neuronal differentiation, eye, limb, lung, kidney and heart development. The patterning of the antero-posterior embryo body axis is also directly regulated by retinoic acid, which controls the expression of several *HOX* genes through RAREs in their regulatory/enhancer regions.

Are there any human diseases related to retinoic acid deficiency? Reduction of vitamin A levels in the diet can lead to a debilitating immune system, anemia or blindness. During pregnancy, insufficient levels of vitamin A lead to fetal vitamin A deficiency-induced syndrome. This results in developmental defects exhibiting many common features with those observed in the RAR/RXR mutations in mouse, including cranio-facial and eye abnormalities.

Retinoic acid as an anticancer drug…? Acute promyelocytic leukaemia is caused by a chromosomal translocation that fuses the promyelocytic leukaemia gene (PML) on chromosome 15 with the RARα gene on chromosome 17. The PML-RARα fusion protein leads to a recruitment of co-repressor complexes that epigenetically silence gene expression. Differentiation therapy with retinoic acid is being used in combination with chemotherapy for the treatment of patients with acute promyelocytic leukaemia, resulting in a 70-80% cure rate.

Where can I find out more?

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Essay

The origins of behavioral genetics

Ralph J. Greenspan

The passing of Seymour Benzer has inspired various retrospectives on his scientific career, and much attention has been paid to his inauguration of single-gene mutant studies of behavior in the fruitfly *Drosophila melanogaster*. Studies of genes and behavior actually go back to the beginnings of genetics. The end of the era marked by Benzer's life offers a good opportunity to look back at the origins of the field he influenced so profoundly.

Origins

Francis Galton is often cited as the first behavioral geneticist. Stimulated by reading his cousin Charles Darwin's *Origin of Species*, he began to survey the concentration of abilities and accomplishments in families. Using the newly developed statistical analysis of quantitative characteristics in populations that he had developed, Galton published the first study claiming to trace inheritance of particular behavioral traits [1]. His failure to consider non-hereditary factors in the familial clusterings that he saw has discredited his findings in the eyes of modern researchers, and his promulgation of eugenic ideology has colored his subsequent treatment by history [2]. His views, however, were entirely consistent with 19th century hereditarianism [3]. Despite these contemporary reservations, Galton stands as the starting point in the long road towards understanding the relation between heredity and behavior.

First single-gene variants

With the advent of Mendelian genetics at the turn of the 20th century and its application to animals, some early attempts were made to trace the inheritance of behavioral traits. Few of the initial efforts were actually directed at understanding behavior. For the most part, they used behavioral phenotypes as tests of Mendelian inheritance.

Mouse strains with characteristic whirling behavior, known as 'Japanese waltzing' mice, were well known during this period as popular curiosities available from pet dealers. Arthur D. Darbishire at Oxford University [4] performed an early experiment to test for Mendelian inheritance of waltzing behavior. He observed that waltzing was recessive, but concluded from the failure to match the expected 3:1 ratio in the F2 (97 waltzers to 458 non-waltzers) that its inheritance did not support a Mendelian model. This is an early case of being misled by pleiotropic effects of a mutation: he failed to consider the possibility of reduced viability of the homozygotes, a common feature of neurological mutants. (Nine years later, when Alfred Sturtevant hit upon the idea of recombination between mutations as indicative of a linear arrangement of genes on the chromosome, he was unperturbed by his much more significant deviation from an expected Mendelian ratio; he was already sold on the idea of Mendelian traits.)

Work on putative single-gene variants in humans was pioneered by Charles B. Davenport at Cold Spring Harbor [5]. These studies suffered, however, from Davenport's propensity to see Mendelian inheritance in every trait he looked at, from Huntington's Disease (which he correctly pegged as an autosomal dominant), to feeble-mindedness (which he claimed was recessive, but we now suspect to be environmentally induced by prolonged contact with academic researchers). Davenport's assumption, appropriate for the day, was that human behavior is determined through and through by 'unit characters' of heredity — single-gene Mendelian factors that are wholly responsible for the determination of a trait. This illustrates a scientific trait that we have seen reemerge in the current genomic era: the tendency to account for any and all unknowns by a newly discovered source of insight.

