Proof of physical exchange of genes on the chromosomes

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Seventy-five years ago, a convincing demonstration that the genes were physically aligned along the chromosome was lacking. Harriet Creighton (1909–2004) and Barbara McClintock (1902–1992) [Creighton, H. B. & McClintock, B. (1931) *Proc. Natl. Acad. Sci. USA* 17, 492–497] showed by an elegantly simple experiment in 1931 that exchange between genes was accompanied by exchange of cytological, i.e., physical, parts of chromosomes. The work has been acclaimed as one of the great experiments in biology. Creighton's doctoral dissertation under McClintock's mentorship provided the basis for the landmark paper, which was unique in merging cytological with genetic data. A companion paper by McClintock, printed and bound back-to-back with the joint paper, set the essential stage with data on the cytological and genetic features that Creighton applied. Following directly from this work, and leading to today's recognition that the genome is a graspable entity, was the knowledge that the genes could be studied as components of a linear structure, the chromosome. Here, we review the data surrounding the Creighton and McClintock paper and provide a perspective on the significance of their findings.

The essential components to the demonstration of cytological and genetic crossing over are (*i*) differential features along the chromosomes that are morphologically (i.e., physically) recognizable and (*ii*) genes in the region of the cytological markers. The question is whether the order of the cytological features directly corresponds with the order of the genes as determined by their frequencies of crossing-over and recombination, that is, in a genetic map. The experiments designed by Creighton and McClintock with *Zea mays* (1) were paralleled by those of Stern (2) with *Drosophila*, published soon afterward. Creighton and McClintock introduce their report with explicit clarity as follows:

> A requirement for the genetical study of crossing-over is the heterozygous condition of two allelomorphic factors [edited in ink on reprints by one of the authors to read 'factor pairs'] in the same linkage group. The analysis of the behavior of homologous or partially homologous chromosomes, which are morphologically distinguishable at two points, should show evidence of cytological crossing-over. It is the aim of the present paper to show that cytological crossing-over occurs and that it is accompanied by genetical crossing-over.

Two cytological features were sufficient for the experiment: (*i*) a dark-staining, heterochromatic "knob" at the end of chromosome 9, and (*ii*) a reciprocal interchange (translocation) of a part of chromosome 9 with a part of chromosome 8 (Fig. 1 *a* and *b*). The knob feature is present in some strains and absent in others, while the interchange had been found as an exceptional type termed semisterile-2, studied by Burnham (3), and subsequently renamed T8-9a. The knob has no effect on the appearance of the plants, but

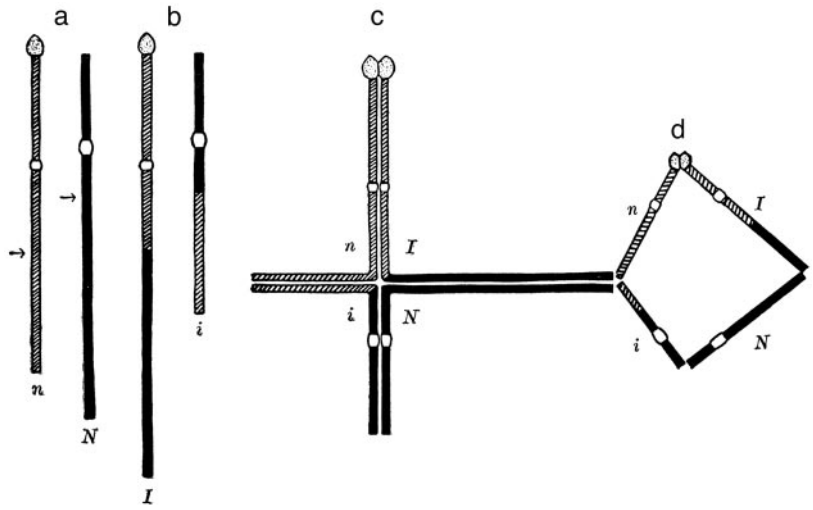

Fig. 1. Chromosomal constitution and cytological features used in the maize experiment. Centromeres are shown as clear circles. In *a*, the two normal chromosomes, number 9 (*n*, barred) bearing a dark-staining knob at the end of its short arm and 8 (*N*, black) are shown with arrows denoting the point of reciprocal interchange of parts to form a translocation. In *b*, interchange chromosome 9 (*I*) has a part of chromosome 8 appended, and chromosome 8 (*i*) bears a part of chromosome 9. In *c*, the normal and interchanged chromosomes are shown diagrammatically in the paired cross formation in early meiosis during the process of gamete formation (see Fig. 3). In *d*, the opening out of the four chromosomes into a ring is diagrammed, from which adjacent or alternate pairs of chromosomes distribute to the division poles, resulting in deficient, inviable gametes or viable ones, respectively. The chromosomes are shown as single rather than double strands in this diagram, for simplicity. For the demonstration of crossing-over, the constitution in *c* and *d* required that one chromosome 9 end be knobbed and the other knobless. [Reproduced with permission from ref. 12 (courtesy of Peter McKinley).]

