Mendel and Lederberg

The first steps towards classical and molecular genetics

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Table of Contents

Introduction

Gregor Mendel is widely recognised as the founder of genetics. His seminal paper “Experiments in Plant Hybridisation" [15] describes how he followed contrasting characters through several generations of crosses and made careful counts of progeny that he converted into ratios. He realised that a pair of differentiated characters followed a binomial algebraic series and that combinations of several series predicted classes in future crosses. Mendel concluded that he had discovered a law of combination for different characters. According to his law, variation is conserved through the generations, in contrast to 19thC theories of heredity, which predict blended variation.

Mendel’s experimental and analytical methods became central to genetics and have been subject to close examination. However, Mendel also turned to the reproductive cycle to explain his law and this explanation has received less attention. He proposed that germ cells in hybrids carry different “elemente” and showed how these account for the ratios. Mendel did not however suggest what the “elemente” might be and almost half a century elapsed before their behaviour was recognised as mirroring that of chromosomes. Since Mendel was working at a time when chromosomes had barely been seen, let alone studied, he was not in a position to envisage the physical basis of his theory. Nevertheless, many revisionist historians see the brevity of his explanation as a shortcoming, rather than a consequence, of information not being available. They claim that Mendel had been merely putting hybridisation onto a quantitative footing and had not had any interest in wider applications of his theory [2, 16, 18].

But few historians consider the state of the mid-19thC cell theory, although this must have influenced Mendel's ideas and how he expressed them. Part 1 of this article looks at his explanation in the light of the incomplete knowledge of cells at the time. Part 2 looks at the birth of E.coli genetics, almost a century later, in the light of the incomplete knowledge of bacterial cells at that time. The E.coli problems have been well documented and make an informative comparison.

Part 1

Mendel and Cells

Mendel's paper goes into some detail as to why peas were suitable experimental material. Their floral structure was ideal for preventing unwanted foreign pollen from entering fertilized flowers and since they had been widely used by plant breeders (though not, in fact, in Moravia), there was plenty of information on performing controlled crosses. Mendel knew that many different varieties had been developed and that "some distinct forms of the genus possess characters that are constant and easily recognisable".

When Mendel came to considering the role of cells, he faced a much less well-informed scenario. The Cell Theory, which states that cells are a universal component of organisms, had been put forward several decades earlier by the the botanist Matthew Schleiden and the zoologist Theodore Schwann; but although the theory was a significant landmark, it had not heralded the arrival of the modern cell [7]. Schleiden's misconceptions were mainly responsible. His attention had originally been attracted by the nucleus, which he thought was involved in forming cells. He renamed it a cytoblast and thought he could see cytoblasts appearing during development, going on to say: "after cytoblasts attain their full size, a delicate transparent material is formed on their surface. This is the young cell". His erroneous view could not support a role for internal structures (at the time mostly invisible) that perform vital functions within a permanent confined space.

Although not everyone was persuaded by free cell formation, cells were not generally recognised as permanent until the 1850s, when Rudolph Virchow pronounced: "every cell is derived from a pre-existing cell". But his pronouncement was not the final word. Cell

division had to be incorporated into the theory and it was assumed that cells and their contents just split in half when the biological mass becomes too big. Virchow offered a description of the nucleus splitting, which he could equally well have applied to cells, since it was entirely fanciful: “First a simple constriction, or groove, is formed ... this groove gradually extends over the surface of the nucleus and from it, the partition wall penetrates right through the interior of the nucleus” [7]. Cell and nuclear division were not addressed seriously until the 1880s, when chromosomes could be properly visualised.

When Mendel was doing his experiments, not only were chromosomes absent to all intents and purposes, but there was also little precise information about cell contents and their functions. Protoplasm’s restless movements had been well documented and there were descriptions of possible internal structures, but there was no consensus on what actually went on. Even cell membranes, indispensable if a cell is to perform essential functions as and when required, were not universally accepted.