Enter the fly

The fruitfly *Drosophila melanogaster* made its research debut in the laboratory of William E. Castle at Harvard University in 1901 (Figure 1). This was the first laboratory to pursue the newly propounded principles of Mendelian genetics in animals, concentrating primarily on the coat color genetics of guinea pigs and

Figure 1. William E. Castle (courtesy of Genetics Society of America).

rats. In parallel with these mammalian studies, however, Castle took the suggestion of his entomologist colleague C.W. Woodworth and began breeding studies with the fruit fly, testing how well it tolerated inbreeding, selection, and probing some of its simple behavioral responses.

The first paper on the subject was a study in 1905 by Castle's student F.W. Carpenter on the fly's phototactic (Figure 2), geotactic and mechanosensory responses [6]. He found that flies are positively phototactic, negatively geotactic, and induced to move by mechanical stimulation. In 1906, Castle and his students published their major work on the fly [7], in which they demonstrated that it tolerated inbreeding to a considerable extent and that it could be selected for improved fertility. Other Castle students soon followed with the first study of olfactory behavior in *Drosophila*, showing that flies like amyl or ethyl alcohol and acetic or lactic acid, and that they find food primarily by smell [8]. The first study of anemotaxis (sensitivity to wind currents) showed that flies respond negatively [9].

None of these behavioral studies involved the use of genetic variants and one may wonder where the idea came from to look at these behaviors. The most likely influence was the German zoologist Jacques Loeb, who had moved to the United States and became a key figure in establishing the University of Chicago as one of the first research universities in America. Loeb's research on tropisms in *Planaria* [10] were well known to all zoology students, and is referenced in these early *Drosophila* papers.

Another first in Castle's lab was the study by his student F.E. Lutz [11] in which flies were selected over more than 40 generations for variation in wing-vein morphology. He also carried out experiments on mating preferences among the various lines, including experiments in which he cut off the male sex combs. The rationale for these mating experiments was framed in the context of Darwin's discussion of sexual selection: had he created reproductively isolated strains? In his description of the work, Lutz makes the first, fateful reference to the richness and detail of this fly behavior: "*There is an elaborate 'courtship', in which the flirting of the wings in front of the prospective mate plays a large part. It seems as though a choice were made on the basis of sight, but I doubt whether that is the case. However, there is no doubt of the choice*."

T.H. Morgan's 'Fly Room' at Columbia was the scene of the first studies of genetic variants in *Drosophila*, which soon became a cottage industry of gene mapping [12]. The two behavioral studies that were produced in this early period followed on the initial reports from Castle's group. A.H. Sturtevant [13] inaugurated the study of genetic variants affecting courtship behavior, as well as the comparison of species differences. He made several key observations that have since been elaborated upon: that males use their wings to stimulate females; and that light (vision) is unnecessary for courtship (in *D. melanogaster*). In the first courtship studies with genetic variants, he tested for mating preference within and between mutant lines and made the first observations on male/female mosaic animals (gynandromorphs) that demonstrated the separability of attractiveness from propensity to perform courtship.