the translocation, when heterozygous with normal chromosomes 8 and 9, results in 50% of pollen grains being sterile and empty and 50% of eggs, embryo sacs, and ovules aborting—consequently, the ear becomes only half-filled, and the kernels are irregularly distributed. This semisterility results from the formation of deficient gametes following synapsis of four chromosomes in a cross-shaped configuration (Fig. 1*c*). This configuration opens out into a ring (Fig. 1*d*), from which the centromeres distribute either two alternate chromosomes, with balanced (viable) genomic constitutions, or two adjacent chromosomes, with deficient-duplicate (inviable) constitutions. Thus, classification of plants for the presence of the translocation can be done either by its effects on fertility or by cytology.

Gabriel and Fogel (4) define the context and the impact of the experiment:

> The relationship between genetic recombination and the occurrence of chromatin exchange between equiva-

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lent segments of homologous chromosomes at the cytological level was first suggested by Morgan in 1911 as an explanation for the genetic phenomenon of linkage. . . . Morgan ingeniously emphasized that if the genes were arranged in a linear fashion on the chromosomes, equivalent blocks of maternal and paternal genes could be exchanged during the period of meiotic synapsis through the formation of chiasmata. These [chiasmata] had been described previously by Janssens [1909]. While the utility of this outlook was abundantly verified in thousands of varied experiments, and no disagreements between theory and observation were reported in the twenty-year period following its introduction, direct proof conclusively validating the theory was notably lacking. That no such proof was obtained for nearly twenty years is more easily appreciated if it is recalled that two homologous chromosomes are identical even in favorable cytological material under ideal conditions. Thus, while chiasmata are directly observable, and while they might be interpreted as due to an exchange between homologous chromosomes, there is no simple way to visually differentiate the maternal and paternal elements in an exchange. . . .

Beyond any question, this is one of the truly great experiments of modern biology, and the conclusion—that pairing chromosomes heteromorphic for two or more regions exchange parts at the same time that they exchange genes assigned to these regions—will doubtless continue to stimulate as much research during the next as they have during the 25 years following its publication.

The experiment of Creighton and McClintock, and the parallel experiment by Stern with *Drosophila* published in the same year, established the commonality in linear order between the chromosome and the genes within it. Only then could it be considered likely that the genetic material extended in a linear tract from one end of the chromosome to the other. This was the point at which 20 years of concentration on the nature of the genetic material was set in motion, brought to fruition by Watson and Crick (5).

Origins of the Components of the Experiment

The morphological markers had been discovered in prior studies and were used for this experiment based on improved knowledge of their chromosome locations. This period was one of very rapid development of cytology, of genetics, and associating genes with the chromosomes that bear

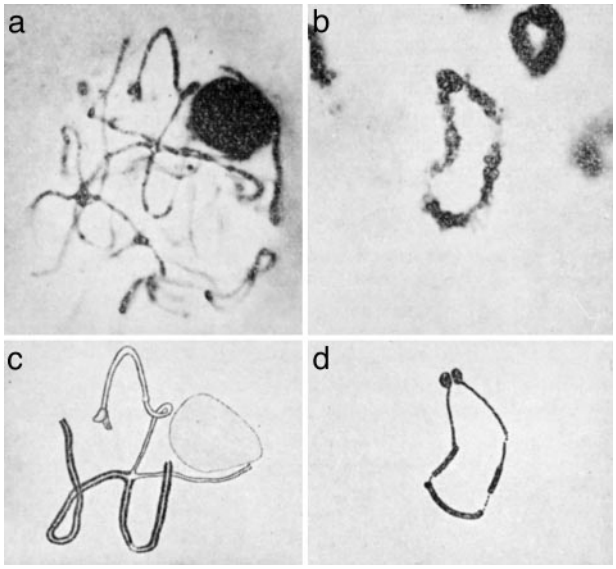

Fig. 2. Photomicrographs of maize chromosomes carrying the 8–9 translocation, at the time of chromosome pairing (*a*) and opening out (*b*), and diagrams (*c* and *d*). At the stage in *a*, heterochromatic regions display differential staining along the lengths and between the chromosomes. *a* is from McClintock (not previously published), and *b* is from Creighton (1933). [Reproduced with permission from ref. 9 (Copyright 1934, McGraw–Hill).]

them, through an intricate cascade of experiments substantially conducted by McClintock at Cornell University (6, 7). The maize chromosomes had been distinguished under the microscope by McClintock in 1929 on the basis of their relative length, arm ratios, and dark-staining knob positions. The knob at the end of chromosome 9, the second smallest chromosome, however, was first specifically described by McClintock (8) in the course of her study on "A cytological demonstration of the location of an interchange between two non-homologous chromosomes of *Zea mays*" as follows:

> Fortunately, the second smallest chromosome possesses, in certain strains of maize, a very conspicuous accumulation of stainable substance at the end of the short arm . . .

