1993). These computer methods are based on the LOD scores and estimates by maximum likelihood, as originally developed for human genetics by Morton (1962).

GENETIC NOMENCLATURE

Gene symbolization began with the development of *Drosophila* and maize genetics. When new organisms, such as *Neurospora*, *E. coli*, and *S. cerevisiae* were introduced, the nomenclature was modified to meet special needs (Boyes et al. 1973). The *Arabidopsis* research beginning in the 1950s did not opt for a special symbolism until the 3rd International Meeting on *Arabidopsis* at Michigan State University. Unfortunately, the term "ecotype" is still incorrectly used in the literature. Ecotype (Turesson 1922) is a genetically ambiguous term, because, despite the homogeneity of the genetic basis of some of the adaptive traits, the genetic background may vary, as was obvious with the original Landsberg "race" (Rédei 1992). Columbia wild type and the so-called Landsberg *erecta* were both isolated from Laibach's Landsberg ecotype, and except for the presence of the X-ray-induced *er* mutation, their RFLP maps are obviously not identical. In addition, *er* may have several "non-wild-type" alleles and rearranged nucleotide sequences because of the exposure to ionizing radiation in 1957.

CHROMOSOMAL THEORY OF INHERITANCE AND *ARABIDOPSIS*

Hybridization studies with plants originated before the nature and function of the gametes were fully understood (Stubbe 1965). The role of the nucleus in heredity and chromosomal mechanics (Coleman 1965) developed steadily during the period between Mendel's discovery (1866) and his rediscovery in 1900 (see Rédei 1974c). To the satisfaction of botanists, the terms pro-, meta-, ana-, and telophase were coined by Strasburger (1884). Strasburger was the major professor of Friedrich Laibach at the University of Bonn. Laibach became the forefather of *Arabidopsis* research by following his mentor's footsteps to study experimentally the continuity of chromosomes. Laibach (1907) used *Arabidopsis* to gain more insight into the problem. Most crucifers display heterochromatic bodies in their interphase nuclei. Laibach found that in the somatic cells of *Arabidopsis* there are 10 prochromosomes, corresponding to the $n = 5$ number of chromosomes observed cytologically during meiosis. He concluded that Mendelian inheritance can be explained on the basis of behavior of chromosomes. In contrast to Laibach, Morgan was very critical of Mendelism, until he discovered the white-eye gene in *Drosophila* in 1910. Thus, at the dawn of genetics, the work with *Arabidopsis* was ahead of that in *Drosophila* regarding the mechanism of heredity.

Laibach also made another important conclusion in 1907. The size of the *Arabidopsis* nuclei appeared to be only about one third of that in *Brassica*. Yet, the former species does not have fewer functions, thus indicating to Laibach that the total amount of chromatin may not be necessary for normal performance. The chromosomes of *Arabidopsis* are smaller than those of other organisms. This might have caused the delay in acceptance of *Arabidopsis* in an era when cytogenetics was prevalent. With the old cytological staining techniques, little was detectable about the structure of the *Arabidopsis* chromosomes. Today, Giemsa C-banding, fluorescent staining, and in situ hybridization permit high-resolution studies in *Arabidopsis* (Ambros and Schweizer 1976; Maluszynska and Heslop-Harrison 1991).

Laibach in *Sisymbrium strictissimum* observed somatic association of the chromosomes. This is apparently the second such observation in plants after Strasburger (1904). Somatic association of chromosomes of *Arabidopsis* was confirmed later (Steinitz-Sears 1962). This may have facilitated the premeiotic exchanges of linked markers in *Arabidopsis* (Hirono and Rédei 1965). In comparison, somatic recombination was first demonstrated in *Drosophila* by Stern in 1936. *Arabidopsis* body sectors occasionally contribute to the inflorescence, and, thus, somatic cross-over products can be recovered in seed progeny. The experiments

showed that the mechanism of exchange in somatic cells is, however, not identical to that in meiosis, because the exchanged strands generally displayed reduced transmission.

Chromosomal aberrations in *Arabidopsis* were first demonstrated cytologically in the early 1960s. Tetraploidy and hexaploidy were first observed in *Arabidopsis* by Rédei (1964), and this material facilitated the isolation of the first set of trisomics (Steinitz-Sears 1963). Trisomics were also isolated by Röbbelen and Kribben (1966) and used for centromere mapping (Lee-Chen and Steinitz-Sears 1967; Sears and Lee Chen 1970; Koornneef 1983). Bouharmont (1965) described tetra-, hexa-, and octaploid *Arabidopsis* obtained by radiation and colchicine. Systemic endopolyploidy was observed by Galbraith et al. (1991). Translocations were induced in *Arabidopsis* (Sree Ramulu and Sybenga 1985) and used for mapping of breakage points (Koornneef et al. 1982b), as was done in maize (Brink and Cooper 1931).

