PERSPECTIVES

T. H. Morgan's resistance to the chromosome theory

Keith R. Benson

The history of science often emphasizes the great discoveries, but neglects to mention that many aspects of these discoveries were frequently known in advance. Such was the case for the chromosome theory of inheritance. Although the behaviour of the chromosome in fertilization and cell development was known before Thomas Hunt Morgan's work, its role in the inheritance of particulate traits was not appreciated. Morgan's relationship with the chromosome theory of inheritance provides a good case study to illustrate how theoretical issues can both impede and facilitate science.

Thomas Hunt Morgan's acceptance, in 1910, of the chromosome as the carrier of heritable traits has been hailed as one of the most important scientific discoveries of the twentieth century[1]. But historical accounts of Morgan's contributions to the emerging discipline of genetics often omit the reason it took biologists so long to appreciate the role of chromosomes in inheritance. After all, chromatin material had been identified over 30 years before Morgan's work on *Drosophila*, the behaviour of the chromosomes in mitosis and meiosis had been well researched, and the association of the so-called accessory (sex) chromosomes with sexual dimorphism had been described. But many descriptions of Morgan's work have neglected the historical context of the period from 1880 to 1910, making the development of chromosome theory seem inevitable. A much more satisfactory history is obtained by critically evaluating not only the growing empirical evidence for the role of chromosomes in inheritance, but also by examining the theoretical milieu in which the empirical studies were embedded. In this manner, we can appreciate the powerful hold of theory over scientific practice, as well as the important conceptual shift that accompanied Morgan's seminal work.

Blending inheritance and variation

Like so many new scientific ideas, the chromosome theory of Mendelian heredity had to overcome well-entrenched conceptual obstacles. That is, for all of the nineteenth century, ideas of inheritance and variation (the two concepts were inextricably bound together during the 1800s) depended on the notion that whatever was passed from parent to offspring had to be contained in the (male and female) seminal material[2]. The offspring, accordingly, was the result of the mixture of these blended materials. This idea, referred to as blending inheritance, explained much of what was observed in reproduction. Normally, offspring were remarkably similar to the parental stock, sometimes seeming to be a complete hybrid of the two contributors. Certainly, reproduction did not seem to produce any characters that were not observed in parental stocks (including distant relatives). So, for most naturalists, reproduction was a conservative process, intended by nature to keep the species true to its type[3,4]. Ideas about species change, offered by a few daring naturalists in the early part of the nineteenth century (for example, the French biologist Lamarck), usually emphasized the role of the environment to produce the needed change — the species was simply incapable of changing on its own.

Similarly, blending inheritance explained the continuous nature of variation, another observation stressed by Charles Darwin. Shown most clearly in his long and tedious work on barnacles, variation was abundant in nature, even in a species that was considered to be clearly distinguished from other species[5,6]. Although he could not explain the cause of this variation, Darwin did highlight its ubiquity. Darwin's cousin, Francis Galton, the founder of the biometrical school in England, supported Darwin by emphasizing how measurable variation gathered about a median level[7]. For example, when soldiers were asked to line up by height, there were a few very short soldiers and almost the same number of very tall soldiers, but most men were of a similar median height. Other examples such as this helped to illustrate the continuous nature of variation, and reinforced the idea of blended traits.

Despite its successes, blending inheritance presented Darwin with one of his most significant problems. When any variation on the parental trait appeared in the offspring, blending inheritance explained how it would soon be 'swamped' by subsequent reproductive acts. After all, the original seminal material would lack the variable trait and, as a result, subsequent mating would restore the variable type closer to the original species type. Well aware of this problem, Darwin spent a considerable part of his career attempting to determine the exact cause and nature of variation, hoping to connect it to inheritance and always finding himself vexed by the idea of blended traits. But in 1865 he struck out in a new direction. In that year, Darwin offered in manuscript form his "Provisional hypothesis of pangenesis", which suggested that the seminal material actually contained tiny gemmules which

