The Embryological Origins of the Gene Theory

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The original support for the gene theory of inheritance came largely from the studies of E. B. Wilson, Theodor Boveri, and Thomas Hunt Morgan. Each of these scientists began his career as an embryologist. In this paper, the emergence of the gene theory out of embryology will be seen in the context of these researchers' attempts to solve the problem of which cellular compartment—the nucleus or the cytoplasm—directed development. Crucial to this transition from embryology to genetics was the discovery of the sex chromosome, a nuclear structure believed to direct sexual development. We shall see that the constant questioning and retesting of the chromosomal theory of sex determination inadvertently formed the basis for Morgan's proof that the genetic factors were physically located on the individual chromosomes.

Finally, the research into the chromosomal models of inheritance displays many examples of how the adherence of scientists to older ideas causes them to interpret new data so as not to conflict with previously held assumptions. This conservative tendency is seen the case of McClung, who insisted on the environmental determination of sex even though he had discovered the mechanism for its intrinsic determination, and especially in T. H. Morgan's ten-year refusal to espouse the Mendelian genetics which he would later champion.

Morgan's refusal to accept the Sutton-Boveri synthesis of Mendelism and cytology becomes a chief concern in this essay. His arguments against this view are seen to arise from his previous embryological experiences, which convinced him that chemical reactions in the cytoplasm were responsible for development, rather than morphological changes within the nucleus. This view contrasts with other analyses, which relate Morgan's refusal to his "empirical" attitude, his dislike for theorizing, or to his "romantic" temperament.

Wilson's rapid acceptance of the Sutton-Boveri hypothesis is seen to result from *his* prior conviction that the *nucleus* controlled development. The reasons for these differences between Morgan and Wilson are traced back to two of Wilson's embryological beliefs which were not

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shared by Morgan. First, Wilson believed that the cell was the primary unit of development. Morgan had insisted that developmental forces molded the embryo irrespective of cellular boundries. Secondly, Wilson believed that the development of all organisms was essentially the same. He abolished the distinction between "mosaic" and "regulative" egg cleavage, stating that this was merely an artifact of how early the nucleus programed the cytoplasm. This allowed him not only to accept Morgan's data, but also to extrapolate from unicellular organisms to embryos. Hence, Wilson was able to see the nuclear control of protozoan morphogenesis as an instructive analogue of those processes occuring during embryogenesis.

The embryological origin of the gene theory demonstrates how the biases of one discipline are effectively carried over into a new field. It shows, too, how a relatively small group of investigators pursuing a problem in one area can generate the foundations of an entirely new science.

Therefore, unlike most histories of genetics, which begin with the experiments of Mendel or other breeders, this essay will maintain that the proper context in which to view the origin of the gene theory is embryology. The entry of Wilson and Morgan into genetics will be seen as an attempt to answer fundamental embryological questions, and their opposing positions—Wilson's acceptance of the chromosome theory and Morgan's long-standing rejection of it—will be seen in the context of their commitments to certain embryological theories.

Other analyses have been made of Morgan's and Wilson's work prior to the gene theory. Garland E. Allen has carefully documented Morgan's disagreements with the chromosomal theory of sex determination,[1] but although he states that this view was typical of other embryologists, he does not relate Morgan's views to their larger embryological context. Allen constructs his analysis from a cytological-genetic perspective rather than viewing Morgan as a participant in, and heir to, recent embryological controversies. As will be shown here, Morgan's rejection of the Sutton-Boveri hypothesis stemmed from his prior belief in the cytoplasmic control of development.

There are two studies which have investigated the embryological researches of Morgan and Wilson as a precondition for their subsequent work. Wagers discusses Morgan's embryological studies, and claims that Morgan became a Mendelian after W. E. Castle's 1909 paper

1. G. E. Allen, "Thomas Hunt Morgan and the Problem of Sex Determination, 1903-1910," *Proc. Amer. Phil. Soc., 110* (1966), 48-57.

formulating a physiological model for Mendelian inheritance.[2] However, there is much evidence against this interpretation. Morgan's 1910 polemic in the *American Naturalist* is a full assault on those who sought to place morphological determinants for heredity within the nucleus, and Castle himself claimed that he had had no effect upon Morgan.[3] Furthermore, although Wagers has pointed to Morgan's work as an embryologist, he does not connect the problem of sex determination with that of the nucleus-cytoplasm controversy.

A recent essay by Alice Levine Baxter shows E. B. Wilson's embryological background as influencing his acceptance of the chromosomal hypothesis.[4] While I agree that Wilson's embryological research led to his agreement with that model, I disagree with the reasons she put forth. Baxter claims that Wilson was a new type of preformationist, whose morphological bias and preference for morphological explanations were crucial in his favoring the chromosomal model. In the present study I seek to show that Wilson was an epigenesist who accepted the Sutton-Boveri hypothesis for the reasons already stated above—his belief that the cell was the primary unit of development and that the development of all organisms was essentially the same. Whereas Baxter sees Wilson as committed to a mosaic model for development after his 1904 experiments, here I view Wilson as destroying the very separation of mosaic and regulative modes of embryogenesis, placing them both within a framework of epigenetic physiology.

Edmund Beecher Wilson (1856-1939), Theodor Boveri (1862-1915), and Thomas Hunt Morgan (1866-1945) were among the first group of embryologists "liberated" by developmental mechanics. Before its metamorphosis, embryology had been studied as an adjunct to evolutionary phylogeny, and both Wilson and Morgan had done excellent studies delineating phylogenetic relationships by cell-lineage analysis. But with the advent of developmental mechanics, many old questions were left behind while new ones took on central importance. Entire methodologies and modes of explanation and evidence were substituted for older ones in what had become a new type of embryology. In the same year that Roux called for "a study of embryonic physiology,"[5]

2. R. Wagers, Ph.D. thesis, University of Oregon, 1973.

3. W. E. Castle, "The Beginnings of Mendelism in America," in L. C. Dunn, ed., *Genetics in the Twentieth Century* (New York: MacMillan, 1951), p. 94.

4. A. L. Baxter, "Edmund B. Wilson as Preformationist: Some Reasons for His Acceptance of the Chromosome Theory," *J. Hist. Biol, 9* (1976), 29-57.

5. W. Roux, "The Problems, Methods, and Scope of Developmental Me-

E. B. Wilson celebrated the reemergence of embryology as a new discipline: "So long as the study of embryology was dominated by the so-called biogenetic law, so long as the main motive for investigation was the search for phylogenetic relationships and the construction of systems of classification, the earlier stages of development were little heeded."[6]

Morgan echoed the call for a "more exact, more profound . . . new embryology,"[7] and Boveri claimed that the day would come when embryology would be a biochemical science.[8] As of 1900, none of these researchers felt the need to ground their work in Darwinism, and neither Morgan nor Wilson felt that natural selection was an adequate explanation for the origins of developmental phenomena.[9] The value of an explanation had moved from its ability to explain the salient features of evolution—constancy with variation, recapitulation, analogies and homologies—to the much smaller realm of being able to account for the physiological capabilities of the egg or embryo itself.

It was precisely in this area of early development that the central problem of developmental mechanics was framed: Which of the two major compartments of the fertilized egg—the nucleus or the cytoplasm—controls heredity and development? This problem did not arise *de novo* but emerged as the extension of the cell-lineage question which had hitherto occupied embryologists. Wilson's 1893 lecture at Woods Hole characterized the new studies as being motivated by recent insights into the fertilized egg which might enable researchers to account for such observations as the "so-called pre-morphological relations of the segmenting ovum" and the differential partition of egg substances by cleavage.[10]

The first conflict between partisans of the nuclear hypothesis and proponents of the cytoplasmic hypothesis involved the localization of preformed hereditary and morphological determinants. That some directing substance or substances had to exist was a necessary assumption, shared even by evolutionary morphologists like William Keith Brooks, the thesis advisor to both Wilson and Morgan. Something must

chanics, "trans. W. M. Wheeler, *Biol. Lectures Woods Hole, 2* (1894).

6. E. B. Wilson, "The Mosaic Theory of Development," *Biol. Lectures Woods Hole, 2* (1894), 1.

7. T. H. Morgan, "Developmental Mechanics," *Science, 7* (1898), 158. This and all other references to *Science* are from the new series.

8. J. Oppenheimer, *Essays in the History of Embryology and Biology* (Cambridge, Mass.: M.I.T. Press, 1967), p. 80.

9. G. E. Allen, "Thomas Hunt Morgan and the Problem of Natural Selection," *J. Hist. Biol., 1* (1968), 113-139.

10. Wilson, "Mosaic Theory," p. 3.

cause the egg of one species to develop differently from that of another species even though the eggs look identical and are in the same environment.[11] This observation linked heredity to development, and the identification and localization of such determinants became the central problem for the new embryology.

Coleman[12] and Churchill[13] have shown that localization and identification indeed constituted a single problem, since hypotheses postulating a determinant assumed a knowledge of where it acted, and hypotheses concerning the location of embryological determinants eliminated certain candidates for that role. Moreover, Coleman's and Churchill's studies highlight a controversy which would be extremely important for the new developmental physiologists: were the hereditary and developmental agents morphological entities (chromosomes, idioblasts, and so on), as O. Hertwig and C. Nägeli claimed, or were they soluble chemicals reacting in a physiological manner, as postulated by E. Pflüger and T. L. W. Bischoff?

The means sought to identify the determinants was to clarify their location. At first, the cytoplasm of the egg had been proposed as the location of these predetermined substances. W. His hypothesized that anlagen were present within the egg cytoplasm that were destined to form specific bodily parts.[14] This theory of *Organbildende Keimbezirke* had several important supporters, among them Flemming, van Beneden, and Lankester, the last of whom said of the egg cytoplasm: "Though the substance of a cell may appear homogeneous under the most powerful microscopy, it is quite possible, indeed certain, that it may contain, already formed and individualized, various kinds of physiological molecules."[15]

C. O. Whitman, who would become the director of the Marine Biological Laboratory at Woods Hole, also supported this theory, extrapolating from his observations on the worm Clepsine:

> While we cannot say that the embryo is predelineated, we can say

11. W. K. Brooks, *The Law of Heredity*, (Baltimore: Murphy, 1883), pp. 32-33.

12. W. Coleman, "Cell, Nucleus, and Inheritance: A Historical Study," *Proc. Amer. Phil. Soc., 109* (1965), 124-158.

13. F. Churchill, "Hertwig, Weismann, and the Meaning of Reduction Division circa 1890," *Isis, 61* (1970), 429-449.

14. W. His, *Unsere Korperform und das physiologische Problem ihrer Entstehong* (Leipzig: Vogel, 1894), quoted in E. B. Wilson, *The Cell in Development and Inheritance* (New York: MacMillan, 1896), p. 297.

15. E. R. Lankester, "Notes on the Embryology and Classification of the Animal Kingdom, " *Quart. J.Micr. Sci., 17* (1877), 399, in Wilson, *Cell,* p. 297.