NUCLEAR GENOME SIZE AND STRUCTURE

Sparrow et al. (1972) examined Feulgen-stained nuclei of *Arabidopsis* by cytophotometric techniques and concluded that the genome size is 1×10^9 bp. Now, this appears too high (Schmidt and Dean 1992), yet these data proved that *Arabidopsis* has less DNA in its nucleus than other angiosperms. Leutwiler et al. (1984), using reassociation kinetics, arrived at an estimate of 7×10^7 bp that was recently revised to about 8×10^7 to 10×10^7 bp with a G+C content of 41.8% (Meyerowitz 1992). *Arabidopsis* has only about 2–5 times as much DNA as the genetically most-used ascomycetes, and only about 20 times more than *E. coli*. Pruitt and Meyerowitz (1986) have demonstrated very low redundancy in the *Arabidopsis* genome. The repetitive component is about 30%, leaving 65–80 Mbp to low-copy-number components. By mutation studies, the minimum number of genes of *Arabidopsis* was estimated at about 28,000 (for review, see Rédei and Koncz 1992). Thus, approximately 2,300 bp may be allocated to an "average" individual gene, including introns and regulatory sequences. Although this may be an underestimate, so far, the putative size of the genome and the number of genes are in reasonably good agreement. So far, about 0.2–0.3% of the transcribed DNA has been sequenced. Thus, a larger fraction of the genome is known in *Arabidopsis* than in any other higher plant. *Arabidopsis* has similar codon usage as other dicots. At the third position, G+C is more frequent when at the second place there is an A or a T. *Arabidopsis* also appears to use the XCG codons more frequently than other dicots (Gasch et al. 1992). These differences may not be significant because of the relatively

small number of genes sequenced, or they may indicate the frequency of methylation, and/or differences in the reliance on particular functions.

MUTAGENESIS OF *ARABIDOPSIS*

Mutation Rates

The availability of genetic variation is the most important requisite for inheritance studies despite Linneaus's famous admonition to his students: "*varietates levissimas non curat botanicus.*" The frequency of overall spontaneous mutations in *Arabidopsis* is low and varies from 0.01% to 3% as measured by the various investigators. These figures are affected by the genes studied, the method of estimation, and the rigor of the classification (Rédei and Koncz 1992). Spontaneous mutation frequencies at specific loci have been recorded (Rédei 1982a), and induced mutation rates for 15 loci of *Arabidopsis* have also been calculated (Koornneef et al. 1982a). Spontaneous mutation rates are greatly influenced by the power of the genetic resolution. If we accept the gene number of *Arabidopsis* as about 30,000, the locus-specific average mutation rate appears to be in the 10^{-7} range. The gene number estimate used is within the range of that of other plants, inferred from single copy sequences (Meyerowitz 1992). For comparison, the latest estimate of human gene number is about 75,000 (Macilvain 1993). The low spontaneous mutability of *Arabidopsis* explains why mutations at "good genes" are rare in natural populations, unlike *Drosophila* and maize, where indigenous active transposable elements may rapidly reorganize the genome. The low mutability might have been the cause of the delays in using *Arabidopsis* for classical genetic studies.

Mutagenesis Techniques

Despite the low spontaneous mutability, *Arabidopsis* responds well to mutagens. Reinholz (1945) found that even low doses of X-rays yielded 36 characterized mutations in a population of 1,600 families. This frequency, on a genome basis, corresponds to an overall mutation rate of about 6×10^{-3}. This was thus an increase by three to four orders of magnitude over the spontaneous rate. Reinholz's experiments also revealed that X-ray doses up to 2,000 kR applied to dry seeds failed to prevent germination. Similar experiments carried out by γ-radiation, combined with measurements of the nuclear volume, also suggested that *Arabidopsis* has the lowest DNA content among angiosperms (Sparrow et al. 1972). Practically all *Arabidopsis* mutants obtained before 1962 were induced by ionizing radiation. The majority of these were considered to be point mutations, because they were not associated with detectable chromosomal alterations and displayed quasi-normal recombination rates and meiotic transmission. The effect of X-rays on the genome was controversial for decades. Some of the *Drosophila* geneticists, including H.J. Muller, considered many of the X-ray mutations to be indistinguishable from the spontaneous ones, whereas the maize geneticists, including L.J. Stadler, concluded that apparently none of the X-ray mutations represented minute intragenic alterations and therefore were of minimal significance for the study of the gene. Today, X-ray mutations have become valuable tools following the development of the genomic subtraction method for gene isolation (Shirley et al. 1992; Sun et al. 1992). This type of gene isolation technique is particularly adaptable to *Arabidopsis* because of its small genome size, and it was used for the first time among higher eukaryotes. These recent studies lend support to Stadler's (1944) conclusion that most X-ray mutants indicated a loss of genetic material. Some other mutants of *Arabidopsis* obtained by ionizing radiation may be true base substitutions, just as appeared to be the case in *Neurospora* (Malling and de Serres 1973).