However, the participation of cells in the reproductive cycle was not in question. There had been well-founded reports of encounters between egg and sperm in frogs and in rabbits and pollen in plants had been seen pushing a tube into the ovary [14]. Although the actual fusion between gametes was out of sight in most animals and plants, some algae despatch their germ cells into the surrounding water where sooner or later they bump into each other. In 1855, Pringsheim saw an actual fertilization between algal germ cells and Mendel knew of the observation, most likely through his friend Johannn Nave, who took a well-informed interest in algae.

But although the reproductive cycle was reasonably well established, it's likely that other possibilities still lingered. Schleiden had claimed that the egg merely helps the pollen tube become the embryo and, although the proposal seems rather obviously wrong, it had gained some support [14]. Mendel pointed out in a footnote that his experiments argued against it, which suggests uncertainty as to whether his readers were up-to-date.

But while cells provided an essential framework for Mendel's theory, he had little to go on when it came to the differentiating elements inside them. When he introduces the reproductive cycle, he speaks of germ cells differing in internal composition, but only once mentions "faktoren"; and while he says that the different cell types are numerically equivalent, he does not suggest how this comes about. However, he returns to the theory in the Concluding Remarks, where he refers to "faktoren" as "elemente" and is more explicit about what might be going on. When egg and pollen cells unite into a single cell, the further development "depends on the material and composition of the elements which meet in a vivifying union". But in variable hybrids, the union is uneasy: "... between the differentiating elements of the egg and pollen cells, there also occurs a compromise, insofar that the foundation of the hybrid has become possible, but nevertheless the arrangement between the conflicting elements is only temporary ... Since in the body of the plant no changes are perceptible during the whole period of vegetation, we must assume that it is only possible for the differentiating elements to succeed to step out from their enforced association during development of the fertilizing cells".

Mendel is pointing out that since hybrid plants are not mosaics, the enforced union is preserved during the vegetative phase and only breaks down in the reproductive tract. Separating the uneasy pairs during germ cell formation nicely accounts for the numbers

of different germ cells being equivalent. Finally, “In the formation of these (that is the fertilizing) cells, all existing elements participate in a totally free and uniform arrangement, while only the differing ones mutually exclude each other”. The free and equal arrangement of equivalent numbers of single elements gives the Mendelian ratios.

Revisionist historians claim that the elements bear little resemblance to the modern gene (2, 18). The “like elemente” do not appear to be in pairs and do not “mutually exclude” each other. And Mendel’s algebraic symbols give homozygotes and heterozygotes as A Aa a, rather than the AA Aa aa in modern text-books.

Their interpretation of the text overlooks the fact that Mendel was not developing a theory, but proposing a new one, and new theories often leave details to be sorted out later. Mendel could deduce that hybrid cells have pairs of differentiating elements, but had no direct evidence for pairs of like elements in cells of constant forms. Van Dijk and Ellis have argued that he might have used single letters for constant forms because the elements were identical [19]. In a recent Perspectives, Kim Nasmyth points out that there was in any case insufficient information to justify AA rather than A.

Pairs of elements in cells, whether like or differentiating, raise several issues that Mendel might have considered. In the first place, during normal growth, the elements have to multiply and distribute themselves into daughter cells. When nuclear division by mitosis was being described several decades later, Wilhelm Roux argued that a homogenous mass could split into two exact replicas, while a heterogenous mass required a mechanism to ensure equitable distribution of component structures. Hence indirect division by mitosis: “The goal of nuclear division is not merely an arbitrary halving of nuclear mass, but is also some sort of

designated separation of ‘qualities’ which comprise this mass” [7]. Roux argued from first principles and his abstract argument also applies to cells. Mendel could therefore have argued for a mechanism that ensures accurate division and distribution of his proposed elements without knowing what that mechanism might be.

However, one suspects that Mendel would have been more exercised by how the differing elements came to mutually exclude each other in a precise and organised series of events. The novelty of his thinking is brought out by a comparison with the French hybridiser Charles Naudin, who had been struck by the release of variation in later generations of hybrid crosses. Naudin turned to the germ cells for an explanation, but his discussion was in terms of disjunction of species essences: “… the disjunction leads to the formation of a pollen identical with that of the father-species, besides the pollen identical with that of the mother-species. This applies also to ovules: the disjunction leads to the formation of ovules identical with those of the mother-species, besides the ovules identical with those of the father-species" [13]. Naudin was on the right track, however his theory does not have a quantitative basis; disjunction between parcels of species essences was little more than a description, which could not accurately predict results of future crosses.