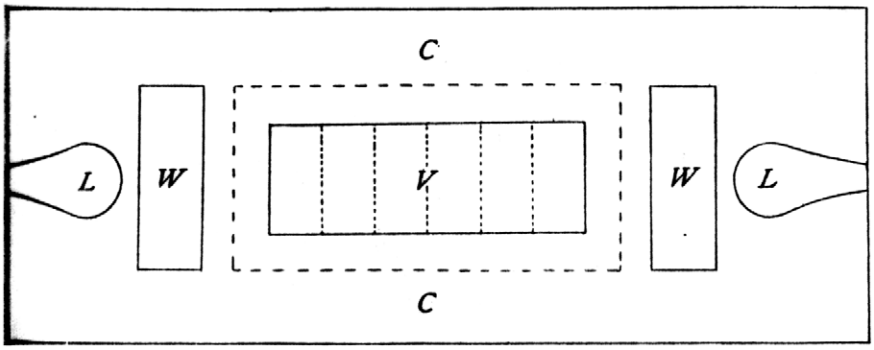
Another Morgan student, R.S. McEwen, studied phototropic and geotropic responses in the fly [14]. He subsequently reported the first behavioral abnormalities in mutants: poor phototaxis in the cuticle pigment mutant *tan* and in the wing morphology mutant *vestigial* [15]. It is fitting that these first two reports of mutant defects were in obviously pleiotropic mutants, thus foreshadowing the course of behavioral mutant studies to come. In the 1960s, Seymour Benzer would stumble upon these same mutants in his inaugural studies of phototaxis [16], but otherwise the testing of fly mutants for behavioral anomalies lay fallow for many years. It is not clear what motivated McEwen to examine behavior in these mutants — certainly not testing for Mendelian segregation; that had already been done in Morgan's lab for the mutants' morphological phenotypes. His work did follow from earlier studies of the response of wild-type *Drosophila* to light and gravity [6,9], and was firmly rooted in the tradition of Jacques Loeb's [10] influential ideas on animal tropisms. In this sense, he was the first to test mutants for behavioral defects.

First strain differences

The first study of strain differences in behavior traces back to one of the original animal behaviorists, Robert Yerkes, who compared tame rats with wild rats differing in such observable traits as biting, teeth gnashing, jumping, hiding, urination, defecation, cowering, and so on [17]. He then went on to analyze F1 and F2 generations and found no simple Mendelian segregation of traits. The F1s showed relatively high behavioral scores, but the F2s were lower and much more variable. A similar study in mice gave correspondingly similar results [18]. Though not analyzable at the time, the results foreshadowed what would become the mantra for studies of strain differences, and eventually for any kind of selected phenotype: the effects were genetically complex.

First selection experiments

The aforementioned early breeding experiments in *Drosophila* by Castle and his students [7] had as a principal goal the establishment of laboratory strains with high fertility and tolerance of inbreeding; hence, their 15 generations of selection. Lutz's experiment on wing-vein morphology [11] went on for over 43 generations. A contemporary experiment was carried out by F. Payne [19] in which flies were raised for 69 generations in the dark.



Sectional Plan of Dark Box × ¼. *C*, dark chamber; *L*, incandescent electric light of 5 c. p.; *V*, cylindrical glass vessel in which flies were contained; length, 15 cm., diameter, 5 cm.; distance of either end of this vessel from light, 7 cm.; the dotted transverse lines indicate the division into six sections by rubber bands; *W*, glass vessel containing water. The broken line surrounding *V* is a projection of the outline of the window of the dark box on the plane of this drawing.

Figure 2. Carpenter's phototaxis apparatus (reproduced with permission from [6]).

Both Lutz and Payne were interested in the question of whether disuse over many generations could cause structures to degenerate — wings in the case of Lutz, and eyes in the case of Payne. In neither case was there any evidence for such an effect.

Animal husbandry's experience in selective breeding for traits was a cornerstone of Darwin's observations in developing his theory of natural selection and had been universally acknowledged through the ages as indicative of the inheritance of parental characters by their offspring. The science of analyzing selectively bred behavioral traits began with E.C. Tolman at Berkeley in the 1920s, and with it arose the first authentic school of thought devoted to the study of the relationship between heredity and behavior. Rats were tested for maze-running ability followed by mating of the brightest to each other and likewise mating of the dullest to each other [20]. Similar multi-generational selection was subsequently carried out by Tolman in collaboration with R.C. Tryon, who went on to analyze inheritance patterns of maze-running ability in F1 and F2 progeny after 18 generations of selection and concluded (you guessed it) that the inheritance was genetically complex [21].

