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Point of View

DID SUTTON AND BOVERI PROPOSE THE SO-CALLED SUTTON-BOVERI CHROMOSOME HYPOTHESIS?

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ABSTRACT

The "Sutton-Boveri chromosome hypothesis" attempted to establish a parallel between cytological chromosome behavior and the principles followed by Mendelian factors. Today, this hypothesis is well accepted; however, it was not completely accepted at its proposal (1902-3). The aim of the present study is to elucidate the meaning of the chromosome hypothesis based on the original scientific works, taking into account the scientific context of that time. The negative treatment this hypothesis received is evaluated. I conclude that it was unfair to include Boveri's name beside that of Sutton's as one of the proponents of the chromosome hypothesis of Mendelian heredity, because he did not publish any hypothesis of that kind during the relevant period (1902-1903). Moreover, no coherent chromosome hypothesis existed during that period. Sutton and other researchers of that time were strongly influenced both by cytological knowledge grounded in observations and theoretical presuppositions that led to interpretations with no observational basis. The chromosome hypothesis was not proposed as a result of experimental cytological research.

INTRODUCTION

Most graduate and undergraduate students of biological sciences study the "Sutton-Boveri chromosome hypothesis" (or theory), proposed in the early 20th century (1902-03). It attempted to establish a parallel between Mendel's laws and chromosome behavior:

"Credit for the chromosome theory of heredity – the concept that genes are parts of chromosomes – is usually given to both Walter Sutton (an American who at that time was a graduate student) and Theodor Boveri (a German biologist). In 1902, these investigators recognized independently that the behavior of Mendel's particles during the production of gametes in peas precisely parallels the behavior of chromosomes at meiosis: genes are in pairs (so are chromosomes); the alleles of a gene segregate equally into gametes (so do the members of a pair of homologous chromosomes); different genes act independently (so do different chromosome pairs). After recognizing this parallel behavior (which is summarized in Figure 3-6)[1] both investigators reached the same conclusion" (Griffiths *et al.*, 1993, p. 58)[2].

At first, from the point of view of contemporary scientists, the issue seems extremely simple. It was enough to know cytology and Mendel's principles, and to show that chromosome behavior is similar to that of Mendelian factors. However, from a historical point of view, things were not that simple.

Textbooks teach us that the chromosome hypothesis admits that genes correspond to special pieces of matter (nucleic acids) that occupy definite places within the chromosomes, that chromosomes retain their individuality except when they exchange pieces in synapsis (crossing over), and that those features explain the independent segregation of Mendelian factors (except for linkage) and the purity of gametes. However, the theory we accept today is not the same hypothesis that was proposed almost one century ago. In addition, textbooks omit that the chromosome hypothesis was first rejected by most of the scientific community.

If the hypothesis was so obvious, how could anyone reject it? What, after all, was the original chromosome hypothesis? Which scientific papers presented it, and how? Was it clearly formulated by Sutton and Boveri? The aim of this paper is to answer those questions. It will elucidate the meaning of the chromosome hypothesis based on the original scientific papers. It will also discuss whether it deserved the criticism it received, taking into account the scientific context of the time it was proposed. Due to space restrictions we will focus our attention specifically on Sutton's work.

The general outlook at the beginning of the 20th century

The reader should recall that we are dealing with the beginning of the 20th century – a time when classical genetics blossomed. In 1900, Mendel's laws were "rediscovered" (Correns, 1900; Tschermak, 1900; De Vries, 1900; Stubbe, 1972; Meijer, 1985; Monaghan and Corcos, 1986). In his famous paper published in 1865, Mendel presented his hybridization experimental results with edible peas (*Pisum sativum*)[3]. He showed that heredity followed

[1]See Griffiths *et al*., 1993, p. 59.
[2]Cf. Burns and Bottino, 1989, p. 2; Russell, 1996, p. 12.
[3]Mendel's paper was translated into English by William Bateson (1902). It was this translation that made Mendel's work accessible to most of the scientific community.

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some simple principles in those vegetables. After the rediscovery of Mendel's work, a flood of experimental research arose to validate or disprove Mendel's principles. Scientists also wanted to know if this theory could be applied to other organisms (animals and vegetables) besides *Pisum sativum*. So, when the chromosome hypothesis was proposed, many cross-fertilization experiments were being performed in several countries.

By the late 19th century, several authors such as August Weismann and Oscar Hertwig, had already proposed that the elements responsible for transmitting hereditary characters were inside the cellular nucleus (Stubbe, 1972, pp. 160, 245). Around 1900, it was generally accepted that each vegetable or animal species had a characteristic number (usually even) of chromosomes in their somatic cells (Wilson, 1900, p. 67). There were, however, several doubts concerning the permanency of those chromosomes throughout the series of cellular divisions. The origin of the chromosomes was also not clear. Cytological data were not sufficiently clear. Chromosomes could be seen only during cell divisions. The number of chromosomes that could be seen during the usual kind of division (now called mitosis) seemed double the number of chromosomes found during some steps of gametogenesis (now called meiosis). During mitosis it seemed that each chromosome was longitudinally split into halves, but the process was not well known.

Chromosome individuality had already been widely discussed. Edmund Beecher Wilson (1856-1939), an American cytological expert working at Columbia University supported that idea, and pointed out several favorable pieces of evidence in his monumental cytology treatise (Wilson, 1900, pp. 294-304). The main argument was that the number of chromosomes seemed constant (at least in well-studied species). In addition, Boveri had been able to study chromosomes in living cells of *Ascaris*, in which he had found another strong evidence. Towards the end of telophase, when the nuclear membrane was building itself and enclosing the chromosomes, he noticed that the chromosome ends produced visible bulges at the membrane. During interphase, chromosomes could not be seen, but those bulges remained at the same place. In the following prophase, chromosomes reappeared at the same places where they had disappeared. It seemed, therefore, that they had identity and permanence throughout the cellular transformations – at least in the specific case of *Ascaris*. That was the strongest evidence available toward the end of the 19th century[4].