would grow to form cells in the new organism. (Gemmules were small particles generated from each bodily part of the organism; they collected in the sexual organs from which they were transmitted by reproduction.) These gemmules, which amounted to an early particulate explanation for inheritance, could be altered under selective pressure to produce change in the offspring of the pressured parental stock. Apparently buoyed by the response to the *Origin of Species*, Darwin dared to append this new idea to his book, *The Variation of Animals and Plants under Domestication*, a two-volume work which investigated the phenomena of inheritance and variation, published in 1868 (REF. 8). Although the book found general favour, the idea of pangenesis (Darwin's theory of inheritance), including its suggestion that traits acquired during the lifetime of an individual could be transmitted to its offspring, was almost uniformly rejected. Galton, who had been such a strong supporter of his cousin's earlier work, scoffed at the gemmules and advised Darwin to drop the idea. In fact, Galton experimented on rabbits with different fur colour to illustrate that gemmules could not be carried in the blood because transfusing the blood between rabbits produced no change, as would be predicted by Darwin's speculative idea.

So, by 1870, biologists in Europe were just as confused as Darwin about the variable character of inherited material. In fact, when Gregor Mendel implicitly offered a new version of inheritance, and referred to "characters" that were passed discretely from one generation to another, his contribution was not fully appreciated by Darwin, or indeed by
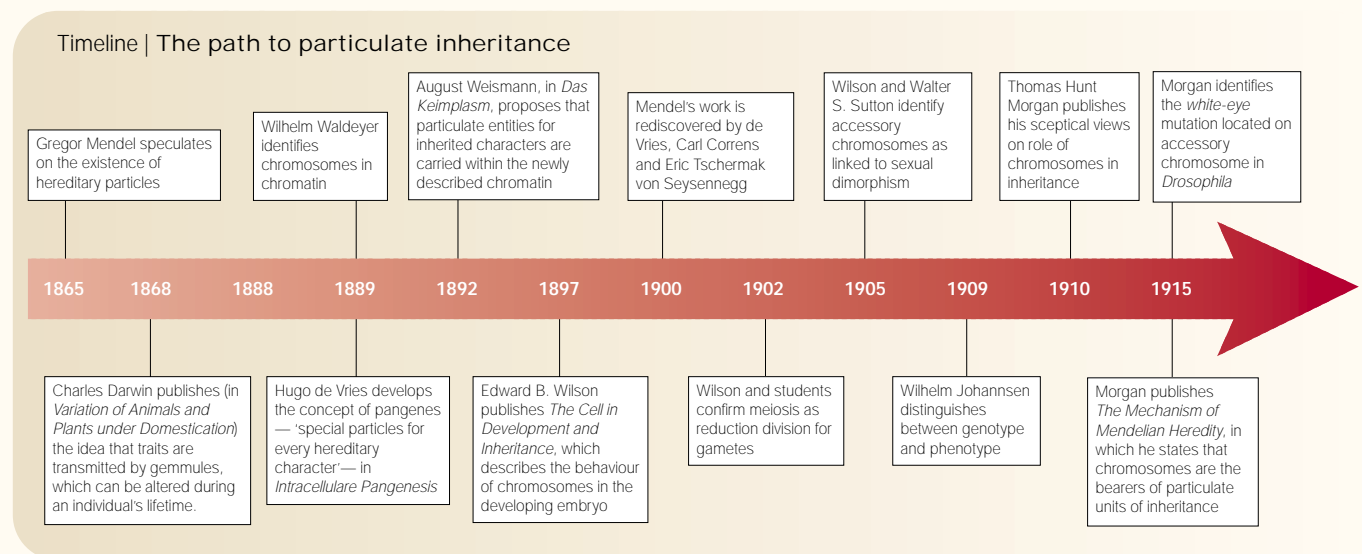
> "The job of the analytical biological researcher was to design an experiment in which nature could be asked a question and, more importantly, to which nature could provide an answer."

most other biologists. This is because Mendel addressed only the passing of traits from one generation to the next, saying nothing about the problem of variation. Instead of following Mendel, many biologists began to pursue work in embryology, following Darwin's suggestion that the embryo retained information of ancestral (evolutionary) relationships[9]. If this were true, the embryo would also provide hints for variation. Fortunately, microscopists developed several new techniques (see below) that enabled biologists to investigate early cell developments. Consequently, the search for answers about inheritance and variation moved into the new biological laboratories and institutes at the end of the nineteenth century, where the exciting techniques offered unique opportunities for experimental manipulation and cutting-edge research[10,11].

