What Determines Sex?

A Study of Converging Approaches, 1880–1916

*By Jane Maienschein**

ORGANISMS ORDINARILY COME IN ONLY TWO SEXES, male or female; there is no third alternative or intermediate sex. This rather obvious fact, so important for the human poetic imagination, has long stimulated scientific curiosity as well. By 1892 Charles Otis Whitman suggested that problems of sex determination held the "highest philosophical interest" in zoology at the time. And Thomas Hunt Morgan wrote in 1906: "Theories of sex determination have flourished like weeds."[1]

Interest in sex determination did not of course begin in 1892 or 1906. All manner of theories had been proffered by all manner of people, beginning with the Presocratics. Geddes and Thomson estimated in their classic work of 1889 that by 1800 more than five hundred theories of sex determination had already appeared.[2] Regarding the quality of these proliferating theories, developmental biologist and evolutionist Edwin Grant Conklin said:

> Hundreds of hypotheses have been advanced to explain this perenially interesting phenomenon. The causes of sex determination have been ascribed to almost every possible external or internal influence and the world is full of people who think they have discovered by personal experience just how sex is determined. Unfortunately these hypotheses and rules are generally founded upon a few observations of selected cases. Since there are only two sexes the chances are that any hypothesis will be right half the time, and if only one forgets the failures of a rule and remembers the times when it holds good it is possible to believe in the influence of food or temperature or age, of war or peace or education on the relative numbers of the sexes, or on almost any other thing. By statistics it has been shown that each of these things influences the sex ratio, and by more extensive statistics it has been proved that they do not.[3]

Around the turn of this century, scientific interest in sex determination intensified for a variety of reasons.[4] Hundreds of papers written by dozens of

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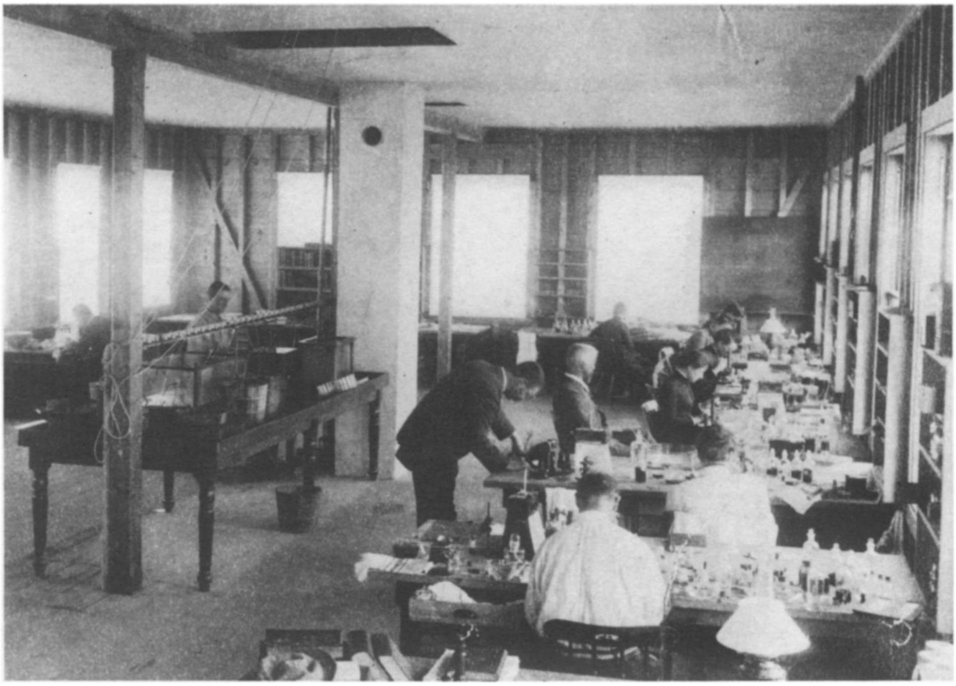
[1] Charles Otis Whitman, *Annual Reports of the Marine Biological Laboratory,* 1892, p. 38; Thomas Hunt Morgan, "Sex Determining Factors in Animals," *Science,* 1907, *25*:382.

[2] Patrick Geddes and J. A. Thomson, *The Evolution of Sex* (London: Walter Scott, 1889), p. 33.

[3] Edwin Grant Conklin, *Heredity and Environment* (Princeton: Princeton Univ. Press, 1915), pp. 139–140.

[4] For discussion of the resurgence of scientific interest in sex determination, see Frederick



The Marine Biological Laboratory (MBL), where much of the work on sex determination was carried out, during its first year of operation (1888). Courtesy of the MBL, Woods Hole, Massachusetts.

researchers appeared in the period 1890–1910. The papers fell into three main clusters which crystallized as three separate research approaches to the question of how individuals come to have one or the other sex. While the approaches overlapped in some respects and underwent changes with time, each remained identifiable prior to 1910: each embraced a cluster of specific theories and had its own assumptions about relevant problems, appropriate methods, and types of acceptable answers. The first, the externalist approach, ascribed sex determination to external conditions that act on the individual in the course of its development. The second, the internalist approach, focused on factors within the individual, maintaining that sex is determined in the egg and manifests itself in morphological and physiological differences within the cytoplasm or nucleus. The third, the hereditarian approach, regarded various inherited "determinants" as basic to sex determination.

The three approaches each had its period of dominance. External factors received the most attention in the 1880s and early 1890s. Internalist studies, inspired by the successes of the German physiological or experimental embryologists, gained importance in the 1890s and 1900s. And the years 1905–1915 brought a stress on heredity, with research efforts focused on chromosomes. This shift should not suggest, however, a triumph of the hereditarian approach. What happened instead is that all three approaches changed, for not one of them could in itself provide a full account of sex determination. The resolution of the problems of sex determination involved a gradual and continual refocusing of questions and approaches. The convergence of different approaches produced a new approach, and by 1915 the result was a reshaped tradition of developmental study with a refined sense of mission and redefined specialty areas. More than a synthesis of previous ideas, the result represents consensus on appropriate directions for future work.

This article will describe the three initial approaches to sex determination, briefly examining the shifting commitments within the groups of biologists subscribing to them as well as the shift of general attention from one group to the next. The individuals chosen for discussion include those whose writings are most often cited and those who best exemplify the assumptions within each approach. I will then discuss the convergence of the three approaches into a new approach that addressed a set of problems not previously regarded as central. This is, then, a story of changing assumptions about what were thought to be appropriate problems and commitments in biology.

I. THE EXTERNALISTS

The externalists held that external environmental conditions act on the developing egg to determine which sex the individual shall actually become. Since the egg is initially capable of becoming either male or female, sex, in their view, is not merely inherited and hence predetermined. These investigators stressed instead the theory of epigenesis, which holds that form is not inherited but emerges only gradually during the course of development in response to external developmental cues. With this belief in the egg's flexibility, the externalists' pri-

Churchill, "Sex and the Single Organism," *Studies in History of Biology,* 1979, *3*:169–171; John Farley, *Gametes and Spores* (Baltimore: Johns Hopkins Univ. Press, 1983).

mary concern was to show that external conditions determine sex. They approached that goal by asking how external conditions affect the ratios of males to females in a population; a change in ratio would, they felt, show a causal connection between external conditions and sex determination.

It is reflective of the externalists' strong epigenetic bias that embryologists at first contributed most significantly to the development of this approach. Various specific theories implicated such external factors as nutrition or temperature in determinating the sex of the egg. Frequently the focus was on nutrition as the determinant of sex. The German zoologist Hermann Landois first brought attention to nutrition and to the externalist position with his widely cited work on the caterpillar *Vanessa* (1867). Landois argued that a population of young caterpillars has more males when poorly nourished and more females when better nourished. While T. H. Morgan later regarded Landois's evidence as "casual," Landois's efforts nonetheless stimulated discussion and support for an externalist viewpoint, especially in the 1880s. By 1896 Edmund Beecher Wilson recorded in his masterful textbook *The Cell* that externalist views had become dominant and suggested that he had sympathy for at least some forms.[5]

Among the other investigators who took up the externalist cause was the German embryologist Gustav Born. Employing the approach of experimental *Entwickelungsmechanik,* which examines the mechanics of development, Born thought he had shown that providing frogs with a rich food supply produces more females and that a greater concentration of spermatozoa in the semen produces more males.[6] Later Born suggested that, at least in higher animals, sex may not be significantly affected by changing food supply or by such factors as age of the parent but is instead determined in the egg. In this respect he moved from a strict externalist position toward an internalist position, but he remained uncertain about how sex determination occurs in lower organisms.[7]

In 1883 and 1885 Emile Yung found that female frogs outnumber males by two to one, a result he attributed to differences in nourishment of the mothers and to other external factors.[8] Like Landois and Born, Yung met with opposition from internalists who maintained that these researchers had only found altered sex ratios, which might be explained otherwise than by externalist theories of sex determination. Critics pointed out that the externalists might simply have witnessed differential mortality, for the results did not positively show that any individual's sex had in fact been changed by the altered environmental conditions. Externalists responded, predictably, that their data did support their

[5] H. Landois, "Gesetz der Entwickelung der Geschlechte bei den Insekten," *Zeitschrift für wissenschaftliche Zoologie,* 1867, p. 17; and T. H. Morgan, *Heredity and Sex* (New York: Columbia Univ. Press, 1913), p. 232; and Edmund Beecher Wilson, *The Cell in Development and Inheritance* (1896; New York: Johnson Reprint, 1966), esp. p. 109.