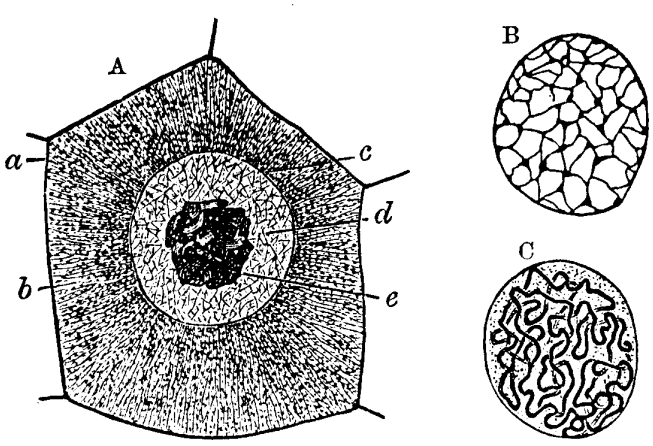

Figure 1 - A drawing from the early 20th century (Thomson, 1992, *The Illustrated Chambers's Encyclopaedia*, Vol. 3, p. 49), showing the structure of the cell (A), and two possible chromatin arrangements in the still (interphase) nucleus: a network (B) or a continuous thread (C).

It was not altogether clear, however, whether chromosomes always maintained their identity, because it seemed to several cytologists that between cellular divisions (at interphase) they all united to build a continuous thread (spireme) or a network[5] (Figure 1). It was even suggested that they could dissolve into a set of chromatin globules. At the beginning of meiosis, instead of seeing pairs of homologous chromosomes moving away from each other, splitting in half, and building a tetrad (as thought today), it was believed that there was initially a set of simple chromosomes with half the number of chromosomes found during normal divisions (mitosis), and that each simple chromosome underwent two divisions – perhaps one of them longitudinal and the other transversal – producing four equal chromosomes (see Wilson, 1900, p. 285, for instance). A. Weismann had suggested that corresponding maternal and paternal chromosomes were joined by their ends in the process of fertilization, and that chromosomes were reduced to their primitive size in gametogenesis (during the so-called "reducing division"). All this shows that it was not altogether clear what happened inside the cell, and chromosome processes were not well understood.

Boveri's study of dispermic fertilization of sea urchin ova

The German zoologist Theodor Heinrich Boveri (1862-1915) is usually regarded as one of the proponents of the chromosome hypothesis. It will be shown, however, that his main contribution, from the late 19th century to 1902, was a defense of the constancy in number and individuality of chromosomes.

What was the role of each chromosome? Were all of them equivalent in terms of their physiological func-

[4]John A. Moore commented that in the 1930's, when he was studying cytology for the first time in his life, Boveri's evidence was still taught as the strongest proof of the constancy of chromosomes (Moore, 1986, p. 654).

[5]According to Arthur Thomson, "The most marked difference of opinion is this, that some describe the framework as distincly of the nature of a network, while others are as emphatic in calling it a much coiled band" (Thomson, 1902, p. 48).

tion? Or did each chromosome perform a specific role? Boveri tried to answer these questions.

In a series of experiments, Boveri established that a single set of chromosomes (either maternal or paternal) was enough for zygote development. First, by inducing artificial parthenogenesis, he noticed that the set of maternal chromosomes alone could lead to normal zygote development (Boveri, 1888). In a second study, he fertilized enucleated ova of *Sphaerechinus* with *Echinus* spermatozoa and noticed that the paternal set of chromosomes was again sufficient for normal development (Boveri, 1889). In this second experiment, the progeny resembled the father, which strongly indicated the essential role of nuclear substances in heredity. In his second paper, Boveri emphasized that "the law, that the substances giving the definite and hereditary characters to the cell are contained in the nucleus, was not known in the phenomenon of fertilization of the egg, nor through the researches already carried out, concerning the role of the nucleus in the protozoa" (Boveri, 1889; Morgan's translation, p. 223).

Besides providing evidence for the relevance of nuclear substances in heredity, Boveri studied the specific role of chromosomes. In a work about fertilization problems (*Das Problem der Befruchtung)*, published in 1901, he expressed himself in a careful way:

"When the nucleus of each cell comes out from the resting stage, the chromosomes become visible as individualized elements always equal in quantity. It is therefore probable that, even during the resting or reproductive period of the nucleus, the chromosomes are at least potentially in existence. The number of chromosomes is characteristic of the particular animal or plant species. Furthermore, as we have just seen, in mitotic division the chromosomes are equally divided and become paired off during fertilization, so that we may feel justified in contending that the chromosomes possess 'individuality'" (Boveri, 1901, pp. 124-125).

When Boveri stated that "it is probable that, even during the resting or reproductive period, the chromosomes are at least potentially in existence" he did not intend to say that they always exist in the same form and structure.

In 1902 Boveri published a paper on multipolar mitosis in dispermic fertilization of sea urchin ova (Boveri, 1902). In that paper he argued from a physiological point of view that chromosomes were not identical[6]. This was a fundamental step towards forming the chromosome hypothesis of heredity.

Oscar Hertwig and Hermann Fol had already observed in 1879 that sea urchin zygotes produced by induced dispermic fertilization did not grow in the usual way, and egg development fell short of the gastrula stage (Wilson, 1925, p. 917; Coleman, 1963, p. 139). This result was confirmed by Hans Driesch in 1892.

Since normal development could occur either with normal fertilization (a double set of chromosomes) or without fertilization (a single set of chromosomes), it was odd that a triple set of chromosomes would result in anomalous development. However, earlier observations had already established that cell divisions following dispermic fertilization are abnormal and produce an irregular chromosome distribution. Could this be the cause of the anomalous development?

Boveri pondered that if all chromosomes were equivalent, no anomaly should occur in the development of dispermic eggs. Abnormal development could be regarded as a hint that chromosomes are not equivalent to each other and that they differ in their effects upon development (Figure 2).