> that it is predetermined. The "histogenetic sundering" of embryonic elements begins with the cleavage, and every step in the process bears a definite and invariable relation to antecedent and subsequent steps... It is, therefore, not surprising to find certain important histological differentiations and fundamental structural relations anticipated in the early stages of cleavage, and foreshadowed even before cleavage begins.[16]

Soon, however, there evolved another germinal localization hypothesis, placing the site of inheritance in the nucleus. Nägeli had proposed that there existed within the egg cell an *idioplasm* which formed the physical substance of heredity, and which was separate from the nutritive *trophoplasma* of the egg. Although Nägeli did not specify the nucleus as the seat of this idioplasm, new evidence of the importance of the nucleus in protozoa regeneration, and of the fidelity of chromosome number, morphology, and transmission, led Hertwig, Strasburger, Kolliker, and Weismann to conclude independently that "the nucleus contains the physical basis of inheritance, and that chromatin, its essential constituent, is the idioplasm postulated in Nageli's theory."[17]

This line of reasoning was further developed by Roux and Weismann. Roux, who certainly championed a physiological approach to embryology, exempted the idioplasm from epigenesis:

> While it is true that the normal operations of development are essentially physiological problems, we must, nevertheless, not lose sight of the cardinal fact that the organization of the idioplasm, which is at the bottom of every such reaction, is an *inheritance from the past.*[18]

He pictured the nucleus as a heterogeneous array of substances, each having a position on the chromatin fibers. Division, then, could be equivalent, each substance being exactly duplicated and passed to the progeny of the cell, or it could be quantitative. In the latter case, the original array of qualities is unequally apportioned between the daughter cells, thereby causing a differentiation to occur. Weismann extended this idea to its logical conclusion: that in a fully differentiated cell, only one of the many original determinants remains present, and

16. C. O. Whitman, "The Embryology of Clepsine," *Quart. J. Micr. Sci., 18* (1878), 215-315.

17. Wilson, *Cell*, p. 302.

18. Roux, "Developmental Mechanics," p. 123.

that only in germ cells are all the determinants retained.

This hypothesis of quantitative nuclear division was severely upset by th experiments of Driesch, who showed, first by completely severing the blastomeres of sea urchin eggs and later by changing their cleavage orientations by pressure, that the nucleus of a sea urchin blastomere destined originally to become ectoderm can retain the ability to become endoderm or even to generate the entire embryo itself. Driesch believed that "the results of ontogenesis come about by chemical phases"[19] and held that the nucleus and cytoplasm interact to produce the harmony of development. The fate of a blastomere was determined by its position rather than by the loss of chromatin material:

> Insofar as it carries a nucleus, every cell, during ontogenesis, carries the totality of all primordia; insofar as it contains a specific cytoplasmic cell body, it is specifically enabled by this to respond to specific effects only... When nuclear material is activated, then, under its guidance, the cytoplasm of the cell that had first influenced the nucleus is in turn itself changed, and thus the basis is established for a new elementary process, which itself is not only a result but also a cause.[20]

Even though Driesch's hypothesis differed greatly from the one proposed by Roux, the nucleus was still deemed the site of the primordia.

But direct proof for the nuclear control over development was still lacking, and critics of this hypothesis were able to point out that it was primarily an interpretation based on the role of the nucleus in fertilization and the constancy of nuclear organization within species. In 1889, in a paper appearing in a German journal, even Boveri acknowledged this limitation:

> Although the law, that the substances giving the definite and hereditary characters to the cell are entirely contained in the nucleus, is at times spoken of as a very much probable hypothesis, but again even as fact, yet it may be easily shown that this can be shown to us neither in the well-known phenomena of fertilization of the egg, or in the researches already carried out, concerning the role of the nucleus in protozoa.[21]

19. H. Driesch, *Analytische Theorie Organischen Entwicklung,* (Leipzig: Wilhelm Engelmann, 1894), quoted in Oppenheimer, *Essays,* p. 76.

20. Ibid., p. 77.

21. T. H. Boveri, "An Organism Produced Sexually without Characteristics

He then appended the results of what he believed to be the definitive experiments proving the determinative role of the nucleus in development.

Boveri fertilized presumed nonnucleated egg fragments of *Sphaerechinus granularis* with the sperm of another sea urchin, *Echinus mircrotuberculatus*. The skeletal axes of their pluteus larvae differ considerably, so that the observation of the skeleton of the larvae produced from such a mating should allow one to infer whether the nucleus (from the sperm) or the cytoplasm (from the enucleate egg fragment) controlled the developing structure. As indicated by the paper's title, "An Organism Produced Sexually without the Characteristics of the Mother," Boveri reported that the hybrid larvae had the skeletal axes of the male parent only; hence, the nucleus controlled development.

This work was translated from the original German into English for *The American Naturalist* by Thomas Hunt Morgan. Morgan recognized the importance of the article, first published in a journal seldom read in the United States,[22] and noted that the article's implications "are of the utmost importance inasmuch as they touch the very heart of the question of heredity."[23] Included in his headnote was also a caveat which would prove extremely important: "Results of this importance must be verified over and over again, until all chance of error (by no means small) are eliminated."[24]

From 1903 to 1905, Morgan undertook a series of investigations to test Boveri's work, and he concluded that it "rests on insufficient and unsound evidence."[25] Moreover, at the end of these investigations, Morgan was convinced that it was the cytoplasm, and not the nucleus, which controlled embryonic development.

Morgan was working at the Smithsonian Institution table at Dohrn's Stazione Zoologica in Naples. His first papers showed that he was expanding the experiments of Driesch, and the two men collaborated on investigations there. Morgan's first papers discussed the minimum size that a blastomere or egg fragment could have and still be capable of

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of the Mother," *Sitz d. Gessell. fur Morph. und Physiol. zur Munchen,* 1889; trans. T. H. Morgan in *Amer. Nat., 27* (1893), 223. Wilson similarly described it as "an open question" in his 1893 lecture at Woods Hole.

22. Ibid., p. 222.

23. Ibid.

24. Ibid.

25. T. H. Morgan, "The Fertilization of Non-Nucleated Fragments of Echinoderm Eggs," *Arch. Entwickelungsmech., 2* (1895-1896), 278.

producing an entire embryo. He found that in three species of urchin, the ability to retain totipotency diminished as the size of the fragment became smaller, such that at the 32-blastomere stage, it was not apparent. Moreover, Morgan observed that "the size of the cell determines the size of the contained nucleus."[26] The inability of the older blastomeres to produce embryos, he claimed, was not due to progressive differentiation, as Roux and Wilson had proposed, but rather to cytoplasmic size: "In the egg fragments and in isolated blastometers, the ultimate size of the cells produced by repeated divisions determines when the division shall come to an end for a certain stage of ontogency."[27] The inability of the smaller blastomeres and fragments to produce embryos was therefore due "to their inability to form the number of cells necessary for the later stages of development."[28] The cytoplasm, by Morgan thought, controlled development, rather than the progressive differentiation of the idioplasm.

At the same time, Morgan collaborated with Driesch on a developmental analysis of the ctenophore (comb jelly) egg. From later comments that Morgan made on this work, it seems that the results of this study settled for him the question of whether the nucleus or the cytoplasm was ascendant.

> I refer to the experiment on the ctenophore-egg, in which a part of the cytoplasm was cut from the unsegmented egg, and the latter gave rise in most cases to an imperfect embryo. Here, although the entire segmentation nucleus is present, yet by loss of cytoplasm, defects are produced in the embryos. The form, therefore, of the early embryo would seem to result from the structure of the protoplasm, or from the arrangement of the blastomeres after cleavage. In either case, the phenomenon is in the first instance cytoplasmic.[29]

Morgan, observing the powerlessness of the nucleus when a segment of cytoplasm is removed, declared the primacy of the cytoplasm:

26. T. H. Morgan, "Studies of the 'Partial' Larvae of Sphaerechinus," *Arch. Entwickelungsmech, 2* (1895-1896), 110.

27. Ibid., p. 121.

28. Ibid.

29. T. H. Morgan, *The Frog's Egg* (New York: MacMillan, 1897), p. 135. Experiments reported in H. Driesch and T. H. Morgan, "Zur Analysis der ersten Entwickelungstadien des Ctenophoreneies. I. Von der Enwickelungeinzeluer Ctenophorenblastomeren," *Arch. Entwickelungsmech., 2* (1895-1896), 204-215.

> a defect in the protoplasm often brings about a modified cleavage and also a defective embryo, and this takes place even though the whole of the nuclear marterial of the unsegmented egg remains present. There seems, therefore no escape from the conclusion that in the protoplasm and not in the nucleus lies the differentiating power of the early stages of development.[30]

But to claim such powers for the cytoplasm (and even to propose that if an enucleated ctenophore egg were to be fertilized by a sperm from another species the hybird would resemble the mother),[31] Morgan would have to refute Boveri's conclusion that the "protoplasm of the egg fragment had no influence upon the form of the resulting larva." Indeed, Morgan had said that Boveri's experiments would have to be repeated, hinting that there was definitely room for error in his study. He now attempted to duplicate those results.

He could not. Morgan found no support for Boveri's claims. First, instead of observing that the nuclei of hybrid larvae were larger than those of the pure parental type, Morgan found, as he had seen before, that the nuclear size varied with the size of the cytoplasm it inhabited. Second, and more important, Morgan demonstrated that Boveri's assumption that a hybird formed from the fusion of two nucleated gametes would have a skeletal morphology intermediate between the two parents was false. Rather, a wide variety of skeletal types appeared, some even looking totally like the male parent. Boveri had assumed these latter types to be the product of the sperm and enucleated egg fragment. Morgan noted that Seeliger had also made the same observation concerning the variety of pure hybrid types of skeletal axes, even using the same species as had Boveri. Morgan concluded that "the other support of Boveri's conclusion was thus also taken away,"[32] leaving open the possibility that the cytoplasm directed early development.

In contrast to Morgan, E. B. Wilson had enormous respect for

30. Ibid., p. 121.

31. Ibid., p. 134.

32. Morgan, "Fertilization," p. 269. Boveri countered with a defense of his paper later in that volume, stating, among other things, that Morgan had not read his earlier paper with reflection. In an article published posthumously (*Arch. Entwickelungsmech., 44* [1918], 417-471), Boveri qualified his earlier work, although it has for the most part been verified subsequently. (For discussion, see E. Davidson, *Gene Activity in Early Development* [New York: Academic Press, 1977), pp. 29-38).

Boveri. His 1896 edition of *The Cell in Development and Inheritance* was dedicated to Boveri, whose "slow and painstaking processes of observation, experiment, and analysis, accomplished the actual amalgamation between cytology, embryology, and genetics–a biological achievement which . . . is not second to any of our time."[33] In this volume, Wilson marshaled the embryological and cytological evidence for the nuclear control over cellular processes and was obviously impressed with Boveri's experiments. Calling Boveri's study "a most ingenious and beautiful experiment," he added: "Boveri's result is unfortunately not quite conclusive, as has been pointed out by Seeliger and Morgan, yet his extensive experiments establish, I think, a strong presumption in its favor."[34]

What was the evidence that convinced Wilson that the nucleus controlled heredity and development? Besides Boveri's work on the sea urchin embryo, there was his exhaustive cytological study on the development of the *Ascaris* nematode. As the cells of the fertilized *Ascaris* egg cleave, the elimination of chromatin was seen from all those cells except those destined to become germ cells. All the somatic cells, therefore, contained only a portion of the original chromatin. Here, then, was nuclear differentiation concomitant with cellular differentiation.