Speculation, particles and chromatin
As mentioned above, ideas concerning particulate inheritance (including Darwin's) were rejected mainly because of the solidity of the concept of blending inheritance; that is, particles seemed to suggest discontinuous variation, whereas blending inheritance under-

scored the continuous nature of variation that was observed. Furthermore, there was no empirical evidence to support the existence of heritable particles. Instead, most interpretations of inheritance pointed to the blending of the variable seminal material (Darwin's idea of gemmules even sought to explain how traits appeared to be the blended result of biparental inheritance). Even Mendel's implied particles garnered little attention. But the new particulate perspective on inheritance, heavily steeped in speculation, did not go away. August Weismann, a dedicated Darwinian biologist working in Freiburg, Germany, who wanted to eliminate any vestige of acquired traits from Darwinian evolution theory, imagined the existence of particulate entities for inherited characters that were probably carried in the newly described chromatin (see TIMELINE). After Wilhelm Waldeyer's identity of chromosomes (literally 'coloured bodies') within the chromatin in 1888, Hugo de Vries proposed that these parts of the nucleus actually consisted of invisible "pangenes," which were "special particles for every hereditary character"[12]. A little more than ten years later, in 1900, Mendel's paper from 35 years earlier was 'rediscovered', and even more interest was directed towards the speculative particles for characters. (Mendel did not speculate on the nature of the characters transmitted from generation to generation, except to note that they designated different traits in germ cells.)

Even William Keith Brooks, one of the founding fathers of American biology and a committed Darwinian, began to dabble with the imagined units. In an address to the American Association for the Advancement of Science meeting in Buffalo, New York, in 1876,

Timeline | **The path to particulate inheritance**

Gregor Mendel speculates on the existence of hereditary particles

Wilhelm Waldeyer identifies chromosomes in chromatin

August Weismann, in *Das Keimplasm*, proposes that particulate entities for inherited characters are carried within the newly described chromatin

Mendel's work is rediscovered by de Vries, Carl Correns and Eric Tschermak von Seysennegg

Wilson and Walter S. Sutton identify accessory chromosomes as linked to sexual dimorphism

Thomas Hunt Morgan publishes his sceptical views on role of chromosomes in inheritance

Morgan identifies the *white-eye* mutation located on accessory chromosome in *Drosophila*

1865 1868 1888 1889 1892 1897 1900 1902 1905 1909 1910 1915

Charles Darwin publishes (in *Variation of Animals and Plants under Domestication*) the idea that traits are transmitted by gemmules, which can be altered during an individual's lifetime.

Hugo de Vries develops the concept of pangenes — 'special particles for every hereditary character'— in *Intracellulare Pangenesis*

Edward B. Wilson publishes *The Cell in Development and Inheritance*, which describes the behaviour of chromosomes in the developing embryo

Wilson and students confirm meiosis as reduction division for gametes

Wilhelm Johannsen distinguishes between genotype and phenotype

Morgan publishes *The Mechanism of Mendelian Heredity*, in which he states that chromosomes are the bearers of particulate units of inheritance

he delivered a paper entitled "A provisional hypothesis of pangenesis", a self-conscious adoption of Darwin's idea[8]. By 1883, he had expanded this into a monograph, *The Law of Heredity*, in which he attempted to strengthen several of the weak points of Darwin's earlier particulate view[13]. In particular, Darwin had suggested a gemmule for each cell of the body, an enormous number that would need to be packed into the germ cells. Brooks minimized the number of gemmules by suggesting that they were "thrown-off" (that is, transmitted to the next generation) only by those parts of the organisms that were experiencing selective pressure, thus minimizing their number but retaining the important role of environmental influence. These ideas, along with those of Darwin and, after 1890, those of Weismann and de Vries, were regularly discussed by Brooks's students in the 'Morphological Seminary' at Johns Hopkins University, the graduate-level seminar in which these biological problems were first considered in the United States[14]. But the discussion was generally not one in which the particulate ideas of inheritance were favourably entertained. Other than Brooks (and perhaps Charles O. Whitman at Woods Hole and Chicago), most of the younger biologists found little sympathy with a biology that championed speculation over observation and experimentation. This was especially true of the hypotheses of particulate units of inheritance, for which there was no empirical evidence. Instead, young American biologists such as Edmund