[6] Gustav Born, "Experimentelle Untersuchungen über die Entstehung der Geschlechtsunterschiede," *Breslauer ärztlichen Zeitschrift,* 1881, *3*:3–28; On *Entwicklungsmechanik* see Frederick Churchill, "Wilhelm Roux and a Program for Embryology" (Ph.D. diss., Harvard Univ., 1966). On experimentation see Jane Maienschein, "Shifting Assumptions in American Biology: Embryology, 1890–1910," *Journal of the History of Biology,* 1981, *14*:89–113; and Maienschein, "Experimental Biology in Transition: Harrison's Embryology, 1895–1910," *Studies in History of Biology,* 1983, *6*:250–286.

[7] Gustav Born, "Die Entwickelung der Geschlechtsdrüsen," *Anatomische Hefte, 2 Abteilung,* 1894, *4*:592–616.

[8] Emile Yung, "De l'influence des variations du milieu physicochimique sur le développement des animaux," *Archives des sciences physiques et naturelles,* 1885, *14*:502–552.

claims and that they had in fact changed the sex of individuals within certain populations. They maintained that their interpretation was just as defensible as any alternatives.

This disagreement underscores the inherent weakness of the externalists' program: all of their studies examined populations, yet they sought to draw conclusions about environmental effects on individuals. Unfortunately, they had no way to prove that an altered environment had changed any individual's sex. Sex remained indeterminate, for one could not both know the sex at one time and know that it had changed at a later time. Once the researcher could observe which sex an individual was, the sex had already been determined. Thus, for pragmatic reasons, externalists were forced to focus on sex ratios within populations. They then sought to correlate those ratios with changes in external conditions, supporting the claim that because the conditions determine the particular ratio, they actually determine an individual's sex.

Entering the debate from what he saw as a different angle, the outspoken cytologist and developmental biologist Richard Hertwig concentrated on one mother and how external changes affect her eggs. Drawing on frog studies, he argued that the temperature of the mother and resulting ripeness of her eggs are crucial in determining the sex of her offspring: lower temperatures at fertilization yield more males. In 1905 he began explaining his theories of sexual development before the Deutsche Zoologische Gesellschaft.[9] There he acknowledged that current opinion regarded sex as fixed in the egg and all expression of sex as simply the result of cell regulation, but he believed nonetheless that external conditions must play a causal role. Because the *Kernplasmarelation,* the relative amounts of nucleus and cytoplasm, varies for the two sexes, he maintained, the sex of an egg depends upon its "ripeness" when fertilized. As a result, eggs left in the uterus for two to three days produce a greatly increased proportion of males. Perhaps the ripeness of the spermatozoa would also prove important, but Hertwig left that as an open question for future work.[10]

In this context Helen King, who had been Morgan's student at Bryn Mawr and was working with E. B. Wilson at Columbia by 1908, decided to examine such results as Hertwig's and possible external influences on frog development. In a series of papers beginning in 1907, she examined the effects of nutrition, right versus left ovary, starvation, ripeness of the egg, temperature, alcohol, changing water content, and acidity. Always an embryologist concerned with changes in development, King found no changes of sex ratios except when she changed the water content. Increased sugar in the water did affect the sex ratio somewhat, producing more males. Yet she felt unclear about the proper interpretation of these results because she could not tell *how* the altered water content had exerted an influence—whether differential sex production or differential mortality had occurred, for example. What was it about the change in water that affected what aspect of sex determination in particular? King's impressive series of detailed experiments thus remained inconclusive in some respects.[11] Both ex-

[9] Richard Hertwig, "Über das Problem der sexuellen Differenzierung," *Verhandlungen der deutschen zoologischen Gesellschaft,* 1905, *15*:186–214; continued in "Weitere Untersuchungen," *ibid.,* 1906, *16*:90–112, and 1907, *17*:55–73.

[10] Hertwig, "Weitere Untersuchungen," pp. 68, 73.

[11] Helen Dean King, "Food as a Factor in the Determination of Sex in Amphibians," *Biological*

ternalists and internalists could find support from different parts of her work.

Two other much-studied organisms raised special questions: the sexually complex rotifer *Hydatina senta* and man. *Hydatina* has three different types of females, distinguished by the eggs they lay: one type produces large eggs, always yielding females, without fertilization; a second produces smaller eggs that develop as males, again without fertilization; and the third produces eggs that are fertilized and yield females. In the 1890s the embryologist Moritz Nussbaum at Bonn began the study of the confusing sex determination in *Hydatina* by demonstrating that the mother's nourishment prior to deposition of her first egg (or during her own early developmental process) determines the type of offspring she will have. Better nourishment yields males, he found. Thus external conditions determine the sex of offspring, though that determination process remains indirect and difficult to interpret. François Emile Maupas (1890) similarly found that temperature affects the results of *Hydatina* offspring by affecting the type of egg that the mother lays.[12]

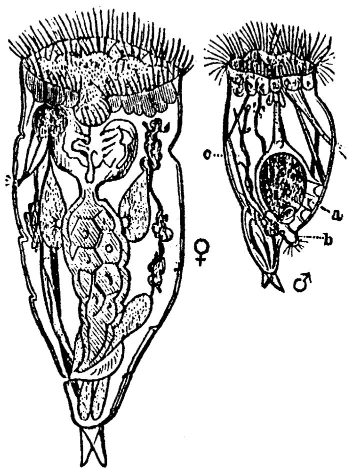


Figure 1. Hydatina senta, *as depicted in Patrick Geddes and J. Arthur Thomson,* The Evolution of Sex *(London: W. Scott, 1901), page 20, showing the relative sizes of male and female.*

The human species raised the same questions about sex determination, with the additional conviction, inspired by the theory of evolution, that controlling man's development might be possible. Numerous papers on human sex determination thus appeared during the period in question, and with them came a changing emphasis within the externalist camp. Embryologists, who had led the externalist cause, gave way in the early 1900s to breeders and to statisticians—to those who were looking at populations and reporting sex ratios at later stages of development than the embryologists had stressed. With this shift came a geographical shift from Germany and the United States to England, for it was

Bulletin, 1907, *8*:40–56; and articles in *ibid.,* 1909, *16*:27–43; 1910, *18*:131–137; 1911, *20*:205–235; and *Journal of Experimental Zoology,* 1912, *12*:319–336.

[12] Moritz Nussbaum, "Geschlechtsentwicklung bei Polypen," *Sitzungsberichte der niederrheinischen Gesellschaft für Natur- und Heilkunde zu Bonn,* 1892, offprint, unpaginated; François Emile Maupas, "Sur la multiplication et la fécondation de l'*Hydatina senta* Elu.," *Comptes-rendus hebdomadaires des séances de l'Académie de Paris,* 1890, *111*:310–312; Maupas, "Sur la fécondation de l'*Hydatina senta* Elu.," *ibid.,* pp. 505–509; and Maupas, "Sur la déterminisme de la sexualité chez l'*Hydatina senta,*" *ibid.,* 1891, *113*:388–390.

largely the British who dominated the breeding tradition and concerned themselves with population statistics.

Carl Düsing at first represented the older group. With comparative studies of humans as well as various animals and plants in 1883 and 1885, he maintained that nutrition determined the sex ratio. Foreshadowing later population work, he concluded that the upper, and hence supposedly better-fed, classes of humans produce more girls, while lower, and hence presumably less well nourished, classes produce more boys. Two decades later, Reginald C. Punnett looked at the London population and found that lower classes have more females and upper classes have more males. While raising the possibility that such differences resulted from nutritional differences, he acknowledged that differential mortality and different breeding habits of different classes might provide a more likely explanation. In 1908 Raymond Pearl and Maud Dewitt Pearl examined births in Buenos Aires (because of the exceptionally accurate records kept there) and found that racially crossed stocks apparently yielded more males than racially uniform stocks. But did this support an externalist position? Not clear, they concluded, since "the chief difficulty involved in maintaining that there is a causal relation between the character of the mating and the sex-ratio lies in the lack of knowledge as to what could be the physiological mechanism by which the causation was effected."[13] Whether external conditions actually cause or merely contribute in a looser way to sex determination had become an open question for some researchers of the externalist approach.

By 1908 consensus had emerged that none of these breeding studies with populations had sufficient control to yield convincing interpretations of sex determination in individuals. Population studies had chiefly served to demonstrate that external factors may change population ratios, but they had not provided direct evidence for external determination of individual sex development. Since the externalist approach had not succeeded in meeting its original goals, it underwent a shift, embracing population studies and deliberately focusing on what sex ratios occur and how those can be changed, rather than on sex determination in individuals. Many externalists began to focus on how changes in populations could be effected and what that might mean for practical breeding work. As for individual sex development, many embryologists moved toward internalist explanations.