Maze learning was not the only behavior that responded to selection in rats or mice. Activity *versus* inactivity [22] and emotionality *versus* non-emotionality [23] were also selected in multi-generational paradigms, and also shown to be genetically complex.

Genetics and eugenics

The 1920s saw the maturation of genetics into a mature scientific discipline, but it was also the heyday of eugenics — a movement that saw the future salvation of humanity in scientifically planned selective breeding [2,3,5]. Started by Galton and championed by Davenport, eugenics spread widely in England and America to the point that county fairs would host booths to promulgate 'social hygiene' through 'fitter families' and 'better babies' contests (Figure 3). The movement had its dark advocates, such as Davenport, who saw great threats to the genetic stock of Americans in the waves of new immigrants from eastern and southern Europe, and more 'progressive' advocates, such as Hermann Muller, who espoused a more optimistic eugenics aimed at improving the health of humanity.

The majority of practising geneticists, however, saw little justification in the wholesale ascribing of all human behavior to simple Mendelian factors. Morgan's fly work had already begun to turn up complexities and pleiotropies in many of the genes they studied. But nearly all scientists felt strongly that wading into the political waters was beneath them, even as the U.S. Congress held hearings on the need for a national origins quota system. Quotas were eventually written into the Immigration Act of 1924, thus ending the great wave of American immigration. Notable exceptions to this scientific reticence were J.B.S. Haldane in England and the protozoologist H.S. Jennings, who distinguished himself as the only American geneticist willing to testify before Congress and challenge the scientific basis of the anti-immigrant claims [2].

The anti-immigrant sentiment that fueled the eugenics movement is visible today in the debates over immigration policy, but the lack of effective opposition back then can be ascribed in large measure to the absence of countervailing explanations. The social sciences of anthropology, sociology, and behaviorism were in their infancy at the time, and there simply was no concept of culture or environmental influence to stand up against long-standing hereditarian assumptions [3,5]. Nurture was out.

The emergence of quantitative behavioral genetics

Just as the new science of Mendelian genetics was quickly seized upon for studies of the inheritance of behavioral traits at the turn of the 20th century, so the advent of quantitative genetics several decades later sparked a new discipline and mode of analysis for behavioral traits with complex modes of inheritance. The analytical techniques developed by Fisher, Wright and Haldane, so crucial in reconciling Mendelian genetics with Galtonian quantitative traits, began to be applied to behavioral traits, such as those seen in selected lines or in strain comparisons. Aside from the ability to model and estimate the number of loci involved, based on the phenotypic distributions in F1, F2 and backcross progeny, the analysis also afforded an estimate of the number and nature of gene interactions.

The problem of the heritability of a behavioral trait in *Drosophila,* and whether it could be assigned to a single gene, seems first to have been addressed by J.P. Scott [24] at Wabash College in Indiana. He recognized that a behavioral difference between wild-type flies and *white* or *brown* mutants might not be due exclusively, if at all, to the visible mutations if the strains contained other differences in genetic background. He tested this by crossing wild-type alleles of *white*

or *brown* into the original genetic background of the mutants, and demonstrated that the background genotypes did exert significant effects.

Jerry Hirsch (Figure 4) was the pioneer who brought quantitative genetic analysis to the study of behavior. As a student in Tryon's lab, he began selection experiments for geotaxis preference in *Drosophila* (Figure 5; and see [25]), which he continued with Dobzhansky at Columbia and then for many years thereafter at U. Illinois (reviewed in [26]). In addition to the standard litany of F1, F2 and backcross experiments, Hirsch also introduced the first truly genetic technique into the mix: chromosome analysis [27]. This technique capitalized on the ability in *Drosophila* to manipulate and track the segregation of whole chromosomes without the complication of recombination, first developed by H.J. Muller [28]. As a result, individual chromosomes from a selected line could be isolated onto a neutral genetic background and tested for their relative contribution to the phenotype. In addition, interactions between the set of loci on different chromosomes could be tested directly, albeit not individually. He also promulgated Tryon's idea of population diversity in behavioral analysis — the concept that individuals in a population are behaviorally variable as part of that population's Darwinian repertoire [29].