McClintock observed these chromosomes from preparations she made from a maize stock she received from Charles Burnham. The photographs she mentioned in her paper were subsequently published (Fig. 2 *a* and *b*) in Sharp's widely used 1934 cytology textbook (9).

The interchange between chromosome 9 and chromosome 8 was first recognized by its effects on fertility, with 50% pollen and kernel abortion, and was named "Semisterile-2" in the studies of Brink and Burnham (10, 11). Recognizing Belling's hypothesis of segmental interchange, they suggested that an interchange of chromosome segments could explain the genetic behavior, and Burnham (3) and McClintock (8) confirmed cytologically that two chromosomes had exchanged parts. The consequences of distribution of chromosomes after pairing of two normal chromosomes with two interchanged chromosomes, leading to 50% sterility (Fig. 3), were mutually recognized by these authors.

The genetic markers of the "*C–wx*" linkage group had been mapped in relation to each other in studies by other scientists, and these data had been compiled by R. A. Emerson and G. W. Beadle in 1929 and 1930 during early cooperation among maize geneticists. Association of these linked markers with chromosome 9 was established by McClintock (12) with experiments involving an extra chromosome, and was doubly reinforced by mapping the knob and genetic markers together (see below).

The Significance of Back-to-Back Papers

The paper by Creighton and McClintock was not presented as a free-standing report. In a paper just preceding it in the journal (both were distributed as one offprint in a single cover bearing both titles), McClintock (12) set the stage with mapping data placing three genes, *c*, *sh*, and *wx* (respectively affecting color, shape, and starch properties of the kernel), on chromosome 9, in order with the interchange and with the knob. First, McClintock established the association of these genes with the chromosome bearing two morphological markers, the knob and the interchanged portion, in plants with an extra chromosome. The correspondence between the presence of the extra chromo-

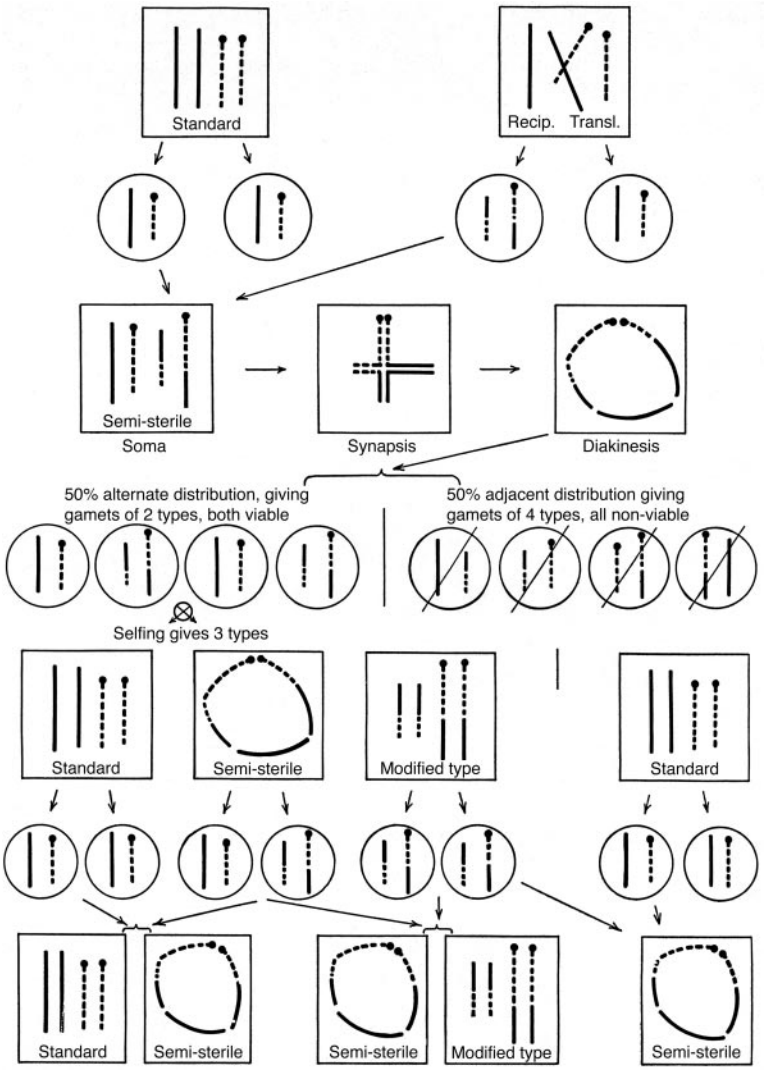

Fig. 3. Consequences of distributions of chromosomes from a heterozygous translocation, showing the arising of viable vs. deficient-duplicate, nonviable gametes and the results of self-pollination. Note that there are three classes in such a progeny, occurring in a 1:2:1 ratio: standard chromosome constitution with normal pollen grains, heterozygous translocation with semisterile pollen grains, and homozygous translocation with normal pollen grains, due to a complete but rearranged set of chromosomes. [Reproduced with permission from ref. 9 (Copyright 1934, McGraw–Hill).]