Figure 1 | **Edmund Beecher Wilson with young boy.** (© Stazione Zoologica Anton Dohrn (ASZN: La. 127.54).)

Box 1 | **Americans and the new biology**
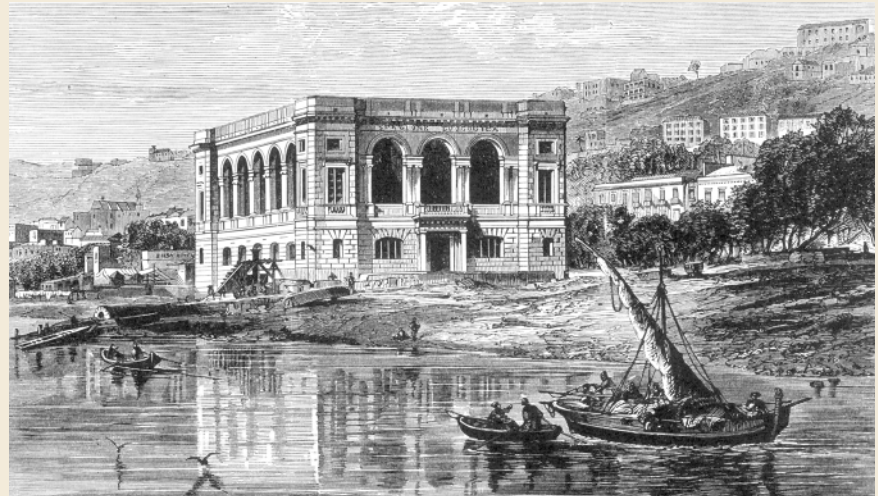
The expansion of American biology that occurred from 1880 to 1915 was directly related to its new institutional setting and the excitement associated with the possibility of experimental and instrumental approaches in biology. Laboratories and experimentation had already been shown to be crucial to the other sciences in Europe, especially the physical sciences, in which the cloud of the occult had been removed from electricity, magnetism, and a host of chemical phenomena. Similarly, in the life sciences, gains had been made in the new science of microbiology, in which instruments were used to discover the role of microbial agents in causing specific diseases. Some biologists argued that these same experiences could be achieved in new investigations into the problems of inheritance and variation, the twin and inseparable problems behind biology's nineteenth-century unifying theory, evolution.

But in a country such as the United States, which lacked any well-defined tradition of biology, how could this be done? Where did one look for exemplars? European science served as the source of models for the creation of new institutions in the United States, and as a source of exposure to new approaches in biology through American visits and graduate work in Europe[10]. For biology, the institution that offered both was the Stazione Zoologica in Naples (see figure), referred to by Charles O. Whitman as the "Mecca for biologists"[11]. It was here that Americans were exposed to the new oil-immersion microscopes that increased the level of resolution in light microscopy. Rotary microtomes — instruments that enabled the biologists to slice tissue into extremely thin sections — were also invented, allowing for close microscopical examination. In addition, a new laboratory technique that involved the fixing and differential staining of tissue allowed the laboratory worker to differentiate between the structures in the tissue, especially the parts of the cell involved in cellular division and embryological development. As a result, the "Naples Method", which emphasized the examination of the details of cellular ultrastructure (which soon included chromatin and chromosomes), was imported back to the United States. (Image © Stazione Zoologica Anton Dohrn.)