Mendel must have been aware that his theory depended on a novel precision mechanism. However an abstract argument could not deduce the state of play that cytologists would eventually uncover. Not only had nuclear division by mitosis not yet arrived, but the reduction of hereditary material by meiosis was so far down the line that it was effectively a blank slate.

While meiosis couples separation of paired genes with cell division, the blank slate of the mid-19th century could have been filled by a 2-step process in which the enforced union is dissolved in step 1, allowing the elements to move into designated separate compartments that only accept singles. Mendel's text seems to imply a physical association that would need to be sundered. Alternatively, he could have seen the "accommodation" as operating at a distance, with step 1 being a break-down in the arrangement. In step 2, simple fission could separate the two compartments, generating reproductive cells carrying alternative elements; or compartments could just be budded off.

The identical elements in constant forms are fully accommodated to each other, so they are not in an uneasy union from which they must extricate themselves. A passive system that does not require pairing could, in principle, distribute single elements to compartments destined to be reproductive cells, provided each compartment is limited in what it can accept.

Chromosomes going through meiosis would later provide a complete, and analysable, mechanism that applies to like, as well as unlike, partnerships. But primitive systems that somehow brought about the required ends could have been envisaged before chromosomes arrived on the cytological scene, albeit with unproven assumptions and gaps as to what kind of mechanisms might be involved.

**Footnote: He does not explicitly state that the vegetative elements are inside cells, but since he describes the pollen and egg cells as uniting into a single cell it is unlikely that he supposed that the elements emerge, to move back later into reproductive cells.*

Part 2

The Birth of E.coli Genetics

Mendel's deductions about transmission of "elemente" led to their being located on chromosomes, so the 20th century gene had a physical presence. Nevertheless, individual genes remained inaccessible and their composition remained indeterminate because chromosomes contained a mix of proteins and DNA. This was the situation that Joshua Lederberg faced when he became interested in genetics. Lederberg, like Mendel, was an academic outsider. In fact, he was at the beginning of a medical degree. He was not, however, a typical medical student; he saw the degree as a useful step towards a career in research. He used to take vacation jobs in Francis Ryan's laboratory, where the main focus was on whether external conditions might influence mutation. The fungus Neurospora crassa was used in the experiments, because it was easy to vary its growth parameters.

A few years earlier Neurospora crassa mutants had played an essential role in George Beadle and Edward Tatum's influential One Gene One Enzyme hypothesis, though the connection with enzymes did not offer clues about the gene itself. Then Avery *et al* reported that the bacterium Pneumococcus could be transformed by DNA extracted from a different type [14]. Finally a possible gene was in the frame, and the young Lederberg saw a prospect of isolating it.

But there was a problem. There were long-standing doubts over whether bacterial genes were directly comparable to those in higher organisms [23], so maybe Pneumococcal DNA was something of a red herring. Lederberg decided to attempt transformation in a higher organism and Neurospora looked like a good choice. There wasn't, in fact, a lot of

choice. Since classical genetics depends on a supply of suitable mutants that can be put through reasonably straightforward crosses, the subject's development had focussed on a relatively small number of organisms, most of which did not lend themselves to DNA transformation.

When Lederberg set about planning transformation in Neurospora he realised that it would certainly be rare, so some kind of selection system was called for. George Beadle and Edward Tatum had pioneered the use of biochemical mutants (auxotrophs) unable to manufacture an essential metabolite and Ryan's Neurospora stocks included one which had lost an enzyme needed to make the amino acid leucine. Since the mutant could not grow on simple defined medium, Lederberg argued that they could transform it with DNA from an normal strain and select for occasional cells that had received a functioning gene. But the mutant turned out to be unstable, with numerous revertants that grew very happily on minimal medium. The realisation that occasional transformants would be hard to detect brought the experiment to a premature end.