some and abnormal ratios for the genes was the key determinant, and this was the point at which the association of the group of linked genes with a specific cytological chromosome, number 9, was defined. The other chromosome in the interchange, chromosome 8, was recognizable by its size and other morphological features. Semisterile-2 was thus defined as a translocation between chromosomes 8 and 9. Mapping data defined the order on chromosome 9 to be knob–*c*–*sh*–*wx*–interchange. The purpose of the first paper is stated in the last sentence: "*It was desired to present briefly the evidence at this time, since it lends valuable support to the argument in the paper which follows*." The paper by Creighton and McClintock refers twice to the "preceding paper" without a citation, assuming the reader will read the two together. In contrast, they refer twice to a relevant "previous paper" by McClintock (8) in the preceding year. The importance of the "preceding paper" is emphasized in an annotation in the "Current list of Barbara McClintock's publications" [L.B.K., *Maize Genetics Cooperation Newsletter* (1999) **73,** pp. 42–48].

Creighton recalled that Thomas Hunt Morgan pushed them to publish their data (Creighton, 1982, taped symposium, courtesy of Rosalind Morris). Emerson sent both papers to PNAS and specifically asked the editor to publish them together and, if they could not, to publish the paper by McClintock first [letter from R. A. Emerson to Edwin B. Wilson, July 3, 1931, Plant Breeding Records, Rare and Manuscript Collections, Carl A. Kroch Library, Cornell University Library, Ithaca, NY (hereafter abbreviated as CU)].

Applying the information from the "preceding paper" (12) on map order of the components, Creighton and McClintock conducted an experimental cross of the constitution shown in Fig. 4. First they presented data showing that the frequencies of recombination, ≈39% between the knob and the interchange and ≈16% between the knob and gene *c*, are consistent with the order and distances provided in the preceding paper. This interpretation is most important for what follows: cytological crossing over between heteromorphic chromosomes (between normal chromosome 9 and the interchange chromosome—specifically the section between the knob on the short arm of chromosome 9 and the attached piece of chromosome 8 in T8-9a) accompanying genetic crossing over between loci (*c* and *wx*). The table of data presented by Creighton and McClintock, reproduced here (Fig. 5), was accompanied by this comment: "*The data are necessarily few since the ear contained but few kernels*." Consideration of each individual plant of the progeny is followed promptly in the paper by a one-sentence final statement and conclusions:

> The foregoing evidence points to the fact that cytological crossing-over occurs and is accompanied by the expected types of genetic crossing-over.
>
> Conclusions.—Pairing chromosomes, heteromorphic in two regions, have been shown to exchange parts at the same time they exchange genes assigned to these regions.

Notably, the "preceding paper" by McClintock relates and cites data from two then-current sources of shared data: A "Mimeographed pamphlet on linkage in maize. Cornell University" (published and unpublished data that were compiled and distributed to colleagues by R. A. Emerson as a part of the nascent Maize Genetic Cooperation in 1929 and 1930, reprinted in Maize Genetics Cooperation Newsletter 53 and 54, respectively—L.B.K. and E.C., unpublished work) and "Unpublished data which Dr. C. R. Burnham has generously allowed me to use . . ." The latter data were subsequently published by Burnham in 1934 (14), accompanied by other data furnished by Creighton, and the data of both were partly incorporated in the monographic 1935 "A Summary of Linkage Studies in Maize" by Emerson, Beadle, and Fraser (15). In this vein, we offer the following informative correspondence relevant to shared data and cooperation among scientists.