Also, since Wilson acknowledged the cell to be the fundamental unit of inheritance and development (something that Morgan, following C. O. Whitman, did not do),[35] he was able to draw analogies between the physiological processes of unicellular organisms and individual cells of a multicellular embryo. The experiments of Nussbaum on *Oxytricha,* Gruber on *Stentor,* and other investigators clearly demonstrated that if these organisms were cut into parts, any piece of cytoplasm could regenerate the entire complex morphological structure of the cell if and only if it contained the nucleus. Lillie had showed that in *Stentor,* a fragment containing only 1/27 of the original volume of cytoplasm could regenerate the entire protozoan if it contained the nucleus.[36] Wilson concluded from these studies that:

> These beautiful observations prove that destructive metabolism, as manifested by co-ordinated form of protoplasmic contractility, may

33. Oppenheimer, *Essays,* p. 79.

34. Wilson, *Cell,* p. 258.

35. Morgan, "Partial Larvae", p. 124. This point will be discussed later. (See the quotation referred to in note 92).

36. Wilson, *Cell,* pp. 248 ff.

> go on for some time undisturbed in a mass of cytoplasm deprived of a nucleus. On the other hand, the formation of new chemical or morphological products by the cytoplasm only takes place in the presence of a nucleus. These facts form a complete demonstration that the nucleus plays an essential part not only in the operations of synthetic metabolism or chemical synthesis, but also in the *morphological determination of these operations,* i.e. the morphological synthesis of Bernard—a point of capital importance for the theory of inheritance.[37]

Wilson linked the protozoan research directly to that of embryology:

> This fact (of the necessity of the nucleus for protozoan regeneration) establishes the presumption that the nucleus is, if not the seat of the formative energy, at least the controlling factor in that energy, and hence the controlling factor in inheritance. This presumption becomes a practical certainty when we turn to the facts of maturation, fertilization and cell-division. All these converge to the conclusion that the chromatin is the most essential element in development.[38]

37. Ibid., pp. 250-251. Claude Bernard claimed that the nucleus was the site of synthetic activity while the cytoplasm was the site of degradative metabolism. Wilson also expressed this notion in appendix to one of his graduate students' papers on cytoplasmic localization. See E. B. Wilson, "On Cleavage and Mosaic Work" (Appendix to H. E. Crampton, Jr.) *Arch. Entwicklungsmech., 3* (1896), 19: "Cytoplasmic organization, while affording the immediate conditions for development, is itself a result in the last analysis of the nature of the nuclear substance which represents by its inherent composition the totality of hereditable potence."

38. Wilson, *Cell,* p. 262. The concept of "formitive energy" was influential during this period, when much of what was known in physiology centered on energy metabolism. C. O. Whitman introduces it into his description of fertilization ("Clepsine", p. 252) stating this process to be "a re-union, not of exhausted, but of complementary energies." To those who favored the environmental determination of sex, these energies were manifest in the anabolism-catabolism ratios which determined the character. Wilson used this concept extensively, linking the "formitive power" directly to Bernard's notions of "chemical synthesis." Wilson's view that sex differences were caused by differences in the intensity or energy, not substance, of the chromosomes, is consistent with his belief that "the nucleus is the formitive centre of the cell in the chemical sense, and through this is the especial seat of the formitive energy in a morphological sense." (*Cell,* p. 261).

He noted that germ cell maturation appeared to be a process preparing for the subsequent union of chromatin from both parents, and he recognized the immense implications of this idea. Observing that chromatin appeared to be identical with nuclein, which chemical analysis had shown to be fairly regularly composed of nucleic acid and albumin, he concluded:

> When this is correlated to the fact that the sperm nucleus, which brings the paternal heritage, likewise consists of nearly pure nucleic acid, the possibility is opened that this substance may be in a chemical sense not only the formative centre of the nucleus but also a primary factor in the constructive processes of the cytoplasm.[39]

Another line of reasoning which enabled Wilson to conclude that the nucleus was dominant was a "habit of thought" characteristic of Wilson as an embryologist. This was his notion of continuity. Wilson did not see nature in terms of dichotomies. Rather, he viewed phenomena that were usually considered to be opposites as poles of a continuous spectrum. This habit of thought can be identified in many of Wilson's most important papers.

First, in an attempt to reconcile Roux's theory of inherent differentiation with Driesch's notion that location determines developmental fate, Wilson destroyed the dichotomy between regulative cleavage (as found in the sea urchins, where any of the early blastomeres can give rise to an entire embryo) and mosaic cleavage (as seen in the ctenophores, where one of the two-cell blastomeres can give rise, essentially, to only half an embryo). He claimed that differentiation may be only the manifestation of covert changes that had already taken place earlier. In this way, the egg of *Amphioxus,* which undergoes regulative cleavage, was no different than that of *Nereis,* an example of mosaic cleavage. The cytoplasm of the *Nereis* egg was merely determined by the nucleus very early, perhaps even before fertilization, whereas in the *Amphioxus* or sea urchin egg, the cytoplasm had not been determined until a few cleavages had taken place. However, it was the nucleus that was the controlling factor in both cases, the cytoplasmic control of mosaic ova being merely an artifact of its early determination by the nucleus.

We may interpret this to mean that in *Amphioxus,* the differentiation

39. Wilson, *Cell,* p. 262.

> of the cytoplasmic substance is at first very slight or readily alterable, so that the isolated blastomere, as a rule, reverts at once to the condition of the entire ovum. In the sea-urchin, the initial differentiations are more extensive or more firmly established, so that only exceptionally can they be altered. In the snail we have the extreme opposite to *Amphioxus,* the cytoplasmic conditions having been so firmly established that they cannot be altered...
>
> The origin of cytoplasmic differentiations existing at the beginning of cleavage have already been considered. If the conclusions there reached are placed beside the above, we reach the following conception. The primary determining cause of development lies in the nucleus, which operates by setting up a continuous series of specific metabolic changes in the cytoplasm.[40]

When Wilson discovered the importance of the pole plasm in the *Dentalium* egg (evidence which would seem to support Morgan's contention that the cytoplasm instructs development), it did not disturb his theory. For even though Wilson discovered that a definite segregation of material existed even before fertilization and that isolated blastomeres were unable to produce a complete embryo, "the contra-

40. Wilson, *"Mosaic Theory,"* p. 320. Throughout his research, Wilson maintained this view that nuclear constancy directed epigenetic events through physiological reactions. Davidson (*Gene Activity,* p. 309) has stated Wilson's position as the idea that "apparently preformed characters can only be regarded as the product of *an earlier epigenetic process originating in the oocyte nucleus during oogenesis.*" Just as Wilson abolished the dichotomy between mosaic and regulative cleavages, so Wilson integrated apparent preformationism into an epigenetic framework. While Morgan was viewing the problems of heredity and development as identical, Wilson separated the two processes (cf. the quotations referred to in notes 117. and 119, below). Thus, like Roux, he could envision a hereditarily stable nucleus exempt from the epigenetic processes of development. Hereditary factors could be preformed and direct epigenetic developmental processes: "Heredity is effected by the transmission of a nuclear *preformation* which in the course of development finds expression in a process of cytoplasmic epigenesis" (Wilson, *The Cell in Heredity and Development,* 3rd ed., [New York: MacMillan, 1925]). This is the same idea Wilson details in the 1896 edition of *The Cell in Development and Inheritance,* p. 320. Wilson is always emphatic that development is epigenetic; and even at the onset of the chromosome controversy, he repeats this position: "Early in its development the egg contains only a few of these specific stuffs... and that as development goes forward, new stuffs are formed and distributed... The actual progressive development of the protoplasm must be conceived as a process of *epigenesis,* not of preformation or evolution (E. B. Wilson, "Mosaic Development in the Annelid Egg," *Science, 20* [1904], 750).

diction disappears upon comparison with certain other forms, which are intermediate in character between the extremes represented by *Dentalium* and the echinoderm egg."[41]

This use of intermediate forms to create a continuum was a characteristic argument of Wilson's. In his 1898 paper "Cell Lineages and Ancestoral Reminiscence," he showed that differences between annelid and molluscan cleavage on the one hand and polyclad flatworm cleavage on the other could be reconciled by the cleavages in species having intermediate patterns, thus helping "to bridge a gap which once seemed hopelessly wide."[42] Similarly, in his papers (to be discussed later) on the chromosomal basis of sex determination, he regarded those species with two types of sex chromosome (X and Y) as intermediate between those having an accessory chromosome (XO) and those having two sex chromosomes identical in morphology. Certainly consistent, Wilson also stated that in all probability "the chemical differences between chromatin and cytoplasm, striking and constant as they are, are differences of degree only."[43] This conceptualization of nature as a continuum is in striking contrast to Morgan's categorizations which, as we shall later see, often viewed disparate phenomena as antitheses.

But Wilson, believing in a progressive (and in part, reversible) determination of the cytoplasm by the nucleus, and Morgan, believing that it is the cytoplasm which controls nuclear function, were but opposite sides of the same coin. Both attempted to define physiologically the material and efficient causes for development. The efficient cause for Morgan was the material cause for Wilson and vice versa. This will also become apparent in their later discussions on chromosomes: Morgan would say that the cytoplasm caused the segregation of chromosomes (as in the hickory aphids), while Wilson would contend that the chromosomes created the segregation of the cell plasm (as in *Dentalium*).[44]

Indeed, Wilson and Morgan were very similar in both background and method. Both men received their doctorates from the Johns Hopkins University in the laboratory of William Keith Brooks (Wilson

41. E. B. Wilson, "Experimental Studies on Germinal Localization, I." *J. Exp. Zool., 1* (1904), 59.

42. E. B. Wilson, "Cell Lineage and Ancestral Reminiscence," *Biol. Lectures Woods Hole,* 1898, pp. 21-42.

43. Wilson, *Cell,* p. 242.

44. As Wilson once put the argument ("The Problem of Development", *Science, 21* [1905], 288): "The protoplasmic stuffs appear to be only the immediate means or the efficient cause of differentiation, and we still seek its primary determination in the causes that lie more deeply."

in 1881, Morgan in 1890). Upon completing their respective theses, both went to the Naples Marine Biology Station and became friends of Dohrn and Driesch. In particular, Wilson became a close friend of Boveri. In 1885, Wilson became the first professor of biology at Bryn Mawr, and when he left to go to Columbia University in 1891, Morgan took his place in Pennsylvania. Later, Morgan would join Wilson at Columbia (1904). Their families were close and even were neighbors at Woods Hole during the summers. (So close were their histories that the pycnogonids on which Morgan worked for his thesis were studied twelve years earlier by Wilson, and both of them worked on invertebrate regeneration in addition to their studies of early embryogenesis).

Ross Harrison, former graduate student of Brooks and a mutual friend of Wilson and Morgan, characterized the elder as "classic," in contrast to Morgan, whom he called "romantic," that is, solving one problem so that he could be free to tackle another.[45] But this distinction does not really seem to hold, as is attested by Morgan's continuous attempts to grapple with the problem of nuclear versus cytoplasmic control of inheritance from his first papers of 1894 through his earliest *Drosophila* work (where he finally resolved the problem) in 1911. His unflagging interests in the physiological mechanisms of regeneration during this period also testify to his doggedness in pursuing a single problem for many years. Likewise, the explanation that Morgan's reluctance to accept the chromosome theory was due to his empirical biases[46] does not fully account for that refusal. Certainly Morgan was empirical, but whether he was significantly more so than Wilson seems doubtful. Wilson's belief in nuclear control was based on solid evidence, and he was constantly seeking ways to test his hypothesis. Experimentation rather than speculation was as important for Wilson as it was for Morgan. Wilson's *Cell in Development and Inheritance* was largely a critical analysis of data, and throughout his work, he acknowledged the limitations of current knowledge, which forbad one to propound general theories. Of many such remarks, this one is of some importance:

> If the hypothesis of formative cytoplasmic stuffs be valid, there seems no escape from the conclusion that in such cases the necessary formative stuffs may be formed anew. But if the potentiality of the cytoplasmic system be primarily given in the nuclear

45. R. G. Harrison, "Response on Behalf of the Medalist" (Accepting the Carty Prize for E. B. Wilson), *Science, 84* (1936), 565.

46. Allen, "Morgen and the Problem of Natural Selection," p. 122.

> organization, and if this be the primary determining source of the initial cytoplasmic localization in the unsegmented egg, this presents no insurmountable difficulty. It is obvious, however, that this question is not one for speculation, but for further experiment.[47]

When Wilson wrote that statement, he probably had a very good idea as to how to take the question of whether "nuclear organization" could determine development out of the realm of speculation; for within a year he published his first papers on the chromosomal basis of sex determination.