Lederberg now decided that finding a bacterial sexual system similar to systems in higher organisms would be strong evidence for bacteria having bona fide genes. Microscopists had seen occasional pairings that appeared to be conjugal, but there were no reports of possible genetic transfer. If there was sexual activity, it must be infrequent. So a selection system was again called for - and Tatum had already started isolating auxotrophic biochemical mutants in Escherichia coli. Lederberg moved to Tatum's laboratory and began preparations for looking for bacterial sex.

Revertants, such as those that had scuppered the Neurospora attempt, were a major consideration, but they could easily be foiled by using a multiply mutant recipient in which the chance of several mutations reverting simultaneously would be vanishingly small. The parents in E.coli's first successful cross each carried three mutations and when a mating yielded several hundred colonies capable of growing on minimal medium, Lederberg and Tatum knew that they were looking at gene transfer [11]. But were the bacteria just spewing out DNA that could enter other cells? Treating the crosses with DNA nuclease had no effect and simultaneous recombination of several genes argued against transformation, though several years elapsed before Bernard Davis obtained unequivocal evidence for the physical contact required by a true conjugation. [4]. However Lederberg was hoping that bacteria were capable of a Mendelian-type cross, or some acceptable equivalent, so he needed to look for Mendelian-type segregation. Initially, this posed a problem because colonies selected on minimal medium could not be analysed for alternative auxotrophic markers. Mutants capable of growing on minimal medium would have to be included in the cross.

Lederberg and Mendel had so far travelled along very different paths. Mendel had made use of a well-established crossing system that had been providing data of one kind or another for over a century, whereas Lederberg was attempting to establish a crossing system in a supposedly asexual organism through an entirely new method. However, when Lederberg set about choosing mutants for analysis his approach was surprisingly similar to that of his distant predecessor, showing the same concern for accurate classification.

Despite E.coli's lack of genetical history, it had plenty of well-documented mutations. Phages had been around since the 1920s and resistant mutants had been widely studied; Lederberg chose four that gave unambiguous results. Bacteriologists used lactose

fermentation as a diagnostic tool, so a tester medium was available in which a dye turned fermenting colonies purple. He isolated several non-fermenting mutants that gave white or pale pink colonies. But mutants unable to use glycerol proved unsatisfactory, and he decided against differences in colony appearance in case these might influence scoring.

When the cross finally got underway, the unselected markers did indeed segregate [12]. But they did not assort randomly, so the fruit-fly genetic map would be an appropriate model. This was directly connected to four chromosomes and the segregation patterns for E.coli's unselected markers also suggested linear chromosomes. Lederberg was so confident that he was on the right path that he borrowed Mendelian terminology for his crosses; parents gave rise to F1 and F2 generations, segregation was seen in the F1 therefore E.coli was haploid and the segregation itself involved some kind of meiosis, albeit possibly not quite as in higher organisms.

The latter caveat was necessary because one parent invariably contributed the majority of genes. Lederberg pointed out that there were examples of oddly-behaved chromosomes in higher organisms, citing the fly Sciara, which sheds many of its chromosomes during development. E.coli's recombinants could be extruding some genes.

The mating system was also difficult to fathom, though in this case, fungi offered a wide range of possibilities. Since the cultures that had produced E.coli's first recombinants had appeared to be identical, the system was supposed to be homothallic. Then Lederberg's wife, Esther, discovered strains that only mated in appropriate pairwise combinations, so heterothallic replaced homothallic [10]. But the Lederbergs abandoned fungal mating-type terminology when they designated the F+ parent as male, and the F- parent as female, though

they did not see any differences in morphological features; and they were surprised when the ability to be “male” turned out to be contagious, so that crosses converted females to maleness, regardless of whether or not any of the male’s genes were transferred. A transmissible fertility factor appeared to be another bacterial peculiarity. They called the factor F.

Lederberg remained confident that the various conundrums would be explained when the system was better understood. But despite his optimism the mapping, which had initially been so promising, was not progressing well. In fact it became so difficult to construct a straightforward and consistent linear map that the possibility of branched chromosomes was raised. Branching had no known analogies in higher organisms.