Each sea urchin gamete carries 18 chromosomes. Therefore, when an ovum was fecundated by two spermatozoa, the resulting zygote had, at first, 54 chromosomes (while the normal diploid number would be 2n = 36). Boveri observed that at the first dispermic egg division each chromosome split longitudinally, as usual, but four spindles appeared, instead of the usual two, resulting in four cells. As a result, the 108 chromosomes were distributed into four groups, originating the nuclei of the four initial blastomeres. Chromosome distribution among the four spindles seemed to occur by chance. Each new nucleus received about 27 chromosomes, but the number could vary. Assuming that distribution was completely random, there was a large number of possible combinations of paternal and maternal chromosomes in the several blastomeres (Boveri, 1902; Baxter and Farley, 1979, p. 163).

Boveri observed nearly 1,500 dispermic eggs, and found only two cases of normal development. He conjectured that normal development only occurred when each cell received an adequate number and kinds of chromosomes – at least one chromosome of each kind. Incomplete sets of chromosomes would be the cause of monstrosities. If this could be confirmed, it would strongly suggest that the properties of each chromosome are different from those of the others.

When Boveri strongly shook the vessel containing sea water and the fertilized ova, he noticed that only three spindles appeared, instead of four. In that case, there would be a larger chance that each blastomere would receive a complete set of chromosomes and development would be normal. Indeed, in those cases Boveri observed 58 normal developments in a total of 719 eggs – that is, about 8% (Boveri, 1902, Wilson, 1925, p. 920).

Afterwards, Boveri tried to decompose the primitive blastulas in cells, to check how each of them would develop. He detached the blastomeres by placing the eggs in calcium free sea water. In the case of normal fertilized

[6]At the turn of the century, August Weismann's theory of heredity was very influential. According to him, all chromosomes of a given species were equivalent, since he assumed that each one contained a complete set of "ids" that were needed to build the whole organism. Those "ids" were associated to the "microssomes", the smallest visible chromatin grains (Hertwig, 1894, pp. 22-23; Délage, 1903, pp. 697-749).

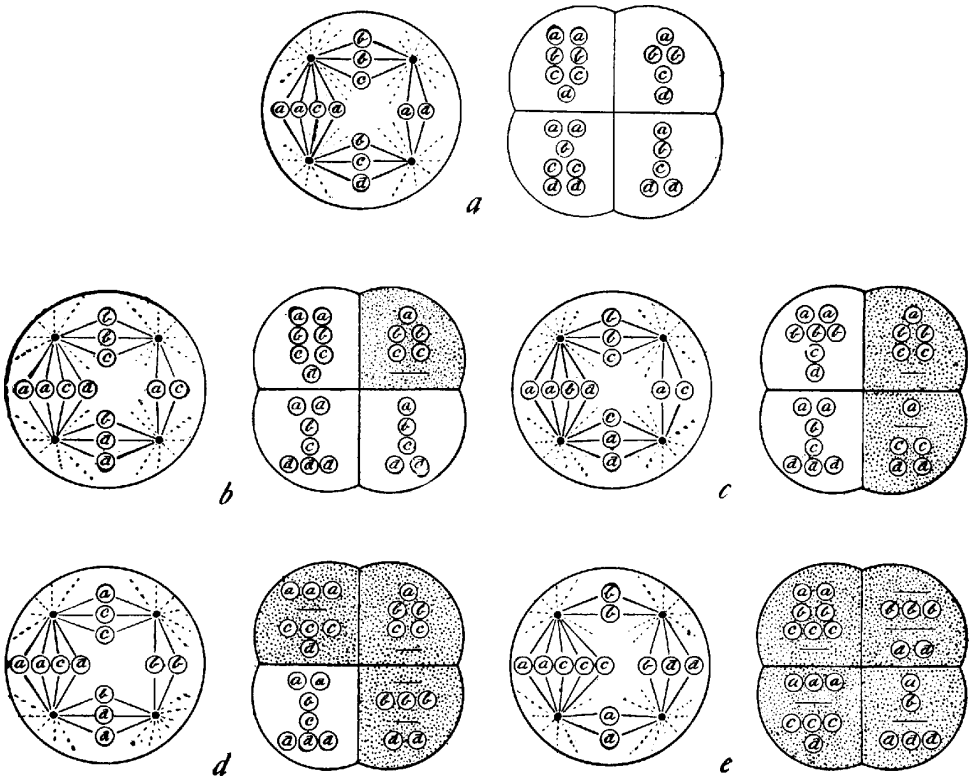

Figure 2 - Boveri's model of multipolar division in dispermic eggs. Irregular chromosome distribution can produce cells with completely different sets of chromosomes (at least one of each kind) or cells with an incomplete chromosome set (gray cells, in the drawing).

ova (by a single spermatozoon) the four cells developed and produced smaller but otherwise normal larvae. Repeating the experiment with dispermic eggs, he observed that the four separate blastomeres underwent pathological development, and that they were usually different from one another. This seemed to indicate that each chromosome combination produced different developmental results. Boveri observed only 17 normal gastrulas (18%) in a sample of 92 separate blastomeres. He also studied 102 separate blastomers in tripolar dispermic eggs, of which 44 produced normal gastrulas (43%) (Boveri, 1902, Wilson, 1925, pp. 921-922).

Boveri developed a mathematical analysis of the different chromosome combinations in the blastomeres, and he showed that the probability that each blastomere received at least one chromosome of each kind, in cases of tripolar and tetrapolar divisions, was very close to the experimentally obtained frequencies of larvae with normal development.

From the agreement between theoretical expectation and observation, Boveri concluded that a definite set of chromosomes is required to produce normal development, and therefore each chromosome is endowed with different qualities. The result conflicted with Weismann's theory, who believed that all chromosomes were equal (Sturtevant, 1965, p. 35).

In this work, Boveri did not follow individual chromosomes. All evidence was indirect – physiological, not visual or morphological. Nevertheless, the results he obtained were favorable to the concept of chromosome continuity, and contrary to the idea that they could merely be temporary chromatin arrangements, as was formerly believed.

Note that Boveri did not attempt to relate chromosome behavior in these studies to Mendel's principles of heredity.