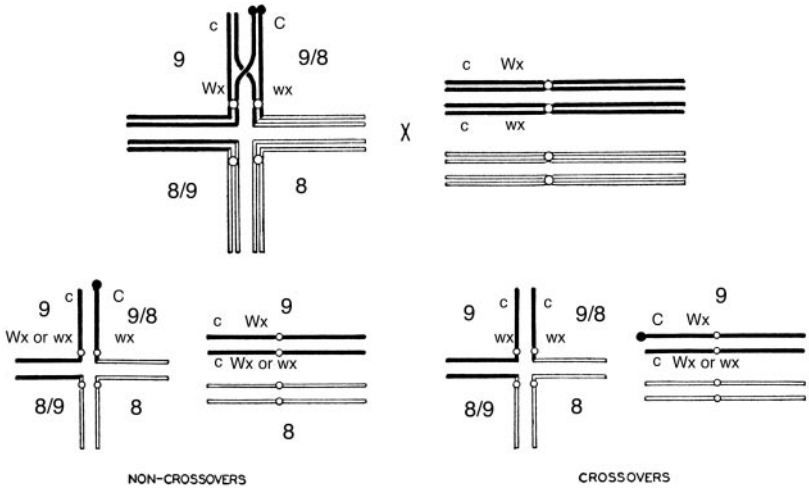

Fig. 4. The experimental maize cross and progeny types designed to test the hypothesis that exchange between genes is accompanied by exchange of physical parts of chromosomes. (*Upper*) a morphologically marked hybrid, knobbed vs. knobless and normal vs. interchanged, and a genetically marked hybrid, *C* (colored kernels) vs. *c* (colorless kernels) and *Wx* (normal starch, blue-staining kernels and pollen) vs. *wx* (waxy starch, reddish-staining seeds and pollen) is crossed with knobless normal chromosomes bearing *c* and heterozygous for *Wx* and *wx*. One crossover in the critical region is shown in the hybrid, exchanging parts between the genes and between the physical markers. (*Lower*) the (viable) products resulting from no crossover or a crossover in the critical region. Note that, because the pollen can be classified for *Wx* vs. *wx*, progeny plants that are *Wx Wx* vs. *Wx wx* vs. *wx wx* can be distinguished by staining samples of the pollen. Note also that, because plants heterozygous for a translocation have 50% aborted pollen and eggs (Fig. 4), progeny plants can be classified for normal vs. interchange-carrying constitution. (Adapted from ref. 13 to reflect the exact experiment.)

Parts of the Data Were Unpublished Work Shared by Charles R. Burnham

McClintock asked Burnham to coauthor the paper on the order of the genes (McClintock to Burnham, May 12, 1931, in the papers of C. R. Burnham, University of Minnesota archives):

> P.S. Would you care to write up the order of the genes of the c-sh-wx linkage group with me? I think it ought to be done soon and should go in the Proc-Nat Acad-Sci. Your unpublished data is [sic] as essential as mine. Let me know what you think.

McClintock told Provine (16) that she first had to show the order of the genes before she could publish the crossing-over data. On June 11, 1931, McClintock wrote to Burnham and enclosed her manuscript on the order of the genes:

> Sharp, Rhoades, & Stadler have worked it over. . . . The paper which goes with it is Harriet's—'A correlation of cytological & genetic crossingover.' I am growing more material to make the evidence wider in scope but I believe that this is not necessary for this paper.
>
> The part marked across the page is the part which you are to do as you like with. I don't know whether you want to put in a table, make a statement or what. The figures I obtained from a letter you wrote in December. [The letter has not been located.] Maybe there is more data now. I think you will see what ought to be put in here to give the meaning intended. If you do not want to go in with me I should feel bad for your data has been a key for me to work with. You may not want to take the responsibility since you were not in close touch with this latter work when it was done. I hope you won't feel that way although be frank about it & say what you please. Don't injure yourself to please me.
>
> I am anxious to get Harriet's data in press as I have been advised to push it. [See story about Morgan pushing them to publish in Kass (17), per Creighton (1982), taped symposium, courtesy of Rosalind Morris. Morgan gave the Messinger Lectures at Cornell in March/April of 1931, before publication of the subject paper (CU) (18).] Since this paper goes first [emphasis added] in the same issue of the Proceedings of the National Academy of Science I am anxious to get it off as soon as possible. I don't know how busy you are now & whether you can spare a few hours during the next few days to do it. I hope so. Let me know by a short note what the situation is so that I will know what to expect.

Two weeks later McClintock wrote to Burnham (June 26, 1931) expressing her disappointment with his decision not to publish collaboratively:

> I was much disappointed that you feel you can't go in with me on the paper. The reasons you gave I do not think are strong enough. I would be glad if you change your mind. I don't want to force you, so you do as you please. I will go ahead now but can insert any changes or additions later if you will come in with me. . . . I saw Robbins of the National Research Council. He said the joint authorship need not hold up the paper so that reason is dispensed with. You can let me know any time soon.

The appreciation is encompassed in their crossing-over paper with a simple acknowledgment that follows their final statement and the conclusions:

> [The authors] are indebted to Dr. C. R. Burnham for furnishing unpublished data and for some of the material studied.

