PNAS SPECIAL FEATURE: INTRODUCTION

Gregor Johann Mendel and the development of modern evolutionary biology

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This year we celebrate the 200th anniversary of the birth of Gregor Johann Mendel, who discovered the missing component of Darwin's evolutionary theory, the genetic mechanism of trait inheritance. The eight articles in this Special Feature collection cover various aspects of Mendel's life, his work, and his contribution to science, with a special focus on his impact in evolutionary biology. In this introductory paper, we provide the context for the eight papers, as well as summarize how Mendel's work has contributed to the development of modern evolutionary biology.

In *On the Origin of Species*, Charles Darwin (1) proposed what he called "descent with modification": what we now refer to as evolution through natural selection. Today, we can describe Darwin's idea as a theory that requires a population with individuals having the following three properties:

(a) Differential reproductive success: each individual produces, on average, more offspring than is needed to replace itself upon its death, thus typically resulting in competition among individuals such that not all individuals contribute equally to the next generation (the ecological component of Darwin's theory).
(b) Inheritance: traits that affect an individual's ability to survive to reproduce (fitness) are transmitted from parents to offspring (the genetic component).
(c) Variation: there is within-population variation in heritable, fitness-related traits (the population-genetic component).

When individuals compete for resources and vary in their competitive ability, heritable traits that affect fitness will in general change in frequency in the population when environmental conditions change. Prior to the publication of *On the Origin of Species*, Darwin dedicated years to thorough observation and careful experimentation to amass data from natural and domesticated populations, both on competition among individuals (the first property) and on phenotypic variation within populations (the third property). However, Darwin glossed over the second property of the theory's underpinnings: how heritable traits (and thus genetic variation) are passed on from one generation to the next. This was a significant omission given that the heart of the theory is the differential probability of between-generation transmission of variants according to their impact on fitness. Darwin struggled long and hard to understand what today we call transmission genetics (2), but ultimately in *On the Origin of Species* had to fall back on an ill-defined claim, derived from his experience as an experimental naturalist and as an animal and plant breeder, that like begets like. Genetics (3)*, then, was for Darwin a black box.

*The term "genetics" was termed by William Bateson in 1902 (3).

Darwin, his defenders, and his critics were all aware that no theory can be considered complete when a mystery, that black box, lurks at its heart. Some scientists proposed models of inheritance that in fact were incompatible with natural selection. Jenkin (4) pointed out, for example, that an intuitive understanding of inheritance, that offspring are a blend of their parents' characteristics, is inimical to natural selection. Blending inheritance, over generations, results in convergence on the population mean, eliminating in the process the distribution's extremes, and yet those extremes—the fastest running antelopes, say—are often what are being promoted by natural selection (5). In 1868, Darwin published his own thoroughly flawed attempt to model the interior workings of the black box, his "provisional hypothesis of pangenesis" (6).

Two years before Darwin's pangenesis theory appeared, Mendel (Fig. 1*A*) had published his now famous (but at the time ignored) results, but Darwin almost certainly never encountered them (2). Darwin, a recluse in his study at Down House, had other concerns [in 1871, for example, he published *The Descent of Man* (7)] and Mendel's promotion to abbot in 1868 severely curtailed his opportunities to do science and publicize his work. The two ideas—natural selection and Mendelian genetics—never had the opportunity to intertwine during their originators' lifetimes.

Mendelian inheritance is generally presented in the form of three laws (8):

(a) Dominance: inherited factors can be dominant or recessive, an individual carrying both a dominant and recessive factor will only show the dominant trait.
(b) Segregation: in a diploid organism, maternal and paternal inherited factors, referred to as alleles, are transmitted randomly to its offspring.
(c) Independent assortment: inherited variants affecting different traits are inherited to the next generation independently of one another.

Collectively, these three laws (which are expounded below) replace and explain Darwin's black box.

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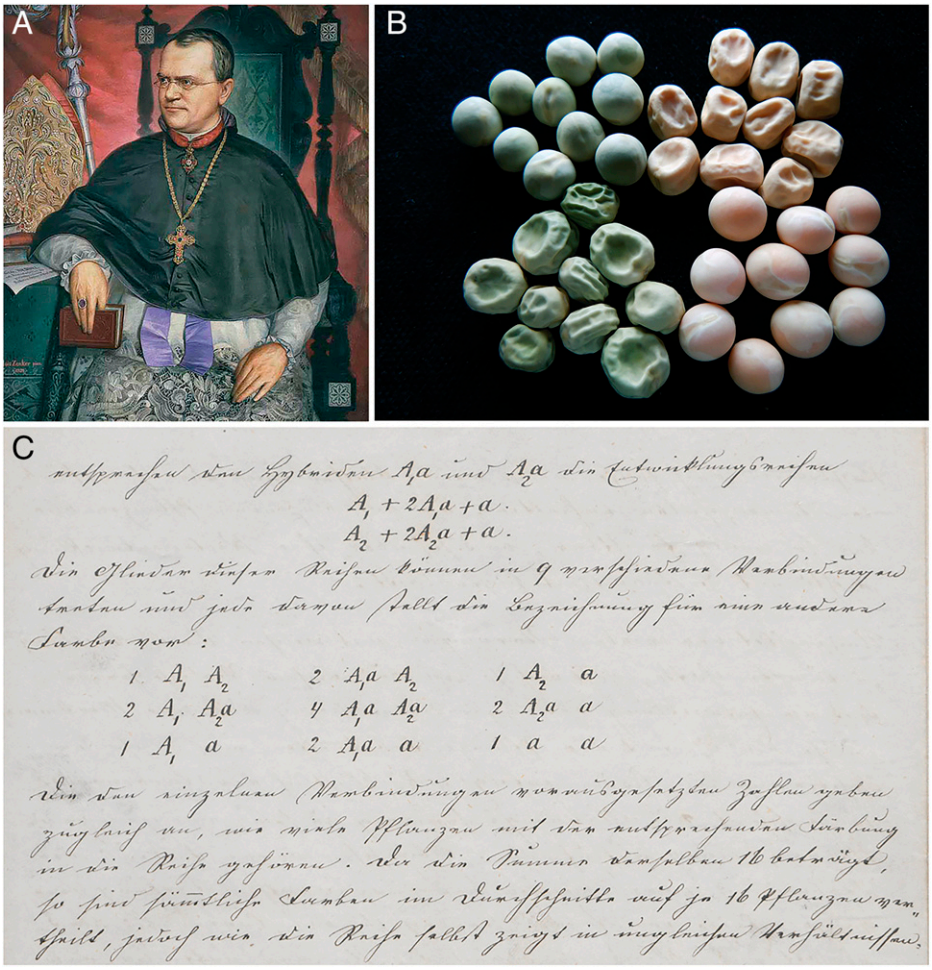

Fig. 1. Mendel and his work. (*A*) Portrait of Gregor Johann Mendel. (*B*) The phenotypes of peas used by Mendel resulting from two independent traits (i.e., the color and shape of the seeds) segregating in a dihybrid cross. (*C*) Facsimile of part of a page from Mendel's manuscript of his 1866 article entitled "Versuche über Pflanzen-Hybriden" ("Experiments on plant hybridization") published in *the Proceedings of the Natural History Society* in Brno (8). (The Mendel portrait was provided by the Old Brno Abbey of the Order of St. Augustine; the photo of the peas was provided by Ortrun Mittelsten Scheid [Gregor Mendel Institute, Vienna] and is reproduced, with permission, from ref. 95; the facsimile from Mendel's 1866 article was provided by the Old Brno Abbey of the Order of St. Augustine).