Sutton's cytological work and hypothesis

Walter Stanborough Sutton (1877-1916) is regarded as the first proponent of an association between Mendelian genetics and chromosome behavior. Sutton began his cytological research as an assistant to Clarence E. McClung. After completing his thesis on spermatogenesis of the grasshopper, *Brachystola magna*, he moved to Columbia University to work with Wilson. It seems that, after hearing a talk delivered during September 1902 by William Bateson (1861-1926) in New York, Sutton suddenly linked his cytological knowledge to the laws of heredity (McKusick, 1960, p. 489). It was not through Wilson's influence that he reached this connection, because Wilson himself declared at a later time: "I well remember

... that at that time I did not at once fully comprehend his conception or realize its entire weight" (McKusick, 1960, p. 490).

Sutton presented his proposal in two articles. In his first paper, he described the morphology of the chromosome group of the great "lubber grasshopper" *Brachystola magna*[7] (Sutton, 1902). This species has large cells and clearly visible chromosomes of different sizes. He first discussed whether those size differences could be due to chance, during division of the spireme thread, or were due to chromosome individuality (Sutton, 1902). He was aware and cited at the beginning of his paper previous studies of Boveri[8] and Montgomery (1898, 1901)[9].

Sutton detected 23 chromosomes in diploid cells of *Brachystola magna*; one was called an 'accessory chromosome' (X). Sutton divided the other chromosomes into two groups: one consisted of the 16 largest chromosomes and the other with the six smallest ones. In the second group, he perceived that chromosomes could be sorted into three pairs of clearly different sizes and volumes (Figure 3). As to the larger chromosomes, the differences were not so evident, but Sutton stated that they could also be divided into eight pairs (Sutton, 1902, pp. 25-26). Some of the drawings presented in his paper, however, do not in any way show that. As Alice Baxter and J. Farley commented: "One might wonder at Sutton's ability to distinguish chromosomes of 11 sizes since, as previously indicated, it was extremely difficult to interpret cytological preparations. But it is clear that he was looking for such differences, influenced as he was by Boveri" (Baxter and Farley, 1979, p. 166).

Sutton studied the metaphases of eight spermatogonia generations, and noticed that there was always the same number of chromosomes, of the same relative sizes (Sutton, 1902, p. 26). This strongly suggested their individuality. There was, however, a much stronger evidence. When chromosomes lost their definite outlines, between successive cell divisions, it was possible to see them as thin threads in the nucleus (spireme). It was essential to decide whether they joined to build a single thread, or remained separate. According to Sutton, it was possible to perceive

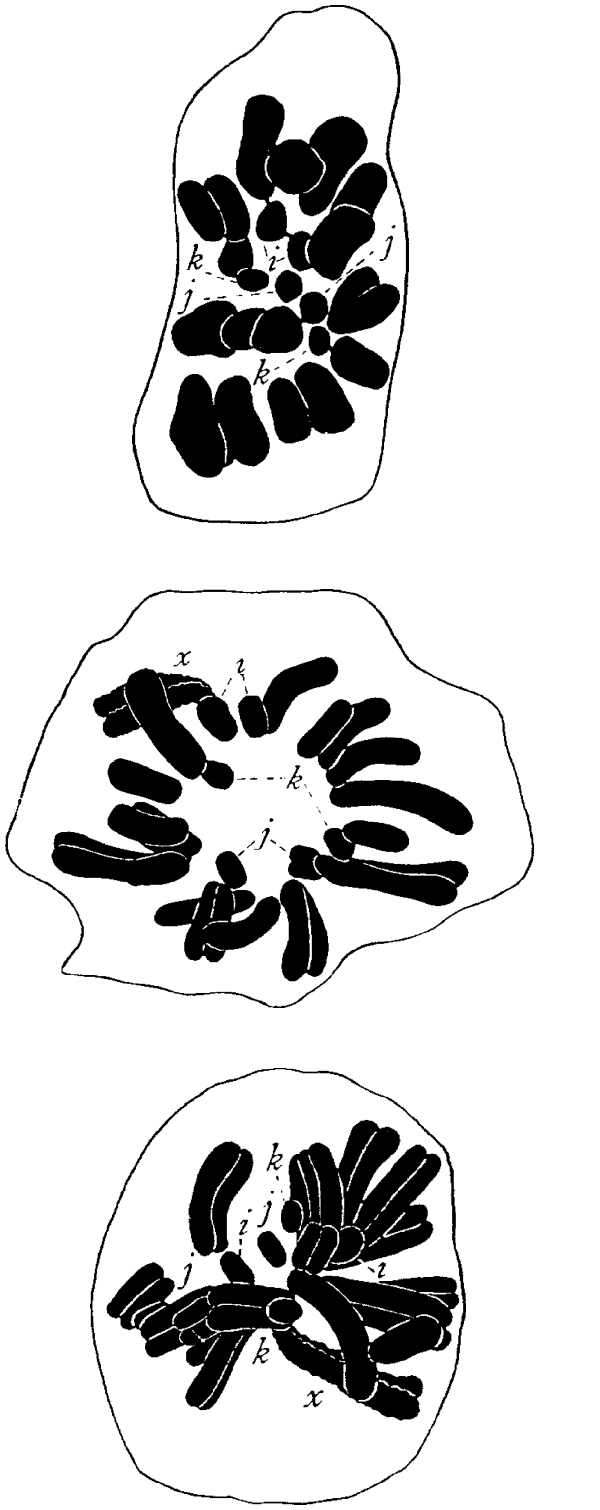

Figure 3 - Sutton's drawings of *Brachystola magna* chromosomes during nuclear division, showing the three smallest chromosome pairs (i, j, k) and the accessory chromosome (x) (Sutton, 1902, figs. 1, 2, 3).

[7]Most of the material contained in this paper came from Sutton's Master's dissertation, which had already been published (McKusick, 1960, p. 491).
[8]He referred to Boveri's work on multipolar mitosis due to dispermic fecundation (Boveri, 1902) that was described earlier in this paper.
[9]First, in a study on the spermatogenesis of a hemipteran (*Pentatoma*), Thomas H. Montgomery believed that chromosomes fused at synapsis, losing their individuality (Montgomery, 1898, p. 20). Three years later he changed his mind when he studied the spermatogenesis of 42 species of Hemiptera and came to believe that chromosomes only formed pairs during synapsis (Mongomery, 1901, pp. 197-198). His change of opinion was due to theoretical presuppositions and not observation. He regarded synapsis as similar to the process of infusorian conjugation, and believed that it rejuvenated the microorganisms. Sutton referred to Montgomery's 1902 work, where he stated that the size relations found among the chromosomes of some Hemiptera were a constant attribute and not merely a result of chance (see Sutton, 1902, p. 24).