By now, E.coli’s new sexual system was attracting a lot of attention. Bacterial cells are so small that cytologists had struggled to make out what they contained and questioned whether indistinct bodies that took-up nuclear stains were in fact nuclei [23]. But improved techniques were changing opinions, in particular on the uncertain nuclear bodies, which appeared to be more organised than previously supposed. The bacteriologist Edward DeLameter saw the arrival of a genetical system, complete with recombination, as opportune. He had recently discovered that breaking open bacterial cells spread-out the contents of the nuclei, making them easier to study, and now he brought bacterial chromosomes into the frame [5]. He and his collaborators published articles on bacterial mitosis throughout the next decade and a possibility that there might be two chromosomes was seen as supporting the quadrivalent pairing proposed by Lederberg. Other researchers focussed on obtaining more genetic data, but more did not bring clarification. On the contrary. When Howard Newcombe and M H Nyholm tried to account for recombination

patterns, they found themselves considering the respective merits of ring chromosomes, the presence of lethals and chromosome losses [18].

In short, instead of delivering the gene, E.coli was offering yet another genetical puzzle. Mendelian genetics had already provided so many unsolved puzzles that its detractors could claim, with some justification, that it added little to the general biological scene. E.coli's mapping anomalies did not look likely to change matters. But this time an answer was just round the corner.

William Hayes was a medical bacteriologist who had run a testing laboratory during WW2. Since Shigella was a major cause of dysentery, it had occupied a lot of space in his files, and he noticed that there were many different types. Some years later he joined the Postgraduate Medical School in Hammersmith and took the opportunity to find out more. Shigella had no genetic system but he might get a few ideas from its close relative E.coli, so he asked the Lederbergs for strains. These arrived with a range of auxotrophic markers and since streptomycin was now widely available, some were resistant to the drug. Hayes mated an F+ normal male with an F- mutant female carrying auxotrophic markers and streptomycin-resistance and prototrophic, strep-resistant recombinant colonies duly appeared. He wondered how long the process took and decided to stop matings at intervals by exposing them to streptomycin. He estimated the time needed for completion as around 2 hours. But when he repeated the cross using a streptomycin-sensitive female, he obtained no recombinants at all. The F+ male and F- female were not just sexually different, they had different roles in forming recombinants [8].

It looked as though the complete F+ and F- genomes did not come together in a zygote, as in a typical Mendelian cross, rather the male F+ parent was a donor that transferred just a few of its genes. Perhaps the actual transfer was not affected by streptomycin, so that it could proceed even when the drug was present; but since the F- female provided most of the recombinant genome, its streptomycin sensitive gene made it vulnerable to attack by the drug. This proposal not only explained the results of the crosses, it also explained the puzzling excess of F- markers in recombinants.

Lederberg agreed that an asymmetric model was a nice hypothesis, but was not convinced that it applied. He had given a lot of thought to E.coli's genetics and could explain divergences from Mendelian expectations, whereas Hayes had only just started. Nor was Esther impressed when Hayes made the mistake of supposing that F was some kind of virus. Her careful experiments had provided no evidence at all for virus activity.

Meanwhile it was no longer necessary to rely on the inefficient F+ males for genetic data. Two new males had emerged that yielded recombinants at efficiencies as high as 10%, though only for some genes and frequencies fell onto a gradient that reduced to around 3%. Recombinants for genes outside the high-frequency polarised segment were at the low levels typical of F- crosses. The new males were called Hfrs and, although the high recombination rates were limited to part of the genome individual progeny, from crosses could be analysed. Lederberg undertook detailed studies of cell lineages, which convinced him that some chromosome segments were lost before or after fertilization, or both; however pairings between remaining segments resulted in segregations and the results seemed to be consistent with meiosis. He accounted for excess of unaffected F- genomes by proposing that some nuclei had not participated in fertilization [13].

Hayes, on the other hand, thought that polarised gradients were strong evidence for transfer from a donor male to a recipient female and concentrated on timing the process. Phage infection destroyed sensitive donors with immediate effect, enabling him to interrupt crosses with resistant recipients at intervals and plot gradients against conjugation times. The graphs were consistent with polar transfer from males to females.