For the next decade, the controversy over whether the nucleus or the cytoplasm controlled heredity and development would focus on the ability of "sex chromosomes" to produce the sexual phenotype. The idea that sex might be determined by such nuclear structures was a critical departure from the dominant view of the 1890's, which held that sex was determined by environmental factors. A critical review of the theories of sex determination up to 1890 was presented in Geddes and Thomson's remarkable book *The Evolution of Sex.* The first point stressed in this review was that any study of sex determination must be backed by physiological data:

> It is recognized that the problem is one for scientific analysis; thus, the constitution, age, nutrition, and environment of the parents must be especially considered. . . That the final physiological explanation is, and must be, in terms of protoplasmic metabolism, we must again remind our reader.[48]

Geddes and Thomson therefore reject most of the hypotheses from Aristotle through Darwin as mere speculation and guesswork. The remaining scientific theories strongly indicated the environmental determination of sex. Yung had shown that the richer the diet of a tadpole, the more likely it was to become female,[49] and others had repeated the same observation with caterpillars. Thury and Dusing had independently shown that older ova tended to produce male offspring, but the best data came from studies of parthenogenetic species of

47. E. B. Wilson, "Experimental Studies on Germinal Localization, II," *J. Exp. Zool., 1* (1904), 265.

48. P. Geddes and J. A. Thomson, *The Evolution of Sex* (New York, 1890), p. 33.

49. Ibid., p. 45.

insects, such as aphids. Here, sex seemed totally a function of nutrition. In the summer, when food was abundant, generation after generation of parthenogenetic females was produced. No males appear until the food begins to get scarce. At this time, a wingless female generation is produced whose eggs give rise to both males and females. These would mate to produce the eggs which could survive the winter, and they would hatch only into females, who thus began the cycle anew. Any theory of sex determination had to explain how male aphids suddenly could arise after generations of females. The idea that the triggering event was the loss of food certainly supported the environmental argument.

It was Geddes and Thomson's contribution to unite these observations into a physiological theory of sex determination. It was based on the predominance of one type of metabolism over the other: either anabolism, the storing up of energy, or catabolism, the utilization of energy. They summarized their theory as follows: "But the general conclusion is tolerably secure—that in the determination of sex, influences favoring katabolism tend to result in the production of males, as those favoring anabolism similarly increase the production of females."[50]

This conclusion, they claimed, was confirmed by the catabolic habits of the adult male (shorter life span, greater activity, smaller size) and by the energy-conserving habits of the females, whom they described as "larger," "more passive," and "vegetative." This view that the adult organism and the germ cell it produces have a macrocosm-microcosm relationship extended, as we shall see, to many investigators.[51]

50. Ibid.

51. Science is being used to justify social mores here, since implicit in this theory is that an active woman is unnatural. A similar degree of male supremacy can be seen in the basic argument of the theory, which holds that when times get rough, only the males survive. In 1914, Geddes and Thomson will restate this argument, with the following additon: "We may speak of women's constitution and temper as more conservative, of man's as more unstable... We regard the woman as relatively more anabolic, man as relatively katabolic; and whether this biological hypothesis be a good one or not, it certainly does no social harm" (*Problems of sex* [Moffat, N.Y., 1914], pp. 205-206). Geddes's views of sex in society are of further value since he was also one of the leading sociologists of his time (and Lewis Mumford's mentor). Geddes sees a distinct sexual dimorphism in the bodies, sensibilities, and aptitudes of men and women. They are not equal but complementary, and he welcomes the advances of women as having the potential of transforming the masculine neotechnic age into a totally human eutechnic era by their humanitarian ideals and inspiration. (I am indebted to

Like Weissman's theory, Geddes and Thomson's hypothesis viewed the cell as the basic functional unit for sex and heredity; but instead of seeing development in terms of particulate idants of the nucleus, they saw it in terms of cellular metabolic processes. Moreover, this theory contradicted the views put forth by Weissman, who had declared that the germ cells were sequestered and isolated from the effects of their environment. Geddes and Thomson argued that they had the data, rather than mere speculation, and that therefore the burden of proof was on Weissman. So strong was this physiological theory of environmental sex determination that E. B. Wilson, in the 1896 edition of *The Cell in Development and Inheritance*, quoted the book approvingly, concluding: "The determination of sex is not by inheritance, but by the combined effect of external conditions."[52]

It was only a year after Geddes and Thomson's book was published that the first step was taken toward the discovery of an intrinsic mechanism for the determination of sex. Hermann Henking, observing spermatogenesis in the plant bug *Pyrrhocus apterus*, noted an intensely staining body which appeared during the first spermatocyte division and which retained these staining properties afterward, when the other chromosomes lost them.[53] Moreover, in the second division, this dark body passed intact into one of the two daughter cells. Not knowing its function, Henking referred to it as "a particular chromatin element" and labeled it "X"; hence, the name later given to the larger of the sex chromosomes. Henking remained unaware of the importance of his discovery until it was pointed out to him as late as 1930 by Richard Goldschmidt.[54] Others did not do much with Henking's observation for a decade. Even in 1900, Wilson followed Paulmier in believing that this peculiar structure represented a functionless chromosome in the process of degenerating.[55]

Indeed, before Henking's observation could hold any interest for those looking for a mechanism of sex determination, the old theory would have to be torn down and a new hypothesis proposed. This

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David Cahan for suggesting the relationship of Geddes the botanist with Geddes the social theorist).

52. Wilson, *Cell*, p. 109.

53. H. Henking, *Z. Wiss. Zool., 51* (1890), quoted in C. E. McClung, "The Accessory Chromosome: Sex Determinant?" *Biol. Bull., 3* (1902), 43-84.

54. R. Goldschmidt, *The Golden Age of Zoology* (Seattle: University of Washington Press, 1956), p. 117.

55. E. B. Wilson, quoted in C. E. McClung, "Notes on the Accessory Chromosome," *Anat. Anz., 20* (1901), 224.

would be done in the course of the decade. T. H. Morgan, in his 1903 review of sex determination, gave credit for the destruction of the environmental hypothesis largely to Hannenburg and Lucian Claude M. J. Cuenót.[56] Hannenburg, by collecting birth statistics from many locales with widely disparate environmental conditions, concluded that the sex ratio was independent of the environment when large enough samples were taken. More important, Cuenót and his colleagues disproved the experimental basis for the environmentalist position.

Repeating Born's and Yung's experiments on tadpoles, Cuenót found that diet did not make a difference. Pflüger also obtained the same results. Careful documentation also disproved several celebrated experiments which claimed that well-fed caterpillars became females while poorly fed larvae became males. Moreover, Cuenót claimed to know the reasons for his predecessors' different results. First, they did not take into account differential mortality. Second, they neglected an important control–size matching. Brocadello had discovered that silkworms lay two types of eggs, large and small. From the large eggs came large larvae which were destined to become female. The smaller eggs produced males around 90 percent of the time. Other insects were soon found to shown a similar pattern of egg and larva size with respect to sex. Cuenót asserted that the earlier investigators, when they wished to starve caterpillars, would naturally take those which were scrawnier to begin with. Those caterpillars which were to receive the enriched diet would be chosen from the plumpest available. But these fatter caterpillars which were to be given the better diet were already determined to be females. When the well-fed and poorly fed groups were matched for original size, feeding or starvation had no effect on the sex ratio, nor did it affect the sex ratio of their offspring. These and other experiments led Cuenót to conclude that sex was determined not by the environment, but by the egg. In no instance was sex determined later than fertilization, and in some species, like the bees, the sperm obviously had some sex-determining agency.

Cuenót's work on animals was quickly paralleled by Edouard Strasburger's observations on dioecious plants; Strasburger claimed he could not change the sex of a plant during its development.[57] By 1902, J. Beard could review theories of sex determinations and state, "In

56. T. H. Morgan, "Recent Theories in Regard to the Determination of Sex," *Pop Sci. Mon., 64* (1903), 97-116. Cuenót's work was reported in *Bull. Sci. France Belg., 32* (1899).

57. E. Strasburger, quoted in J. Beard, "The Determination of Sex in Animal Development," *Zool. Jahrb., 16* (1902), 744.

the present writing, the experiments of Yung, Born, Maupas, Mrs Treat and others have received no mention, because at the best their researches only prove what percentage of either sex will survive under given conditions."[58]

Although this reversal of attitude was not as complete as Beard claimed, there certainly had been a major switch from an environmental account of sex determination to an internally focused approach. What caused the dissatisfaction with the environmental hypothesis? To a large extent, this change may have resulted from new theories about development. As previously mentioned, the researchers of *Entwickelungsmechanik* sought the determinants of heredity and development within the fertilized egg. Therefore, if sex was considered to arise by developmental processes, certainly it, too, would be internally directed. Straburger, for example, was especially concerned with the role of fertilization and after much experimentation had become convinced that the nucleus alone transmitted hereditary traits from one generation to the next. Development was the realization of these potentials.[59] He therefore accorded the nuclear substance a large degree of freedom from environmental conditions. Indeed, as research became more concerned with cellular control over hereditary and developmental processes, a retesting of environmental theories became essential.

In addition, the rediscovery of Mendel's paper in 1900 provided a powerful alternative to the environmental model for sex determination. Soon after it became known, various proposals were published attempting to explain sex inheritance as a Mendelian character. Correns, a codiscoverer of Mendel's work, believed that sex could be thought of as a unit character, and from his work on the plant *Bryonia,* characterized the male as a sex hybrid where maleness was dominant to femaleness.[60] That one of the sexes would have to be a hybrid was apparent from the 1:1 ratio which was produced when a heterozygote (hybrid) was mated with a homozygous (pure-bred) recessive individual:

Male	X	Female		1 male :	1 female
A a		a a	⟶	A a	a a

His experiments determined that the male was a hybrid.

58. Ibid., p. 709.

59. Coleman, "Cell, Nucleus, and Inheritance", pp. 124-158.

60. C. Correns, quoted in T. H. Morgan, "A Biological and Cytological Study of Sex Determination in Phylloxerans and Aphids," *J. Exp. Zool, 7* (1909), 33 ff.

The difficulty with this theory was that it could not explain the numerous cases, especially in parthenogenetic species such as aphids, where males emerged without fertilization after generations of females. Nor could it explain the fact that in bees unfertilized eggs gave rise to males while fertilized eggs became females.

In Castle's theory, each sex was a hybrid, but some sort of selective fertilization prevented two gametes of the same sex from uniting.[61] Therefore, the offspring remained hybrid, and whether the offspring became male or female would be determined by which germ cell bore the dominant character. The difficulty, again, came in describing the mechanism of sex determination for the parthenogenetic insects. In addition, Castle's theory invoked a selectivity principle which had never been observed. Punnett and Bateson's hypothesis that the males were the homozygous sex did nothing to alleviate these difficulties.[62] In fact, this view was made less tenable by the new observations, following those of Henking, that male insects may produce two types of sperm.

The peculiar chromatin element which Henking observed in the plant bug was found to be present in the maturing spermatocytes of numerous insects. One of the researchers investigating male gametogenesis was C. E. McClung of the University of Kansas. It is often assumed that his demonstration of the correlation between sex and the accessory chromosome freed sex determination from the environmental approach. As we shall see, however, McClung held fast to the view of Geddes and Thomson and integrated his results into an environmental theory of sex determination.