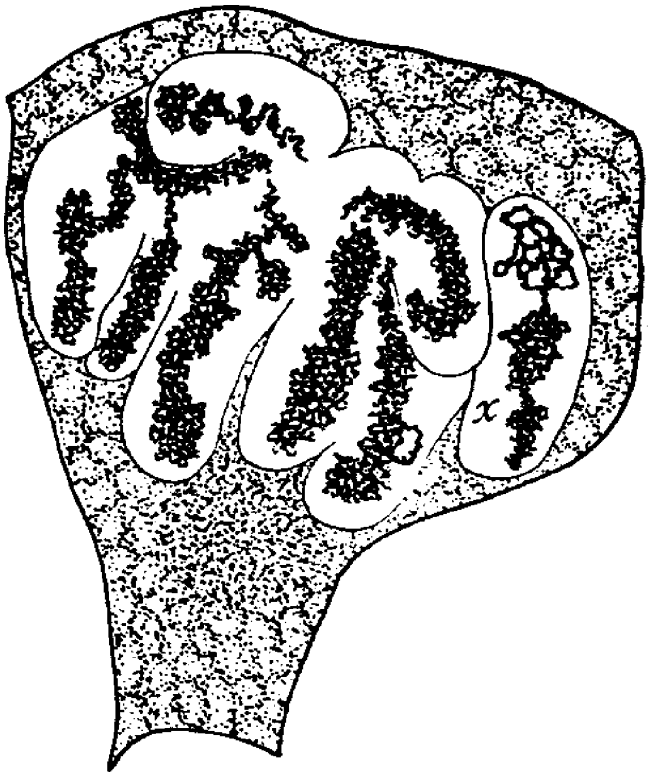

Figure 4 - Sutton's drawing of *Brachystola magna* chromosomes during interphase, showing their separate vesicles.

in the nucleus, during this phase, some vesicles that in his drawing looked like fingers of a rubber glove, united together by their ends (Figure 4). Sutton stated that each of the 16 largest chromosomes was kept in a separate vesicle, which united to another vesicle that held the remaining six chromosomes (Sutton, 1902, p. 27). Although it was not possible to see clearly whether the threads were united or not, Sutton believed they remained detached.

Sutton's description of the first steps in spermatocyte formation completely agreed with Montgomery's interpretation of synapsis (see Montgomery, 1901, pp. 197-198): he described that both chromosomes of each pair had united, producing 11 double chromosomes, in which each original chromosome remained distinct. In the same way as Montgomery, Sutton described that the double chromosomes underwent two successive divisions, one of them longitudinal, and the other transversal (Sutton, 1902, pp. 32-33). Finally, each spermatid received only one chromosome of each type. Sutton also studied oogenesis and reported a process exactly the same as that of spermatogenesis. It was also possible to identify 11 different chromosome pairs (Sutton, 1902, p. 35). He concluded:

"Taken as a whole, the evidence presented by the cells of *Brachystola* is such as to lend great weight to the conclusion that a chromosome may exist only by virtue of direct descent by longitudinal division from preexisting chromosome and that the members of the daughter group bear to one another the same respective relations as did those of the mother group – in other words, that the chromosome in *Brachystola* is a distinct morphological individual" (Sutton, 1902, p. 36).

Sutton concluded that there was no qualitative division (a break in different parts) of chromosomes in *Brachystola*, but only a separation:

"There is, therefore, in *Brachystola* no qualitative division of chromosomes but only a separation of the two members of a pair which, while coexisting in a single nucleus, may be regarded as jointly controlling certain restricted portions of the development of the individual. [...]" (Sutton, 1902, p. 39).

In the first article, the author called attention to the probability that the association of paternal and maternal chromosome pairs and their subsequent separation during division could constitute the physical basis of the Mendelian law of heredity (Sutton, 1902, p. 39). However, he did not draw any explicit parallel between chromosome behavior and Mendelian factors.

Cannon's proposal

Another researcher who contributed to the chromosome hypothesis, at the same time as Sutton, was William Austin Cannon, a botanist who also worked at Columbia University. It is curious that Cannon worked independently of Sutton, and that he was also led to search for a cytological basis for Mendel's law under the influence of William Bateson's work.

Cannon's first paper, published in December 1902, was very short and contained only a few suggestions concerning the relation between Mendel's laws and cytological phenomena (Cannon, 1902). First, he stated the problem:

"We now arrive at the interesting question, Is there a cytological basis for Mendel's law of the splitting of the hybrid race?

Bateson has recently suggested the idea that "*the essential* part of the discovery (of Mendel – the italics are my own) is the evidence that the *germ cells or gametes produced by cross-bred organisms may in respect of given characters be of pure parental types and consequently incapable of transmitting the opposite character."* (The italics are in the original). This notion has also been expressed by others, or may be implied from their conclusions. Assuming such to be the case, how may we account morphologically for the purity of the sex cells?" (Cannon, 1902, p. 659).

The main question was: what happened in the production of gametes, *especially in the case of hybrids*? There was no reason to assume that cytological phenomena in hybrids were equal to those in organisms of pure lines, because their offspring usually varied and were sometimes sterile. There seemed to be cytological evidence confirm-

ing botanists' suspicion that gametogenesis in hybrids was "irregular, abnormal and peculiar to each organism" (Cannon, 1902, pp. 659-660). Such an irregular production of gametes could not explain the regular results obtained by Mendel.

Studying the formation of pollen in a cotton hybrid, Cannon observed both regular and irregular cell divisions. In the latter case, the resulting pollen grains were abnormal and, in the opinion of this author, they could never fertilize ova. He therefore suggested that when hybrids produce fertile gametes, a regular cell division must take place, as in pure lines.