Creighton's Role

Harriet Creighton carried out this widely cited crossing-over experiment as part of her 1933 doctoral thesis (19), in which she acknowledged "*indebtedness to Dr. Barbara McClintock for her aid and constant encouragement during the course of this study, which she suggested*." Therein, she summarized the background papers by McClintock (8) and Burnham (3) and included photographs that had been taken by Barbara McClintock. She specifically used the microscopic photograph of maize showing eight paired chromosomes and a ring of four chromosomes, carrying the 8–9 translocation and opening out at diakinesis (late prophase of meiosis). A close-up of the latter (Fig. 2 *b* and *d*) was published by her major professor L. W. Sharp (9) along with the photograph by McClintock mentioned above (Fig. 2 *a* and *c*; see also Fig. 1*d*). It was this stage of the division process that played an important part in their cytological observations in 1931: "*It is clear that these two chromosomes which synapse along their homologous parts during prophase of meiosis in the resulting individual are visibly different at each of their two ends*" (1). Creighton (interview by L.B.K., August 23, 1994) recalled in 1994 that because of her inexperience she really did not appreciate the significance of the study when it was initially proposed to her by McClintock. She was also quite surprised when she learned recently that their paper had been so widely cited. [A cited reference search for their 1931 publication in the Science Citation Index Expanded (1945 to the present) (20) recovered 61 citations between 1945 and 2004. By way

PLANT NUMBER	KNOBBED OR KNOBLESS	INTERCHANGED OR NORMAL	
	KNOB-*C-wx*-INTERCHANGED / KNOBLESS-*c-Wx*-NORMAL ×	KNOBLESS-*c-Wx*-NORMAL / KNOBLESS-*c-wx*-NORMAL	
Class I, *C-wx* kernels			
1	Knob	Interchanged	
2	Knob	Interchanged	
3	Knob	Interchanged	
Class II, *c-wx* kernels			
1	Knobless	Interchanged	
2	Knobless	Interchanged	
Class III, *C-Wx* kernels			*Pollen*
1	Knob	Normal	*WxWx*
2	Knob	Normal	....
3	....	Normal	*WxWx*
5	Knob	Normal	....
6	Knob	.....	....
7	Knob	Normal	....
8	Knob	Normal	....
Class IV, *c-Wx* kernels			
1	Knobless	Normal	*Wxwx*
2	Knobless	Normal	*Wxwx*
3	Knobless	Interchanged	*Wxwx*
4	Knobless	Normal	*Wxwx*
5	Knobless	Interchanged	*WxWx*
6	Knobless	Normal	*WxWx*
7	Knobless	Interchanged	*Wxwx*
8	Knobless	Interchanged	*WxWx*
9	Knobless	Normal	*WxWx*
10	Knobless	Normal	*WxWx*
11	Knobless	Normal	*Wxwx*
12	Knobless	Normal	*Wxwx*
13	Knobless	Normal	*WxWx*
14	Knobless	Normal	*WxWx*
15	Knobless	Normal	*Wx*—

Fig. 5. Data presented by Creighton and McClintock, 1931, Table 3. Kernels were classified as *C wx* (colored waxy kernels, non-crossover—see Fig. 4), *c wx* (colorless waxy kernels, crossover), *C Wx* (colored non-waxy kernels, crossover), and *c Wx* (colorless non-waxy kernels, non-crossover). Progeny plants may be classified for the knob by cytology at meiosis or in postmeiotic divisions, for the interchange by cytology or by semisterile vs. normal pollen, and for *wx* constitution by staining samples of pollen with an iodine solution (IKI), as described in Fig. 4. Plants from Class I carried the knob and the interchange, that is, without genetic or physical exchange, while those from Class II were knobless and carried the interchange, that is, with a physical exchange accompanying the genetic exchange. In Class III, those individuals that could be classified showed a physical crossover and accompanying genetic exchange. In Class IV, all of the individuals were knobless (having no exchange between the knob and gene *c*), and those without physical exchange (Knobless and Normal) were consistent with no genetic exchange, while those with physical exchange (Knobless and Interchanged) were due either to genetic exchanges in the critical region or between *wx* and the interchange. [Reproduced with permission from ref. 1 (courtesy of Peter McKinley and the Creighton estate).]

of contrast, the companion paper by McClintock (12) elicited 12 citations. Stern's 1931 crossing-over paper (2), which appeared within months of Creighton and McClintock's paper, was cited 38 times during this same time span—27 citations overlapping with those of Creighton and McClintock.]

Concise Reports of High Quality

Perhaps because the most essential background information was presented in a separate but companion paper, and likely because of confusion between the words "preceding paper" and "previous paper," some subsequent writers, while crediting it with its place in biological history, have considered the report difficult to absorb. For example, Robbins (21), commenting with the reprinting in the Classical Genetics papers of Electronic Scholarly Publishing (www.esp.org), states that the authors "do not take much time to help readers understand the underlying logic or to appreciate the subtleties of their analysis." Peters (22), reprinting the paper among a selection of classics, comments, "This paper has been called a landmark in experimental genetics. It is more than that—it is a cornerstone. It is not an easy paper to follow, for the items that require retention throughout the analysis are many, and it is fatal to one's understanding to lose track of any of them." The experiment is very widely covered in textbooks and histories, although admittedly most presentations are over-simplified or inaccurate. The focus of the crossing-over paper was placed on the specific theoretical issue by defining the elements of the experiment in the "preceding" paper by McClintock (12). The experiment, in fact, was exemplary and elegant in its simplicity.