Hirsch epitomized the approach of those studying 'genetic architecture'. The philosophy of this approach can be summarized as follows: characterize quantitatively a behavioral phenotype in a given population (strain), whether a natural population or a strain resulting from artificial selection, and infer its genetic architecture (number of responsible genes and their interactions) from the analysis of the phenotype and its variance in sets of progeny from test crosses between different populations (strains). The consistent conclusion from nearly all of Hirsch's (and everyone else's) studies of the genetic architecture of behavior is that it is complex and multigenic.

Figure 3. Eugenics pavilion at 1929 Kansas State Fair (courtesy of the American Philosophical Society).

Genetics and behaviorism

Hirsch's work represented a first attempt at reinstating the relevance of genetic influences to the study of behavior. As described above, the high water mark of the eugenics movement occurred in the 1920s, only to subside with the rise of the social sciences. No school of thought was more influential in replacing hereditarian thinking than behaviorism, most closely associated with the psychologist John B. Watson [5]. Watson and his student B.F. Skinner promulgated a scientific view of human nature diametrically opposed to genetic determinism, epitomized by Watson's assertion [30]: "*Give me a dozen healthy infants, well-formed, and my own specified world to bring them up in and I'll guarantee to take any one at random and train him to become any type of specialist I might select — doctor, lawyer, artist, merchant-chief and, yes, even beggar-man and thief, regardless of his talents, penchants, tendencies, abilities, vocations, and race of his ancestors*." With the ascendant social sciences, the dominance of behaviorism, and revulsion at the atrocities associated with the Nazi version of eugenics, the 1950s represented the low ebb for hereditarian explanations of behavior. Genes were irrelevant; nature was now out.

Hirsch's effort to win recognition for the role of genes was based on his recognition that behavior had to be understood in the context of evolution, a concept that goes back to Darwin and which had been revived in the 1920s in the ethological work of Nikolaas Tinbergen and Konrad Lorenz. By introducing the element of population genetics, Hirsch brought the modern evolutionary synthesis to behavioral studies.

First 'genetic dissection' of behavior

Up to this point, the only conclusion that one could draw from studies of heredity and behavior was that aspects of the phenotype could be affected by genotype. Some of the first steps in the direction of genetic dissection of behavior were taken in studies of phototaxis and optomotor response. Brown and Hall [31] at the University of Illinois studied *white* and *Bar* mutants' phototactic responses. They systematically studied the effects of varying light intensity and

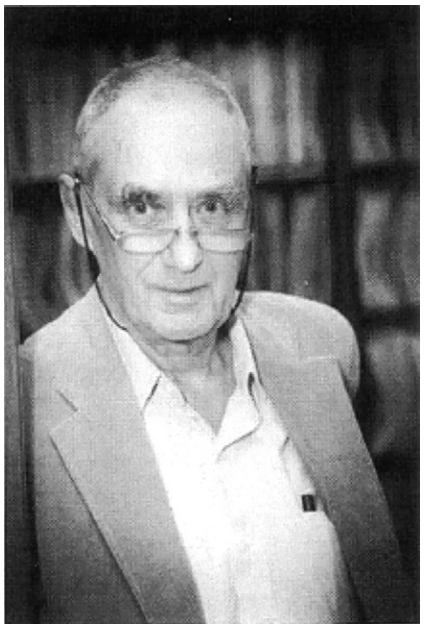


Figure 4. Jerry Hirsch (courtesy of U. Illinois).

wavelength, generating data on the threshold of a fly's response as well as an action spectrum. By counting facets in *Bar* versus normal flies, they were also able to demonstrate a correlation between surface area of the eye and speed and sensitivity of response.