Beecher Wilson (FIG. 1) and Thomas Hunt Morgan wanted to base their new understanding of inheritance and variation on experimental and laboratory evidence, especially evidence from microscopical studies. After the encouragement of their mentors, they extended their quest to Europe (BOX 1).

Cytology, Wilson and Morgan

Wilson and Morgan (FIG. 2) are perhaps the best-known students of Brooks at Johns Hopkins. Wilson, who was Brooks's first graduate student, was drawn to questions of inheritance and variation, and to the microscopical approaches that seemed to provide the most promising attack on them. Adept with both the microscope and embryological materials, he frequented Hopkins's Chesapeake Zoological Laboratory and then, in 1882, left the United States for the biology laboratories of Europe. Here, Wilson saw the new approaches first-hand, and spent part of the year at biology's Mecca, the Stazione Zoologica in Naples. Ten years later, he once again went abroad, on this occasion spending most of his time working with Anton Dohrn at Naples. During this period, he also met the German embryologist Hans Driesch.

Back in the United States, Wilson settled at Columbia University in the 1890s, where he worked during term time, and at the Marine Biological Laboratory (MBL) at
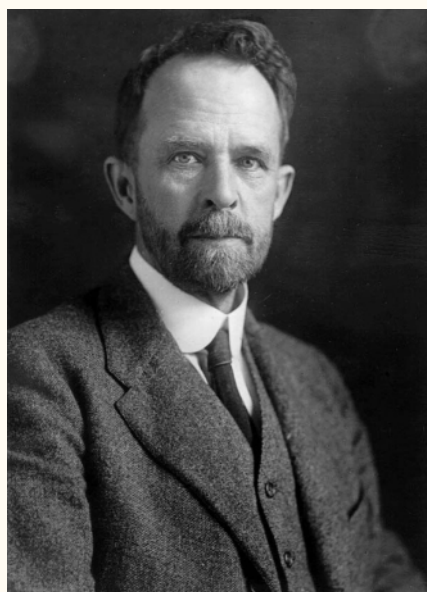
Figure 2 | **Thomas Hunt Morgan.** (Image courtesy of The Marine Biological Laboratory Archives.)

"… not in sympathy with all this modern way of referring everything to the chromosomes and I am continually in hot water, for I live in an atmosphere saturated with chromosomic acid and blue dyes."

Woods Hole (located on the Atlantic Coast at Cape Cod, Massachusetts); here, he taught cytology and microscopical technique, and worked with Edwin G. Conklin to refine their studies of cell lineage[15]. By tracing the developmental events from fertilization through late stages of blastula formation, cell-lineage studies offered a new approach to investigate how inheritance and variation operated in the newly fertilized embryo. It was their hope that such careful studies of many different organisms could reveal patterns of development, leading to new perspectives on the epigenetic processes of inheritance and variation. Wilson was well acquainted with the European work on cellular ultrastructure, in particular the studies of the orderly performance of chromosomes in the developing cell. But he was not too impressed with the idea that these structures could provide a comprehensive explanation for inheritance and variation. Much of this information found its way into Wilson's first book, *The Cell in Development and Inheritance*, first published in 1896 (REF. 16).

During the summer sessions of the MBL, Wilson and Morgan discussed the important problem of development with each other and with many of their colleagues. All of them wanted to know what controlled the growing specificity of the embryo as it emerged from a fertilized but undifferentiated egg to a highly organized structure. In the 1896 version of his book, Wilson showed the scepticism characteristic of American biologists for any explanation that pointed to an isolated part of the cell, and rejected any theoretical position that emphasized only the role of the nucleus. Even when he and his students were able to associate the meiotic events leading to gamete formation with the newly rediscovered Mendelian principles (work published from 1902), Wilson still did not expand the role of the chromosomes[17]. In fact, in 1905, he published a work in *Science* which illustrated the relationship between sexual dimorphism and differences in chromosome structure[18], but concluded only by stating that there was "no doubt that a definite connection of some kind between chromosomes and the determination of sex exists in these animals". Wilson's use of the phrase "connection of some kind" and his specific reference to "these animals" reveals his hesitancy to ascribe too much to these observations. Clearly, the evidence pointing to the role of chromosomes in inheritance was growing, but it was evidence that had not fallen on receptive ground.