While his larger analysis was in press, McClung sent to the *Anatomischer Anzeiger* a summary in which he gave credit for some of the work on the earlier stages of spermatogenesis to his student W. S. Sutton.[63] It was Sutton, trained by McClung (who was only seven years his senior) to observe chromosomes in meiosis, who would enunciate the theory that the chromosomes are the physical carriers of Mendelian factors. Here, however, he was assisting McClung in his observations on the chromosomal morphology of the lubber grasshopper in regard to sex determination, and in this work we see the first example of how research into sex determination led to the gene theory.

61. W. E. Castle, "The Heredity of Sex," *Bull. Mus. Comp. Zool., 40* (1903), 189-218.

62. R. C. Punnett and W. Bateson, "The Heredity of Sex," *Science, 27* (1908), 785.

63. McClung, "Notes," p. 220.

McClung and Sutton noted that in the lubber grasshopper an "accessory chromosome" appeared at the first meiotic metaphase. Others before them had been uncertain whether this deeply staining structure was a chromosome or a nucleolus. Henking and Montgomery both equivocated, sometimes calling it by one term, then by the other. It was McClung and Sutton who were able to trace the formation of this structure from the spermatogonial cells to the spermatocytes, and thereby definitely state that it was a true chromosome. Sutton noted that "the accessory chromosome, however, though showing a clearly-defined longitudinal split, does not divide, but passes entire to one pole".[64] Therefore, only half of the developing spermatocytes receive this accessory chromosome. It was this 1:1 ratio which caused McClung to theorize that this chromosome was the determinant of sex. Fertilization with the reduced gametes of the egg would restore the original chromosome number, but McClung and Sutton were both mistaken in their view that the male had the extra chromosome. Noting, in the development of the egg, that "none of these behaved in the characteristic manner of the accessory," they proclaimed it to be missing.

This correlation of sex with the fusion of two reduced gametes, although given experimental validity by Sutton and McClung, was not a startlingly new departure. Montogomery had speculated about such a possibility, and in the same volume that McClung published his summary report, J. Beard of the University of Edinburgh asserted this theory (along with other less tenable conclusions) on theoretical grounds.[65]

Although McClung and Sutton demonstrated the chromosomal basis of sex determination in the grasshopper (the details were cleared up by both Wilson and Stevens in 1905), McClung still believed that the role of the environment was decisive. Following Dusing's statements, McClung declared that the egg "is able to attract that form of spermatozoon which will produce an individual of the sex most desirable to the welfare of the species."[66] In his larger paper, published 1902, he elaborated this argument using a courtship analogy, and he directly related his conclusions to the anabolism-catabolism theory of Geddes and Thomson:

The ovum determines which sort of sperm shall be allowed entrance

64. W. Sutton, "On the Morphology of the Chromosome Group in Brachystola Magna," *Biol. Bull., 4* (1902), 24.

65. H. Beard, "The Determination of Sex in Animal Development," *Anat. Anz., 20* (1901), 556.

66. McClung, "Notes," pp. 225-226.

> into the egg substance. In this we see an extension, to its ultimate limit, of the well-known role of selection on the part of the female organism. The ovum is thus placed in a delicate adjustment with regard to the surrounding conditions and reacts in a way as to best subserve the interests of the species. To it come two forms of spermatozoa from which the selection is made in response to environmental necessities. Adverse conditions demand a preponderance of males, unusually favorable environments induce an excess of females, while normal environments apportion an approximately equal representation of the sexes.[67]

Furthermore, "Those theories regarding sex determination which contain any truth within them will be found dependent upon this principle. It is expressed by Geddes and Thomson."[68] Here, McClung quoted their conclusion as stated earlier in this paper, that catabolism favors male production while anabolic tendencies favor the birth of females. Like Geddes and Thomson, he envisioned a manly sperm and a stay-at-home egg, stating that the egg "is to determine whether the germ cells are to grow into passive, yolk-laden ova or into minute mobile spermatozoa."[69] Moreover, as is in the courtship analogy, it is the egg that ultimately decides which of her visiting suitors will penetrate it.

The link between cytology and embryology can be symbolized by Sutton's leaving McClung's laboratory to work for E. B. Wilson. Writing from New York in 1902, Sutton was compelled by new work by Boveri to publish his theory that the segregation of Mendelian factors had its cytological analogue in meiosis. This provided a framework for those investigators who sought to localize these factors in the nucleus. Such a theory could not be ignored by the embryologists who had postulated nuclear control even before the rediscovery of Mendel. In coming to Wilson's laboratory, Sutton brought with him not only his theory for the chromosomal basis of Mendelism, but detailed

67. C. E. McClung, "The Accessory Chromosome-Sex Determinant?" *Biol. Bull., 3* (1902), 76-77.

68. Ibid., p. 77.

69. Ibid., p. 72. The language of McClung's and Sutton's correspondence also demonstrates this conscious analogy they saw between courtship and fertilization, eggs and women, etc. Victor McKusick ("Walter S. Sutton and the Physical Basis of Mendelism," *Bull. Hist. Med., 34* [1960], 457) has published portions of their letters wherein the male lubber grasshoppers are referred to as "the gentlemen."

knowledge of accessory chromosomes, a nuclear determinant postulated for that most obvious and important of developmental characteristics–sex. Here was a correlation between nuclear organization and development which could finally be tested.

These developments evoked an immediate response from Morgan. He belittled the accessory chromosome theory as mere speculation. There was no evidence of a causal relationship, he said: "McClung has urged that this difference is connected to the determination of sex; but there is nothing more than supposition that this may be so to go on at present. . . It has not been shown that a difference of this kind would have any value in the determination of sex."[70] But Morgan would still have Boveri's new paper to contend with. For Boveri had also discovered the individuality of the chromosomes, and he had linked them to the Mendelian factors in a way that confronted Morgan directly.

During his formative years in Naples, Morgan had published his own observations on abnormal mitoses in the sea urchin egg. Driesch had noted that dispermic eggs developed aberrantly, and Morgan extended these observations to show that the cause of this abnormal development was the unequal apportionment of chromosomes in the blastomeres:

> Towards some of the centers are drawn more chromosomes than toward others. In one case for instance of fourfold cleavage, one center got seventeen chromosomes, another fourteen, another thirty-three, and one center got none at all. We can understand then why such eggs do not produce normal larvae, for the resting cells will contain very different numbers of chromosomes, and the chances are that none of them will contain the normal number.[71]

Morgan interpreted his results to show merely that chromosomes, like any other cell constituent, were necessary for development; but he insisted that it was the cytoplasm which controlled them. "The results go to show, if I mistake not, that even prior to division (perhaps only after fertilization) the proptoplasm of the egg is not all alike so that a region of special protoplasm, which later goes into the micromeres, is set aside at an early period."[72] If anything was important about the chromosomes, Morgan insisted it was the *amount* present.

But in 1902, Boveri placed a totally different interpretation on

70. Morgan, "Recent Theories," p. 107.

71. T. H. Morgan, "A Study of a Variation of Cleavage," *Arch. Entwicklungsmech, 2* (1895-1896), 76.

72. Ibid., p. 79.

Morgan's results through experiments of his own. He fertilized sea urchin eggs and observed some of them being fertilized by two spermatozoa. These eggs never developed into normal larvae. He then surpassed Morgan's procedures by separating the four blastomeres from a dispermic quadripolar egg by placing them in calcium-free sea water. Herbst and Driesch had demonstrated that normal blastomeres treated in such a way gave rise to whole, if slightly smaller, larvae. Boveri found, however, not only that the separated blastomeres from the dispermic egg failed to form normal larvae, but that each blastomere seemed to develop differently! "Whereas, therefore, the four blastomeres of a normally dividing egg are equivalent, the properties of the blastomeres of a dispermic egg differ from each other in many respects and to varying degrees."[73]

Boveri also noted that the tripolar eggs obtained, but not explained, by Morgan were artifacts resulting from the attempt to remove the fertilization membrane by shaking the eggs. This caused the failure of one of the two sperm centrosomes to divide. He also claimed to have analyzed over nine hundred such specimens as compared to Morgan's ten.

But for all these lesser thrusts at Morgan (Boveri had claimed that Morgan's attack on his earlier paper was due to the latter's failure to understand what he had done), Boveri's real triumph was his ability to restate, with even more proof, the conclusion of his earlier paper: that the nucleus controls inheritance. Different developmental fates could not be cytoplasmically directed, since the cytoplasm was found to divide perpendicularly to the axis of the egg, thereby distributing various longitudinal plasms equally. This attacked Morgan's assertion that the cause for differentiation lay in the unequally divided cytoplasm. Moreover, Boveri's conclusions undermined Morgan's notion that a minimal number of chromosomes was all that was necessary for the formation of a normal larva. This, said Boveri, could not be the case, since it was known that parthenogentically activated sea urchin eggs could develop normally with only half the normal number of chromosomes. In a tetrapolar mitosis, at least two of the blastomeres would get more than the minimal number of chromosomes. Therefore, if minimal number were the only criterion, two of the four separated blastomeres from such a dispermic egg should have been able to form normal larvae. Since none ever did, Boveri concluded that "not a

73. T. Boveri, "On Multipolar Mitosis as a Means of Analysis of the Cell Nucleus" (1902), in B. H. Willier and J. M. Oppenheimer, *Foundations of Experimental Embryology* (Hafner, N.Y., 1974), p. 77.

definite number, but a *definite combination of chromosomes* is essential for normal development, and this means nothing else than that *the individual chromosomes must possess different qualities.*"[74]

The idea framed by Sutton and Boveri that each chromosome was distinct and bore part of the genetic and developmental program of the gametes was now a testable hypothesis bearing directly on whether or not the nucleus controlled heredity. The ability to focus on a single chromosome caused the emphasis to be switched from the analysis of early cleavage in marine embryos to the investigation of how sex is determined in a wide variety of species.

In 1905, Wilson published two papers on the idiochromosomes (accessory chromosomes) of the true bugs. Here, he confirmed McClung's view that the accessory chromosomes, at least in some cases, were correlated with sex, and he corrected McClung's notion that the accessory chromosome was the male determinant. The female, he said, had the extra chromosome. This assertion was based on his observation of chromosome morphology in the bug *Anasa* and on the theory that in some bugs there existed in the male both large and small idiochromosomes (later to be termed by Wilson X and Y, respectively). The smaller one, he argued, which was always found in the male, could be absent altogether in some species. From the sperm of the males, then, half would receive the large idiochromosome and half would receive either the small idiochromosome or no sex chromosome at all, depending on the species. Wilson was very much aware of the consequences that his confirmation and extension of McClung's work had for embryology and genetics: "It is hardly necessary to point out, finally, how strong a support the foregoing observations lend to the general hypothesis of the individuality of chromosomes, and to the conception of synapsis and reduction first brought forth by Montgomery and developed in so fruitful a way by Sutton and Boveri."[75]

In same year, Nettie M. Stevens of Bryn Mawr published her work on sex determination in insects. Her first paper, published in the same volume of the *Journal of Experimental Zoology* as Wilson's, claimed that in two species of aphids, no accessory chromosome could be seen during spermatogenesis.[76] However, by observing spermatogenesis in an organism with only five clearly distinct chromosomes, she confirmed Sutton and Boveri's theory that the homologues each went

74. Ibid., p. 84.

75. E. B. Wilson, "Studies on Chromosomes II," *J. Exp. Zool. 2* (1905), 540.

76. N. M. Stevens, "A Study of the Germ Cells of *Aphis rosae* and *Aphis oenotherae*," *J. Exp. Zool. 2* (1905), 371-405, 507-545.

to separate cells during meiosis. By September 1905, the Carnegie Institution of Washington began publishing her complete study of the mode of sex determination in over fifty species of insects and one primitive chordate. Most important of these studies were her observations on the meal work beetle, *Tenebrio molliter.* Here, somatic cells in the females and twenty large chromosomes, while those of the male had nineteen large chromosomes, plus one small one. The unfertilized eggs had ten large chromosomes, whereas the sperm had either ten large chromosomes or nine large and one small chromosome. She related her findings to those of Wilson on *Lygaeus,* calling the process she observed a "clear case of sex determination, not by an accessory chromosome but by a definite difference in the character of the elements of one pair of chromosomes of the spermatocyte of the first order, the spermatozoon which contains the small chromosome determining the male sex."[77] She, too, corrected the details in McClung's theory. By September 1906, Stevens had discovered the mode of sex determination for over forty-two species of beetles. Of these species, 85.7 percent had their sex determined by the method of unequal partners (what Wilson was to call Type B determination), whereas 14.3 percent had it determined by the single accessory chromosome method (Type A determination).