It took almost 20 years after the discovery of the mutagenic effect of X-rays to induce mutations in *Arabidopsis*. The use of chemical mutagens was also somewhat delayed (for review, see Rédei and Koncz 1992). Ethylmethane sulfonate (EMS), an alkylating agent, was first applied to *Arabidopsis* by Röbbelen (1962a), and McKelvie (1963) used EMS and ethyleneimine. EMS turned out to be a real "supermutagen," a term coined by Rapoport et al. (1946) for chemicals that on a molar basis have low toxicity yet are highly mutagenic without causing much chromosome breakage. Müller, Gichner, and Velemínsky tested hundreds of compounds for mutagenicity in *Arabidopsis*, and they found several mutagens of about the same efficiency as EMS (for review, see Rédei 1970). An assay for mutations was developed by Müller (1963), based on exactly the same principle as Mendel's use of the yellow versus green, wrinkled versus smooth, embryo characters to identify segregation in the pods of heterozygotes. This procedure is valuable for the rapid identification of mutagens, and indirectly carcinogens, with about 88% effectiveness (Rédei et al. 1980). Reducing the costs of mutation experiments by effective planning, as well as the statistical bases of economical mutant screening in *Arabidopsis* and other autogamous plants, were worked out (for review, see Rédei and Koncz 1992). *Arabidopsis* was the first plant in which mutation rate was expressed on a genome basis in a generally applicable form, and, thus, mutation rates of homoeologous genes could be compared across phylogenetic boundaries (Li and Rédei 1969a).

Mutant Selection Techniques

A most effective selective mutant isolation technique involves allyl alcohol (AA), which is converted to highly toxic acrylaldehyde by alcohol dehydrogenase (ADH). Mutants lacking ADH thus survive, whereas the wild type dies on AA. This type of mutant isolation was first applied to yeast, then adapted to maize pollen, and proved to be successful also in *Arabidopsis* (Megnet 1967; Schwartz and Osterman 1976; Jacobs et al. 1988). *ADH* became the first cloned and sequenced *Arabidopsis* locus (Chang and Meyerowitz 1986), and base substitutions were first identified in *adh* alleles (Dolferus et al. 1990).

Somerville and Ogren (1982) developed very successful selection schemes in a controlled carbon dioxide atmosphere for screening of photorespiratory mutants. By 1986, *Arabidopsis* emerged as a premier organism in the field (Somerville 1986), attesting to the joint power of genetic selection, biochemistry, and molecular biology. The efficiency of selection was shown by the isolation of sulfonylurea herbicide-resistant mutants by plating up to 10,000 seeds per petri dish (Haughn and Somerville 1986). Although this population is smaller than in bacterial mutagenicity tests (10^8 cells), it is much larger than the approximately 500 kernels per ear of maize. In addition, the *Arabidopsis* screening may be repeated several times per month (for reviews, see Rédei 1970, 1974b; Meyerowitz 1987; Rédei and Koncz 1992 and references therein).

GENETIC TRANSFORMATION OF *ARABIDOPSIS*

Genetic transformation of higher plants has a controversial history. Ledoux and Huart (1961) considered the introduction of various macromolecules into growing barley embryos. Subsequently, the genetic correction of thiamine auxotrophs of *Arabidopsis* was reported after treating seeds with bacterial DNA containing the thiamine gene cluster (Ledoux and Jacobs 1974). The transfer and expression of the β-galactosidase gene of *E. coli* has been reported under the term *transgenosis* by Doy et al. (1973). The correction of the thiamine deficiency carried out in the Ledoux laboratory could not be confirmed by either genetic or molecular analyses (Lurquin 1976; Rédei et al. 1976). "If the work is critically evaluated, one is tempted to find more explanations than corrections by exogenous DNA" (Hess 1977).