In noting these shifts I wish to stress that externalist approaches nonetheless persisted. Leonard Doncaster reported that externalists were still well represented at a 1908 meeting of the zoology and botany sections of the British Association for Advancement of Science in Dublin.[14] A few still sought to establish external conditions as determinants of individual sex, and even those externalists who changed their focus continued to provide an alternative perspective on

[13] Carl Düsing, "Die Faktoren, welche die Sexualität entscheiden," *Jenaische Zeitschrift für Naturwissenschaft,* 1883, *16*:428–464; Düsing, "Die Regulierung des Geschlechtsverhältnisses bei der Vermehrung der Menschen, Tiere, und Pflanzen," *ibid.,* 1884, *17*:593–904; R. C. Punnett, "On Nutrition and Sex-determination in Man," *Proceedings of the Cambridge Philosophical Society,* 1903, *12*:262–273; and Maud Dewitt Pearl and Raymond Pearl, "On the Relation of Race Crossing to the Sex Ratio," *Biol. Bull.,* 1980, *15*:194–205.

[14] Leonard Doncaster, "Recent Work in the Determination of Sex," *Science Progress,* 1909, *4*:90–91.

sex ratios. For not all respectable researchers jumped on the internalist or chromosomal or Mendelian bandwagons shortly after 1900, as some histories of this period imply. Different researchers continued to adopt revised externalist approaches to slightly different problems, and these approaches eventually converged with others into a new approach.

What the externalists had provided was an awareness of population studies and a demonstration of the way external factors can act on the proportion of characters in a population. Population studies did seem to provide information where individual studies could not, including information about how external factors might act (if they did act) in determining sex. But they could *only* tell about populations, not about the fates of individuals within the group: they provided no useful information about what an individual inherits or how that inheritance is translated into actual characters. Those concerns required other, parallel approaches to sex determination problems, particularly those of experimental embryology and cytology.

II. THE INTERNALISTS

The internalists also believed that an individual is initially capable of becoming either male or female, and that the epigenetic process of development determines which. Yet for the internalists the cause of sex determination lies with factors within the egg, not outside it. The egg retains some flexibility and may respond to changed internal conditions with developmental changes. The primary concern for the internalists was to show what happens inside the egg that determines sex. In seeking an answer to this question, internalists divided into two different groups, both concerned with epigenetic development. The first group, the embryologists, concentrated on the egg cytoplasm as locus for determining factors. To this end they used experiments with regeneration, with selective destruction of embryonic parts, and with transplantation of embryonic parts. The second group, the cytologists, focused on the nucleus, relying on traditional microscopic cytological examination of the nucleus and chromosomes.

Unfortunately, neither of the above sets of techniques provides direct information about sex determination. F. H. Pike, an American, suggested separating blastomeres to produce two organisms and then trying to change the sex of one, but that intriguing experiment proved unfeasible. Even Pike evidently did not seriously try it himself.[15] Regeneration of sexual organs, readjustments of the body after cells had been selectively destroyed, and transplantation of sexual parts constituted the methods of the experimental embryologists. These methods could not succeed in showing how sex is determined, however; they yielded information only about changes in the later physiological production of sex. Unfortunately, it seemed that sex might be determined at a very early stage, before secondary sexual characteristics had actually appeared, a stage that proved difficult to study in detail in most organisms. Experimental embryological approaches thus could not illuminate how and why sex is irreversibly determined. The best hope for experimental embryology in the 1890s lay with unraveling the

[15] F. H. Pike, "A Critical and Statistical Study of the Determination of Sex, particularly in Human Offspring," *American Naturalist*, 1907, *41*:319.

way an embryo develops from the egg cell stage and elucidating the patterns and processes of individual development generally. These general rules would presumably also hold for sex production.

As the young American zoologist Shozabura Watasé clarified the matter in 1892, two closely related phenomena of sex differentiation needed to be distinguished: (1) heredity, or "mixture of parental characteristics in the offspring," however that happens, and (2) "sexual differentiation in the organism, in which the parental characters have already been mixed."[16] Others later termed these problems of sex determination and sex production, or heredity and development. Precisely when the determination took place or when the production process began was not at all clear in 1892, but Watasé's distinction helped provide some clarity to the discussions of sex. The internalists began by addressing Watasé's second question, the hereditarians his first.

At a meeting of the American Society of Naturalists at Columbia University in 1906, in contrast to the British meetings of 1908 on which Doncaster reported, the tone was positive toward internalist views and skeptical of externalist approaches. In fact, by 1903 Morgan had already recorded that "In the last few years opinion has begun to turn in the opposite direction, and several attempts have been made to prove that the sex of the embryo is determined in the egg" and not by external factors acting on either the egg or the later developing embryo.[17]

Developmental Approaches: The Cytoplasm and Embryology

The French zoologist Lucien Cuénot admitted in 1899 that he did not know whether sex is determined before or at fertilization, though he was certain that it is determined at least by the latter time. But is the egg a latent hermaphrodite or are eggs sexually dimorphic from the beginning?[18] About this he was not yet sure.

A number of American biologists, usually considered embryologists, did feel certain. They maintained that at first eggs remain potentially of either sex, hence effectively hermaphroditic or indeterminate. The action of the entire organism then determines which sex the individual shall become. An individual, therefore, does not inherit its sex but develops it. Thus one must understand what Watasé called sex production in order to explain sex determination.

On this point the biologist-historians Scott Gilbert and Garland Allen have suggested that the employment of the terms heredity and development changed in the period 1890–1910.[19] In 1890 a satisfactory account of sex production, or development, would have had to explain both Watasé's heredity and his differentiation. An account of inherited material alone could only suggest how the individual became *predisposed* to become one sex or the other but could not

[16] S. Watasé, "On the Phenomena of Sex-Differentiation," *Journal of Morphology,* 1892, *6*:481.

[17] The American Society of Naturalists met at Columbia University on 28 December 1906, with papers appearing in *Science,* 1907, *25*:366–384. See also Morgan, "Recent Theories in Regard to the Determination of Sex," *Popular Science Monthly,* 1903, *64*:97.

[18] Lucien Cuénot, "Sur la détermination du sexe chez les animaux," *Bulletin scientifique de la France et de la Belgique,* 1899, *32*:462–527, esp. pp. 525–526.

[19] Scott Gilbert, "The Embryological Origins of the Gene Theory," *J. Hist. Biol.,* 1978, *11*:307–351; Garland Allen, "T. H. Morgan and the Split Between Embryology and Genetics, 1910–1926," paper delivered at the British Society for Developmental Biology, Nottingham, 1983.

provide a satisfactory explanation of sex production. The type of explanation sought was broader, with the concept of heredity embracing development as well, as Allen suggests, and with development encompassing both also, as Gilbert demonstrates. This way of integrating problems of heredity and development led proponents to emphasize the organism as a whole and the role of the entire cytoplasm in particular.

For example, although Charles Otis Whitman did not address sex determination directly, he urged consideration of the "biological economy of organisms." Biologists cannot separate physiology from morphology or heredity from development, Whitman believed, but must examine the way physiological action of inherited factors brings about development of morphological characteristics.[20] In the 1890s sex differentiation offered a particularly exciting area of research at the Marine Biological Laboratory at Woods Hole (MBL), of which Whitman was the first director. Whitman saw possibilities for such studies of "biological economy," or complementary physiology and morphology.

Edwin Grant Conklin, who taught at the University of Pennsylvania, then at Princeton, and carried out research during the summers at the MBL, agreed with Whitman. In particular, Conklin always stressed that one must examine the role of cytoplasmic processes. Without denying that some of the localization in cytoplasm is inherited, Conklin nonetheless argued for the importance of developmental responses to internal and external conditions as "determining" characteristics. He found preformation, or predetermination by inherited determinants, unacceptable; he always considered himself "a friend of the egg"—the whole egg.[21]

The American zoologist Frank Rattray Lillie, also doing research at the MBL, similarly remained an outspoken proponent of the view that the cytoplasm and whole organism cause sex determination. He maintained that at first the organism definitely exhibits a stage of sexual indifference; then the physiological factors, directed by the egg and balanced by those from the sperm, express themselves. Lillie concluded in 1906: "It seems to me that this conception is as necessary and fundamental today as it ever appeared to be, and that we cannot depart from it without involving ourselves in absolutely hopeless theoretical difficulties."[22] It might be, as Lillie acknowledged, that the gametes are physiologically, even if not morphologically, differentiated. Perhaps they are predisposed to become one sex or the other. But it is only the balance of the whole organism, responding to external and internal physiological demands, that actually produces and fixes the sex.

Militantly, the American nonconformist Charles Manning Child agreed. He consistently emphasized that characteristics, including sex, cannot properly be said to be inherited. Rather, he argued:

> It is the fundamental reaction system which is inherited, not a multitude of distinct, qualitatively different substances or other entities with a definite spatial localization. Development is not a distribution of the different qualities to different regions, but

[20] Whitman. *MBL Annual Reports* (cit. n. 1), p. 35.

[21] Conklin, "Mosaic vs. Equipotential Development," *American Naturalist,* 1933, *67*:296.

[22] See Frank Lillie, "Sex Determination in Relation to Fertilization and Parthenogenesis," *Science,* 1907, *25*:375, 376; quoting from Lillie, "The Theory of Individual Development," *Pop. Sci. Month.,* 1909, *75*:252.