Wilson attempted to relate sex determination to physiological differences arising from different chromosome constitutions. He believed that the chromosomes determined the sex of the individual, and that the smaller chromosome of the male represented a degenerate female chromosome. The sex characteristics, he held, would arise from differences in the degree or intensity of chromosomal activity rather than from qualitative differences between the two chromosomes. He based this belief on the differences in activity of the accessory chromosome in the male and female germ line; in the male germ line the accessory chromosome was condensed (hence, inactive), while in the female it was normal. Only the active chromosomes would be functional in making products, and the amount of products synthesized would determine the sex of the offspring. Type B determination (X,Y) was therefore viewed as a transition to Type A (X, O). Here, said

77. N. M. Stevens, *Studies in Spermatogenesis with Especial Reference to the "Accessory Chromosome"* (Washington, D.C.: Carnegie Institution, 1905). A study of Stevens's work according it priority over Wilson's has been prepared by Dr. Stephen G. Brush and will appear in *Isis.* He notes that Morgan, while disagreeing with her theory, gave Stevens unqualified support in his recommendation letter to the Carnegie Institution.

Wilson, sex determination could be summarized as follows:

$$\text{Egg}\frac{n}{2} + \text{Sperm}\frac{n}{2} \longrightarrow n \qquad \text{(female)}$$

$$\text{Egg}\frac{n}{2} + \text{Sperm}\frac{n}{2} - 1 \longrightarrow n - 1 \qquad \text{(male)}^{78}$$

As previously mentioned, by maintaining a bias toward continuity, Wilson was able to link disparate phenomena. Moreover, his insistence upon quantitative differences in activity rather than qualitative differences in substances underlines Wilson's epigenetic stance.

Stevens, however, believed that it was more probable that qualitative differences existed between the large and small asymmetrically paired chromosomes, and that these were the differences which determined sex.[79] More important, though, was her belief that a dominance-recessive Mendelian inheritance of sex was possible through selective fertilization. Here she differed radically from Wilson:

> Here we know that such a combination of gametes must occur to give the observed results, but we are not certain we have a right to attribute sex characters to these particular chromosomes or in fact to any chromosome. It seems, however, a reasonable assumption in accordance with observed conditions. The scheme also assumes either selective fertilization or, what amounts to the same thing, infertility of gametic unions where like sex chromosomes are present. It assumes that the large sex chromosome is dominant in the presence of the male sex chromosome, and that the male sex chromosome is dominant in the presence of the small female sex chromosome... This theory of sex determination brings the facts observed in regard to the heterochromosomes under Castle's modification of Mendel's Laws of Heredity.[80]

For Stevens, the small and large heterochromosomes (idiochromosomes) did not determine sex by their presence alone, but by Mendelian

78. E. B. Wilson, "The Chromosomes in Relation to the Determination of Sex in Insects," *Science, 22* (1905), 501-502: "It is more probable, for reasons that will be set forth hereafter, that the difference between eggs and spermatozoa is primarily due to differences of degree or intensity, rather than of kind, in the activity of the chromosome groups in the two sexes."

79. Stevens, *Studies,* p. 55.

80. Ibid.

relationships in hybrid individuals! Wilson, however, viewed selective fertilization as "*a priori* very improbable"[81] and defended himself against those, like Geoffrey Smith, who claimed that he was a proponent of such a belief.[82] Garland Allen has also alluded to Wilson's support of selective fertilization,[83] but nowhere in his papers does it become apparent during this time.

The chromosomal determination of sex for which Wilson was the major spokesman and Nettie Stevens the major source of evidence could not be completely substantiated without an explanation of how it was accomplished in the parthenogentically reproducing species. It was what Wilson called "the brilliant discoveries of Morgan and von Baehr" that showed that sex was determined by chromosomes in these species; but as we shall see, even as late as 1910, Morgan refused to believe in what he called the "McClung-Stevens-Wilson hypothesis."[84]

Morgan's first paper on sex determination was a review of the subject published in the 1903 volume of *Popular Science.* In it, Morgan argued the position that sex is determined by internal factors, either in the ovary or at fertilization. Much of his discussion either pointed out inconsistencies in the environmental approach or presented the embryological evidence suggestive of internal mechanisms. Identical twins, for instance, are always of the same sex and are derived from the same egg, whereas two-egg twins can be of different sexes. A similar situation, he observed, is found in the Paraguayan armadillo (where all of the eight to eleven litter mates come from the same egg and are the same sex) and in the chalcid bee. As mentioned earlier, Morgan shrugged off McClung's work as inconsequential. His general conclusion was that sex was internally determined and that recently proposed chromosomal theories did some good in that they directed attention to the early determination of sex. However, he went on, "those of them which have attempted to connect this conclusion with the assumption of the separation of male and female primordia in the germ cells have failed to establish their point of view.[85]

In 1905, the year that Stevens and Wilson presented their data on chromosomal sex determination, Morgan published two articles

81. E. B. Wilson, "Selective Fertilization and the Relation of Chromosomes to Sex-Production," *Science, 32* (1910), 242-244.

82. Smith, quoted in Wilson, ibid.

83. Allen, "Morgan and Sex Determination," p. 50.

84. Morgan, "Sex Determination in Phylloxerans and Aphids," 334.

85. Morgan, "Recent Theories," p. 116.

rebutting the idea. One of these was a short review and interpretation of Cuenót's new data, which struck at the heart of the Sutton-Boveri marriage of Mendelism and cytology, asserting that there was now evidence contrary to the belief that primordia separate in the germ cells. Cuenót had discovered that a yellow-haired variant in the mouse, when bred to normal mice, produced both black and yellow mice. The yellow mice of this new generation, when mated to each other, always produced litters containing both colors of mice. Never did a pure-breeding strain of mice develop, as would be expected from Mendelian ratios. (In other words, each yellow mouse was a hybrid, whereas Mendelian ratios would predict that one out of every three of them would be pure-bred). Cuenót interpreted his inability to obtain pure-bred yellow mice from heterozygotes having a recessive black trait as being due to selective fertilization. Yellow-bearing sperm could not fertilize a yellow-bearing egg. Morgan, however, interpreted his results differently. The reason for Cuenót's observation, he said, was that the color yellow was never dissociated from black, and this proved the inadequacy of the Sutton-Boveri model, which would have predicted the segregation of these factors in the second filial generation.[86]

The irony is that recent studies have shown that the yellow color (Agouti) in mice is an embryonic lethal when homozygous. Any mouse embryo homozygous for yellow does not survive to be born. Morgan, who had pointed out Cuenót's earlier successes by demonstrating differential mortality, failed to take this into account. Cuenót's own version of selective fertilization (in this case, the selective abortion of just those conceptuses) was closer to the truth.

Morgan's other 1905 paper on sex determination, also a review, criticized the theory of sex determination proposed by H. E. Ziegler. Ziegler's contention was that although each person received equal numbers of chromosomes from both parents, each received different numbers of chromosomes from his four grandparents. If each chromosome had a sex-determining factor on it, sex would be determined by the number of chromosomes received from the male versus the female grandparents. If the sum of the male grandparental chromosomes was greater than the sum of all the female grandparental chromosomes, the offspring would be male. If female grandparental chromosomes predominated, the offspring would be female. Morgan easily disposed of this theory by invoking aphids, bees, *Daphnia,* and the now familiar

86. T. H. Morgan, "The Assumed Purity of the Germ Cells in Mendelian Results," *Science, 22* (1905), 877.

menagerie of parthenogenetic species. He then launched into a more general critique.

> Ziegler's failure to give a satisfactory account of sex determination on the *differential* chromosome basis raises the wider question as to whether, at this time, we are really obliged to look in this direction for a solution of the question . . . The only value that such a conception might have at the present would be to indicate that *sex determination may not be the result of differential nuclear divisions that locate sex determining chromosomes in different cells, but that the process is chemical rather than morphological.*[87]

It soon became apparent that when Morgan wrote about chemical processes, he meant physiological reactions occurring in the egg cytoplasm. His bias was the same as he had had in the embryological controversy as to whether nuclear or cytoplasmic factors controlled inheritance and development. He related this search for sex determination directly to the earlier embryological controversy:

> In the higher animals, at least, sex is determined by internal, not external, factors. What the nature of the internal mechanism may be we do not know, but it is a curious and significant fact that in modern attempts to account for the nature of the change that takes place, the biologist finds himself trying once more to steer his course between the inevitable alternatives of preformation and epigenesis.[88]

Morgan saw Mendelism, in the Sutton-Boveri model, as a return to preformationism, whereas a physiological approach would assure epigenesis. Indeed, Morgan was against Mendellism *because* he thought it was preformationist (and in a very direct sense, morphological). Earlier in his career, Morgan had criticized His's theory of *Organbildenden Keimbezirke* for the same reasons, even though its preformed determinants were cytoplasmic. Wilson, however, could accept this theory, provided that the cytoplasmic determinants were epigenetically directed by elements in the nucleus.[89] Morgan's "epigenesists" were those who believed, with him, that each germ cell was a sex hybrid

87. T. H. Morgan, "Ziegler's Theory of Sex Determination and an Alternative Point of View," *Science, 22* (1905), 839 (italics mine).

88. T. H. Morgan, "Sex Determining Factors in Animals," *Science, 25* (1907), 382-384.

89. Morgan, "Variation of Cleavage," p. 79.

(therefore, each zygote was a double hybrid) and that sex was determined by internal physiological conditions which caused an unfolding of events like that seen in the development of any other embryological characteristic: "My own preference—or prejudice, perhaps—is for the epigenetic interpretation, but the whole truth may like somewhere in between these two modes of thought that are the Scylla and Charybdis of biological speculation."[90] Even as late as 1910, Morgan could not see how anyone could say that sex was due to one nuclear element "when we have every evidence that in embryologic development the responsive action of the cytoplasm is the real seat of changes at this time, while the chromosomes remain constant throughout the process."[91] Morgan's dichotomies take the following form:

Epigenesis	Preformation
Cytoplasm	Nucleus
Physiological process	Chromosomal morphology
Embryologic	Mendelian genetic

Indeed, one observes that Morgan's arguments against Wilson were the formal descendants of those used by Geddes and Thomson against Weismann. Like these earlier authors, Morgan claimed that metabolic balances determined the fate of the offspring, and he similarly attacked those who posited morphological elements as controlling heredity from the nucleus. (Interestingly enough, both of these controversies echo an even earlier dispute between Nageli, who insisted on the morphological continuity of hereditary material, and van Beneden and Pflüger, who proposed that heredity and development were controlled by the interactions of molecules in solution.[92])

But Morgan does not accurately portray Wilson's beliefs concerning epigenesis or physiology. For Morgan, physiology meant the metabolic reactions in the cell cytoplasm. For him, the nuclei of early embryos were equivalent (as had been shown by Driesch), and only their cytoplasms differed. Morgan believed, for instance, that each germ cell carried the potentials for both sexes, thus making the zygote "a double-barrelled sex hybrid."[93] The sex of each embryo would be determined

90. Morgan, "Sex Determining Factors," p. 383.

91. T. H. Morgan, 'Chromosomes and Heredity," *Amer. Nat., 44* (1910), 453.

92. Coleman, "Cell, Nucleus, and Inheritance," pp. 147-148.

93. Morgan, "Sex Determining Factors," p. 383. This view recalls van

not by the equivalent nuclei, but by internal conditions which would favor the expression of one or the other alternative.