Direct DNA transfer to plant protoplasts succeeded by employing Ti plasmid DNA (Davey et al. 1980; Draper et al. 1982; Krens et al. 1982). *Arabidopsis* protoplasts were first transformed by plasmid DNA in 1989 using polyethylene glycol treatment (Damm et al. 1989). Delivering functional DNA segments into plant cells by microprojectiles was discovered by Klein et al. (1987), and the method was successfully applied to *Arabidopsis* by Seki et al. (1991). Although eventually protoplast transformation became the most important means of gene transfer during the 1980s, today gene transfer vectors based on the T-DNA of *Agrobacterium* Ti or Ri plasmids are used preferentially. The plant pathogen *Agrobacterium* induces crown gall by a plasmid, called TIP (tumor inducing principle) by Braun (1947), before anything was known about its substance. In 1974, the laboratory of Schell demonstrated that the tumor induction by *Agrobacterium* is due to its large Ti plasmid (Van Larebeke et al. 1974). Chilton et al. (1977) have shown that crown-gall formation is the direct consequence of T-DNA incorporation into the plant genome. An *Arabidopsis* tumor line (Aerts et al. 1979) provided important basic information on the T-DNA structure (DeBeuckeleer et al. 1981). In a systematic approach, the pGV3850 vector was constructed (Joos et al. 1983; Zambryski et al. 1983) by deletion of oncogenes from the natural nopaline Ti plasmid pTiC58. The new plasmid carried pBR322 sequences, allowing homologous recombination between the Ti plasmid and common *E. coli* cloning vectors. This Ti plasmid vector was suitable for introduction of any gene into plant cells. In the same laboratory, within the same year, antibiotic resistance genes (kanamycin, methotrexate, chloramphenicol) of bacterial transposons were linked to the nopaline synthase promoter and polyadenylation signals to facilitate large-scale selection of transgenic plant cells (Herrera-Estrella et al. 1983a,b). Simultaneously, Schilperoort's laboratory constructed a non-oncogenic Ti plasmid vector (Hille et al. 1983).

Transformation of *Arabidopsis* with disarmed Ti plasmid vectors (Hooykaas 1989; Walden et al. 1990) started relatively late. The first successful transformation of *Arabidopsis* was reported by the Monsanto group (Lloyd et al. 1986). The same year, transgenic *Arabidopsis* plants, produced by infection of leaves, stems, and roots with different binary vectors, were obtained (An et al. 1986; Rédei et al. 1988). A root transformation technique was developed by Valvekens et al. (1988). Feldmann and Marks (1987) infected seeds of *Arabidopsis* (Wassilewskija) with a C58 *Agrobacterium* strain carrying the cointegrate vector pGV3850::1003 (Velten et al. 1984) and obtained large numbers of transformants. In the laboratory of Pelletier and Caboche, an extremely efficient procedure has been developed for the transformation of soil-grown *Arabidopsis* by infiltration with agrobacteria (Bechtold et al. 1993).

The advantages of transformation are manifold: It can be used to tag genes, as well as to identify cloned genes by reintroducing them into mutant hosts. From the viewpoint of basic genetics, insertional

mutagenesis was probably the most important gain from transformation. Insertional mutations are quite common in plants, and many of the recessive genes contain inserts. One of the most famous plant genes, the *r* allele of peas, responsible for the wrinkled-seed character studied by Mendel (1866), contains an insert of about 0.8 kb showing homology with the *Ac* (maize), *Tam3* (snapdragon), and *Tpc1* (parsley) transposable elements (Bhattacharyya et al. 1990). In *Arabidopsis*, silent retrotransposons were observed in several ecotypes (Voytas and Ausubel 1988; Voytas et al. 1990; Peleman et al. 1991). The *Tag1* element, recently discovered in *er* background, was mobilized in *Arabidopsis* after transformation with the *Ac* transposable element of maize. The authors concluded: "We think it unlikely that the *Ac* transposase directly mobilizes *Tag1*, as no *Ac* transposase binding site (AAACGG) is found adjacent to the inverted repeats of *Tag1* as it is in *Ac*" (Tsay et al. 1993).

T-DNA TAGGING

For gene tagging by insertional mutagenesis, two alternatives were used until 1993: T-DNA or alien transposable elements. Teeri et al. (1986) and André et al. (1986) tagged *Nicotiana* genes by promoterless *aph(3′)II* genes and generated in vivo fusions of reporter genes. In *Arabidopsis*, transcriptional and translational in vivo gene fusion vectors provided highly efficient gene tagging: About one third of the hundreds of transformants expressed the reporter gene (Koncz et al. 1989). Feldmann et al. (1989), using seed transformation, reported 36 different mutations that cosegregated with T-DNA. From thousands of morphological mutations obtained through seed infection, several have already been analyzed at various levels of depth (Herman and Marks 1989; Marks and Feldmann 1989; Yanofsky et al. 1990; Feldmann 1991; Oppenheimer et al. 1991). Using tissue culture transformation with a binary gene fusion vector, Koncz et al. (1990) have shown with a comprehensive analysis that T-DNA can indeed induce mutations by an insertion at the 3′ end of the *CH-42* locus. This analysis included genetic recombination with a resolving power of less than 10 kb and in vivo complementation of the T-DNA-induced *cs* mutation through retransformation by the wild-type gene.