Hans Kalmus of University College London used mutants to test for the functional components necessary for the optomotor response. He built on a behavioral assay developed ten years earlier by two of the pioneers in vision science, who were neither fly biologists nor geneticists: Selig Hecht at Columbia, the premier biophysicist of vision in his day, and his student George Wald, who later went on to identify rhodopsin and describe the photochemical cycle of visual pigment excitation and regeneration. Hecht and Wald [32] measured responses of *Drosophila* to moving stripes — the 'optomotor' response — testing different stripe widths and different intensities of illumination to determine the flies' visual acuity. Perhaps the fact that Hecht had been recruited to the Zoology Department at Columbia University by T. H. Morgan prior to the departure of the fly group ten years earlier, and that Jack Schultz had spent time in his lab learning to isolate photopigments from the fly [12], had something to do with the choice of *Drosophila* for these studies. In the paper, they claim that flies were used because of their genetic uniformity (for a change) and their year-round availability.

Following Hecht and Wald, an extensive and detailed investigation of visual acuity and the optomotor response was conducted by Lotte von Gavel [33] at the University of Königsberg, and then by Kalmus [34] who showed, not surprisingly, that *eyeless* flies have no optomotor response, and that *Bar*-eyed flies, with a reduced number of ommatidia, have a correspondingly reduced optomotor response. More significantly, Kalmus reported that white-eyed flies failed to respond to stripe movement, despite their normal phototactic behavior. He attributed this (correctly, as it turns out) to the loss of the screening pigments between ommatidia. This line of research was resumed twenty years later by Karl G. Götz [35] at the Max-Planck Institut fuer Kybernetik in Tübingen with a more sophisticated and analytical approach to the optomotor response.

Evolutionary perspectives

The Darwinian notion of sexual selection made mating behavior and the attendant species barriers to mating an important subject of evolutionary study. Sturtevant [13] initiated studies of courtship and mating behavior in *Drosophila*, documenting the distinctive courtship behaviors of males vs. females, and performing the first mosaic experiment on behavior with male/female mosaics (gynandromorphs). His observations, along with those of Duncan [36], provided the first evidence that sexual behavior was not correlated with the sex of the gonads — a finding that would be confirmed sixty years later with the identification of brain regions governing courtship behavior [37]. J.M. Rendel in Edinburgh took courtship studies into the realm of mutants by testing for differences in male courtship or female receptivity in *yellow* mutants of *D. subobscura* [38]. This was followed by a series of studies on a more extensive series of mutants in *D. melanogaster*: *yellow, cut*, *vestigial*, *ebony*, *tan*, and *black* [39]. Sexual selection and the conditions for mating that affected it were a focus of studies in a variety of *Drosophila* species by Herman Spieth [40].

The first ethological perspective on fly behavior came, appropriately, out of Tinbergen's laboratory at Oxford, where Margaret Bastock [41], together with her colleague Aubrey Manning [42], performed the first detailed behavioral analysis in *Drosophila* of courtship and the effects of mutants on it. This work gave rise to the division of courtship into the canonical 'steps' of orientation, following, tapping, wing extension and vibration, licking, attempted copulation, and copulation [41].

A similar ethological and evolutionary perspective motivated the initial studies of aggression in flies. These began (as did everything else) with an early description by Sturtevant [13], but were not seriously picked up until Jacobs gave the first detailed description of the behavior [43]. Dow and von Schilcher studied territoriality and its correlation with mating success [44] and Hoffmann conducted the first thorough quantitative analysis of territoriality in *D. melanogaster* and its sibling species *D. simulans* [45]. Since then, aggression in *Drosophila* has become something of a cottage industry.

The legacy of early studies in behavioral genetics

All of the studies described up to this point were carried out in blissful ignorance of any mechanistic explanation for the genes' actions. In the case of selection, strain difference and quantitative genetic studies, the blissful ignorance applied not only to the genes' mechanism of action but also extended to their identity. For the single-gene variants that were studied, none had actually been isolated as a behavior mutant. Instead, mutants had been isolated for some visible characteristic — for example, *yellow* body color, *vestigial* wing — and were later tested in various behavioral paradigms. As a result, neither approach had much to contribute to an understanding of the nervous system. What they did suggest, for those who were observant enough to notice [29,46], was that genes affecting behavior are often pleiotropic, interactive, and part of a much larger conglomeration of genes that produce any given phenotype.