In the case of pure forms (non-hybrids), Cannon accepted the conclusions of J. Rückert, Montgomery and Wilson:

"The chromosomes derived from the father and the mother unite in synapsis and separate in the metaphase of one of the maturation divisions, and also a single longitudinal division occurs, so that the end is attained that the chromatin is distributed in such a way that two of the cells receive pure paternal, and two cells pure maternal chromosomes, and no cells receive chromosomes from both the father and the mother. In this manner *it has been demonstrated that pure races of animals may, and normally do, organize sex cells of pure descent*.

Now since such is shown to be the case in *pure* races of animals, I suggest that the sex cells of *fertile* animal hybrids *are formed in a similar way,* and thus we may have in animals a cytological basis for variation in accord with Mendelian conception. And I further suggest that this is the case in plants as well" (Cannon, 1902, pp. 660-661).

Notice that, following Van Beneden (1883) and probably Montgomery and Sutton, Cannon believed that there was no intermixture of paternal and maternal chromosomes – each gamete would have either one or the other. This concept, which is not accepted today, could not explain the independent segregation of the Mendelian factors. Perhaps that author did not perceive, at the time, that independent segregation was a central aspect of Mendelian genetics. If Cannon's hypothesis was correct, it would be able to explain only crosses in which the parents differ by a single character. Furthermore, it would conflict with all the rest of Mendelian theory.

Cannon's ideas were grounded upon Rückert's fragile work. At that time, the very continuity of chromosomes was still held in doubt. There was no cytological basis for Cannon's hypothesis, as he, himself recognized: "This notion is, I am well aware, squarely opposed to the present conception of the nature of the maturation mitoses in plants [...]" (Cannon, 1902, p. 661). Indeed, Cannon was defending an idea opposite to that of most botanists, who believed that transverse or reducing divisions never occurred during gametogenesis of superior plants (Wilson, 1902, p. 993).

Besides that, in two later cytological studies on the gametogenesis of cotton and pea hybrids (Cannon, 1903a,b), he did not assume the permanency or individuality of chromosomes – he only referred to maternal or paternal *chromatin*, not chromosomes (Cannon, 1903a, p. 164 and Cannon, 1903b, p. 532).

Wilson's contribution

Sutton's first paper was written in October 1902. It was published in December of the same year, in the *Biological Bulletin*. Cannon's first paper was independently published in the same month, in the *Bulletin of the Torrey Botanical Club*. Sutton was working with Wilson, who read the paper before it was published. Cannon also showed his original to Wilson, before publication. After that, Wilson wrote a short note, that was also published in December 1902, in *Science* (Wilson, 1902).

When Wilson decided to publish his paper, it is likely that he had perceived how important the issue was. His aim was not to merely announce the ideas of the two students from his university (Sutton and Cannon) in a widely circulated journal; it is likely that he also intended to take partial credit for the proposal.

In his note, Wilson made use of Sutton's and Cannon's papers, and also referred to some of Sutton's ideas that were published only later, in a more detailed form (Sutton, 1903).

Wilson's starting point is a reference to Bateson's book *Mendel's Principles of Heredity – A Defense*, where the author suggested that the symmetrical result in the offspring of cross-bred forms "must correspond with some symmetrical figure of distribution of gametes in the cell divisions by which they are produced[10]." Wilson then commented that cytologists did know a mechanism of the type Bateson required (Wilson, 1902, p. 991).

According to Wilson, germ cells are formed in groups of four, produced by two successive divisions of different kinds. One of them would be a common mitosis, with longitudinal chromosome division. The other would be a special division that "separates whole chromosomes by a transverse division ('reducing division' of Weismann)" (Wilson, 1902, p. 992). In other words, Wilson still interpreted meiosis in the old Weismannian sense. On the other hand, Wilson also seemed to accept the conclusions of O. von Rath, Rückert, V. Häcker and especially Montgomery, who claimed that in synapsis a union of paternal and maternal chromosomes occurred (at their ends) and that later "The ensuing transverse or reducing division, therefore, leads to *the separation of paternal and maternal ele-*

[10]Wilson did not present the full citation, but it was published in Sutton's second paper (Sutton, 1903, p. 232): "It is impossible to be presented with the fact that in Mendelian cases the cross-bred produces on an average *equal* numbers of gametes of each kind, that is to say, a symmetrical result, without suspecting, that this fact must correspond with some symmetrical figure of distribution of gametes in the cell divisions by which they are produced" (Bateson, 1902, p. 30).

ments and their ultimate isolation in separate germ-cells" (Wilson, 1902, p. 992). It seems that Wilson was also thinking of paternal and maternal chromosomes as whole, inseparable groups, and that each gamete could only receive paternal or maternal chromosomes.

Wilson admitted that cytological evidence was still incomplete, and the suggested interpretation was a conjecture, not a well-grounded conclusion (Wilson, 1902, p. 992). He thought, however, that Sutton's cytological study of grasshopper chromosomes had provided strong evidence for that interpretation.

Throughout the rest of his article, Wilson describes Sutton's and Cannon's works, without adding much of his own.

We can conclude that in December 1902 the hypothesis supported by Sutton, Cannon and Wilson had a weak cytological basis, and was unable to explain some basic features of Mendelian theory – such as the independent segregation of characters.

Sutton's explanation of Mendel's laws

In his second paper, Sutton discussed the relationship between chromosomes and Mendel's laws (Sutton, 1903). At the very beginning of the article, he admitted the "speculative character" of his work, but claimed that such a style was acceptable because in the future it would be possible to check the validity of the conclusions he presented (Sutton, 1903, p. 231). He made it clear that he only intended to explain the simplest cases, or "typical Mendelian cases", and suggested that "many of the known deviations from Mendelian type may be explained by easily conceivable variations from the normal chromosomic processes" (Sutton 1903, p. 231).

"At first, the author presented the main results of his former paper in a clearer way:

1. The chromosome group of the presynaptic germ-cells is made up of two equivalent chromosome-series, and that strong ground exists for the conclusion that one of these is paternal and the other maternal.
2. The process of synapsis (pseudo-reduction)[11] consists in the union in pairs of the homologous members (i.e., those that correspond in size) of the two series.
3. The first post-synaptic or maturation mitosis is equational[12] and hence results in no chromosomic differentiation.
4. The second post-synaptic division is a reducing division, resulting in the separation of the chromosomes which have conjugate in synapsis, and their relegation to different germ-cells.
5. The chromosomes retain a morphological individuality[13] throughout the various cell-divisions" (Sutton, 1903, p. 232).