The *New Synthesis*, led by Fisher (9), Haldane (10), and Wright (11), was the culmination of attempts to combine Darwin's and Mendel's contributions after the rediscovery of Mendel's work in 1900 (2). This initial Darwin–Mendel coupling was further developed by a large number of evolutionary biologists, including Dobzhansky (12), Mayr (13), and Simpson (14) [for an exposition of the development of the *New Synthesis*, also see Mayr (15)]. The key insight that allowed the two areas to merge synergistically was that heritable variation within populations for traits that do not show discrete classes like Mendel's peas, such as height in humans, can be explained by a large number of independent genetic factors that are individually inherited according to Mendel's laws, with each factor only accounting for a small portion of the overall variation (5, 16). In fact, most biological traits show polygenic inheritance, rather than discrete classes like those observed for traits following strict Mendelian monogenic inheritance. Today, this Darwin–Mendel marriage is the foundation of evolutionary biology. Mendel's contribution was not, as it is sometimes characterized, the missing jigsaw piece in a complex, sprawling Darwin-dominated scientific puzzle. Rather, a better analogy is a lock and key, where each of two contributions is equally critical to the whole.

Celebrating the 200th Anniversary of Gregor Johann Mendel's Birth

The 200th anniversary of Gregor Johann Mendel's birth on July 20th in 1822 (17, 18; see also refs. 19–22)[†] is, quite

[†]There is uncertainty whether Gregor Johann Mendel was born on July 20th or July 22nd. With the help of Dr. Jiří Sekerák (Head of the Mendelianum Centre, Moravian Museum, Brno, Czech Republic) the following information is of some help in this respect: The literature provides two dates for Mendel's birth, July 20th and 22nd, 1822 (to be presented at the *Mendel200* conference in Brno 20 to 24 July 2022 and later published (17) in *Folia Mendeliana*, Brno). First, Anna Matalová (18) points out that, in the surviving documents, the date of Mendel's birth is consistently given as July 22, 1822. There are only two exceptions to this in numerous archival documents: the parish register of the village of Vražné and a baptismal certificate derived from it 12 y later, in 1834. In both of these documents, the date July 20, 1822 is given as the day of Mendel's birth. No date of birth is included in any other documents, such a passport. Matalova gives July 22nd as the probable correct date of birth and accepts the claim of Mendel's nephew Alois Schindler that, for Mendel's family, this was the correct date. This is primarily because Mendel's mother, Rosina Mendel (1794–1862), claimed so. She always associated the day of Mendel's birth with the feast day of St. Mary Magdalene, July 22nd. However, second, in an older publication from 1997, Matalová et al. (19) offer another explanation for the existence of two dates. Mendel's baptismal certificate, issued by the parish priest, Johann Edmund Schreiber, in 1834, was based on the original entry in the parish register. In the baptismal certificate, Schreiber confirms the date of birth in the parish register as being July 20, 1822. Schreiber was a conscientious priest and teacher, and followed the government requirement that he give the date of birth rather than the date of baptism. Therefore, Mendel's baptismal certificate (Taufschein) is, in fact, his birth certificate with a date of birth of July 20th and not a baptismal date of July 22nd. However, neither Mendel himself nor his family respected this date and consistently gave the date of baptism instead of the date of birth. Our conclusion: Mendel was born on July 20 and baptized on July 22, 1822. Mendel himself always celebrated his birthday on July 22nd, the feast of St. Mary Magdalene. For further reading on this topic, see refs. 20–22.

appropriately, focused on his contribution to the field of genetics, and thus molecular biology and medical genetics.

This PNAS Special Feature collection of articles, however, focuses on Mendel's impact on evolutionary biology. The collection of papers in honor of Mendel starts with a history of Mendel himself (23): his life, including his career as a scientist, and finally as an abbot in Brno (Moravia), a center for agricultural research and selective breeding since 1800 (see Table 1 for an overview of the chronology of Mendel's life). Berry and Browne (2) continue with an exploration of the (non)relationship between Darwin and Mendel, dismissing as myth, for example, the popular claim that Darwin owned an uncut copy of the journal issue in which Mendel's paper appeared. Barton (5) then discusses the development of the *New Synthesis*, which reconciles Darwin's theory of evolution and Mendel's ideas on heredity in a mathematical framework. The Special Feature collection continues with articles on the use of model organisms (24), the genetics of domestication (25), the genetics of adaptation (26), the genetics of behavior (27), and the genetics of speciation (28), all topics that highlight Mendel's profound impact on modern evolutionary biology.

The Three Laws of Mendelian Genetics

A diploid organism, like a human or the garden peas Mendel studied, carries two copies of each "inherited factor," which are now referred to as gene variants or alleles (Fig. 1*B* and *C*). The term "gene" was introduced well after Mendel and initially referred to genetic factors affecting a phenotypic trait. In modern genetics, a gene is typically defined as a piece of DNA that codes for an RNA molecule. When genes are protein-coding, messenger RNA (mRNA) molecules are then translated to proteins. Each of the traits Mendel studied was controlled by a single gene. This simple pattern of inheritance is now referred to as "Mendelian genetics" (monogenic inheritance), in contrast to polygenic inheritance, when a trait is influenced by many genes.

In his garden peas, Mendel observed—when considering the inheritance patterns of a single trait (e.g., seed color)—that the ratio of progeny from hybrid plants, with respect to that trait, was 3:1, namely three offspring with the dominant trait to every one with the recessive trait. He further observed that when two independent traits were inherited simultaneously (e.g., the color and shape of the seeds), that the ratio of the offspring phenotypes from such dihybrid crosses was, on average, 9:3:3:1 (Fig. 2). Namely, 9 offspring showed both dominant traits, 3 offspring showed one dominant and one recessive trait, 3 other offspring showed the complementary dominant and recessive combination, and 1 of every 16 progeny showed both recessive traits. This observed pattern can be explained by what has come to be known as Mendel's three laws of inheritance, which we outline in detail below.

The Law of Dominance. All the traits Mendel studied showed complete dominance: that is, an individual that carries both the dominant and recessive alleles (a heterozygote, A/a) has the same phenotype as the homozygote carrying two dominant alleles (A/A). To express the recessive trait, an individual must inherit the recessive allele from both parents (a/a). Complete dominance is often observed for inherited disorders in humans (Online Inheritance in Man; https://www.omim.org/): that is, heterozygotes (e.g., carriers of a recessive "disease allele") show no sign of disease because one functional copy is sufficient to avoid a defect. Today, we know that some traits show incomplete dominance, which means that heterozygotes show an intermediate phenotype somewhere between the two parental trait values.

The Law of Segregation. Mendel demonstrated that individuals inherit one allele from each of the male and female parent, and they transmit these alleles randomly to the next generation.