GENE TAGGING BY ALIEN TRANSPOSABLE ELEMENTS

Zhang and Somerville (1987) introduced the *Mu1* mutator element of maize (Robertson 1978; Barker et al. 1984) into *Arabidopsis*. Although the transformation was successful, *Mu1* failed to increase the mutation rate in *Arabidopsis*. Van Sluys et al. (1987) introduced into *Arabidopsis* the *Ac* transposable element of maize using an Ri plasmid T-DNA vector. The *Ac* element (identical to *Mp*, described by Brink and Nilan 1952) was discovered by Barbara McClintock (1952) and isolated by Fedoroff et al. (1984). It was used first for transformation of alien (tobacco) cells by Baker et al. (1986). *Ac* induced no visible mutation in the first experiments with *Arabidopsis*, but the DNA analysis indicated excision and transposition of *Ac*. Schmidt and Willmitzer (1989) were first to genetically detect the movement of *Ac* in *Arabidopsis*. The vector, developed by Baker et al. (1986) and Coupland (1992), contained an *aph(3′)II* gene, inactivated by an *Ac* insertion in the 5′ untranslated sequences. Unless *Ac* left the leader sequence of this reporter gene, the transgenic plants stayed kanamycin-sensitive. In about 0.2–0.5% of the population, resistance was observed, indicating the excision of *Ac*. A similar procedure, using a streptomycin resistance gene (Dean et al. 1992), and *gus* (*uidA*) with the *Ac-Ds* (Bancroft et al. 1992), also indicated high *Ac* transposition in *Arabidopsis*. The transposed *Ac-Ds* elements tend to remain in the vicinity of their original insertion site in *Arabidopsis* (Bancroft and Dean 1993), as it was first observed in maize (Van Schaik and Brink 1959). The state of methylation of *Ac* apparently did not affect much the transposition frequency (Keller et al. 1992). The *En-I* system was also used with success to tag a male sterility locus (Aarts et al. 1993), and by application of the *Cre-Lox* site-specific recombination system of *E. coli*, high frequencies of chromosomal aberrations were obtained in *Arabidopsis* (Osborne et al. 1993).

GENETICS OF SOMATIC CELLS

Genetic study of somatic cells is of particular interest in low-fecundity multicellular organisms and/or without means of controlled matings. *Arabidopsis* has neither of these problems, and body sectors may develop into inflorescence tissue, thus allowing somatic chromosome exchanges to be analyzed in the generative offspring (Hirono and Rédei 1965). When plants heterozygous for eight "visible" markers were X-irradiated, all displayed somatic sectoring, indicating that the "visible" mutations are generally cell-autonomous and involve nondiffusible gene products (Rédei 1967).

Barski et al. (1960) used another approach to cell genetics: They fused different cultured mammalian cells. Later, the laboratory of Cocking (Power et al. 1970) fused plant protoplasts, and Carlson et al. (1972) produced interspecific tobacco hybrids by protoplast fusion. An *Arabidopsis*/turnip somatic hybrid was obtained by Gleba and Hoffmann

(1978). In animal cells, somatic hybridization by cell fusion (Ephrussi and Weiss 1965) became one of the most important tools for the analysis of synteny of genes. In plants, the lack of efficient means of chromosome elimination prevented the use of this approach.

Mutant isolation in haploid *Antirrhinum* cell suspension cultures was reported quite early (Melchers and Bergmann 1959), and by the 1980s a wide variety of mutants were claimed in plant cells (for review, see Maliga 1984). Resistance to metabolite analogs (Negrutiu et al. 1978) and nitrate reductase deficiency (Scholten and Feenstra 1986) were selected in suspension cultures of *Arabidopsis*. Through radiation induction, exogenous hormone-independence has been observed (Campell and Town 1991; Persinger and Town 1991). Protoplasts permit the large-scale transformation and regeneration of *Arabidopsis* cells (Damm et al. 1989) and gene replacement (Halfter et al. 1991; Altmann et al. 1992).