At this stage, Francois Jacob and Elie Wollmann, in the Pasteur Institute, became involved. They were not interested in genes, bacterial or otherwise; they were investigating E. coli's temperate phage lambda, which can remain quiescent in the cells for many generations. Since it was likely that the quiescent state was in, or near, the chromosome, it might be possible to locate it on E.coli's new genetic map. Jacob visited Hayes and returned with strains and protocols. It was soon obvious that E.coli mapping was not the cutting-edge tool they had hoped for, and they would have to look into methods and arguments before attempting to make use of the system.

** Footnote: the F factor had moved into the chromosome and mobilised this during crosses. The chromosome is in fact incapable of self-mobilisation, and transient F integrations are responsible for the rare recombinants in F+ x F- crosses.*

Jacob and Wollmann liked the donor/recipient model, but realised that Hayes' gradients were open to interpretation. They wondered whether they could obtain more accurate information by separating conjugating pairs mechanically; a kitchen blender had recently been used to shear phages from their host cell; maybe it would serve their purpose. The blender was acquired and tested and Jacob and Wollmann were pleased that they could indeed plot gradients more accurately. They were even more pleased by an unexpected bonus. The system was so successful at stopping conjugation that it gave accurate entry times for the different markers. E.coli's genetic map would be in minutes, not recombination units [22].

Timed entries looked like convincing evidence for the donor-recipient model, however Lederberg was still reluctant. He pointed out that violent agitation in a blender was not what bacterial cells were accustomed to, so the crosses might not reflect the normal process. Jacob and Wollmann had checked against untoward effects of the blender, but they found it difficult to make a watertight case and they had no direct evidence for unilateral physical transfer [23]. The scenario was not unlike what Mendel had faced a century earlier, when he had had to argue from abstract genetic data. In this case, abstract genetic data supported two different scenarios, maybe even a third, and while some arguments were more convincing than others, none was definitive. Eventually electron micrographs showed a DNA molecule, or rather one strand of a DNA molecule, travelling through a conjugation tube. By that time E.coli had a well-established circular time map, Lederberg had long conceded and DeLameter had retracted claims about mitosis [6].

Discussion

Mendel and Lederberg were both trying to make deductions in the absence of adequate information about physical contents of cells, and neither arrived at the complete picture. Mendel's study of pea crosses specified paired elements in hybrids but left open the state of cells in constant forms, though the omission did not affect the analysis. Lederberg's interpretation of E.coli conjugation assumed that complete genomes were coming together, but since transfer was in fact partial the misreading resulted in discrepancies between theory and data. Ploidy was the culprit in each case. It was unknown in the 19thC so Mendel could not apply it, but was so well-established by the mid-20thC that Lederberg took it as the default position.

Although there is little documentary evidence on how Mendel arrived at his theory, the lay-out of the Versuche is suggestive. He introduces differences among reproductive cells in the Results, but though he makes the important point that the numbers of different cells must be equivalent, he does not suggest how the equivalence comes about; he merely points out that the pattern of fertilisations accounts for the ratios. Later, in the Concluding Remarks, he furnishes hybrid cells with paired elements and now halving each pair gives equivalent numbers of different germ cells.

It is unlikely that the Remarks were included in the lectures. Peter van Dijk has demonstrated that there wasn't time, and in any case the mixed audience of professors, teachers and amateur naturalists would have struggled to take on board a role for intracellular elements, followed by applications of the new law to hybridisation data in the literature.

Possibly Mendel did not introduce the elements until he was writing the paper, but whatever his timetable, his argument looks very like the birth, or maybe the gestation, of the gene.

The gene was still out of sight almost a century later, when Lederberg turned his attention to it. Lederberg could call on plenty of information about cells and molecules, perhaps too much since he tried to interpret the results in terms of known systems. Since recombination in bacteria has much in common with recombination in higher organisms the initial comparisons seemed to vindicate his approach; however attempts to treat conjugation as a cross between equal partners had to be abandoned in the face of mounting evidence for transfer from donor to recipient. Nevertheless Lederberg's original aim of isolating genes was eventually realised, though not for several decades and by an unexpected route. Bacterial plasmids would play a key role, and the mysterious F factor was the first representative of the class.

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