The Law of Independent Assortment. Mendel also established that different genetic traits are inherited independently of

Table 1. Mendel chronology

Year	Event
1822	Johann Mendel was born in Vražné in the Austro-Hungarian Empire (now the Czech Republic) on July 20th and baptized in a church in Hynčice on July 22nd[†]
1831 to 1833	Went to elementary school in Hynčice
1833	Continued school in Lipnik
1834 to 1840	Went to gymnasium in Opava
1843	Started in St. Thomas monastery in Brno; takes the ecclesiastical name Gregor (hence the full name Gregor Johann Mendel)
1847	Adopted as monasterian brother in the Order of Saint Augustine
1851 to 1853	Student at the University of Vienna
1856	Start breeding experiments with garden peas (*Pisum sativum*)
1862	Visits the world exhibition in London
1863	Read the German translation of Darwin's *The Origin of Species* (second edition of 1860)
1865	Presents the results of the pea experiments in two lectures (February and March) entitled "Versuche über Pflanzen-Hybriden" ("Experiments on Plant Hybridization"), at the Natural History Society in Brno
1866	Publishes his experimental results on peas in the society's proceedings (8) (the paper was sent to 120 recipients; 40 reprints are ordered, 1 of which was sent to the Swiss botanist Carl Wilhelm von Nägeli)
1868	Elected abbot in the Saint Augustine monastery in Brno
1870	Starts breeding experiments on hawkweed (*Hieracium*) as suggested by the Swiss botanist Nägeli; results published in the Societies proceedings (no reprints ordered)
1872	Emperor Franz Joseph I awarded him the Commander's Cross of the Order of Saint Francis Joseph
1873	In a letter to Nägeli the Darwinian term "the struggle for existence" was used (Nägeli was skeptical to Darwin's theory)
1875 to 1884	New demanding duties in the monastery making it difficult to follow up the scientific experiments; entertained hobbies like beekeeping, gardening, meteorology, and registration of sun spots

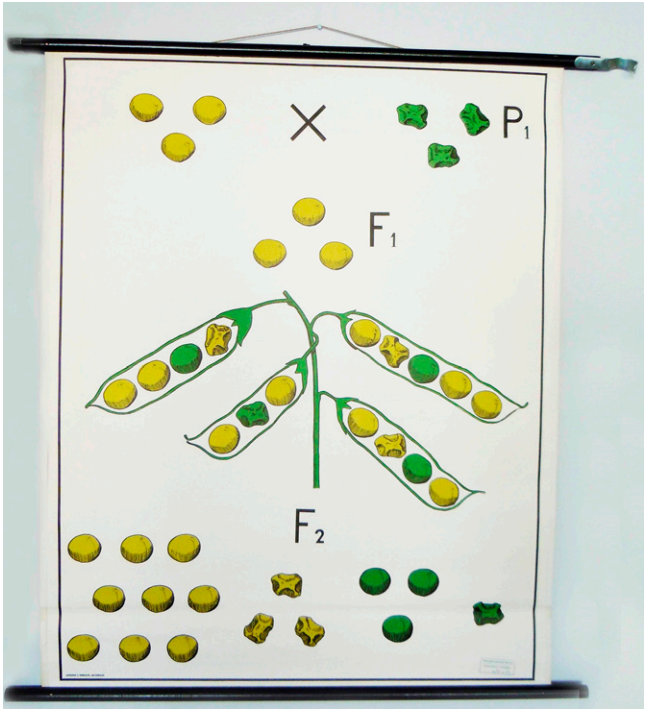

Fig. 2. Mendel's breeding experiments on garden peas (*Pisum sativum*). An image illustrating the phenotypes of the parents (P_1), the first-generation offspring (F_1) and second-generation (F_2) phenotypes illustrating the 9:3:3:1 ratio among F_2 progeny of a dihybrid cross: 9 offspring exhibiting both dominant traits, 3 offspring exhibiting one dominant and one recessive trait, 3 other offspring exhibiting the complementary dominant and recessive combination, and 1 of every 16 progeny exhibiting both recessive traits. (The poster has been obtained from Ortrun Mittelsten Scheid [Gregor Mendel Institute, Vienna] and is reproduced, with permission, from ref. 95).

each other, resulting, for example, in the classic segregation ratio 9:3:3:1 in a dihybrid cross (Figs. 1*B* and *C* and 2). Today we know that this is true for all genes except for those that are located close to each other on the same chromosome (i.e., linkage); then the proportion of different phenotypes will depend on the frequency of recombination between the two genes.

These three laws constitute a cornerstone for modern biology, and indeed for evolutionary biology. Although most traits typically are determined by many genes, and thus not as simple as with Mendel's peas and certain heritable diseases, the general principles still hold. Below we provide a synoptic presentation of Mendel and modern biology with a particular focus on modern evolutionary biology.

Gregor Johann Mendel and Modern Genetics

Our current understanding of genotype–phenotype relationships and, in particular, of how mutations in specific genes affect trait variation, is largely the product of research on model organisms, humans, and domesticated species. The impact of this work on evolutionary biology cannot be overstated. For example, basic knowledge of gene function and variation is critical to evolutionary analysis.

The Role of Model Organisms. Developmental biology, until recently, played little if any role in post-Darwinian evolutionary theories. However, Darwin used the fact that general features that characterize a species develop earlier in embryogenesis than specialized features as strong support of his theory of common descent. A focus on only a few organisms, which are accessible to systematic genetic investigations, so called model organisms, resulted in the discovery that many genes that direct embryonic development are conserved across animal phyla. Thus, model organisms have played a crucial role in the development of modern biology. Soon after the rediscovery of Mendel's laws of inheritance in 1900, the first model organisms—fruit fly (*Drosophila melanogaster*) and mouse (*Mus musculus*)—were established (24). They have been followed by the development of additional model organisms, such as the bacterium *Escherichia coli*, yeast *Saccharomyces cerevisiae*, the plant *Arabidopsis thaliana*, the nematode *Caenorhabditis elegans*, zebrafish *Danio rerio* (see Fig. 3), and, in recent years, many more that are applicable to particular biological research questions. For example, the liverwort *Marchantia polymorpha* is used in explorations of the evolution of plants (29), and the salamander axolotl *Ambystoma mexicanum* is used as a model for regenerative medicine because it can redevelop lost limbs (30). Irion and Nüsslein-Volhard (24) summarize the advances made through the use of model organisms leading to the convergence of developmental and evolutionary biology (31) and discuss how this knowledge set the stage for exploring genetics in natural populations.

Genetics of Humans and Domesticated Species. In humans, more than 6,000 traits and disorders, which are inherited according to Mendel's laws and controlled by a single gene, have been documented (Online Inheritance in Man; https://www.omim.org/). For the majority of these, the gene causing the Mendelian trait has been identified: many of the tools of molecular genetics have been developed for biomedical purposes. With the discovery of the genetic basis of a disease comes improved diagnosis and the development of new therapies for the condition. Similarly, thousands of traits showing Mendelian inheritance in animals have been cataloged (Online Mendelian Inheritance in Animals, OMIA: https://omia.org/home), with important applications in veterinary medicine. Genetics and genomic analyses of domesticated plants and animals have been used to advance our understanding of genotype–phenotype relationships, capitalizing on the rich phenotypic diversity that has accumulated in these species subsequent to domestication (25). Although domesticated plants and animals have been largely replaced by model organisms like *Arabidopsis* and *Mus* in basic biology, they still have a prominent role as models for evolutionary change because they have gone through an evolutionary process over the last 10,000 y during domestication and diversification (25).