> simply the realization of possibilities, of capabilities of the reaction system. The process of realization differs in different regions because the conditions are different. Neither characters nor factors as distinct entities are inherited, but rather possibilities, which are given in the physico-chemical constitution of the fundamental reaction system, but not necessarily localized in this or that part of it. [23]

Though the details of Child's own theories found little support, they did help keep an important physiological epigenetic viewpoint alive.

Jacques Loeb likewise held that the physiological expression of characters, through internal secretions and hormonal action, explains sex development and hence sex determination. As late as 1916 Loeb suggested that inheritance may "determine or favour in a way as yet unknown, the formation of the specific internal secretion" that produces sexual differentiation. And yet, in keeping with his general goal of controlling development, Loeb concluded that "it may be clear that when it is possible to modify secretions by outside conditions or to feed the body with certain as yet unknown specific substances the influences of the sex chromosomes upon the determination may be overcome."[24] With more information, the embryologist could hopefully override the hereditary directive.

In their belief that productive research was to be carried out only on the physiological processes of character production, such developmental biologists as Child and Loeb generally set aside questions about heredity as that subject was later understood. Geoffrey Smith's series of studies on internal secretions illustrates this attitude, as does Oscar Riddle's work on melanin or J. T. Cunningham's emphasis on chemical stimuli as causes of development.[25] Others, like Richard Goldschmidt, later tried to unite heredity and physiology of development along the unifying lines envisioned by Whitman and other Americans at the Marine Biological Laboratory in the 1890s.[26] Such efforts to account for development of the organism as a whole have often failed to provide results that attract attention or convince others, and they are therefore often overlooked in the history of biology. Yet the internalist emphasis on cytoplasm kept attention focused on the problems of sex production and expression of characteristics. The emphasis underlines the conviction, dominant prior to 1910 among embryologists, that an adequate explanation of character determination must be developmental and not "merely" hereditary. Today this emphasis is gradually reentering parts of developmental biology.[27]

[23] Charles Manning Child, *Individuality in Organisms* (Chicago: Univ. Chicago Press, 1915), p. 202.

[24] Jacques Loeb, *The Organism as a Whole* (New York: Putnam, 1916), p. 228; on Loeb, see Philip Pauly, "Jacques Loeb and The Control of Life: An Experimental Biologist in Germany and America, 1859–1924" (Ph.D. diss., Johns Hopkins Univ., 1980), p. 228.

[25] Geoffrey Smith, "Studies in the Experimental Analysis of Sex," *Quarterly Journal of Microscopical Science,* Pts. 1 and 2, 1910, *62*:577–604; Pts. 3 and 4, 1910, *63*:225–240; Pt. 5, 1911, *64*:591–612; Pt. 6, 1911, *65*:45–51; Pt. 7, 1911, *65*:251–265; Pt. 8, 1912, *65*:439–471; Pt. 9, 1912, *66*:159–170; Pt. 10, 1913, *67*:267–295; Oscar Riddle, "Our Knowledge of Melanin Color Formation and Its Bearing on the Mendelian Description of Heredity," *Biol. Bull.,* 1909, *16*:330; and J. T. Cunningham, "Sex and Sexual Characters," *Sci. Progress,* 1910, *4*:459, 467.

[26] Richard Goldschmidt, *The Mechanism and Physiology of Sex Determination* (London: Methuen, 1923); and Garland Allen, "Opposition to the Mendelian-Chromosome Theory: The Physiology and Developmental Genetics of Richard Goldschmidt," *J. Hist. Biol.,* 1974, *7*:49–92.

[27] Supported by Allen, "T. H. Morgan and the Split," pp. 29–30, and by my own observations and conversations with developmental biologists, such as Rudy Raff at Indiana University. Jane Oppenheimer has correctly pointed out, in private correspondence, that the term "developmental biology" was not used in the early part of this century. In using this and corresponding terms, then,

Foremost among the turn-of-the-century developmental biologists was T. H. Morgan, who concluded in 1903 that both male and female "elements" exist in all kinds of eggs, so that eggs are not prefixed as either males or females. Further, Morgan felt that evidence remained inconclusive as to whether the nucleus or cytoplasm provided "the determining influence on sex." Therefore:

> Our general conclusion is that while recent theories have done good service in directing attention to the early determination of sex in the egg, those of them which have attempted to connect this conclusion with the assumption of the separation of male from female primordia in the germ-cells have failed to establish their point of view. The egg, as far as sex is concerned, appears to be in a sort of balanced state, and the conditions to which it is exposed, even when it is not fully formed, may determine which sex it will produce. It may be a futile attempt to try to discover any one influence that has a deciding influence for all kinds of eggs. Here, as elsewhere in organic nature, different stimuli may determine in different species which of the possibilities that exist shall become realized.[28]

In 1906, despite recent cytological advances by his Columbia colleagues Nettie Stevens and E. B. Wilson, Morgan still maintained that "whether this cytoplasmic difference can be traced to a preexisting cytoplasmic basis, or to nuclear influence, or to the influence of external conditions is quite unknown, but in the absence of any nuclear difference it seem[s] questionable whether we should assume that such exists."[29]

In his textbook *Experimental Zoology,* Morgan acknowledged that there are two types of theories of sex determination: morphological and physiological. The former saw preexistence of sex in the germ cells, while the latter cited unfolding of sex in accordance with individual physiological processes of development. "For myself," he concluded, "the physiological conception seems more in accordance with our general ideas concerning development, and above all to be a conception that is more stimulating and suggestive as a working hypothesis than the morphological idea, which seems to be quite sterile as a point of view leading to further investigation."[30] Even in 1910, after the advent of his Nobel Prize–winning research in genetics and sex-limited inheritance, Morgan remained disinclined to regard chromosomes as responsible for *determining* development. While he thought the chromosomes might play some directive role, he still did not believe they should be seen as determinants.

To the end Morgan remained attached to the internalist developmental search for a theory of sex determination *and* production. In his view, such a theory should not operate in the world of theoretical determinants or even observed morphological units, like chromosomes, without a clear understanding of how those units exercise effects on embryonic development. Like his fellow embryologists, Morgan longed for a physiology of development in line with Whitman and the spirit of the Marine Biological Laboratory in the 1890s. His commitment followed in part from a view of science that stressed the importance

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I only wish to identify those interested in developmental problems and not to suggest that they identified themselves as developmental biologists.

[28] Morgan, "Recent Theories," pp. 115, 116.

[29] Morgan, "The Male and Female Eggs of Phylloxerans of the Hickories," *Biol. Bull.*, 1906, *10*:206.

[30] Morgan, *Experimental Zoology* (New York: Macmillan, 1910), p. 422.

of asking narrow questions, beginning with working hypotheses and experimental tests, seeking clear results, and producing a unified set of theories. But, unlike some of his developmentally oriented colleagues, Morgan had become persuaded by 1910 that a revised program of study was desirable, as discussed below.

Developmental Approaches: The Chromosomes and Cytology

The second group of developmental biologists emphasized the importance of the nucleus, and especially the chromosomes, for development of sex. Concerned with describing nuclear changes, including the complex "dance" of chromatin material at different developmental stages, cytologists used traditional histological methods of sectioning and staining rather than the more experimental techniques of transplantation or isolation adopted by many developmental biologists. Clearly related to embryologists in their goals of understanding the developmental significance of nuclear changes, these investigators sought first to describe, rather than to find causal accounts for, nuclear changes.

After 1891, cytologists had also to address the significance of H. Henking's discovery of an unusual body. Not certain whether it was a chromosome or some other nuclear variation, Henking vaguely called his discovery a "nucleolus" and a "chromatin element." Pointing out that in insect spermatogenesis this one body was distributed unequally during cell division, he remained unclear about how to interpret this phenomenon, which others soon documented as well.[31]

In 1902 an American in Kansas, Clarence Erwin McClung, maintained that Henking's discovery, which McClung termed the "accessory chromosome," bore some relation to sex. Acknowledging the preliminary nature of his theoretical suggestions, McClung cited the need for a working hypothesis. He concluded that two kinds of spermatozoa must have arisen, by natural selection, which determine the two different types of individuals after fertilization. He tentatively suggested that the accessory chromosome is the bearer of sex: males have the accessory, females do not.[32] His was essentially a quantitative theory, maintaining that the existence rather than the particular nature of the extra chromosome determines sex. Unfortunately, McClung's belief that males must have one more chromosome than the female does not actually hold true for the insects he studied. Yet his hypothesis that spermatozoa were dimorphic and led to two different fertilized egg forms did focus attention on the accessory chromosome and its possible importance for sex determination.

Chromosomes might determine sex; that is, the particular quantitative union of chromosome material at fertilization might in some sense cause the organism to become either male or female. This was McClung's suggestion, for which he offered a clearly stated, testable hypothesis. Concentration on accessory chro-

[31] H. Henking, "Üntersuchung über die ersten Entwicklungsvorgänge in den Eiern der Insekten, II: Über Spermatogenese und deren Beziehung zur Eientwicklung bei Pyrrhocoris apterus," *Z. wiss. Zool.*, 1891, *51*:685–741.