GENETICS OF CHLOROPLASTS AND MITOCHONDRIA

Röbbelen found that nearly 1 in 100,000 cells of *Arabidopsis* had two or more types of plastids, and after X-irradiation their frequency increased by two orders of magnitude (Röbbelen 1962b). The first plastid mutator gene was discovered in barley (Sô 1921), then the *iojap* mutation of maize was characterized (Rhoades 1943). Röbbelen (1964) discovered an X-ray mutation (*am*) that acted as a plastid mutator. The plastid mutations were maternally inherited until they were thinned out by selection. A similar mutation (*chm*) was obtained by Li and Rédei, and subsequently two additional alleles of the locus were discovered in chromosome 3 (Rédei 1973). Genes *am* and *chm* were never tested for allelism, but they do not appear identical (Rédei and Plurad 1973). By the removal of the mutator gene, apparently homoplastidic mutants could be fixed (Rédei 1975b). It is intriguing that genetic defects induced by *chm* were attributed to rearrangements in the mitochondrial DNA (Martínez-Zapater et al. 1992). Plastid gene recombination has not been observed yet in *Arabidopsis*, but in the unicellular green plant, *Chlamydomonas*, map construction based on genetic recombination of chloroplast genes has long been feasible (Sager and Ramanis 1970). Recently, image analysis permitted the screening for chloroplast mutants involved in control of plastid division and DNA replication (Pyke and Leech 1992).

GENETICS IN METABOLIC AND DEVELOPMENTAL PATHWAYS

The first auxotroph of any higher plant was discovered in *Arabidopsis* by Langridge (1955), and subsequently, Rédei's laboratory identified more than 200 mutations in several steps of the thiamine pathway. Fink's laboratory isolated the first amino acid auxotrophs of plants in *Arabidopsis* (for review, see Rédei and Koncz 1992). Space limitations allow the inclusion of only a few of the recent milestones.

Studies of cell cycle and signaling emerged by the late 1980s. Cell cycle regulatory genes, such as protein kinases, phosphatases, and cyclins, were identified first in yeast, *Xenopus*, and mammals, and are now found and studied also in *Arabidopsis* (see, e.g., Ferreira et al. 1991; Hemerly et al. 1992; Nitschke et al. 1992). An analysis of tubulin genes revealed that the small genome of *Arabidopsis* has at least six expressed α-tubulin genes and nine β-tubulin genes, more than the much larger mammalian genomes (Snustad et al. 1992). The studies of the central elements of signaling cascades revealed the existence of small GTP-binding proteins (Anai et al. 1991), the α-subunit of trimeric G proteins (Ma et al. 1990), several tyrosine-, serine/threonine-specific protein kinases (see, e.g., De Guen et al. 1992; Kohorn et al. 1992), and a rapidly increasing number of transcription factors acting on hundreds of different genes in *Arabidopsis*. Among these, the TATA-box-binding general transcription factor, TFIID, isolated from *Arabidopsis* became the first plant transcription factor with the crystalline structure determined (Nicolov et al. 1992).

As a part of impressive progress in studies of metabolic pathways, different techniques for isolation of lipid mutants were developed, and the function and regulation of many such mutants were characterized (Browse and Somerville 1991; Somerville and Browse 1991). Mutants in the phytohormone pathways became essential tools for studies of metabolism and signaling. Following the pioneering efforts of Maher's laboratory (Maher and Martindale 1980), a large number of mutants displaying auxin resistance, anomalous gravitropic response, and/or pleiotropic cross-resistance to auxin, abscisic acid, and ethylene were isolated and characterized (see, e.g., Pickett et al. 1990; Okada et al. 1991). In addition to several genes encoding putative auxin receptors (Palme 1992), the auxin resistance mutation, *axr1*, was cloned (Leyser et al. 1993). Because of the pioneering work of Koornneef et al. (1982c, 1984, 1985), the gibberellin biosynthetic pathway of *Arabidopsis* is well mapped by mutations, and major functions in the abscisic acid response are defined (Finkelstein and Somerville 1990; Talón et al. 1990). Genes *GA1* and *ABI3* are the first from these pathways that were characterized molecularly (Giraudat et al. 1992; Sun et al. 1992). The analysis of the ethylene biosynthesis and signaling pathways provides an example of how a complex signaling cascade can be effectively rationalized by the use of combined biochemical and genetic methods (for review, see Chang et al. 1993; Kieber et al. 1993; Kieber and Ecker 1993). Although a number of interesting mutations affecting cytokinin biosynthesis and/or

regulatory action were isolated (see, e.g., Moffatt et al. 1991; Su and Howell 1992), a closer insight into a signaling pathway(s) in *Arabidopsis* is still awaited. Many mutations influencing cytokinin action have a pleiotropic effect on the mechanisms involved in light response.