However, most traits in biology, including many common diseases in humans, like diabetes and inflammatory disorders, show more complex, polygenic inheritance. Many genes as well as environmental factors contribute to the risk of developing disease. Thus, an important area of research in human medicine is to identify genetic factors that may contribute to an individual's disease risk. Such studies are based on quantitative genetics theory, which deals with the inheritance of polygenic traits. This theory has also revolutionized breeding programs in agriculture; it would not have been possible to feed 8 billion people

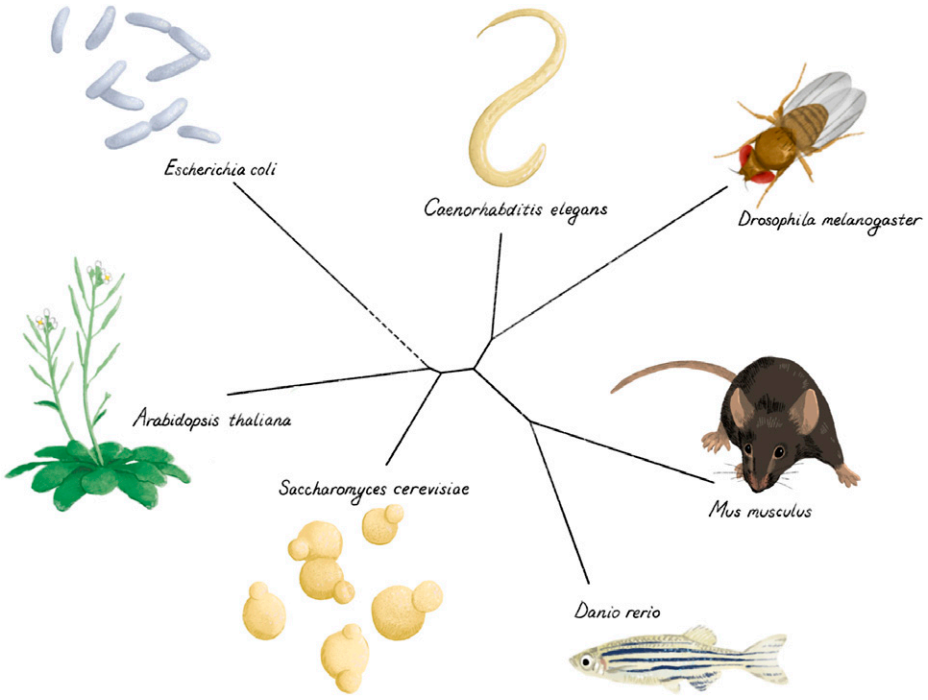

Fig. 3. Examples of some common model organisms (see ref. 24) representing different branches of the Tree of Life (http://doi.org/10.1126/science.1123061 and https://doi.org/10.1093/nar/gkab301).

with the crop varieties and farm animal populations available before the genetics revolution (25). A recent advance is the development of genomic selection—with genome-wide genetic markers used to enhance the effectiveness of artificial selection (32)—now widely used in crops and domestic animals.

Genome Sequencing. Genomics has revolutionized the field of genetics because we now can study (nearly) all genes in the genome, and we can carry out genetic studies on (almost) any species. A genome sequence provides a complete catalog of all genes, their specific locations, polymorphisms within those genes and in neighboring regions, as well as other structural changes in the genome (deletions, duplications, inversions, transposable elements, and so forth). Genome sequencing was initially pioneered in bacteria (33). In 2001, the first human genome sequence was published, and recently, a near complete sequence was released (34). Since then, the speed of sequencing has increased while sequencing costs have dropped, allowing for genome sequencing of both more species and more individuals within species. Given the importance of comparative sequence information, especially to evolutionary biology, genomics today has the ambitious goal to move beyond single-species sequences and instead produce genome sequences for all fish (10kfish), all vertebrates (VGP), or even all eukaryotes on earth (EBP). Equally informative, population resequencing projects have allowed evolutionary biologists to also study intraspecific genetic variation. Finally, genome sequencing has also unleashed the full potential of ancient DNA, making it possible to reconstruct the evolutionary history of archaic and modern humans (35), and under favorable conditions study up to 1 million-years-old DNA (36), providing a direct time dimension to evolutionary studies.

Gregor Johann Mendel and Modern Evolutionary Biology

Analyses of model species in laboratory environments left many key questions about evolution unanswered: we needed studies of genetic variation in natural populations. In the 1960s, the first survey of genetic variation was performed in a natural population of *Drosophila pseudoobscura* using protein electrophoresis (37, 38). These two studies not only raised their own questions (How is so much genetic variation maintained in populations?) but also opened the floodgates to future studies of genetic variation and ultimately to a focus on the connections between genes and specific traits—from adaptations and behaviors to those leading to speciation—in wild populations of a wide range of species.

The Genetics of Adaptation. Modern genetics has allowed us to work at the intersection of Darwin's and Mendel's ideas to identify genes (or even specific mutations) that give rise to phenotypic variation underpinning adaptation. In recent years, the number of genes now implicated in fitness-related differences has dramatically increased due, in large part, to the rapid development of powerful and cost-effective genomics tools. Today, we can scan the genome of almost any organism as a first step in uncovering the genetic basis of its fit to its environment. This has resulted in a rich list of fascinating examples of how genetic variation contributes to variation in evolutionarily significant phenotypic variation in natural populations (26, 39). Based on these studies, a better understanding of the genetic architecture of adaptive traits is emerging. For example, one important question is to what extent genetic adaptation is based on de novo mutations vs. standing genetic variation. The emerging picture is that standing genetic

variation often plays an especially prominent role in rapid bouts of adaptation (28, 40), likely because adaptive haplotypes accumulate multiple favorable mutations, similar to what is seen in the evolution over time of key alleles during domestication (25). That a single de novo mutation may have a small effect compared with that of existing adaptive haplotypes is a strong argument for the importance of maintaining genetic diversity in natural populations. An important focus for future research is to go from the identification of genes contributing to adaptation to understanding the mechanism of action of these gene variants. This will require interdisciplinary collaborations combining studies of selection in the field with experimental work in the laboratory (26).

The Genetics of Behavior. In chapter seven of *On the Origin of Species* (1), Darwin shifts his focus from morphological characters to behavior or, to use his preferred term, instinct. Specifically, he discusses the inheritance of instinct, providing many examples of species that have innate, adaptive instincts, and concluding that inherited behaviors, like morphology, can evolve by natural selection. However, the difficulties associated with studying behavior—for example, behaviors seldom fall into discrete categories—have delayed attempts to uncover the genetic basis of behavior. This is only now becoming feasible. For example, new high-throughput, cost-effective genotyping methods (complemented by advances in our ability to measure behavior) are enabling researchers to use forward-genetic approaches to localize regions of genomes that contain causal alleles contributing to behavioral variation. In some cases, this work can be facilitated by using controlled crosses akin to Mendel's experiments with peas. Genomic approaches are also being used to study how dynamic changes in gene expression contribute to behavioral variation, such as in the complex behavioral differences among castes of social insects that Darwin describes in detail. These two approaches are complementary: one searching for specific alleles contributing to behavioral diversity, the other working to understand the downstream transcriptional consequences. Hoekstra and Robinson (27) highlight how both approaches are necessary to further our understanding of how genes influence behavior. What is already clear, however, is that many behaviors have a complex genetic basis, underscoring the need to move away from "gene for" thinking, which has plagued early studies in behavioral genetics, sometimes with disastrous societal consequences.