[32] C. E. McClung, "The Accessory Chromosome—Sex Determinant?" *Biol. Bull.*, 1902, *3*:43–84; McClung, "Notes on the Accessory Chromosome," *Anatomische Anzeiger*, 1901, *20*:225. Gilbert suggests that McClung actually held an externalist position ("Embryological Origins," pp. 328–330), but I think it more likely that he was simply not clear about what he thought.

mosomes and their action provided a direction for productive research. What did they do in the course of development? Was their importance quantitative, because they represented an imbalance in the number of chromosomes, or did they have some special nature, some structural significance?

Equally stimulating to internalist cytological work was Theodore Boveri's theory, soon endorsed by Walter Sutton, that chromosomes maintain their individuality in the course of development and therefore hold morphological significance. They do not simply provide convenient, albeit changing, strings of material. Chromosomes actually maintain individuality or, more helpfully, "genetic continuity" (Wilson's term). By 1902 Boveri and Sutton both felt they had shown that chromosomes remain autonomous and distinct.[33] Further, according to their hypothesis, chromosomes segregate at cell division; that is the two chromosome pairs of one paternal and one maternal member join at synapsis, and then each separates lengthwise, along the same longitudinal lines. The material of the two does not mingle together and compete in some way, as August Weismann had suggested.[34] Rather, each chromosome maintains its autonomy. This continuity was not obvious in prepared sections, however, since the nucleus, and especially chromatin, becomes quite fuzzy and indistinct; the Boveri-Sutton hypothesis thus constituted something of a speculation. But Boveri's work on the large chromosomes of *Ascaris* and Sutton's confirmation of Boveri's observations strongly supported their interpretation. If they were correct, then chromosomes might very well hold more hereditary and determinant significance than was popularly thought within the still predominantly epigenetic biological community.

Although chromosomes seemed a promising subject of scientific inquiry generally, not even all cytologists agreed with the Boveri-Sutton hypothesis. Thomas Montgomery, at the University of Pennsylvania, disagreed in particular with the suggestion that a chromosome pair separates along its original longitudinal lines of conjunction at synapsis. Instead, in 1904 Montgomery focused on the accessory chromosome (which he called the "heterochromosome"), specifically in spiders. One from each parent joins its partner; then they separate. They do not separate along the same lines, however, but "longitudinally" and then "equationally" (that is, lengthwise, then across the center). As a result, the originally distinct heterochromosomes only more or less retain their individuality; that is, each chromosome remains as a morphological unit, but it represents only "a part of a particular chromosome of the preceding generation."[35] Montgomery thus held that chromosomes do not maintain genetic continuity, and he did not agree with Boveri and Sutton that the division processes of the chromosomes are significant for the process of sex determination.

[33] Walter Sutton, "On the Morphology of the Chromosome Group in *Brachystola magna*," *Biol. Bull.*, 1902, *4*:24–39; Theodore Boveri, "Über mehrpolige Mitose als Mittel zur Analyses des Zellkerns," *Verhandlungen der physikalisch-medizinischen Gesellschaft zu Würzburg*, 1902, *35*:67–90; also reprinted in B. H. Willier and J. M. Oppenheimer, eds., *Foundations of Experimental Embryology* (Englewood Cliffs, N.J.: Prentice Hall, 1964), pp. 76–97.

[34] On Weismann see Frederick B. Churchill, "August Weismann and a Break from Tradition," *J. Hist. Biol.*, 1968, *1*:91–112; Churchill, "Hertwig, Weismann, and the Meaning of Reduction Division circa 1890," *Isis*, 1970, *61*:429–457.

[35] Thomas Montgomery, "Some Observations and Considerations upon the Maturation Phenomena of the Germ Cells," *Biol. Bull.*, 1904, *6*:137.

By 1904, then, investigators had presented two different views of chromosomes. According to the first, the chromosomes have morphological significance so that their structural arrangements themselves carry information for development. According to the second, the chromosomes are instead the vehicles for information or physiological stimulants, and their structure holds no major developmental significance. Proponents of both views believed that chromosome study would prove fruitful, but their assumptions and the directions they thought appropriate for research varied somewhat. The first group thought that there might be hereditary units arranged along the chromosomes, for example. The second group thought that hereditary units might be floating around or might depend on epigenetic development rather than on predetermination of the kind that hereditary units suggest. Both possibilities remained viable. Those who endorsed the ability of chromosomes to influence such characters as sex were not necessarily hereditarians, for a hereditarian position must hold that some inherited factor determines sex. These internalists simply claimed that they had found correlations between chromosomes and sex production. Some began to suggest, but not all agreed, that the chromosomes themselves, because of their structural individuality, do cause sex determination.

In 1905 and 1906 several researchers began to contribute directly to that discussion. Nettie Stevens's paper of 1905 attracted particular attention. According to Morgan, he and Stevens had begun work on aphids in 1903 at Bryn Mawr.[36] Stevens performed the cytological studies, while Morgan and Stevens together carried out experimental explorations (on living rather then prepared organisms). The latter experiments, which attempted to demonstrate how changing external conditions of temperature or food could affect sex determination, proved uncertain; they always yielded negative results and were in any case insufficiently controlled. In contrast, Stevens's cytological results reflected a detailed and comparative approach that avoided the confusion and uncertainty of so many earlier works. She carefully recorded results and cautiously suggested interpretations.

Stevens concluded, for example, that for all the cases she had studied, spermatozoa are "distinctly dimorphic, forming two equal classes, one of which either contains one smaller chromosome or lacks one chromosome." She reported no exceptions and decided that "it is therefore evident that an egg fertilized by a spermatozoon (1) containing the small member of an unequal pair or (2) lacking one chromosome, must develop into a male, while an egg fertilized by a spermatozoon containing the larger element of an unequal pair of heterochromosomes or the odd chromosome must produce a female." Yet she remained cautiously conservative as to possible physiological and developmental interpretations of this chromosomal significance, concluding: "Whether these heterochromosomes are to be regarded as sex chromosomes in the sense that they both represent sex characters and determine sex, one cannot determine without further evidence."[37] The evidence did strongly suggest that chromosomes do

[36] T. H. Morgan, "A Biological and Cytological Study of Sex Determination in Phylloxerans and Aphids," *J. Exp. Zool.*, 1909, 7:240.

[37] Nettie Stevens, *Studies in Spermatogenesis*, Part II: *A Comparative Study of the Heterochromosomes in Certain Species of Coleoptera, Hemiptera, and Lepidoptera, with Especial Reference to Sex Determination* (Carnegie Institution of Washington Publication 26, Pt. II, Oct. 1906), p. 53. On Stevens see Stephen Brush, "Nettie Stevens and the Discovery of Sex Determination," *Isis*,

play some hereditary role in affecting sex. But just how remained unclear. Stevens's studies and Wilson's collaborative work (discussed below) did not provide "crucial" support for a chromosome theory of sex determination, as both recognized.

Until this point, these nuclear internalist theories held that the morphological units, the chromosomes, were central; they did not adopt Mendelian or any alternative theory of hereditary units. Yes, chromosomes and sex seemed correlated, but the internalists maintained the epigenetic convictions of their developmental internalist approach. This began to change with Stevens's work, however, and a shift occurred in the nuclear internalist position. The move took those internalists closer toward regarding the chromosomes as *cause* of sex determination.

Careful about her interpretations and acknowledging the need to work within the context of the internalist developmental approach, Stevens remained equally alert to the value of pursuing the best available hypotheses. In the conviction that one should pursue even a problematic "working hypothesis," she concluded in 1906: "Here we know that such a combination of gametes must occur to give the observed results, but we are not certain that we have a right to attribute the sex characters to these particular chromosomes or in fact to any chromosomes. It seems, however, a reasonable assumption in accordance with the observed conditions. . . . On the whole, the first theory, which brings the sex determination question under Mendel's Law in a modified form, seems most in accordance with the facts, and makes one hopeful that in the near future it may be possible to formulate a general theory of sex determination."[38] Here, then, Stevens at least tentatively endorsed a Mendelian position and thereby helped initiate convergence of the nuclear internalist and hereditarian approaches.

E. B. Wilson also contributed to that shift within the nuclear internalist camp and helped effect the move toward heredity. Yet he began firmly as an internalist, demanding accounts in terms of both heredity and development. In 1900 Wilson had found Jacques Loeb's work on artificial parthenogenesis exciting, concluding that developmental rather than nuclear factors might be the more significant:

> The possibility is thus opened [by work on nutrition] that we may yet succeed not only in fertilizing the egg by chemical means but also in rendering the organism male or female by analogous methods. A highly interesting question, still undetermined, is whether organisms produced by artificial parthenogenesis, as above, are capable of reaching the adult condition and of further reproduction. Individuals thus produced lack the paternal nuclear material and must possess but half the normal number of chromosomes. What the ultimate result of this deficiency may be is still a matter of conjecture.[39]

In a short paper evidently written in 1904 but published in 1905, he again evinced this developmental bias, denying that chromosomes hold sex "determinants."

1978, *69*:163–172; and Marilyn Ogilvie and Clifford Choquette, "Nettie Marie Stevens (1861–1912): Her Life and Contributions to Cytogenetics," *Proceedings of the American Philosophical Society,* 1981, *125*:292–311.