The contemporary, systematic approach of using mutants and genetic manipulations to analyze the

nervous system — sometimes referred to as 'neurogenetics' — began in the mid-1960s when Seymour Benzer, William Pak, Martin Heisenberg and their students and postdocs all began inducing and studying new mutants affecting various behaviors [47–49]. Their philosophy was simple: screen randomly induced mutations for behavioral phenotypes that differ drastically from those of the starting strain, then subject them to the available armamentarium of techniques for analyzing individual genes and their functions. From these beginnings, the field has expanded into the large-scale enterprise that we see today.

Mouse genetics and behavior

The Japanese waltzing mouse described at the beginning of this essay was the first of many mutants with ataxia or otherwise abnormal gait that arose spontaneously in mouse colonies and were shown to have a Mendelian mode of inheritance. These represented the majority of mouse behavioral mutants prior to the current era of mouse genetic engineering. One of the exceptions to this trend was a blind mutant, 'rodless', which was discovered accidentally in 1923 by a doctoral student in William Castle's Bussey Institute at Harvard, while examining pups from his own pet mice as part of a morphological comparison of retinal development in vertebrates [50]. In addition to the histological characterization of the retina in these mice, Keeler showed that the trait was inherited as a Mendelian recessive, and showed that the mutant mice were behaviorally blind in a series of choice maze tests.

In the following decades, new ataxic or blind mutants were noticed sporadically, but they were not studied seriously until the 1960s when Richard Sidman at Harvard began systematically to examine such mutants as they cropped up at the Jackson Laboratory. In keeping with Keeler's original analysis, these neurological mutants of the mouse were shown to have anatomical defects often traceable to developmental or physiological abnormalities [51].

Genomics and behavior

With the dawn of the 21st century, we have entered the era of Genomics.