As mentioned earlier, Morgan also believed that these metabolic reactions were unrelated to the cellular compartmentalization of the developing organism. This notion came from Driesch's cellular transposition experiments and from numerous studies which showed the ability of individual blastomeres to produce entire, though smaller, larvae. This work had severely crippled the Roux and Weismann hypothesis of a purely mosaic development. By 1894, Wilson acknowledged that all schools of thought agreed that the cell could not be considered a totally independent unit and that its differentiation was influenced by its environment.[94] However, Driesch's claim that the prospective value of a blastomere was a function of its location[95] did not go far enough for Morgan; for it would have posited that the blastomeres of smaller embryos (that is, those derived from the separated blastomeres of earlier embryos) would have the same relationships to each other as the blastomeres of normal embryos. Morgan believed that these relationships could not hold in the smaller forms, and he claimed that the crucial matter was the "organic continuity" of the embryo cytoplasm. The embryo still gastrulated whether it had 150 cells or 500 cells. Morgan's view was very similar to that of C. O. Whitman, who regarded cell boundries as convenient divisions of the cytoplasm. This is the context in which Morgan interprets his own results.

> "The plastic forces heed no cell boundries but mold the germ-mass regardless of the way it is cut up into cells. That the forms assumed by the embryo in successive stages are not dependent on cell division may be demonstrated in almost any egg." Whitman's conclusions

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Beneden's hypothesis that each cell is hermaphroditic, containing both male and female chemical determinants. Each unfertilized egg, however, would exclude the male material in its polar bodies. After a similar process occured in the formation of the sperm, the union of gametes would yield a new hermaphroditic assembly whose component materials would interact physiologically to produce a new organism. By the time Morgan was writing, however, Hertwig had already shown that a process analogous to polar body extrusion did not happen in the male, so the resulting union might well be expected to create "double-barreled sex-hybrids."

94. Wilson, "Mosaic Cleavage," p. 9.

95. Driesch, quoted ibid., p. 10.

> receive, I think, strong support from the results of the experiments recorded on the preceding pages.[96]

Wilson, however, sought to reintroduce Roux's notion of cell autonomy into the scheme of development. To be sure, Driesch had done embryology a great service, but the cell was not to be viewed as passive in development. Referring to the theories of Driesch and Hertwig, Wilson lectured: "It seems to me, however, that they may be modified in such a way as, without sacrificing the principle of epigenesis for which they contend, to recognize certain elements of truth in the mosaic hypothesis."[97] Using marine animals as his examples, Wilson finds

> a reconciliation between the extremes of both rival theories . . . that we may constantly hold with Driesch that the prospective value of a cell may be a function of its location, and at the same time hold with Roux that the cell has, in some measure, an independent power of self-determination due to its inherent specific structure.[98]

One of the major influences on Wilson's view of the cell was Claude Bernard. In addition to sharing Bernard's view that "cells are the primary elements of living matter,"[99] Wilson also followed Bernard's notions on the metabolic specialization within the cell. The nucleus, said Bernard, was the site of synthetic metabolism, whereas degradative metabolism was confined to the cytoplasm. Thus Wilson could accept all of Morgan's results by stating that these were only secondary phenomena, occurring at a certain place and time because they were directed by "the nucleus which operates by setting up a continuous series of specific metabolic changes in the cytoplasm."[100]

Both Morgan's and Wilson's views of physiology came from their embryological studies. As they moved into cytology, these views were

96. Morgan, "Partial Larvae," p. 124.

97. Wilson, "Mosaic Cleavage," p. 10.

98. ibid., p. 12.

99. C. Bernard, *Lecons sur les propietes des tissus vivant* (Paris, 1866), p. 22, quoted in E. Mendelsohn, "Physical Models and Physiological Concepts: Explanation in Nineteenth-Century Biology," *Brit. J. Hist. Sci., 2* (1965), 201.

100. Wilson, *Cell.* p. 320. It should be noted that even at this time, Wilson viewed metabolism as entailing a specific series of reactions, the sex differences being caused by quantitative rather than qualitative variation in cell metabolism. Such hypotheses show Wilson's inclination to be physiological rather than morphological, epigenetic rather than preformationist.

largely retained, and in 1908, they were sharply contrasted in the conflicting interpretations of Morgan's brilliant experiments on parthenogenetic sex determination. In 1906, Morgan had initated a purely cytological study of the phylloxerans (hickory aphids), a parthenogenetic species, in order to see whether or not the chromosomal basis of sex determination would hold for such organisms. Certainly if there were any organisms in which such a hypothesis should fail, they would be parthenogenetic species.

Morgan was able to show that in the eggs of the stem mother, only one polar body was extruded from the developing ovum, so that the normal diploid (somatic) number of twelve chromosomes remained in the egg. All the winged females that developed from these eggs had twelve chromosomes per somatic cell. These females, however, could lay eggs that became either male or female. In those eggs destined to become female, only one polar body was extruded and the egg contained twelve chromosomes. But in the male-producing eggs, after the polar body was extruded, only ten chromosomes remained in the egg! An entire chromosome pair had entered the polar body in addition to the usual amount, thereby causing the males to have only ten chromosomes per somatic cell. During male meiosis, two types of sperm were formed—one type having six chromosomes and one type having only four. The latter type of sperm degenerated, so that only the sperm bearing six chromosomes survived to fertilize the six-chromosome-containing ova. This process resulted in offspring with twelve chromosomes—that is, females—who began the cycle over again.

Wilson regarded these findings as a great victory for the chromosomal theory of sex determination, but Morgan interpreted his results in a far different manner. If the total number of chromosomes were present in the germ cells of a winged female, he reasoned, why should some of them give rise to ten-chromosome-bearing eggs and others give rise to the larger twelve-chromosome eggs? Whatever was determining sex could not be chromosomal since all the chromosomes were present at the true point where sex was established—the formation of the egg. Morgan believed that the sex determinant was whatever cytoplasmic factor moved the chromosomes. Indeed, his line of reasoning had changed little since his analysis of the ctenophore egg, in which he noticed that aberrations in the cytoplasm could occur in the presence of the entire nucleus; for he now stated: "Clearly, I think, the results show that changes of profound importance may take place without change in the number of chromosomes."[101]

101. T. H. Morgan, "Sex Determination and Parthenogenesis in Phylloxerans and Aphids," *Science 29* (1909), 236.

Morgan's analysis of phylloxeran sex determination went on until around 1909, when he began his studies of *Drosophila.* In 1910, he published the first of his series of papers involving sex-limited inheritance in these fruit flies.[102] A white-eyed fly had appeared in his stocks (Morgan was looking for examples of saltatory mutations at the time), which Morgan subsequently bred to normal red-eyed females. The first generation encompassed 1,237 red-eyed offspring of both sexes. These flies were inbred to obtain a second generation, which had red-eyed males, red-eyed females, white-eyed males, but no white-eyed females! He then mated a white-eyed male to the red-eyed females of the first generation and obtained all the possible results, including white-eyed females. In tabular form, his findings were:

Cross		Progeny
(a) $X^eY \times X^+X^+$	$\longrightarrow$ $X^+X^e + X^+Y$	First generation all red-eyed
(b) $X^+X^e \times X^+Y$	$\longrightarrow$ $X^eX^+ + X^eY + X^+X^+ + X^+Y$	No white-eyed females in second generation
(c) $X^eY \times X^+X^e$	$\longrightarrow$ $X^eX^+ + X^eY + X^eX^e + X^+Y$	All combinations

To account for these results, Morgan posited that all the sperm from white-eyed flies carried the factor W for whtie yes. Half of these spermatozoa carried the factor X for sex. (At this time *Drosophila* was believed to have an XO mode of inheritance).

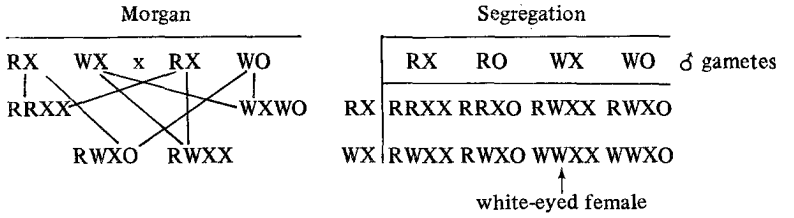
Male = WWX and can form two types of sperm: WX and WO
Female = RRXX and each egg gets and R and an X (R is for red eyes)

White-eyed male × red-eyed female = WX WO × RX RXand yields 50% RWXX (red females) and 50% RWXO (red males)

When these are mated together one obtains:
25% RRXX + 25% RWXX + 25% RWX + 25% WWX
red, female red, female red, male white, male, and no white-eyed females

102. T. H. Morgan, "Sex Limited Inheritance in *Drosophila*," *Science, 32* (1910), 121. Stevens had not observed the small Y-chromosome of these species, hence it was believed at that time to acquire sex in the XO manner.

Allen has pointed out that Morgan purposefully wrote his symbols as though they were in no way physically connected. Yet, if we analyze the results, we can see that Morgan's explanation leaves no other alternative but to link them, since the dihybrid RWXO males do not segregate their factors independently:



Faced with this evidence, Morgan admitted "It now becomes evident why we found it necessary to assume a coupling of X and R in one of the spermatozoa of the red-eyed Fl hybrid RXO. The fact is that the R and X are combined and have never existed apart."[103]

But this did not necessarily mean that these were linked physically together on a chromosome. Morgan avoided any conceptualization of them as nuclear factors, for even after these data were published, he could still criticize those who would "reduce the problem of development to the action of specific particles in the chromosome."[104] Again, Morgan looked to the cytoplasm:

> Our general conclusion is, therefore, that the essential process in the formation of the two kinds of gametes of hybrids in respect to each pair of contrasted characters, is a reaction or response in the cells, and is not due to a material segregation of the two kinds of materials contributed by the germ cells of the two parents... This conclusion is epigenetic, while the contrasting view, that of separation of materials, is essentially that of preformation.[105]

By the summer of 1911, however, Morgan had shown that factors affecting eye color, body color, wing shape, and sex all segregated together with the X-chromosome. To explain these drastic deviations from random assortment, Morgan was forced to espouse the Mendelian

103. Morgan, "Sex Limited Inheritance," p. 122.
104. Morgan, "Chromosomes and Heredity," p. 453.
105. Ibid., p. 497.

preformationism against which he had contended for over a decade. First, Morgan formulated a principle of association: "By this I mean that during segregation certain factors are more likely to remain together than to separate, not because of any attraction between them, but because they lie near together on the same chromosome"[106] And he concluded that "sex-limited inheritance is explicable on the assumption that one of the material factors of a sex-limited character is carried by the same chromosome that carries the material factor femaleness."[107]

It is obvious from the above statements not only that had Morgan obtained direct evidence for the determination of sex by the chromosomal mechanism, but that in doing so, he had come to formulate the gene theory.