The Genetics of Speciation. This golden age of genetics has also allowed breakthroughs in understanding the process of speciation (28), a topic captured in Darwin's book title, *On the Origin of Species* (1). The identification of so called "speciation genes" in various organisms teach us how reproductive isolation can be established either by prezygotic isolation, when interspecies fertilization does not take place, or by postzygotic isolation, when hybrid progeny are either not viable or are sterile, often due to genetic incompatibility. One important insight that has emerged as more genomes are sequenced is that gene flow between populations (at various stages of reproductive isolation) is much more widespread than previously thought. One especially intriguing example is that of gene flow between archaic and modern humans (35). Gene flow may be adaptive if favorable variants introgress from one population to another. However, gene flow may also be detrimental for local adaptation as extensive gene flow tends to homogenize populations adapted to different environmental contributions. Suppression of recombination may facilitate local adaptation and speciation despite gene flow because it inhibits the disruption of adaptive haplotype blocks [i.e., what Dobzhansky and Wright (41) referred to as "coadapted gene complexes"]. Inversions are a prime mechanism causing suppression of recombination, and there is currently an increasing number of examples of supergenes in which multiple adaptive mutations are inherited together by an inversion, thereby contributing to adaptation and phenotypic diversity (28).

The Historic and Conceptual Development of Modern Evolutionary Biology from Darwin and Mendel until Today

The *New Synthesis* (5) brought Darwin's theory of evolution through natural selection together with Mendelian genetics. A key element in Darwin's thinking is competition for resources (in a wide meaning of the term), a key concept of ecology. In this section, we summarize the historic and conceptual developments of the fields of genetics, ecology, and evolutionary biology: three fields that have partly developed independent of, and partly in combination with, each other (Fig. 4).

Dobzhansky (42) stated that "[n]othing in biology makes sense, except in the light of evolution." It is also well known that the ecological interactions both between individuals and between individuals and their abiotic environment cause selective pressures, thus we should also acknowledge that "very little in evolution makes sense, except in the light of population ecology" (43). Whenever evolutionary change occurs, the ecological interactions change, implying a feedback process whereby selective pressures may in turn change (Fig. 5). The molecularization of genetics that followed discovery of the double helix structure of DNA by Watson and Crick in 1953 (44), based on key insights made by Franklin (45), provided mechanistic detail into Darwin's "missing" mechanism of inheritance. The technologies spawned by these advances continue to have a huge impact on studies of evolution and ecology. But, in the midst of all the technological enthusiasm, we must remember that an understanding of ecological and evolutionary processes is critical to our understanding of all life on this planet. Shortly after the discovery of DNA's three-dimensional structure, one of the pioneers of the *New Synthesis*, Fisher, recommended that, even in the frenzy of molecular excitement, we should not lose sight of "a little-known book of nearly one hundred years ago called *The Origin of Species*" (46). Williams' *Adaptation and Natural Selection* (47) reemphasized the importance of ecological thinking in evolutionary biology. We should heed that warning: The basics still matter.

The Genetic Strand. For thousands of years, humans have been aware that many traits are to some extent inherited, as revealed by the patterns of phenotypic variation (height,

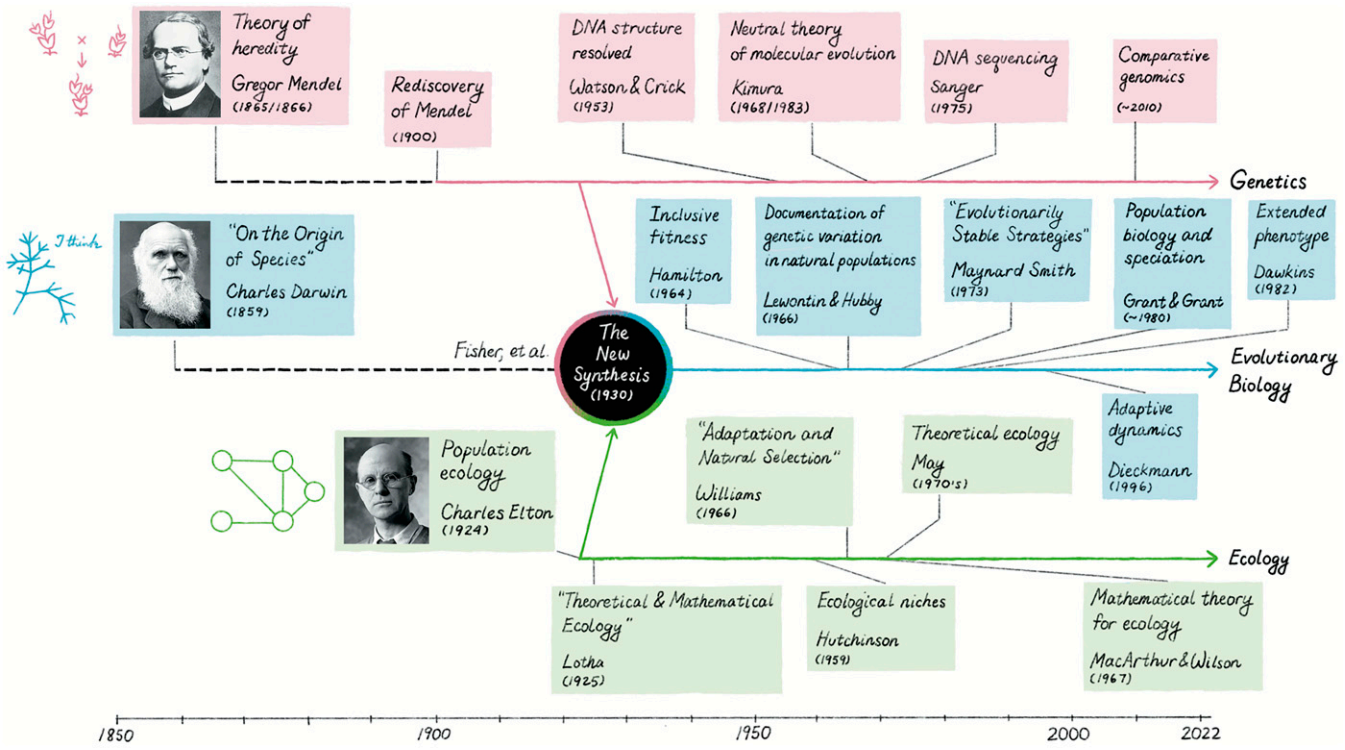

Fig. 4. Bringing genetics, ecology and the process of natural selection together into the field of evolutionary biology. The development of the field of genetics (the genetic strand) starting with Mendel (8), the field of ecology (the ecology strand) starting with Elton (61), and the combination of genetics and ecology in the field of evolutionary biology (the evolution strand) starting with Fisher's (9) and others' pioneering work.

skin, hair, and eye color) within and between families across generations. Based on the observation that like begets like, our ancestors were able to successfully develop crops and domestic animals and thus make the transition from hunter/gathering to agriculture.

Sutton (48, 49) and Boveri (50) established chromosomes as the carriers of genetic information. Avery et al. (51) then established DNA as the critical carrier of genetic information. Modern genetics starts with the description of the structure of the DNA helix (44), which led to the understanding of DNA replication and the genetic code. This in turn led to the development of methods to survey genetic variation: from protein electrophoresis, to DNA-based polymorphisms, to DNA sequencing methods. Gel-based sequencing methods have now largely been replaced by "next-generation" methods for highly parallelized sequencing. Our knowledge of the genetic underpinnings of biological diversity has undergone a revolution.