In this paper, Sutton changed his opinion on the absence of mixture between maternal and paternal chromosomes during gametogenesis. His initial belief, that he now acknowledged as false, had been based on observations of several authors who had described that the two chromosome groups remained distinct for many cleavages, after fertilization – and hence he had been led to think that only two kinds of gametes could be formed, one with paternal and the other with maternal chromosomes (Sutton, 1903, p. 233). He now rejected this idea, not because of new cytological evidence, but because it would conflict with the known facts of heredity: a recombination of characters would be impossible, if chromosomes remained in groups, without mixture (Sutton, 1903, p. 233). Although Sutton's work was essentially cytological, he was led to distrust and review the cytological knowledge of his time, to reconcile it with the facts of heredity – otherwise, it would be impossible to explain Mendel's laws. This attitude shows the strength of his reliance in Mendel's theory, only two years after its rediscovery.

Sutton asserted that he made a more careful study of the cell division process, especially chromosome position before division, spindle origin and formation, the relative positions of chromosomes and centrosomes, and the contact between spindle fibers and chromosomes. He concluded that bivalent chromosome position, before the reducing division, was due to chance, and therefore when the cell divided paternal and maternal chromosomes mixed (Sutton 1903, pp. 233-234).

It is hard to imagine how Sutton could distinguish between paternal and maternal chromosomes. Furthermore, how could he follow them after synapsis and interphase to the following cellular division, in order to conclude that they separate in a random way? Even being benevolent, it is necessary to question the possibility that Sutton could make such observations.

Notice that a completely *random* distribution of chromosomes was unacceptable. To make this point clear, let us suppose for simplicity that instead of 23 chromosomes the male had 7 chromosomes. Let us represent them by a, a', b, b', c, c', x, where a, b, c, x are of maternal origin and a', b', c' are of paternal origin. If during gametogenesis this set of chromosomes were radomly divided into two groups containing 3 and 4 chromosomes, there could arise gametes with combinations such as:

	First cell:	Second cell:
(1)	a, b, c, x	a', b', c'
(2)	a, b', c'	a', b, c, x
(3)	a, a', b, b'	c, c', x
(4)	a, b', c, c'	a', b, x

[11]The phrase "pseudo-reduction" meant, here, that the observable number of chromosomes was reduced, not by their disappearance or by being expelled, but by uniting in pairs.

[12]That is: in the first division, chromosomes were longitudinally split into two equal parts.

[13]'Morphological individuality' means that whenever the chromosomes can be seen, they have the same forms and relative sizes as in the previous stages.

In examples (1) and (2), the result would be "normal" gametes, containing one of each kind of chromosomes. In examples (3) and (4), the result would be "anomalous" gametes, lacking one or two kinds of chromosomes. Therefore, if all chromosomes (of paternal and maternal origin) were shuffled and distributed by chance between the two daughter cells, both in spermatogenesis and in ovogenesis, one should expect something similar to what Boveri observed in his sea urchin experiments: a large proportion of anomalies and monstruosities, because the zygotes could contain combinations lacking one type of chromosome (for instance: a, a', a'', b, b', b'', x). It was necessary to suppose, therefore, that one of each pair of homologue chromosomes went to each pole of the spindle. This is not *random* division, in the sense explained above. Besides that, it was difficult, in the context of that time, to conceive a cellular mechanism that could choose one chromosome of each kind, and at the same time mix maternal and paternal chromosomes. Sutton did not discuss this kind of problem, however.

If one accepts the independent segregation of chromosomes, it is possible to associate them to Mendelian factors and explain the independent segregation of characters. That was what Sutton did; he associated one factor to each chromosome (Sutton, 1903, p. 234). Of course, this would only work if the number of chromosomes was greater than that of factors.

Sutton discussed several specific examples, and concluded that independent distribution of maternal and paternal chromosomes could account for the facts studied by Mendel. Let us remark that in this part of his paper the author neither hinted at the possibility of linkage between factors carried by the same chromosome, nor suggested that chromosomes could exchange parts (when they pair at synapsis), as current theory teaches. After all, it would be incoherent to devote so much effort to support the individuality and constancy of chromosomes, and then accept that they could exchange parts among themselves. In all the instances that Sutton discussed, he assumed that chromosomes were unchangeable. That idea is explicit in a few sentences, such as: "*Thus the phenomena of germ-cell division and of heredity are seen to have the same essential features, viz., purity of units (chromosomes, characters) and the independent transmission of the same*" (Sutton, 1903, p. 237, his italic). Therefore, Sutton regarded chromosomes as *units*, and assumed that they did not exchange parts (they were *pure*).

In another section of his paper, Sutton discussed whether the basis for each hereditary character was the chromosome as a whole or only part of it. Now he seemed to favor the second alternative, and suggested the existence of a coupling between some factors:

"If then, the chromosomes permanently retain their individuality, it follows that all the allelomorphs represented by any one chromosome must be inherited together" (Sutton, 1903, p. 240).

Mendel's experiments had not shown any coupling between characters, but Sutton referred to recent experiments by Bateson and Saunders with *Matthiola* (Bateson and Saunders, 1902, p. 81), where they found a correlation between the green color of seeds and hoary flowers, and between brown seeds and glabrous flowers. Sutton suggested: "Such results may be due to the association in the same chromosomes of the physical bases of the two characters" (Sutton, 1903, p. 241).

As Sutton defended the retained individuality of chromosomes, he did not consider the possibility that they could exchange parts between themselves, although that idea had already been suggested by M.F. Guyer (Sutton, 1903, pp. 450-451). At that time, the concept of interchanges between chromosomes was not accepted, because it was believed that during synapsis chromosomes became united *by their ends*, and it would be difficult to imagine any regular exchange in this condition. Hence, Sutton supposed that any chromosome breaks would constitute pathological anomalies tending to produce infertility.