Morgan followed a similar pathway to Wilson, his elder colleague, soon finding himself along the shores of the Bay of Naples in the summer of 1894, where he enjoyed the science of the Stazione Zoologica and the company of Dohrn, the laboratory's enthusiastic and sophisticated director[19]. Morgan, who earlier had been exposed to Wilson's new orientation in cytology at the MBL, took a keen interest in what regulated the growing specificity of an organism as it developed. Although all organisms began as single cells, what happened to the cells as they divided? Did they all receive the same information or did development result in a growing specificity of the actual cellular material, explaining differentiation and, perhaps, inheritance? He also stressed that any explanation for these problems had to be rooted in the organism and in what could be observed, not in any speculative particles. He was fortunate to find a kindred spirit in Wilson's German friend Driesch, who was interested in the same set of problems[19].

Driesch was an experimentalist *par excellence*. Along with Wilhelm Roux, he had pioneered a new orientation in developmental biology, which they referred to as *Entwicklungsmechanik*, or "developmental mechanics". The job of the analytical biological researcher was to design an experiment in which nature could be asked a question and, more importantly, to which nature could provide an answer. Morgan became an immediate adherent to this new approach because it highlighted empirical observations, not speculative meanderings. When Morgan returned to his teaching position at Bryn Mawr College, Pennsylvania, he published his distaste for Weismann, and his speculative ideas about inheritance and his own desire to construct an "experimental embryology" in the United States[20]. Furthermore, he became a self-proclaimed champion of the methods of *Entwicklungsmechanik*, and a tireless critic of colleagues who emphasized "old Darwinian notions" (Conklin) or who retained "all the old worn-out themes of the metaphysicians" (Brooks)[21]. Even Driesch came in for Morgan's criticism when he attempted to explain the workings of a totipotential embryo as coming under the influence of vital forces. Also under attack were any hypothetical extensions of the cytological evidence, especially those particulate explanations for heredity that pointed to a role for the newly described chromosomes. Such explanations seemed to Morgan to smack of the outmoded idea of preformation, or the inheritance of wholly formed parts from the parent. As a modern biologist trained in embryology, epigenetic development (from undifferentiated and unformed matter) was the only acceptable position.

Early in the twentieth century, Morgan expressed his first scorn for speculative nuclear particles when he claimed to Driesch that he was having a "beastly time" with Karl W. von Nägeli's "idioplasm" — a nominalistic term for some unspecified portion of the nucleus that was involved in the intricate interaction between inheritance and variation[22]. By 1905, the chromosomal structures had received the same sceptical response from the American experimentalist. This reaction was notable, because it indicates how powerful a hold the former ideas of the blending of inheritance had over American biologists. At the very least, the lack of a clear alternative to blending inheritance, and one that was based on observational evidence, blocked the consideration of ideas too reminiscent of nineteenth-century speculations concerning particulate units. Even more notable is the fact that Morgan's own close colleague, Wilson, was now working on chromosomal

behaviour in insects, first finding a connection between the chromosomes and Mendel's idea of unit characters, and then associating them with insect sexual dimorphism. Walter S. Sutton, Wilson's student, even claimed in an article in the 1903 edition of *Biological Bulletin* that the new information could explain how heritable units could be particulate, but that the characters could retain the continuous variation observed in nature[23].