Molecular approaches to measure genetic variation were first applied to populations in the 1960s (38), demonstrating extensive genetic variation in natural populations (see above). To explain this variation, the neutral theory of molecular evolution argued that a considerable portion of the molecular variation present in genomes has no effect on fitness and are therefore selectively neutral (52). This theory provided a null hypothesis for studies of molecular evolution, which has been critical for the detection of the sequence variants that are subject to selection.

In addition to exploring intraspecific variation, genomic data also provide opportunities to compare sequences among species. In a landmark study prior to the genome era, comparisons between humans and chimpanzees showed that their proteins were remarkably similar, raising the hypothesis that much of the phenotypic differences between these species are due to changes in the regulation of genes (53). More recent comparisons of whole genomes between humans and other mammals identified genomic regions that are ultraconserved in humans (54), deleted in humans (55), or show accelerated sequence evolution in humans (56). These few examples serve to highlight the power of comparative-genomic approaches in making connections between genes (both coding and noncoding regions) and phenotypes.

Another important innovation has been the development of methods to alter genomes, which allowed for experimental tests of the effects of particular mutations on phenotype. First approaches focused on transgenic animals and plants generated by random integration of gene constructs (57). This was followed by more precise methods to inactivate or make specific changes in genes, in particular using embryonic stem cells and homologous recombination in mice (58, 59). Most recently, the development of the CRISPR/Cas9 technology provides a very precise gene scissor for gene editing in essentially any organism (60). These methods are of paramount importance for basic research and for future practical applications, such as gene therapy in humans and development of improved crops in agriculture.

The Ecology Strand. A key feature of the *New Synthesis* is population-ecological thinking that emerged from both empirical (61) and theoretical (62) studies during the 1920s (1, 2; see also, refs. 5 and 63). A fundamental insight in ecology (and evolutionary biology) extending back to Darwin is that the major part of any organism's environment is other coexisting organisms and implies that rate of evolutionary change will depend in their competition for

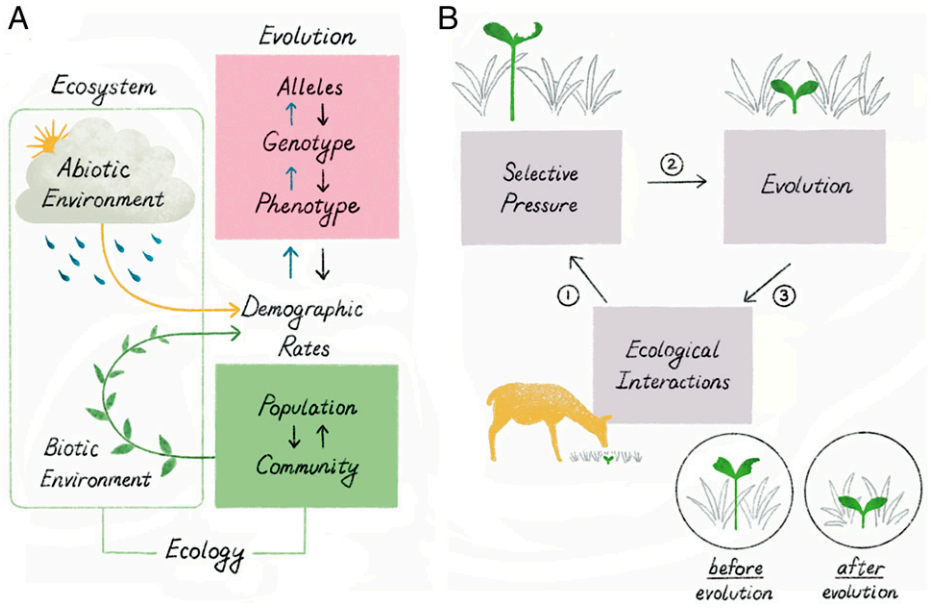

Fig. 5. Modern evolutionary biology. (*A*) The interaction between ecology (green) and evolution (blue arrows); the red box represents the genotype–phenotype mapping (corresponding to the genetic strand in Fig. 4). Evolution, typically inferred from phenotypic changes, represents the changes of allele frequencies in population across generations. The selective pressure is determined by the internal biotic interactions between individuals within and among species (green box and arrows) in combinations with external abiotic forces (yellow arrows) within the ecosystem (including both biotic [all living individuals within an area] and abiotic [including air, soil, water and climate] components). This ecologically determined selective pressure acts through the demographic rates of the genetically determined demographic rates (survival and reproduction). The ecological interactions refer to within population interaction, within community (the assembly of all coexisting species) interactions and the ecosystem level interactions (the combined biotic and abiotic interactions). [For similar, although more detailed figures, see Coulson et al. (96, 97)]. (*B*) The interaction between biotic and abiotic ecological interactions defining the evolutionary selective pressure (arrow #1) leading to evolutionary changes (arrow #2) in populations, which in turn feeds back to the ecological interactions (arrow #3).

resources on the biotic component of the environment (1, 9, 64–67), albeit in combination with the prevailing abiotic conditions (such as climate; see below and Fig. 5). Both ecologists and evolutionary biologists emphasize the importance of competition for resources. Thus, the concept of the niche, as presented by Hutchinson (68), was a very important development within the fields of both ecology and evolution, and emphasizing how ecology links to evolutionary biology through the selective pressure.

The development of mathematical modeling within the field of ecology, during the latter part of the 1960s and 1970s, was critical in making ecology a more predictive branch of biology as well as linking it more closely to the field of evolutionary biology. *The Theory of Island Biogeography* by MacArthur and Wilson (69) is, in this respect, a, milestone within the field of ecology, a development in which May (70, 71) together with several other theorists (72–76) played instrumental roles by further bringing mathematics into ecology. These contributions focused on understanding ecological dynamics in time and space, including both within-biotic forces (such as competition) and external abiotic forces, which together determine selective pressure.

The Evolutionary Biology Strand. The main determinant of evolutionary change within a population is its demography, specifically, the relative rates of birth and death (Fig. 5*A*). These rates are determined by the individuals' phenotypes, which in turn are determined by their genetic composition and their environment: in short, by the genotype–phenotype relationship (see ref. 77). Populations that split may eventually diverge genetically enough to develop reproductive isolation (and thus undergo speciation). Several populations of different species in one location constitute a biological community, and including the abiotic environmental setting, an ecosystem (78–80). As summarized in Fig. 5*B*, the selective pressures potentially leading to evolutionary changes generally lead to changed ecological interactions within the ecosystem, which again changes the selective pressure. There is thus a tight feedback between ecological and evolutionary processes.

With his 1930 book (9), Fisher played a key role, not the least with what is now called Fisher's Fundamental Theorem (see also ref. 81). This states that the rate of increase in the mean fitness of any organism, at any time, due to changes in gene frequencies caused by natural selection, is exactly equal to its additive genetic variance in fitness at that time (for an exposition of this theorem, see ref. 82). Since absolute fitness must remain close to constant, this increase due to selection must be offset by deleterious mutations, and more importantly, by changes in the physical and biological environment, including adaptation by competing species. Fisher's theorem is thus fundamental in evolutionary biology (Fig. 5), emphasizing that the rate of evolution is the product of the (additive) genetic variance and the strength of selection, and thereby highlighting the coupling of genetics with ecology.

A major advance within evolutionary biology following the New Synthesis was the introduction of the concept of inclusive fitness (83, 84; see also ref. 85). This asserts that an individual might promote the representation of its own gene variants in future generations through increasing reproductive success of relatives. Another conceptually important contribution to evolutionary biology was the concept of the extended phenotype (86), whereby an individual can increase its own fitness by manipulating other

individuals to promote the representation of its own genes to future generations.