Sutton discussed a fundamental problem: heredity studies involved hybridization (or crosses between different pure types), and cytological studies used pure lines. Could they be compared to one another? He answered that "the correlation of the two is justified by the observation of Cannon that maturation mitoses of fertile hybrids are normal" (Sutton, 1903, p. 238). However, this was far from established – it was just a *conjecture* suggested by Cannon.

Finally, let us discuss how Sutton answered a serious cytological problem. He believed (as many other cytologists of the time) that chromosomes united by their ends, in synapsis, and separated afterwards. This belief was supported by spermatogenesis studies in lower animals. However, Mendel's laws had been tested and confirmed in higher vertebrates and vegetables, and in those cases no transversal division of chromosomes had been observed. According to the current interpretation, there was therefore no separation of maternal and paternal chromosomes (Sutton, 1903, p. 247). To avoid this objection, Sutton suggested that, in those cases, chromosomes united side by side in synapsis (instead of end to end); thus, the cytological appearance would be of two successive longitudinal divisions. Although there was no observational evidence for this interpretation, he announced that he intended to present favorable observations relative to *Brachystola magna* (Sutton, 1903, p. 248). Those observations have never been published and, had they been published, they would have been irrelevant, since the main problem was to know what happened in *higher animals and vegetables.*

Sutton's work of 1903 was full of difficulties, but it was much better than the brief proposals of Cannon and Wilson. We can state that he was the first to publish a detailed proposal of a chromosome hypothesis of heredity that was roughly compatible with known cytological and hereditary phenomena.

Now, if it was Sutton who proposed this hypothesis for the first time, from where did the designated "Sutton-Boveri hypothesis" come?

This name was created and advertised by Wilson (1925, p. 923). As shown above, Boveri did not publish any proposal similar to Sutton's at that time[14]. When he declared, in 1904, that he had reached a similar conclusion at the same time as Sutton, Wilson (a friend of Boveri, to whom he dedicated all editions of his book *The cell*) accepted his claim and created the expression "Sutton-Boveri hypothesis" (McKusick, 1960, pp. 490-491). However, Wilson himself described Boveri's contribution as: "Boveri had provided two of the fundamental postulates of Sutton's theory, namely, the individuality or genetic continuity of the chromosomes (which he had done more than any other to establish) and especially their qualitative differences in respect to development, for which he alone was responsible" (Wilson, 1925, p. 928). This is very far from a cytological interpretation of Mendel's principles.

CONCLUSION

First of all, it seems unfair to include Boveri's name beside that of Sutton's as one of the proponents of the chromosome hypothesis of Mendelian heredity, because he did not publish any hypothesis of that kind during the relevant period (1902-1903). Boveri did provide several relevant ideas that were used by Sutton, but so did Montgomery, Cannon and other scientists of the time – Hugo de Vries, for instance. Of course, the development of the chromosome theory was a collective work, but Sutton alone should be credited with the first chromosome explanation of Mendel's laws.

Was there a coherent chromosome hypothesis in 1902-03 that established a parallel between the behavior of Mendelian factors and cytological behavior of chromosomes? All evidence presented here leads to a negative answer. There were several types of problems.

- Cytological studies used pure types and heredity experiments used cross breeds. Cytological phenomena could be different in those cases; consequently, there was no cytological basis for Mendel's laws.
- Cytological processes were still obscure. Nobody really knew what happened during synapsis, which was a central point of the whole hypothesis.
- Individuality and constancy of chromosomes were still doubtful. Boveri's research only presented indirect evidence. This problem was solved only in 1909.
- Without assuming individuality and constancy of chromosomes it was difficult to explain the constancy of Mendel's factors and the purity of gametes; on the other hand, those who believed in the individuality and constancy of chromosomes had difficulty in explaining the independent segregation of factors admitted by Mendel.
- Mendel's laws of heredity were still being submitted to tests and criticism. It was premature to assume that the laws of heredity were well known.

One can clearly see that Sutton and other researchers of the time were strongly influenced both by cytological knowledge grounded on observations and by theoretical presuppositions that led to interpretations without an observational basis. They certainly did not propose the chromosome hypothesis as a result of experimental cytological research (Sandler and Sandler, 1986, p. 767). We can say that the chromosome hypothesis was an imaginary model: most of its assumptions could not be observed, at that time.

For those reasons, the attitudes of those scholars who denied it, such as Thomas Hunt Morgan (Martins, 1998) or those who adopted an attitude of critical expectation, such as William Bateson (Martins, 1997 a,b) can be regarded as scientifically sound.

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RESUMO

A chamada "hipótese cromossômica de Sutton-Boveri" foi uma tentativa de estabelecer um paralelo entre o comportamento citológico dos cromossomos e os princípios seguidos pelos fatores mendelianos. Embora seja aceita atualmente, ela teve uma pequena aceitação por ocasião de sua proposta (1902-3). O objetivo deste artigo é elucidar o significado da hipótese cromossômica a partir dos trabalhos originais, levando em conta o contexto científico da época. Além disso, procura verificar se ela mereceu o tratamento negativo que recebeu. Este estudo levou à conclusão de que é injusto incluir o nome de Boveri lado a lado ao de Sutton como sendo um dos proponentes da hipótese cromossômica, porque ele não publicou nenhuma hipótese deste tipo no período relevante (1902-3). Além disso, não havia uma hipótese cromossômica coerente nesse período. Sutton e outros pesquisadores daquela época foram fortemente influenciados tanto pelo conhecimento citológico baseado em observações como por pressuposições teóricas que levaram a interpretações sem uma base observacional. Eles não propuseram a hipótese cromossômica como resultado de uma pesquisa citológica experimental.

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[14]Boveri only published a similar hypothesis in 1904 (Baxter and Farley, 1979, p. 167). Besides that, according to Stubbe, it was only in 1904 that Boveri provided strong evidence for qualitative differences between chromosomes (Boveri, 1904; Stubbe, 1972, p. 250), and only in 1909, with his research on *Ascaris megalocephala univalens* (that has only two chromosomes) that he confirmed the individuality of chromosomes (Boveri, 1909; Stubbe, 1972, p. 250).

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