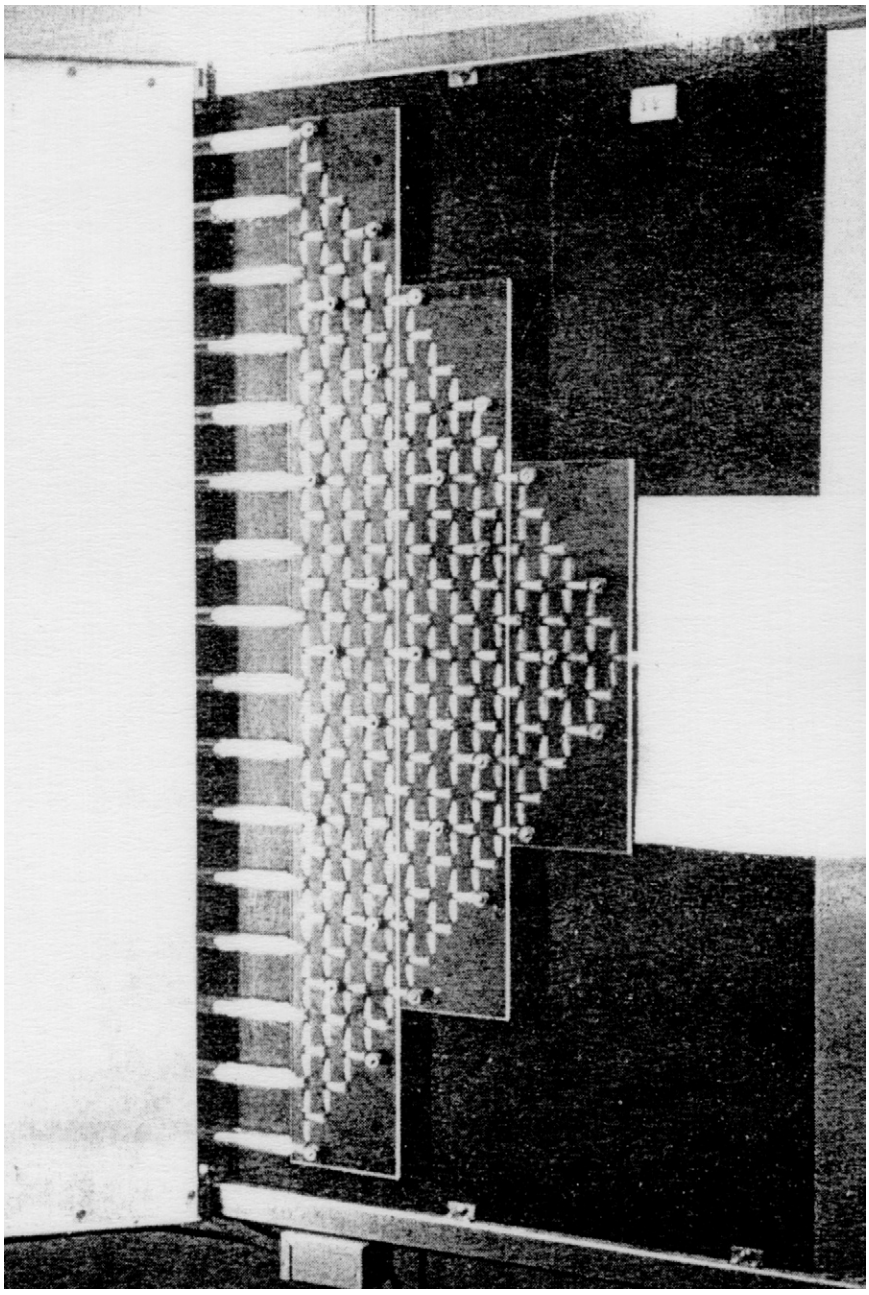


Figure 5. Hirsch's geotaxic apparatus (reproduced with permission from [53].

In an echo of the previous century when genetics made its public debut, we now see a strong tendency to account for any and all unknowns by this newly discovered source of insight. Since the 1960s, the revival of genetic thinking about behavior has received a major boost from the isolation and successful analysis of behavioral mutants in *Drosophila*, from the genetic engineering of behavioral mutants in mice, and from the mapping and identification of human genetic polymorphisms affecting behavior. The study of environmental influences and gene-environment interactions, particularly in humans, has also become much more sophisticated than it was 100 years ago (see [52], for example). We now have a better idea of the scope of the problem. The genetics of behavior is complex, the role of environment is important, and the path from gene to behavior is generally a convoluted one.

Acknowledgments

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Primer

The Price equation

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George Price (1922–1975; Figure 1) was an American scientist whose brief but productive career as an evolutionary theorist during the late 1960s and early 1970s is one of the most fascinating episodes in the history of the discipline. Price trained as a chemist and had worked on the Manhattan Project before becoming a science writer. Self-funded by a large insurance settlement after a botched medical operation, he relocated to London at the end of 1967 and began teaching himself the basics of evolutionary theory, working first in libraries and then at the Galton Laboratory at University College London. Bringing a fresh perspective to the discipline, Price discovered an entirely novel approach to population genetics, and the basis for a general theory of selection — the Price equation. Other accomplishments followed, but the period of discovery was cut tragically short by Price's suicide, after which his name faded into obscurity. However, the Price equation has come to underpin several key areas of evolutionary theory, and is beginning to illuminate difficult issues in other disciplines.

The Price equation

The Price equation is a simple mathematical statement about change. In its usual formulation, it describes how the average value of any character — body weight, antler size, proclivity to altruism — changes in a biological population from one generation to the next. Price denoted the individual's character value as z, its number of offspring as w, and the discrepancy between the character values of itself and its offspring as Δz, and showed that the change in the population average value of the character between parent and offspring generations is:

$$\Delta \bar{z} = \mathrm{cov}(w/\bar{w}, z) + \mathrm{E}((w/\bar{w})\Delta z) \qquad (1)$$

where overbars denote population averages (see Box 1 for a simple derivation).