[38] Stevens, *Studies in Spermatogenesis,* Pt. II, p. 55.

[39] E. B. Wilson, "Some Aspects of Recent Biological Research," *The International Monthly,* July 1900, *17*:1–22.

He attributed sex to metabolism, and perhaps to growth specifically, rather than to chromosomes as sex determinants.[40]

Yet in a general lecture he gave in 1904, Wilson discussed the "definite architecture" of the nucleus. Although still stressing the importance of cytoplasm, he cited the nuclear chromosomes as representing "a kind of microcosm or original preformation," corresponding to parts of the future organism. The chromosomes represent "an original controlling and determining element," he maintained, and the accessory chromosome seemed of particular importance. He thought the nucleus might direct the course of development. Wilson did not, however, assert either that determinants (or "determining elements") exist or that they reside on the chromosomes. Nor did he accept a Mendelian interpretation in 1905. In 1906 he discussed plausible alternatives to Mendelian theory, alternatives in which the sex chromosomes would not be strictly sex determinants. It seemed reasonable to Wilson that "either or both forms of gametes may be predetermined as males or females (or at least male-producing and female-producing) prior to fertilization and irrespective of the chromosomes."[41] Sex would be determined in the gametes but not by chromosomes and not in a Mendelian manner. Accessory chromosomes did not seem to be involved.

By 1907 Wilson had become bullish on chromosomes and even on Mendelian explanations, believing that those had become the preferred working hypotheses, the best "point of attack" for problems of sex determination. "It is entirely possible," he wrote, "that we are on a wrong track, that the so-called sex chromosomes are only associated in a definite way with the sexual characters, and have in themselves no causative influence on sex production. The whole chromosome theory of heredity, for that matter, stands unproved before the judgment seat." Nonetheless, he continued, "I believe that the chromosome theory as applied to the sex problem presents a sufficiently plausible force to be taken for a time as a guide to further examination of the facts. Perchance the true explanation may be found on the way, even should our working hypothesis prove a false leader."[42] By 1907, then, Wilson had moved toward accepting a chromosomal account of sex determination, an account that led some developmental biologists deeper into the nucleus and chromosomes.

Eventually the internalists set aside explicit concern about physiological expression in development as chromosomes assumed greater importance and promised research results that would successfully address what these researchers still saw as developmental questions. For Wilson, Morgan, Stevens, and other developmental biologists continued to stress the importance of full developmental accounts and to insist that even if chromosomes did represent morphological arrangements of inherited determinants, their existence did not

[40] E. B. Wilson, "The Chromosomes in Relation to the Determination of Sex in Insects," *Proceedings of the Society for Experimental Biology and Medicine,* 1905, *3*:19–23. On Wilson see Alice Baxter, "Edmund Beecher Wilson and the Problem of Development" (Ph.D. diss. Yale Univ., 1974); and Baxter, "Edmund B. Wilson as a Preformationist: Some Reasons for His Acceptance of the Chromosome Theory," *J. Hist. Biol.,* 1976, *9*:29–57.

[41] E. B. Wilson, "The Problem of Development," *Science,* 1905, *21*:292. Wilson, "Studies on Chromosomes, III: The Sexual Differences of the Chromosome Group in Hemiptera, with Some Considerations of the Determination and Inheritance of Sex," *J. Exp. Zool.,* 1906, *3*:32–33.

[42] Wilson, "The Biological Significance of Sex: Sex-Determination in Relation to Fertilization and Parthenogenesis," *Science,* 1907, *25*:378, 379.

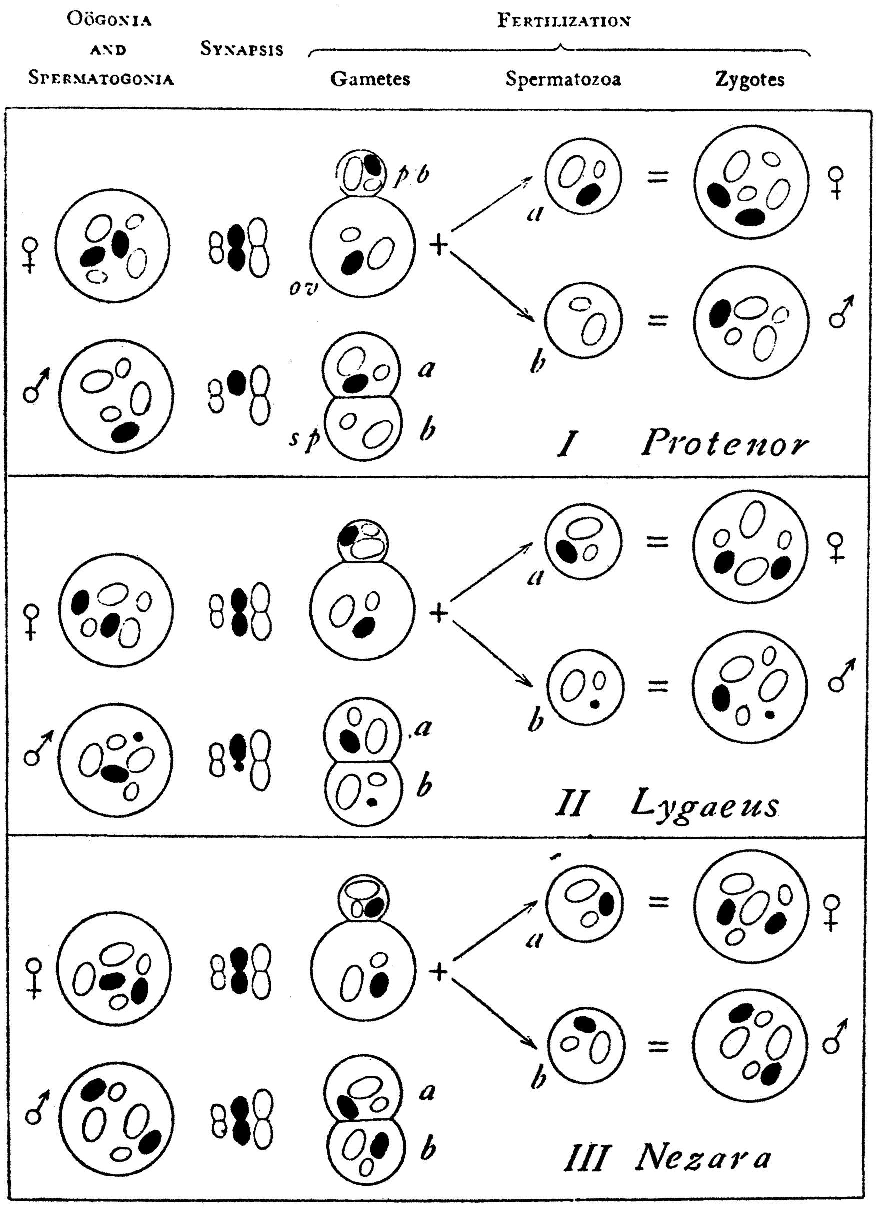

Figure 2. *Demonstration of different chromosomes in different species and sexes. From Edmund B. Wilson, "Studies on Chromosomes,"* Journal of Experimental Zoology, *1906,* 3:*25.*

explain development and character production adequately. They endorsed the old union of heredity and development.

Nevertheless, with the continued study of chromosomes we see a willingness in some internalists to move beyond the ardent epigenetic stand of the 1890s and to embrace the possibility that inherited units in the nucleus—or factors or genes or whatever—also play a decisive role. The traditional preformation-epigenesis dichotomy had been reformulated in the 1890s and began to dissolve in the early years of the twentieth century. Some internalists had begun to work on Watasé's first problem, that of heredity, instead of concentrating on sex production. Thus the second group of internalists, the cytologists working on the nucleus, shifted in their problems and solutions. And the first group, the developmental biologists, had to acknowledge that chromosomes as well as cytoplasmic arrangements affect development. Nonetheless, leading American developmental biologists stressed that development, though influenced somehow by the chromosome, remained essentially epigenetic.

That "somehow" remained the puzzling point. According to experimental embryologists, chromosomes and cytoplasm give some direction to development, providing physiological directives to the system, which is also primed for response to feedback from the whole organism and from the environment. An alternative answer came from the hereditarians, who argued that development is strongly determined by inherited units or factors. After 1900 the Mendelian account of heredity assumed special importance. Few biologists supported Mendelian theories in the first decade of this century, but those few generated their own influential accounts of heredity and of sex determination.

III. HEREDITARIAN APPROACHES: MENDELISM AND DETERMINANTS

The third approach to sex determination centered on Watasé's first problem, heredity, and entailed a focus on units of heredity and the resulting characters. After 1900 and the rediscovery of Mendel's work, discussion took place in the context of Mendelian inheritance, variously interpreted. According to the hereditarian approach, sex is determined at fertilization, because of fertilization. Since fertilization is an internal process, this approach remained essentially internalist. Hereditarians did not view the organism as initially flexible or sexually indeterminate, however, since they claimed that eggs are dimorphic from the point of fertilization. Their approach was thus more predeterminist than epigenetic. The chief goal was to understand how factors come together from both parents (in "normal" or fertilized cases) to determine the egg's sex. Researchers asked, therefore, what the relation is of determinants to expressed sex, or what combination of factors determines sex; they did not ask what the process is by which the determinants become expressed or how the factors determine sex. The stability of that process was taken for granted as a "mere" embryological problem. Nor did hereditarians in 1900–1910 concentrate on the nature or location of the determinants.