With regard to the brevity of the paper, the fact is that the PNAS was a forum to get new results published quickly and was not supposed to include all details of the investigations. Articles were originally limited to six (small) pages and occasionally went over this limit when funds were available. This is clear from the correspondence in Emerson's files at Cornell. On December 14, 1933, Edwin B. Wilson wrote to Emerson (CU) about a subsequent article he had sent for Creighton:

> I am afraid it will set more than 6 pages. . . . I am wondering how we can modify this so that it will set under 6 pages. . . . [Around 1925–26] a special grant became available to enlarge the size of the Proceedings and take some articles in excess of 6 pages provided they were still short. The money . . . has been spent. . . . The reason we have to go back to 6 pages is that the old rule of the Proceedings. . . . limited articles to those which the Managing Editor thought would set within 6 pages. The idea was in a mixed journal it was important to have a variety of sciences represented.

Wilson goes on to suggest limiting papers to members of the academy if longer than six pages. He explains why he has to reject articles over six pages, and ends with an appeal to discuss the matter with other members of the Academy at Cornell. Emerson replied on December 18 that he was returning Creighton's revised manuscript

> . . . within the six page limit.

He added that he would like to get

> prompt publication of brief papers of some of my students and former students who are, as it happens, turning out relatively important contributions in the field of cyto-genetics.

Wilson wrote to Emerson on December 20, 1933 (CU), from the Office of Editors of the PNAS, regarding limiting the Proceedings to papers that

> . . . come under the very carefully written rule which is in the second paragraph of our information to contributors on the 3rd page of our cover . . . It wanted little philosophic specific articles showing the relation of the new discoveries to previous work of the authors and others and if possible their implication for other branches of science or for future work. They wanted some evidence of how the work was obtained but specifically said that elaborate tables and graphs and the description of details should not be permitted. . . . there was every desire to avoid competition with purely professional technical journals. . . . I note you want the proceedings kept open to non-members and I interpret this to mean that of the two alternatives for cutting . . . that we should go back strictly to our 6 page limit but not ex-

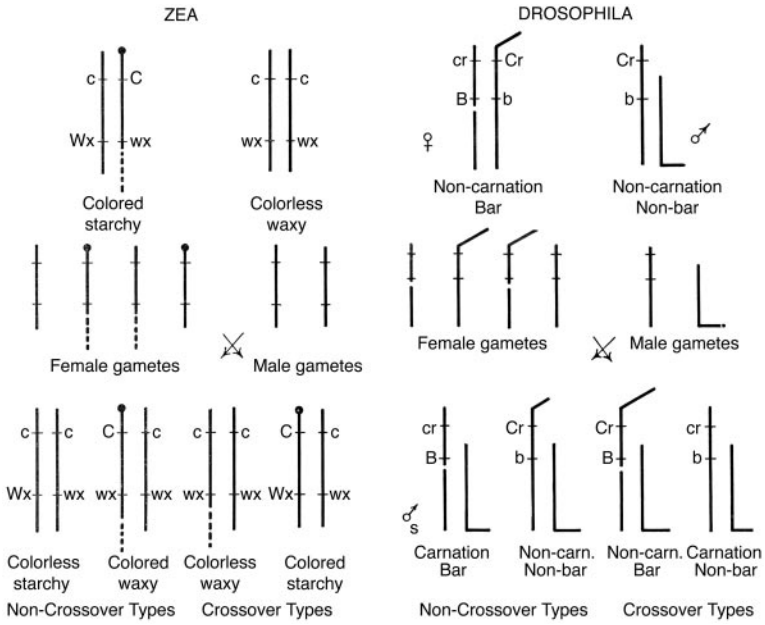

Fig. 6. Comparative diagrams of the experiments of Creighton and McClintock with maize and of Stern with *Drosophila*, mutually supporting the hypothesis of physical and genetic exchange in two key experimental species. [Reproduced with permission from ref. 9 (Copyright 1934, McGraw–Hill).]

> clude non-members. . . . In other words, the university people will want to include the best work of their best students . . .

The parallel experiment by Stern with *Drosophila*, also published in 1931, involved a translocation on one side of a gene-marked segment, and a differential broken chromosome on the other. Sharp (9), in displaying the two experiments side-by-side (Fig. 6), demonstrates the cunning simplicity of each experiment. The pared-down diagram presented by Creighton and McClintock (Fig. 7) displayed only the essential components of the cross, excluding nonessential complementary segments.