Despite the excitement across the hallway at Columbia University, Morgan remained convinced that particles could not explain inheritance and variation. At the end of 1905, he wrote his own interpretation of the work in an article in *Science*[24], suggesting that sex determination was chemical, not morphological. In other words, the chromosomes did not settle the issue until the physical explanation of their operation was known. In letters to Driesch, he expressed this same agnosticism about the chromosomes. Claiming that Wilson was "wild over chromosomes", he suggested that the cytoplasm was just as active in inheritance and development as the nucleus[25]. In a second letter in 1905, Morgan wrote "As to chromosomes I am in the thick of it here … On the contrary I argue that the *protoplasm* may account for the results"[26]. In other words, it was the blending of the two protoplasms, one male and one female, that explained inheritance and variation, not the sole operation of particulate chromosomes. By 1906, Morgan had become antagonistic, arguing that he was going after chromosome theory and that he personally was "… not in sympathy with all this modern way of referring everything to the chromosomes and I am continually in hot water, for I live in an atmosphere saturated with chromosomic acid and blue dyes"[27]. In 1907, Morgan reminded readers in *Science* of the old problem with preformation, an issue that would be resurrected with the idea that chromosomes were passed from generation to generation as heritable particles. That is, just like the eighteenth-century mechanical philosophers who adopted preformation, biologists who held that chromosomes were responsible for inheritance would have to confront the idea that this material existed, fully formed, before development. He encouraged his readers to look for internal factors (chemical and physical) not external factors (preformed chromosomes) for inheritance and variation[28]. And to underscore his position, he reminded Driesch that the two of them "have been very sceptical always about chromosomes"[29].

A few years later, Morgan still expressed doubts about the role of chromosomes in inheritance, but now his doubts contained openings for a new interpretation. Part of his slow conversion to a new attitude about chromosomes came from work he began on *Drosophila*, a fruitfly with exceptionally large and malleable chromosomes. In 1910, after working for more than a year on these animals, he noted in an article in *American Naturalist* that the new attention to "chromosomal behaviour", although not completely convincing, "is nevertheless, I think, worth considering"[28]. In fact, in this same article, Morgan began to separate, for the first time, issues of inheritance from developmental processes. To Driesch, he confided that he needed more experimental evidence, but that sex-linked characters "may throw further light on the process of heredity"[31]. And throw light they did! By the end of the year, he published the paper that would begin the eventual but inexorable shift from blending ideas to particulate ideas, "Sex limited inheritance in

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"… the new attention to 'chromosomal behaviour', although not completely convincing, 'is nevertheless, I think, worth considering.'"

Drosophila"[32]. In this paper, Morgan notes that a new character, white eye, could not be explained by normal Mendelian patterns of inheritance, unless the part of the chromosome responsible for eye colour was carried on the accessory (sex) chromosome. If it were, then the experimental results he obtained in the "fly room" at Columbia could be explained. Additional evidence corroborated his supposition and now, for the first time, Morgan had physical evidence (phenotype) for the heritable units (genotype of the chromosome). To Driesch, he wrote that his analytical work "bears fundamentally on the problem of development" in addition to inheritance, and that he now viewed "the chromosomes to be the bearers of the hereditary materials"[33]. So, by 1912, Morgan had emerged as an experimental biologist who no longer refrained from speculative extensions of experimental work. More importantly, he did this only after he had accumulated enough experimental evidence to show that blending inheritance (based on the chemical role of the protoplasm) could no longer be supported. Instead, the laboratory work that he had conducted at Columbia and Woods Hole had clearly illustrated the role of the chromosomes as the bearers of particulate units of inheritance. In 1915, he and his graduate students published the principal conceptual work, *Mechanisms of Mendelian Heredity*, to explain this shift in allegiance; he associated chromosome theory with Mendel's principles, and impressively constructed the first chromosomal maps, with genetic units to explain traits[34].

Conclusion

I have argued that historical accounts of the development of chromosome theory by Morgan that ignore his long resistance to nuclear explanations for inheritance, fail to appreciate both the hold of blending inheritance on *fin de siècle* biologists, and the American distrust for speculation. Evidence of the continuous nature of variation was supported by the idea of blending inheritance, and alternatives to blending inheritance were considered far too speculative. It was only after Wilson and Morgan amassed considerable experimental and observational evidence that they were able to move beyond their shared conceptions of nineteenth-century ideas.