This concern with heredity rather than development represented a fundamentally distinct, though manifestly related, line of research. What the determinants are like and where they exist in the real organism remained of less importance to the hereditarians than unlocking the patterns of hereditary distribution of characters according to Mendel's predicted 1:2:1 ratio. These researchers thus began with a leading assumption that characters arise because of inherited determinants, and considered that the behavior of these theoretical entities constituted the problem for research. Methodologically, the hereditarians worked with populations of offspring from the same parents (pure lines) rather than mixed populations, and they studied sex ratios rather than individual sex expression. Their methods thus paralleled externalist work on populations, except that the hereditarians were driven by the assumption that it is precisely the internal structure of inherited material that determines sex and not external factors.

The British hereditarian William Bateson and his collaborator E. R. Saunders first developed the suggestion that sex is a quality, inherited according to Mendel's laws.[43] Yet they had no satisfactory solution to the problem that the expected 3:1 ratio never occurs. In most animal species under most conditions sex is roughly equally distributed; exceptions tend to be explicable deviations from the rule rather than counterexamples. Some other laws of heredity or additional factors had to be figured in to explain the regularity of this unexpected 1:1 ratio. Bateson and Saunders therefore concluded that Mendelism could not be adequate. In contrast, the American William Castle offered an alternative, but still essentially Mendelian, account in 1903, then ardently developed and defended it for the next decade. Castle served as an outspoken advocate for the hereditarian approach.

According to Castle, his "new theory of sex development" could unite three lines of scientific theory: Darwin's idea that the nonexpressed sex is latent in each organism; Mendel's recognition that gametes segregate and yield different dominant and recessive trait-producing gametes; and August Weismann's interpretation that with maturation of the gametes comes segregation of the ancestral characters and accompanying visible reduction in the number of chromosomes. This theory began with the assumption that sex is inherited.[44] Thus Castle concluded that the best approach to sex determination would be by way of the "laws of sex-heredity," beginning with Mendel's law. Breeding studies provided the starting point for interpretation.

Castle believed that each gamete carries a sex determinant. Since parthenogenetic species yield some unfertilized offspring that nonetheless have a sex, he reasoned, sex determination cannot require some physiological action of fertilization. Rather, both sexes produce two types of gametes, male and female, which remain segregated, so that each gamete already has a determined sex. But here arises that important difficulty for Mendelism: if either male or female were dominant and the gametes combined at random, a 1:2:1 distribution of determinants or 3:1 distribution of sex would result. In 1903 Castle met the problem by assuming that selective fertilization occurs. He hypothesized that only a male spermatozoon can fertilize a female egg, and vice versa, meaning that each fertilized egg constitutes a sex hybrid. Still a problem remained, for if either male or female were uniformly dominant or recessive, the result would obviously be the production of only that one sex. Castle therefore modified the dominant-recessive requirement of Mendel's law. With a complex set of auxiliary hypotheses governing interaction of determinants, he explicated a system

[43] William Bateson and E. R. Saunders, *Reports to the Evolution Committee of the Royal Society: Report I* (London: Harrison & Sons, 1902), pp. 1–160; and subsequent reports. Reprinted in part, along with other relevant papers, in John Moore, ed., *Readings in Heredity and Development* (New York: Oxford Univ. Press, 1972).

[44] William Castle, "The Heredity of Sex," *Bulletin of the Museum of Comparative Zoology,* 1903, *40*:189–218; Castle, "Yellow Mice and Gametic Purity," *Science,* 1906, *24*:275–281; and Castle *et al.,* "The Effects of Inbreeding, Cross-breeding, and Selection upon the Fertility and Variability of Drosophila," *Proceedings of the American Academy of Arts and Sciences,* 1906, *41*:732–786.

in which sometimes male and sometimes female dominates in dioecious animals, while females always dominate in parthenogenetic species.

Castle's hypothesis of selective breeding and the impurity of the dominance-recessivity caused trouble and carried him away from a strict Mendelian interpretation. In fact, he continued to modify his interpretations so that by 1909 he admitted that his previous conclusions of uniform sex-heterozygosity had proven untenable.[45]

In 1909 Castle suggested instead that maleness and femaleness are not paired factors, with both existing in any individual, but that sex results from the presence or absence of one or the other factor. The female thus results from the male condition plus something extra, he felt. In other words, a unit character determines the existence of a female if it is present, a male if absent. According to Castle, sex does not result, as Wilson said, from the quantitative relations of such morphological units as X-chromosomes, where one produces a male and two a female. Rather, Castle saw the absence or presence of the special unit character as decisive.

Before 1910, a Mendelian interpretation of sex heredity, even one as modified as Castle's, found relatively little support. As Morgan pointed out, Castle's theory, with its assumption that all fertilized individuals are actually sex hybrids, did not explain the very problem of sex determination.[46] For Morgan, the embryologist, Castle had not explained what made some individuals become male and others female. Yet Castle had provided a theory that could account for a 1:1 sex ratio in a population and for other hereditary phenomena that the developmentalists did not hold as central. The hereditarian and developmental lines of research remained largely distinct, with most supporters mutually unconvinced prior to 1910.

Yet once Castle and others had made the clear theoretical suggestion that Mendelian interpretations about "unit characters" might fit the data of sex determination, they had set the stage for a convergence of hereditarian and developmental lines of research. We will return, then, to Columbia and T. H. Morgan's laboratory, where the convergence was effected.

IV. THE CONVERGENCE

By 1909 the lines of disagreement had been drawn and redrawn. Those remaining old-style externalists continued to reject internalist and hereditarian accounts of sex determination. They maintained that all such accounts failed to consider the flexibility of individuals in responding to changing environments. All the externalists continued to emphasize the effects of altered environments on sex ratios in populations. The embryologists among them continued to stress the role of cytoplasm and the epigenetic developmental responses of individuals. While increasingly focused on sex production, or the establishment of sexual characteristics, they held that sex determination must also be an epigenetic process. They found the cytologists' stress on chromosomes, especially the accessory chromosome, to be too fixed, too deterministic, and unsatisfying. The ex-

[45] W. E. Castle, "A Mendelian View of Sex and Heredity," *Science*, 1909, *29*:399.
[46] Morgan, "A Biological and Cytological Study," p. 339.

istence of different chromosomes in the two sexes does not satisfactorily explain sex determination, they insisted. The cytologists regarded the embryologists as too vague and as fiddling around with sexual characteristics but not getting at the *cause* of sex differentiation. The cytologists believed that this cause was linked with the chromosomes, particularly the accessory or sex chromosomes, but they saw the Mendelians, who sought to localize the cause of sex differentiation, as too speculative. Again, the cytologists found selective breeding unacceptable, yet the Mendelians seemed unable to achieve the predicted 1:2:1 ratio and random segregation of factors unless they resorted to selective breeding. The Mendelians themselves, of course, felt that inherited factors must hold the secret of the cause of sex differentiation, but they had to cope with the problems mentioned above.

Thus there coexisted different groups that attempted to account for differentiation of individuals as either males or females. Not directly in conflict on all issues, they focused on different problems and held different goals. The types of explanation as well as definition of the phenomena to be explained varied. Prior to 1910 each had unresolved difficulties. Yet, partly because of shifts within each group, lines of discussion among the groups had opened. Especially in the United States, communication brought cooperation and progress.

Against this background, Morgan's work on *Drosophila,* in which he established the existence of sex-linked traits, began to appear in 1910. This work, reinforced by Wilson's cytological research and related work, gave the study of sex determination a new focus. John Farley has suggested that Morgan changed the question asked from how sex is differentiated to how sex is inherited.[47] The latter question was at the time answerable, and thus a productive starting point for answering the former. Evidently Morgan remained convinced that full and adequate explanation of sex determination and sex differentiation demanded more than the answers he provided to the new question, for he continued to work as a developmental biologist on explaining how the inherited chromosomal material becomes translated into two different sexual forms. But, as Farley and Allen have stated, Morgan was willing to set aside questions of development and turn to heredity as a related problem that was separable for practical reasons.

The subsequent discoveries of Morgan and his coworkers facilitated a move beyond the earlier proliferation of theories to agreement on shared assumptions. Knowledge of sex-linked traits made specialized studies of sex differentiation possible. Morgan's work changed far more than the approaches to problems of sex determination alone, for it stimulated changes in assumptions and shifting specializations within studies of heredity and development generally.