It may seem surprising that 20 years elapsed between the suggestion by Morgan that chromosomes might exchange physical parts as part of the exchange of genes, and the tests of his suggestion. Morgan was unquestionably an influential leader in genetic thinking and experimentation; so one might ask, "What deferred the appropriate experiment?" The answer lies in biological components, which had to be discovered or defined first. The technology for microscopic study of chromosomes was already well developed but was in need of refinements for viewing individual haploid and paired maize chromosomes, for example by McClintock (8, 23). As specific cytological markers, knobs were first described in the study of McClintock (8); reciprocal translocations were recognized in *Drosophila* by Painter and Muller (24) and by Sturtevant and Dobzhansky (25), and in maize by Burnham (3) and McClintock (8). Extensive gene-marked segments were available in *Drosophila* by 1916 (26), and in maize by 1929 (15). What was required, as in most groundbreaking experiments, was the intersection of tools with knowledge, and their ingenious combination. The experiments both in *Drosophila* and in maize, the two principal genetic species of the time, attained the intersection at nearly the same time and were mutually reinforcing. The remarkable nature of reinforcement of proof in experimental science is that it sometimes advances in coincidences and sometimes in competition, rarely by sheer volume of data.

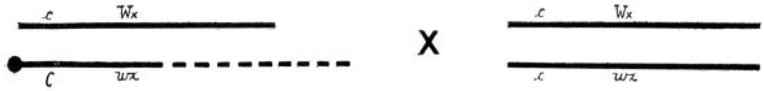

Fig. 7. Simplified diagram of the cross as presented by Creighton and McClintock, 1931, as a text diagram (p. 495). Note that in this diagram, interchanged chromosome 9 (*l*) carries the knob and normal chromosome 9 (*N*) is knobless. Centromeres are not identified, and nonessential segments are excluded. [Reproduced with permission from ref. 1 (courtesy of Peter McKinley and the Creighton estate).]

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1. Creighton, H. B. & McClintock, B. (1931) *Proc. Natl. Acad. Sci. USA* **17,** 492–497.
2. Stern, C. (1931) *Biol. Zent. Bl.* **51,** 547–587.
3. Burnham, C. R. (1930) *Proc. Natl. Acad. Sci. USA* **16,** 269–277.
4. Gabriel, M. & Fogel, S. (1955) *Great Experiments in Biology* (Prentice–Hall, Englewood Cliffs, NJ), pp. 267–268.
5. Watson, J. D. & Crick, F. H. C. (1953) *Nature* **171,** 737–738.
6. Rhoades, M. M. & McClintock, B. (1935) *Bot. Rev.* **1,** 292–325.
7. Kass, L. B. & Bonneuil, C. (2004) in *Classic Genetic Research and Its Legacy: The Mapping Cultures of 20th Century Genetics*, eds. Rheinberger, H.-J. & Gaudilliere, J.-P. (Routledge, London), pp. 91–118.
8. McClintock, B. (1930) *Proc. Natl. Acad. Sci. USA* **16,** 791–796.
9. Sharp, L. (1934) *Introduction to Cytology* (McGraw–Hill, New York), pp. 303, 330, 333.
10. Brink, R. A. (1927) *J. Hered.* **18,** 266–270.
11. Brink, R. A. & Burnham, C. R. (1929) *Am. Nat.* **63,** 301–316.
12. McClintock, B. (1931) *Proc. Natl. Acad. Sci. USA* **17,** 485–491.
13. Sturtevant, A. & Beadle, G. (1939) *An Introduction to Genetics* (Saunders, Philadelphia), pp. 185–186.
14. Burnham, C. R. (1934) *Genetics* **19,** 430–447.
15. Emerson, R. A., Beadle, G. W. & Fraser, A. C. (1935) *Cornell Univ. Agric. Exp. Stn. Mem.* **180,** 1–83.
16. Provine, W. B. & Sisco, P. (1980) *Interview with Barbara McClintock at Cold Spring Harbor Laboratory, Long Island, New York* (Division of Rare and Manuscript Collections, Carl A. Kroch Library, Cornell Univ. Library, Ithaca, NY).
17. Kass, L. B. (2003) *Genetics* **164,** 1251–1260.
18. Morgan, T. H. (1932) *The Scientific Basis of Evolution* (Norton, New York).
19. Creighton, H. B. (1933) Ph.D. thesis (Cornell Univ., Ithaca, NY).
20. Science Citation Index ISI Web of Science/Science Citation Index Expanded (2004) http://isi4.isiknowledge.com/portal.cgi. Accessed September 24, 2004.
21. Robbins, R. J. (2003) www.esp.org/foundations/genetics/classical/holdings/m/hc-bm-31.pdf. Accessed September 15, 2004.
22. Peters, J. A. (1959) *Classic Papers in Genetics* (Prentice–Hall, Englewood Cliffs, NJ), pp. 155–156.
23. McClintock, B. (1929) *Science* **69,** 629.
24. Painter, T. S. & Muller, H. J. (1929) *J. Hered.* **20,** 287–298.
25. Sturtevant, A. & Dobzhansky, T. (1930) *Proc. Natl. Acad. Sci. USA* **16,** 533–536.
26. Bridges, C. B. (1916) *Genetics* **1,** 1–52.