Major advances in our understanding of evolutionary dynamics and the characterization of the evolutionary trajectories were the introduction of evolutionarily stable strategies (87–89) and later adaptive dynamics (90, 91), both of which emphasized the coupling of ecology and evolution (see, e.g., ref. 92). Furthermore, long-term studies of natural populations have provided additional insight into the population dynamics and genetics of adaptation (93, 94).

Evolutionary Biology Today: Concluding Remarks

Evolutionary biology today is an active field of biology, generating insights not only into ourselves but also the biodiversity around us. Importantly, however, both the insights derived from evolutionary biology as well as the approaches used in evolutionary biology are also highly applicable in practical ways. Evolutionary principles underlie plant and animal breeding programs, which have made it possible to feed 8 billion people currently and possibly 10 billion people in the future. Evolutionary perspectives help us manage the planet's threatened biodiversity, providing insight into how to achieve sustainable use of biological resources. Evolutionary thinking helps us predict where zoonotic diseases are most likely to emerge and predict their spread in time and space. Understanding the evolution of our own species also helps us better understand human nature and health.

Thus, this century has the potential to become the century of biology with two main nineteenth-century pillars: Darwin's theory of evolution through natural selection and Mendelian genetics. Mendel provided the insight about inheritance, which Darwin needed to make his evolutionary theory complete.

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1. C. Darwin, *On the Origin of Species* (John Murray, 1859).
2. A. Berry, J. Browne, Mendel and Darwin. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2122144119 (2022).
3. W. Bateson, *Mendel's Principle of Heredity: A Defence* (Cambridge University Press, 1902).
4. F. Jenkin, Review of *The Origin of Species*. *North Br. Rev.* **46**, 277–318 (1867).
5. N. H. Barton, The "New Synthesis." *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2122147119 (2022).
6. C. Darwin, *The Variation of Animals and Plants Under Domestication* (John Murray, 1868).
7. C. Darwin, *The Descent of Man* (Wordsworth Editions Ltd, 1871).
8. G. J. Mendel, Experiments on plant hybridization [Versuche über Pflanzen-Hybriden] [in German]. *Proc. Natl. Hist. Soc.* **119**, 3–47 (1865).
9. R. A. Fisher, *The Genetical Theory of Natural Selection* (Clarendon Press, 1930).
10. J. B. S. Haldane, *The Causes of Evolution* (Princeton University Press, 1932).
11. S. Wright, Evolution in Mendelian populations. *Genetics* **16**, 97–159 (1931).
12. T. Dobzhansky, *Genetics and the Origin of Species* (Columbia University Press, 1937).
13. E. Mayr, *Systematics and the Origin of Species* (Columbia University Press, 1942).
14. G. G. Simpson, *Tempo and Mode in Evolution* (Columbia University Press, 1944).
15. E. Mayr, *The Growth of Biological Thought: Diversity, Evolution and Inheritance* (Harvard University Press, 1982).
16. R. A. Fisher, The correlation between relatives on the supposition of Mendelian inheritance. *Trans. R. Soc. Edinb.* **53**, 399–433 (1918).
17. S. Sekerák, Mendel's birth date *Folia Mendeliana* (2022). In press.
18. A. Matalová, The date of birth of Johann Gregor Mendel. *Folia Mendeliana* **48**, 25 (2012).
19. A. Matalová, V. Nippert, J. Zezulčík, *Johann Gregor Mendel/život a dílo. [Johann Gregor Mendel/Life and Work] [in Czech].* (Obec Vražné, Mendelianum MZM, Okresní vlastivědné muzeum Nový Jičín, 1997).
20. H. Iltis, *Gregor Johann Mendel, Leben, Werk und Wirkung* (Springer, Berlin, 1924).
21. J. Klein, N. Klein, *Solitude of a Humble Genius–Gregor Johann Mendel. Formative Years* (Springer, 2013).
22. V. Orel, *Gregor Mendel: The First Geneticist* (Oxford University Press, 1996).
23. D. L. Hartl, Gregor Johann Mendel: From peasant to priest, pedagogue, and prelate. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2121953119 (2022).
24. U. Irion, C. Nüsslein-Volhard, Developmental genetics with model organisms. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2122148119 (2022).
25. L. Andersson, M. Purugganan, Molecular genetic variation of animals and plants under domestication. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2122150119 (2022).
26. K. Bomblies, C. L. Peichel, Genetics of adaptation. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2122152119 (2022).
27. H. E. Hoekstra, G. E. Robinson, Behavioral genetics and genomics: Mendel's peas, mice, and bees. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2122154119 (2022).
28. D. Schluter, L. H. Rieseberg, Three problems in the genetics of speciation by selection. *Proc. Natl. Acad. Sci. U.S.A.* **119**, e2122153119 (2022).
29. J. L. Bowman, The liverwort *Marchantia polymorpha*, a model for all ages. *Curr. Top. Dev. Biol.* **147**, 1–32 (2022).
30. K. Echeverri, J. Fei, E. M. Tanaka, The Axolotl's journey to the modern molecular era. *Curr. Top. Dev. Biol.* **147**, 631–658 (2022).
31. P. Calow, *Life Cycles: An Evolutionary Approach to the Physiology of Reproduction, Development and Ageing* (Wiley, London, 1978).
32. T. Meuwissen, B. Hayes, M. Goddard, Accelerating improvement of livestock with genomic selection. *Annu. Rev. Anim. Biosci.* **1**, 221–237 (2013).
33. N. J. Loman, M. J. Pallen, Twenty years of bacterial genome sequencing. *Nat. Rev. Microbiol.* **13**, 787–794 (2015).
34. S. Nurk *et al.*, The complete sequence of a human genome. *Science* **376**, 44–53 (2022).
35. M. Hajdinjak *et al.*, Reconstructing the genetic history of late Neanderthals. *Nature* **555**, 652–656 (2018).
36. T. van der Valk *et al.*, Million-year-old DNA sheds light on the genomic history of mammoths. *Nature* **591**, 265–269 (2021).
37. J. L. Hubby, R. C. Lewontin, A molecular approach to the study of genic heterozygosity in natural populations. I. The number of alleles at different loci in *Drosophila pseudoobscura*. *Genetics* **54**, 577–594 (1966).
38. R. C. Lewontin, J. L. Hubby, A molecular approach to the study of genic heterozygosity in natural populations. II. Amount of variation and degree of heterozygosity in natural populations of *Drosophila pseudoobscura*. *Genetics* **54**, 595–609 (1966).
39. A. Martin, V. Orgogozo, The loci of repeated evolution: A catalog of genetic hotspots of phenotypic variation. *Evolution* **67**, 1235–1250 (2013).
40. R. D. Barrett, D. Schluter, Adaptation from standing genetic variation. *Trends Ecol. Evol.* **23**, 38–44 (2008).
41. T. Dobzhansky, S. Wright, Genetics of natural populations. X. Dispersion rates in *Drosophila pseudoobscura*. *Genetics* **28**, 304–340 (1943).
42. T. Dobzhansky, Nothing in biology makes sense except in light of evolution. *Am. Biol. Teach.* **35**, 125–129 (1973).
43. M. Begon, J. L. Harper, C. R. Townsend, *Ecology. Individuals, Populations and Communities* (Blackwell, Oxford, 1986).
44. J. D. Watson, F. H. C. Crick, Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* **171**, 737–738 (1953).
45. V. Percec, Q. Xiao, The legacy of Rosalind E. Franklin: Landmark contributions to two Nobel Prizes. *Chem* **7**, 530–536 (2021).
46. R. A. Fisher, Polymorphism and natural selection. *J. Ecol.* **46**, 289–293 (1958).
47. G. C. Williams, *Adaptation and Natural Selection: A Critique of Some Current Evolutionary Thought* (Princeton University Press, 1966).
48. W. S. Sutton, On the morphology of the chromosome group in *Brachystola magna*. *Biol. Bull.* **4**, 24–39 (1902).
49. W. S. Sutton, The chromosomes in heredity. *Biol. Bull.* **4**, 231–251 (1903).
50. T. Boveri, *Ergebnisse über die Konstitution der chromatischen* (Substanz des Zelkerns. Fisher, Jena, 1904).