Morgan's own conception of the problem developed as follows. In 1906 he had asserted that "in the absence of any nuclear difference it seem[s] questionable whether we should assume that such exists." Instead, he said, let us look

[47] On Morgan see Garland Allen, *Thomas Hunt Morgan* (Princeton: Princeton Univ. Press, 1978); Allen, "Thomas Hunt Morgan and the Problem of Sex Determination, 1903–1910," *Proceedings of the American Philosophical Society,* 1966, *110*:48–57; and Ernst Mayr, *The Growth of Biological Thought* (Cambridge: Harvard Univ. Press, 1982), pp. 744–776; on sex determination see Farley, *Gametes and Spores,* pp. 218–234.

to the cytoplasm to explain development of sex in the phylloxerans. In 1907 he remained convinced that "the physiological conception seems more in accordance with our general ideas concerning development, and above all to be a conception that is more stimulating and suggestive as a working hypothesis than the morphological idea, which seems to be quite sterile as a point of view leading to further investigation." From this point of view, epigenetic or physiological development, not heredity, should explain sex differentiation as well as other kinds of development. In 1909, moreover, Morgan concluded that "if a sex-determining factor is present we have found no clue to such in our study of the chromosomes." Perhaps sex is determined in some sense in the egg but not by chromosomes, he insisted, again looking to the cytoplasm for the cause of sex determination.[48]

By 1910 Morgan acknowledged that the egg initially must have "something" in it responsible for later development. Rejecting theories that the "something" was particulate as "less stimulating for further research," Morgan concluded that exploring the physicochemical reactions of development held the most promising line of research. "There is no need to assume that X is the *sex chromosome* in the sense of carrying sex," Morgan insisted, even though chromosomes were somehow implicated in sex determination. Morgan's closing words reveal his attitudes about how science should proceed:

> Science advances by carefully weighing all of the evidence at her command. When a decision is not warranted by the facts, experience teaches that it is wise to suspend judgment, until the evidence can be put to further test. This is the position we are in to-day concerning the interpretation of the mechanism that we have found by means of which sex is determined. I could, by ignoring the difficulties and by emphasizing the important discoveries that have been made, have implied that the problem of sex determination has been solved. I have tried rather to weigh the evidence, as it stands, in the spirit of the judge rather than in that of the advocate. One point at least I hope to have made evident, that we have discovered in the microscopic study of the germ cells a mechanism that is connected in some way with sex determination; and I have tried to show, also, that this mechanism accords precisely with that the experimental results seem to call for. The old view that sex is determined by external conditions is entirely disproven, and we have discovered an internal mechanism by means of which the equality of the sexes where equality exists is attained. We see how the results are automatically reached even if we can not entirely understand the details of the process. These discoveries mark a distinct advance in our study of this difficult problem.[49]

At this point, then, it seemed to Morgan that even though chromosomes play some role, they do not themselves directly determine sex.

Then Morgan's experimentation with *Drosophila* populations began to produce evidence linking white-eyed mutations with the male sex. Though uncertain what this phenomenon signified, Morgan acknowledged that he must look to the chromosomes for an explanation of both. But hereditarian views in the form of

[48] T. H. Morgan, "The Male and Female Eggs of Phylloxerans of the Hickories," *Biol. Bull.*, 1906, *10*:206; Morgan, *Experimental Zoology* (New York: Macmillan Co., 1907), p. 422; and Morgan, "A Biological and Cytological Study of Sex Determination in Phylloxerans and Aphids," *J. Exp. Zool.*, 1909, *7*:272.

[49] T. H. Morgan, "Chromosomes and Heredity," *American Naturalist*, 1910, *44*:451, 494, 495–496.

Mendelism appeared unacceptable to Morgan. They still had too many problems. Perhaps selective fertilization does occur, as Castle had suggested, yet experimental mixing of sperm and eggs produced no evidence of such selective fertilization and seemed to deny its occurrence. Morgan therefore found it difficult to see how a Mendelian theory could fit the data.[50]

In his publications of 1911, however, Morgan began to assert the view that sex determination is directly caused in some way by chromosomal inheritance. His most recent work had changed his opinions, and he endorsed Mendelian inheritance of factors as a useful hypothesis: "In the same sense in which our ideas concerning variation and heredity have been entirely revolutionized since 1891, so has a similar change taken place in regard to our theories of sex determination. Sex is now treated by the same methods that are used for Mendelian characters in general."[51] Except that in the case of sex, one sex represents a pure line (homozygote, with factors from both parents the same), the other a heterozygous character. This latter distinction resolved some of the earlier objections to a revised Mendelian interpretation of inheritance.

In this crucial work Morgan still urged his readers not to think that development had been explained simply because a correlation had been demonstrated between characters and chromosomes. He argued that in order to explain the correlation of inherited factors with developing characters, it is important to work with physicochemical substances and not just to examine the structure of chromosomes or ascribe the activity to abstract particles. It is probably not the X-chromosome itself, then, that determines sex, but some material on the chromosome. To explain development of sex or any other character, we must ultimately understand the nature of this material and the way it acts to produce the character in the organism. Chromosomes are merely the "bearers of materials essential for the production of characters."[52]

Although Morgan felt that a fully satisfactory explanation would require discovering the nature and action of that material, he never achieved that goal. His very real disappointment at this failure is revealed in his later *Embryology and Genetics* (1934).[53] But his strength lay in his ability to move beyond the three separate research approaches and combine elements of all three. He united strands of the external approach, using population studies and examining ratios of characteristics; the internal, epigenetic approach, emphasizing physicochemical and cytological factors and expression of inherited material; and the hereditarian approach, making reference to inheritance of factors that determine characteristics. He did not believe that population studies could show everything. He did not fully endorse the cytologists' emphasis on morphological units, the chromosomes, as explaining development. Nor did he believe that a Mendelian view of inherited factors satisfactorily explained what happened afterward

[50] T. H. Morgan, "Sex-linked Inheritance in *Drosophila*," *Science*, 1910, *32*:120–122; Morgan, "The Method of Inheritance of Two Sex-linked Characters in the Same Animal," *Proc. Soc. Exp. Biol. Med.*, 1910, *8*:17–19; and Morgan, F. Payne, and E. N. Browne, "A Method to Test the Hypothesis of Selective Fertilization," *Biol. Bull.*, 1910, *18*:76–78.

[51] T. H. Morgan, "The Application of the Conception of Pure Lines to Sex-limited Inheritance and to Sexual Dimorphism," *American Naturalist*, 1911, *45*:65–78, quoting p. 65.

[52] T. H. Morgan, "An Attempt to Analyze the Constitution of the Chromosomes on the Basis of Sex-limited Inheritance in *Drosophila*," *J. Exp. Zool.*, 1911, *11*:403, 409.

[53] T. H. Morgan, *Embryology and Genetics* (New York: Columbia Univ. Press, 1934).

in epigenetic development. Rather, he perceived that biology needed a combination of all three, a convergence of elements from all traditions.

After the work in Morgan's laboratory on sex-linked characteristics, embryologists had a better-defined starting point and a clearer task in delineating epigenetic development from the organized egg. Cytologists had clearer answers about what was inherited and knew that the chromosomes maintain structural individuality and that there must be some sort of subchromosomal morphological "factors" to be explored. Geneticists could explore the nature, function, and effects of the inherited factors and show that they are located on the chromosomes.

In 1914 and 1916, the American Calvin Bridges offered what he and others regarded as conclusive proof that determinants, or genes, are unquestionably located on the chromosomes.[54] The exciting new genetics research program that resulted gained prominence, achieving wide publicity and striking results. Subsequently, biologists and historians of biology have tended to focus on that particularly visible research program and to see the problem of sex determination as solved by 1916. Yet all the problems that had been associated with sex determination were not solved entirely, as evidenced by the continued literature on the subject. The success of a research program in genetics tells only part of the larger story. In brief, a redefined set of assumptions and a refined picture of sex inheritance provided a foundation for mutually compatible specialized substudies of sex production. Far from having all the answers, Morgan had only established a starting point for further work. The period might be seen as one of establishing new paradigms, to use Kuhnian terminology, or new research programs, to use Lakatos's term.[55]

V. CONCLUSION

This article, then, has not described the way in which several approaches to sex determination gave way to a dominant genetics program after 1910, nor even the triumph of one theory over its competitors; for the approaches had focused on different questions and none triumphed entirely. Rather, in this case at least, science changed through a gradual convergence of previously disparate elements. This change entailed the reworking of assumptions, reformulation of problems, and continual correlations of theory with new experimental and descriptive results. The new research tradition that emerged seemed to solve some problems of sex determination, even while it left unsolved others previously thought to be central. Thus a gradual convergence of older traditions resulted in a reformulated foundation for several new specialty studies with different orientations, transformed problems, and shared central assumptions about the nature of science.

[54] Calvin Bridges, "Direct Proof through Non-Disjunction that the Sex-linked Genes of *Drosophila* are Borne by the X-chromosome," *Science,* 1914, *40*:107–109; Bridges, "Non-disjunction as Proof of the Chromosome Theory of Heredity," *Genetics,* 1916, *1*:1–52, 107–163.

[55] See Thomas Kuhn, *Structure of Scientific Revolutions* (Chicago: Uniy. Chicago Press, 1970); Imré Lakatos, "History of Science and Its Rational Reconstruction," *Studies in the Philosophy of Science,* 1971, *8*:91–126; Lindley Darden, "Discovery of the Emergence of New Fields in Science," *Philosophy of Science Association,* 1978, *1*:149–160; "Theory Construction in Genetics," in *Scientific Discovery: Case Studies,* T. Nickels, ed. (Dordrecht/Boston: Reidel, 1980); and Larry Laudan, *Progress and Its Problems* (Berkeley: Univ. California Press, 1977).