Various effects of light, other than photosynthesis, have been studied since the middle of the 19th century. Photoperiodism was discovered in 1918, phytochromes were identified in 1952 (Borthwick and Hendricks 1960). The first mutations affecting photomorphogenesis and photosynthesis in *Arabidopsis* were isolated in the 1960s. Mutants displaying long hypocotyl (*hy*) and etiolated or green color in light were isolated by Rédei (1965). Koornneef et al. (1980b) found five new loci including a series of *hy1* to *hy8*. Genetic dissection of photomorphogenic and skotomorphogenic responses advanced with great speed. New classes of regulatory mutants were isolated, such as the *det, cop,* and *blu* series (for review, see Liscum and Hangarter 1991; Quail 1991; Deng and Quail 1992; Deng et al. 1992; Chory 1993). Epistatic relations between these mutants facilitated the formulation of the first models of the pathways of light signaling (Chory 1992).

The *im* mutant causing red-light-dependent formation of white leaf sectors (Rédei 1963; Röbbelin 1968) has remained so far resistant to molecular approaches. Interestingly, the white leaf sectors of *im* can be suppressed by X-irradiation and azauracil without reverting the mutation. The white sectors appear to overproduce a ribonuclease and can be normalized by 6-azauracil, although the ultrastructure of plastids remains modified. Azauracil suppresses orotidylic acid pyrophosphorylase and inhibits orotydilic acid decarboxylase (Chung and Rédei 1974). Perhaps *im* will soon be better understood through progress in the characterization of ribonucleases of *Arabidopsis* (Yen and Green 1991).

Müller (1963) provided the first detailed study of the embryogenesis of *Arabidopsis*. Although the embryos of *Arabidopsis* are very small, the expression of approximately 80% of all "visible" mutations can be detected before germination of the seeds (Rédei 1981). Meinke and Sussex (1979) began to use lethal embryo mutations for the analysis of early development of *Arabidopsis*. By the early 1990s, more than 300 different mutations influencing morphogenesis, nutritional requirements, and homeotic changes were isolated and mapped (Jürgens et al. 1991; Mayer et al. 1991; Meinke 1991, 1992; Patton et al. 1991). From the dozen seed coat color mutations listed by Bürger (1971) and by Koornneef (1990), the *tt3* (dihydroflavonol-4-reductase), *tt4* (chalcone synthase), and *tt5* (chalcone flavonone isomerase) loci were molecularly characterized (Feinbaum and Ausubel 1988; Shirley et al. 1992). Complementation of the hairless phenotype of the *ttg* (*transparent testa*) mutation by the *R*

gene of maize has raised an intriguing question about complex regulatory interactions between anthocyanin biosynthesis, trichome development, light, and metabolic regulation (Lloyd et al. 1992). A large number of mutants affecting root and root hair development were collected (Schiefelbein and Somerville 1990), and methods were developed for the isolation of mutants with defects in geotropic and touch responses of root (Okada and Shimura 1990). Studies of cell lineages of the shoot apex (for review, see Rédei and Li 1969; Rédei 1970, 1992) were continued (Irish and Sussex 1992; Medford et al. 1992).

Laibach (1940, 1951) recognized that *Arabidopsis* is a long-day plant without a critical day length. Both early- and late-flowering mutants were observed by Reinholz (1945). At three loci, five different flowering time mutants were isolated by Rédei (1962a). These late-flowering mutants were demonstrated to flower very early in darkness in sugar-containing liquid media, as well as in the presence of halogenated pyrimidine nucleoside analogs. On the basis of this information, the conclusion was made that the onset of flowering in *Arabidopsis* is constitutively regulated in darkness, but under short-day conditions, a repressor is made that decays under continuous illumination; i.e., the process is under negative control (Rédei et al. 1974). These data, together with the characterization of a series of late-flowering mutants isolated by Koornneef et al. (1991), may provide the initial material for current approaches aiming at the isolation of genes regulating the process of photoperiodism and vernalization. Klaus Napp-Zinn, John Langridge, John Brown, and others contributed valuable information to this area in the early years (for review, see Rédei 1970).

Attention to flower differentiation dates back to Braun, who described the first *agamous* mutation in 1873 (cited by Yanofsky et al. 1990). Homeotic mutations *ap1* (McKelvie 1962), *ap2* (Koornneef et al. 1980a), *ap3* (Bowman et al. 1989), *pi* (Koornneef et al. 1983), *pin* (Gôto et al. 1987), *lfy* (Haughn and Somerville 1988), *sup/flo10* (Schultz et al. 1991; Bowman et al. 1992), and *tfl* (Shannon and Meeks-Wagner 1991) became central targets of developmental studies. Based on a simple genetic model (Meyerowitz et al. 1991), recent advances in characterization of the function of these genes provide insight into the complex regulatory interplay of functions determining cell fate and organ identity during flower development (Weigel and Meyerowitz 1993) and may be a "trendsetter," as Laibach predicted.