However, it is even more interesting to note that both Wilson and Morgan continued to position themselves gingerly about the new particulate views. In the 1925 edition of his influential book[16], Wilson noted that the gene was "an hypothetical elementary entity that is essential to, or determines the development of, a particular character". Indeed, when he referred to the new particulate nature of heredity, he opted to emphasize the chromosome, with only rare references to the gene. This was the same attitude that Morgan retained for his entire career. *The Mechanism of Mendelian Heredity* did not mention the word 'gene', probably because of its long association with speculative ideas of particulate heredity. Instead, Morgan adopted the Mendelian term 'factors'. In 1919, when he published *The Physical Basis of Heredity*, Morgan wrote a chapter on "The Particulate Theory of Heredity and the Nature of the Gene"[35]. Interestingly, discussions of the chromosome predominate in the chapter. In fact, his later book, *The Theory of the Gene*, published in 1926, is significant in the paucity of references to the nature of the gene, referring instead to chromosomal events[36]. But then, by the 1920s, Morgan and his colleagues knew a lot about the operation of chromosomes; genes remained speculative units.

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FURTHER INFORMATION Thomas Hunt Morgan | August Weismann | Edmund Beecher Wilson | Stazione Zoologica in Naples | Hans Driesch | Marine Biological Laboratory at Woods Hole | Bryn Mawr College | Preformation | Karl W. von Nägeli | Walter S. Sutton

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TIMELINE

The natural history of *Caenorhabditis elegans* research

Rachel A. Ankeny

The nematode *Caenorhabditis elegans* is well known to practising biologists as a model organism. Early work with *C. elegans* is best understood as part of a descriptive tradition in biological practice. Although the resources that have been generated by the *C. elegans* community have been revolutionary, they were produced by traditional methods and approaches. Here, I review the choice and use of the worm as an experimental organism for genetics and neurobiology that began in the 1960s.

The announcement of the nearly complete sequencing of the genome of the nematode *Caenorhabditis elegans* at the end of 1998 was hailed as a milestone in genomics[1]. Although the genomes of several other organisms had been sequenced by that time[2,3], *C. elegans* was the first multicellular organism to be completely sequenced. Arguably more biological information was available on 'the worm' (as it is commonly termed) than on any other relatively complex organism. This was due to the intense studies of its genetics, development and neurobiology that had been underway since the late 1960s. Here, I examine the choice and use of this nematode as an experimental organism for genetics, with particular focus on the period in the 1960s when the brain was declared to be the "last remaining frontier" for biological investigation. The worm was first chosen for investigation into the nervous system, but proved to be useful for exploring many other biological processes. I argue that early work with *C. elegans* can best be viewed as part of a descriptive tradition in biological practice, and that such descriptions are essential as the basis for successful subsequent experimental and explanatory work, as becomes evident on a close examination of the history of the field.

Choosing *Caenorhabditis elegans*
In June of 1963, Sydney Brenner (FIG. 1) wrote in a letter to Max Perutz, the then director of the Laboratory of Molecular Biology (LMB) in Cambridge, UK, that "nearly all the 'classical' problems of molecular biology have either been solved or will be solved in the next decade … the future of molecular biology lies in the extension of research to other areas of biology, notably development and the nervous system"[4]. Brenner had done extensive work primarily in bacteria and bacteriophage genetics at what came to be known as the LMB. He and Francis Crick, head of the Division of Molecular Genetics at the LMB and Brenner's long-time office partner, had a series of conversations in late 1962 to decide in which direction to take their research. These conversations were in part spurred on in early 1963 by institutional factors, such as the interest of the Medical Research Council (MRC) in expanding the LMB[5] and the trends in biology at that time, which were leading away from molecular biology. During this era and after various successes in molecular biology, notably the identification of the structure of DNA and the details of the coding mechanisms associated with it, several prominent biologists had begun to use particular organisms to study behaviour and the nervous system. These biologists shared Brenner's view that many, if not most, of the 'interesting' problems of molecular biology were solved or close to being solved. Ralph Greenspan claims that the almost unanimous convergence on the nervous system as the new problem of interest "was not by design or agreement, but reflected the sense that here lay the greatest challenge and mystery"[6]. So, what has come to be known as "the worm project" arose in the context of a framework greatly influenced not only by the successes and limitations of previous work with bacteria and bacteriophage, but also by a particular vision of biology, including what molecular