In his July 7, 1911 speech at Woods Hole, Morgan did not give a reason for his sudden conversion, and the exact reasons for the change still remains unclear. Certainly, Morgan acknowledged a type of associative inheritance in his *Science* paper of 1910, when he stopped just short of physically linking the hereditary factors for sex and eye color. It would not be surprising, then, if the combined weight of eye color, body color, wing shape, and sex factors cosegregating with the X-chromosome had convinced him that the best way to explain his data was to posit the physical connection of these traits on the chromosome.

In addition, the chromosomal theory of heredity had strong partisans in Morgan's group, for nearly all of Morgan's early *Drosophila* researchers had also been undergraduates at Columbia University. H. J. Muller has described how Wilson, who was then chairman of biology there, exerted an enormous influence over the program. Incoming freshmen would be taught biology from Sedgewick and Wilson's textbook and by Wilson's students Calkins and McGregor. As sophomores, they could take Wilson's course on heredity, chromosomes, and evolution, where they read Lock's *Recent Progress in the Study of Variation, Heredity, and Evolution* (1906), a book even more unreserved in its advocacy of the chromosome theory of heredity than was Wilson. As upperclassmen, biology majors could enroll in Wilson's course in cytology.[108] Indeed, Muller reported that it was a combination of

106. T. H. Morgan, "An Attempt to Analyze the Constitution of the Chromosomes on the Basis of Sex-Limited Inheritance in *Drosophila*," *J. Exp. Zool., 11* (1911), 365-414.

107. Ibid., p. 345

108. H. J. Muller, Edmund B. Wilson–An Appreciation," (part. 2), *Amer. Nat., 77* (1943), 142-172.

Morgan's own data and his students' interpretations that forced him to capitulate. These students, Muller claimed, brought the arguments of Wilson and Lock to their teacher:

> The results [of his studies] proved, however, to be at glaring variance with his views, and at the same time he found himself pressed in his interpretations by a small group of younger co-workers occupying the official position of "student" whose ideas, despite their officially subordinate position, Morgan realized that he should take seriously. These "students" had been influenced greatly by their studies under Wilson, and even more by Lock's remarkably prophetic book... Slowly, and against his will, Morgan was forced to give way to the double pressure of facts and arguments.[109]

By demonstrating the associative inheritance of hereditary determinants on a chromosome, Morgan had resolved the embryological controversy of the previous decade. Ironically, the theories he vindicated were not his own, but those of his "preformationist" opponents, Boveri, Sutton, and Wilson.

In this paper I have tried to show the emergence of the gene theory from a fundamental controversy in embryology. The sex-determination problem is seen here in its larger context as being the critical test of whether the nucleus or the cytoplasm controlled development and heredity. The Investigations of the mechanism of sex determination during these years eventually gave rise to the gene theory in three ways. First, observations on meiosis to determine the origin of the accessory chromosome led to Sutton's hypothesis that Mendelian ratios could be explained by a chromosomal mechanism which allowed for both the transmission and the purity of traits in each germ cell. Second, chromosomal individuality was observed, at least in the case of X-chromosome. And Morgan, who for over a decade refused to accept the evidence of Sutton, Wilson, and Stevens, finally linked certain hereditary factors physically to the X-chromosome.

The study of sex determination during these years also demonstrates the profound nature of scientific conservatism. Earlier ideas concerning

109. H. J. Muller, "Lenin's Doctrines in Relation to Genetics," quoted in E.A. Carlson, *The Gene: A Critical History* (Philadelphia, 1966), pp. 233-234. Elsewhere (ibid.), Muller has stated, "Thus it is likely that only those *Drosophila* workers of the earliest years fully realize to what extent modern genetics traces its descent from Wilson."

sex had to be withdrawn, and previous public statements had to be recanted. Wilson, in becoming one of the most ardent spokesmen for the theory of chromosomal determination, certainly came far from his 1896 statement in which he said sex was environmentally determined. McClung changed his mind about the importance of the environment in sex determination, as is clear from his 1910 review, which was highly critical of a theory that proposed an environmental mechanism very similar to the one he had formerly outlined.[110]

Others, however, were not as quick to change. Thomson, a coauthor of the famous environmental theory, retained his earlier views about sex determination. Along with Geddes, he asserted, as late as 1914:

> To the view of sex expounded in the *Evolution of Sex* in 1889, a reference must again be made, for we find ourselves unable to get away from the conviction that there is no sex-determinant or factor at all, in the morphological or in the Mendelian sense, but that what settles sex is an initial difference in the rate or rhythm of metabolism . . . Influences which favor a predominance of anabolic processes, which affect the nucleus-cytoplasm relation in a way favoring cytoplasmic assimilation, tend to the increase of female-producing eggs. Influences that operate in the opposite direction favor the increase of male-producing eggs.[111]

Allotting only a small paragraph to Wilson's work and all that had been done in the intervening quarter of a century, Geddes and Thomson still maintained their preference for a more physiological explanation: "What we are suggesting is a physiological way of looking at the problem, and the idea that the sex-contrast expresses a physiological alternative."[112] Indeed, Wilson's idea of sexual physiology, that an egg with one X-chromosome can make enough of some substance for a male but note a female, was the weakest point in his theory; and even today, the metabolic reactions directed by the sex chromosomes for sex determination are still largely unknown.

For Morgan, there was no evidence which could compel him to favor the chromosomal theory until his own evidence forced it upon him in 1911. The reason, alluded to earlier, was that he refused to accept the synthesis of Mendelism and cytology which located the hereditary and

110. C. E. McClung, Review of A. Russo's *Studien Ueberdie Bestimmung des Weiblichen Geschlechtes, Science, 32* (1910), 429-432.

111. Geddes and Thomson, *Problems of Sex*, p. 113.

112. Ibid., p. 114.

developmental factors in the chromosomes. To him, this was a preformationist heresy, contrary to the observations of embryology. He found no clear-cut evidence that Mendelism was necessarily true, as is obvious from his analysis of Cuenót's work, and saw nothing to connect chromosomes causally with sex or any other characteristic. The true determinants moved the chromosomes.

What enabled Wilson to accept the chromosomal theory so readily, while Morgan refused to give it credence? Certainly their graduate education was similar. Brooks, their teacher, threw up his hands at the problem of sex determination, observing that "sex is not determined by any constant law."[113] This is not to say that he was not interest in the problem. He noted that the parthenogenetic species were the key to understanding the problem, and, more important, he held that "the characters of each sex was potential and latent in the organism of the opposite sex.[114] He called the belief that hereditary factors existed in the chromatin "metaphysical" and a throwback to pre-Darwinian science.[115]

We have seen that Morgan's and Wilson's attitudes toward sex determination reach back further to their positions in the dispute over cytoplasmic or nuclear control of develop. Wilson's acceptance of the chromosome theory stemmed largely from his former championing of the nuclear control of embryogenesis. His position in this controversy was based largely on two sources—the experiments on protozoan regeneration and the embryological data gathered by Boveri, Roux, and himself, among others. We can further trace Wilson's acceptance of these investigations to two more factors—his view that the cell was the unit of heredity and development (a view that enabled him to extrapolate from protozoans to individual blastomeres) and his view that all animals shared the same basic pattern of heredity, the mosaic and regulative cleavage difference being explained away as differences in the temporal activity of the nucleus. Neither of these basic concepts of nature was shared by Morgan, and that is perhaps why Wilson was so ready to propound the chromosome theory while Morgan was so repelled by it.

Morgan became a geneticist not out of enthusiasm for the new discipline, but only because he wanted to test certain embryological hypothesis. He entered genetics as an embryologist, and later in his

113. Brooks, *The Law of Heredity,* pp. 316-317.

114. Ibid., p. 104.

115. W. K. Brooks, *Are Heredity and Variation Facts?* (Baltimore, 1907), p. 15.

life he returned to those problems of marine embryology which he had abandoned for his *Drosophila* studies. His biases were rooted in earlier disputes, and in this new phase of his research, he equated the hereditary and ontogenetical processes: "We have come to look upon the problem of heredity as identical with the problem of development. The word heredity stands for those properties of the germ cells that find their expression in the developing and developed organism."[116] Here, too, we can see the difference in attitude between Morgan and Wilson. According to Coleman, Morgan was able to advance so greatly after his initial *Drosophila* experiments because he was able to separate the problem of heredity (transmission) from that of development.[117] But Wilson had made that distinction much earlier, as early as 1896:

> The nucleus cannot operate without a cytoplasmic field in which its peculiar powers may come into play; but this field is created and modeled by itself. Both are necessary to *development;* the nucleus alone suffices for the inheritance of specific possibilities of development.[118]

Certainly, Muller was right when he claimed that Morgan accepted the implications of his *Drosophila* experiments "against his will."[119] Nor was Morgan alone in withstanding the chromosomal theory. Bateson, another protégé of Brooks, held out even longer, although he was forced to compromise on the possibility that the X-chromosome might be involved in sex. Physiologically oriented geneticists like R. F. Goldschmidt and W. E. Castle refused to credit all power over sex determination to the nucleus, even after Morgan and his coworkers linked sex cytologically to the physical X-chromosome.[120]

Morgan became the great spokesman and researcher in the field of chromosomes and heredity. His turn-around was complete, and he acknowledged it in an obituary he wrote for his former colleague Nettie Stevens. Like the "devil's advocate" doing penance before the newly canonized, Morgan identified his attitude not with caution, but with conservatism:

116. Morgan, "Chromosomes and Heredity," p. 449.

117. W. Coleman, "Bateson and Chromosomes: Conservative Thought in Science," *Centaurus, 15* (1970), 228.

118. Wilson, *Cell,* p. 327.

119. Muller, "Lenin's Doctrines," p. 327.

120. G. E. Allen, "Opposition to the Mendelian-Chromosome Theory," *J. Hist. Biol., 7* (1947), 49-92.

> The profound significance of the results were by no means generally appreciated, and it is not going too far to say that many cytologists assumed a sceptical or even antagonistic attitude for several years towards the new discovery. No doubt this will be attributed to scientific caution, but conservatism may better account for the slowness with which a recognition of this discovery was received. It was said, for example, that the unequal distribution of the sex chromosomes is only an index of more profound changes taking place, and is not itself the real differential. . .[121]

The latter view, of course, had been Morgan's; yet by 1913, he and Sturtevant produced the first physical genetic map of the X-chromosome of *Drosophila,* and his book *Heredity and Sex* became the major statement of the gene theory that has dominated biology ever since.

The embryological origin of the gene theory demonstrates how the biases of one discipline are effectively carried over into a new field. It also demonstrates a phenomenon that N. C. Mullins has recently noted in his analysis of the origins of molecular biology: that a relatively small group of investigators working on a specific problem in one field can generate the foundations for an entirely new science.[122] Indeed, since the researchers mentioned here were trained under a similar set of conditions and in a very small number of institutions, the science of genetics may owe as much to Naples and Woods Hole as it does to the fly room of Schermerhorn Hall.

121. T. H. Morgan, "The Scientific Work of N.M. Stevens," *Science, 36* (1912), 469.

122. N. C. Mullins, "The Development of a Scientific Specialty: The Phage Group and the Origins of Molecular Biology," *Minerva, 10* (1972), 51-82. It is interesting to note that disciplines seem to change according to their own vocabularies, as if sensitive to their own metaphors. Copernicus's theory of celestial orbits occasioned a "revolution" in astronomy, while the history of evolutionary thought lends itself readily to terms of natural selection. In embryology, change did not occur as a revolution nor were new ideas selected by a changing social environment. Rather, embryology underwent a metamorphosis. There was continuity of substance between the old and the new disciplines, a small portion of the old structure expanding rapidly to produce a new one from within. During this period, embryology underwent two metamorphoses–once in the group of physiological embryologists who created developmental mechanics out of the descriptive embryology, and again when the group of developmental physiologists concerned with nucleus-cytoplasm relationships created the gene theory.

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