The process of fertilization and elements involved are also subjects of molecular genetic studies. The role and structure of the stigmatic surface is anatomically described (Elleman et al. 1992), and the early characterization of ovule and embryo sac (Vandendries 1909) is now well ex-

tended (Mansfield and Briarty 1991a,b). Sterile ovule mutants were isolated, and both ovule and megagametophyte mutations were observed (Robinson-Beers et al. 1992). These studies follow the earlier analysis of an unusual female gametophyte mutation characterized by lack of female transmission, significantly higher than 50% seed set, and the histological observation of twin megaspore tetrads (Rédei 1965). This feature permits megaspore selection when the tetrads are in opposite orientation and therefore produce 64% seed set in the complete absence of female transmission. The time course of microsporogenesis and cytochemical analysis of pollen development were also described (Polyakova 1964; Regan and Moffatt 1990). Androgenesis was induced by pollinating *Cardaminopsis arenosa* ($2n$=32) by diploid *Arabidopsis* (Měsíček 1971), and for safe identification of androgenic seedlings, a genetic construct was developed (Barabás and Rédei 1971). The frequency of androgenesis seems to be somewhat lower in *Arabidopsis* than in maize. In the latter, the frequency is increased by orders of magnitude through a single mutation (Kermicle 1969). Haploids can also be obtained in *Arabidopsis* from anther culture, although their use is so far very limited (Amos and Scholl 1978). Male gametophytic factors occur commonly after treatments with mutagens that cause chromosomal rearrangements and deletions (for review, see Rédei and Koncz 1992). These defects cause deficiency or excess of the recessive class, depending on the linkage phase of the breakage points. Male sterility caused by point mutations or insertions is characterized by high penetrance and expressivity in the male, but good fertility in the female organs (Van der Veen and Wirtz 1968; Aarts et al. 1993).

GENETICS OF POPULATIONS

Theoretical population genetics got off the ground with the recognition of the Hardy (1908) and Weinberg (1908) equilibrium. The law is based on panmixis, and almost all the theoretical developments since deal with panmictic populations. *Arabidopsis*, an autogamous species, did not fit well into the framework based on allogamy. Many of the theoretical solutions to autogamous populations deserve future studies. The topic of this section was reviewed by Rédei (1975a) and Griffing and Scholl (1991).

QUANTITATIVE INHERITANCE

Genetics of quantitative characters does not discriminate against the breeding system of *Arabidopsis* (Rédei 1975a; Griffing and Scholl 1991). Griffing and Langridge (1963) selected thus for phenotypic stability of 38 *Arabidopsis* ecotypes at six different environments. Later, an even more precise analysis of heterozygote advantage (Pederson 1968) followed. Competition studies were also conducted with a number of controlled variables (Griffing and Zsiros 1971). Langridge (1961) interpreted heterosis on the basis of interaction of temperature-sensitive alleles. Overdominance in isogenic background was demonstrated (Rédei 1962b), and biochemical evidence was provided on the basis of allelic complementation of temperature-sensitive pyrimidine genes (Li and Rédei 1969b). It was calculated that overdominance at larger numbers of loci cannot be maintained without danger of extinction, although at a few loci, it may be responsible for heterosis (Rédei 1982b). For a better understanding, the cloning of genes encoding quantitative characters will be required. Alternatively, a better insight into signal transduction mechanisms may help resolve the relations of epistasis, pleiotropy, and polygenic systems.

THE FUTURE OF *ARABIDOPSIS* AS A BIOLOGICAL TOOL

Predictions regarding the future of science are risky because basic science is concerned with the unknown. Friedrich Laibach (1965), the founder of research with *Arabidopsis,* was right by pointing out, "I am certain, the small *Arabidopsis*... will be a trendsetter." Laibach's prediction appears to have been fulfilled. The road to success was not easy, but the goal remained clear and the progress has been impressive.

The major contributions of *Arabidopsis* are in biochemical genetics and in the control of differentiation and development. In the future, the most significant progress may come on a broad front of basic biology. We can expect *Arabidopsis* to be the first higher plant to have its total genome sequenced. The functions of many more genes will be understood in *Arabidopsis* than in other higher plants. It is predictable that a new level of understanding will be gained on the coordinated system of genes involved in receiving and transmitting signals and executing instructions of the genetic blueprint. Although in the past, genetics was characterized by biochemical, morphological, and statistical type dissections, the future will permit an understanding of the functional integration of the genetic elements. In short, the major developments will come in developmental genetics. Yet, today, 30 years later, the question of Chargaff (1963) is still unanswerable: "Will man discover the 'molecular structure of God'?"

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We bequeath this review to the critics (as Goethe did with Faust) so they may have fun in finding the mistakes incurred by omission or judgment,

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