51. O. T. Avery, C. M. Macleod, M. McCarty, Studies on the chemical nature of the substance inducing transformation of *Pneumococcal* types induction of transformation by a desoxyribonucleic acid fraction isolated from *Pneumococcus* type III. *J. Exp. Med.* **79**, 137–158 (1944).
52. M. Kimura, Evolutionary rate at the molecular level. *Nature* **217**, 624–626 (1968).
53. M. C. King, A. C. Wilson, Evolution at two levels in humans and chimpanzees. *Science* **188**, 107–116 (1975).
54. G. Bejerano *et al.*, Ultraconserved elements in the human genome. *Science* **304**, 1321–1325 (2004).
55. C. Y. McLean *et al.*, Human-specific loss of regulatory DNA and the evolution of human-specific traits. *Nature* **471**, 216–219 (2011).
56. K. S. Pollard *et al.*, Forces shaping the fastest evolving regions in the human genome. *PLoS Genet.* **2**, e168 (2006).
57. R. D. Palmiter, R. L. Brinster, Transgenic mice. *Cell* **41**, 343–345 (1985).
58. T. Doetschman *et al.*, Targetted correction of a mutant HPRT gene in mouse embryonic stem cells. *Nature* **330**, 576–578 (1987).
59. K. R. Thomas, M. R. Capecchi, Site-directed mutagenesis by gene targeting in mouse embryo-derived stem cells. *Cell* **51**, 503–512 (1987).
60. M. Jinek *et al.*, A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science* **337**, 816–821 (2012).
61. C. S. Elton, Periodic fluctuations in the numbers of animals–Their causes and effects. *Br. J. Exp. Biol.* **2**, 119–163 (1924).
62. A. J. Lotka, *Elements of Physical Biology* (Williams and Wilkins, Baltimore, 1925).
63. S. E. Kingsland, *Modeling Nature: Episodes in the History of Population Ecology* (University of Chicago Press, Chicago, 1985).
64. N. C. Stenseth, Where have all the species gone? On the nature of extinction and the Red Queen hypothesis. *Oikos* **33**, 196–227 (1979).
65. N. C. Stenseth, J. M. Smith, Coevolution in ecosystems: Red Queen evolution or stasis? *Evolution* **38**, 870–880 (1984).
66. L. Van Valen, A new evolutionary law. *Evol. Theory* **1**, 1–30 (1973).
67. L. Van Valen, A theory of origination and extinction. *Evol. Theory* **7**, 133–142 (1985).
68. G. E. Hutchinson, Homage to Santa-Rosalia or why are there so many kinds of animals. *Am. Nat.* **93**, 145–159 (1959).
69. R. H. MacArthur, E. O. Wilson, *The Theory of Island Biogeography* (Princeton University Press, 1967).
70. R. M. May, *Stability and Complexity of Model Ecosystems* (Princeton University Press, 1973).
71. R. M. May, Simple mathematical models with very complicated dynamics. *Nature* **261**, 459–467 (1976).
72. E. C. Pielou, *Introduction to Mathematical Ecology* (Wiley-Interscience, 1969).
73. S. A. Levin, Community equilibria and stability, and an extension of the competitive exclusion principle. *Am. Nat.* **104**, 413–423 (1970).
74. J. E. Cohen, A Markov contingency-table model for replicated Lotka-Volterra systems near equilibrium. *Am. Nat.* **104**, 547–560 (1970).
75. S. A. Levin, Dispersion and population interactions. *Am. Nat.* **108**, 207–228 (1974).
76. J. Roughgarden, *Theory of Population Genetics and Evolutionary Ecology: An Introduction* (Prentice Hall, ed. 1, 1979).
77. R. C. Lewontin, *The Genetic Basis of Evolutionary Change* (Columbia University Press, 1974).
78. C. S. Elton, *Animal Ecology* (Sidgwick and Jackson, London, 1927).
79. C. S. Elton, *Animal Ecology And Evolution* (Oxford University Press, 1930).
80. A. G. Tansley, The use and abuse of vegetational concepts and terms. *Ecology* **16**, 284–307 (1935).
81. A. W. F. Edwards, The fundamental theorem of natural selection. *Biol. Rev. Camb. Philos. Soc.* **69**, 443–474 (1994).
82. S. A. Frank, M. Slatkin, Fisher's fundamental theorem of natural selection. *Trends Ecol. Evol.* **7**, 92–95 (1992).
83. W. D. Hamilton, The genetical evolution of social behaviour. II. *J. Theor. Biol.* **7**, 17–52 (1964).
84. W. D. Hamilton, The genetical evolution of social behaviour. I. *J. Theor. Biol.* **7**, 1–16 (1964).
85. L. A. Dugatkin, Inclusive fitness theory from Darwin to Hamilton. *Genetics* **176**, 1375–1380 (2007).
86. R. Dawkins, *The Extended Phenotype* (Oxford University Press, 1989).
87. J. Maynard Smith, G. R. Price, Logic of animal conflict. *Nature* **246**, 15–18 (1973).
88. J. Maynard Smith, *On Evolution* (Edinburgh University Press, 1972).
89. J. Maynard Smith, *Evolution and the Theory of Games* (Cambridge University Press, 1982).
90. U. Dieckmann, M. Doebeli, J. A. J. Metz, D. Tautz, *Adaptive Speciation* (Cambridge University Press, 2004).
91. U. Dieckmann, R. Law, The dynamical theory of coevolution: A derivation from stochastic ecological processes. *J. Math. Biol.* **34**, 579–612 (1996).
92. J. Reed, N. C. Stenseth, On evolutionarily stable strategies. *J. Theor. Biol.* **108**, 491–508 (1984).
93. P. R. Grant, B. R. Grant, *40 Years of Evolution. Darwin's Finches on Daphne Major Island* (Princeton University Press, 2014).
94. S. Lamichhaney *et al.*, A beak size locus in Darwin's finches facilitated character displacement during a drought. *Science* **352**, 470–474 (2016).
95. O. Mittelsten Scheid, Nicht-Mendelsche Genetik. *Nova Acta Leopoldina NF* **413**, 231–250 (2017).
96. T. Coulson, Environmental perturbations and transitions between ecological and evolutionary equilibria: An eco-evolutionary feedback framework. *Peer Community J.* **1**, article 6 (2021).
97. T. Coulson *et al.*, Modeling adaptive and nonadaptive responses of populations to environmental change. *Am. Nat.* **190**, 313–336 (2017).