Part1

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Genetics

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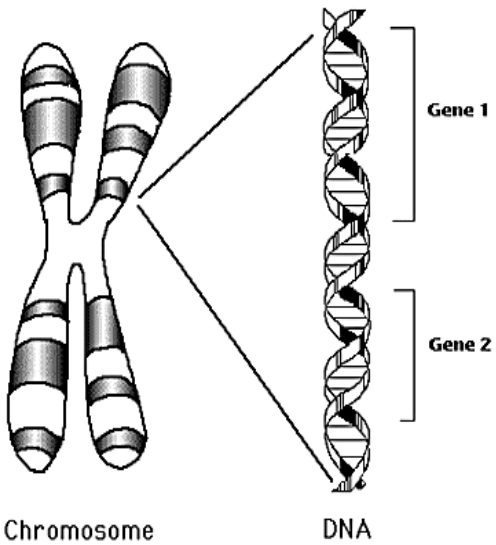
Table of contents

Basic Concepts of Genetics

- Gene – basic unit of genetic information. Genes determine the inherited characters.
- Genome – the collection of genetic information.
- Chromosomes – storage units of genes.
- DNA - is a nucleic acid that contains the genetic instructions specifying the biological development of all cellular forms of life
- Locus – location of a gene / marker on the chromosome.
- Allele – one variant form of a gene / marker at a particular locus.
- At each locus (except for sex chromosomes) there are 2 genes. These constitute the individual's genotype at the locus.
- The expression of a genotype is termed a phenotype. For example, hair color, weight, or the presence or absence of a disease.
- A dominant allele is expressed even if it is paired with a recessive allele.
- A recessive allele is only visible when paired with another recessive allele.



Genes

History of genetics

In keeping with the concept that people of earlier ages were not stupid, it was long understood that most reproduction produced offspring that somehow displayed combinations of the traits of the parents. If you bred individuals with some particular trait in common, you increased the chance that such a trait would be prominent in the offspring, but it didn't always work that way. You could make plant cuttings and pretty much get a duplicate plant, but pollination produced the same sort of mixtures that animal reproduction gave. How did it all work? Were there hidden rules that could be discovered and applied?

Gregor Mendel was fascinated with science and Nature, but in order to get enough training he had to enter a monastery in what was then Austria. In a classic example of using the materials at hand, Mendel took advantage of the monastery's production of peas: for years he bred peas in special separate plots, focusing on a few one-or-the-other features (such as Tall / Short, or Wrinkly Pea / Smooth Pea) that he could isolate in a "pure" form. After hundreds of tests, with new plots of hybrid plants and plots of hybrid-hybrid crosses, Mendel developed the first basic rules of what would come to be called genetics.

Mendel decided that traits were determined by some sort of internal code pieces which he called ***genes.*** For any particular trait, there might be code variations that changed the nature, like leaf color, or degree (height) of the trait, such as a variation in the Height Gene for Tall and one for Short. These variations he called ***alleles,*** which are carried in each individual in pairs (although there may be way more than two allele variations in a whole population, each individual just gets two, one from each parent), of which only one is passed on to each offspring. For each trait that is determined by a single gene, an individual's particular version of that trait is a product of their two alleles. Mendel thought that every single allele pair was sorted separately for reproduction, which turned out later to not be true, but many of them do sort independently.

As a side effect of Mendel's choice of pea traits, he also discovered a genetic feature called ***dominance,*** where the presence of a dominant allele can completely hide the presence of a recessive allele. This either-or condition was necessary to his working out genetic rules, but it has since

been found (and he probably realized) that many traits don't follow such a pattern. Many allele effects are not that strong or weak, but rather blend to produce the trait. (In human eye color, very dark alleles can be dominant over very light alleles - brown can dominate blue - but middle-strength alleles blend, such as when green and light brown produce hazel) It also turns out that many traits, in fact most traits, are a product of at least two genes working together, two alleles per gene; these ***multiple-gene traits*** do follow rules based upon Mendel's discoveries, but the complex mixing of many alleles makes predictions of offspring traits a matter of complex probability. With all that we know of genetics, breeding racehorses is still a matter of mating parents with desired traits and hoping everything mixes properly in the offspring (running ability is a multiple-gene trait), which is what they have been doing since before Mendel was born.

Mendel wrote and published several papers on his discoveries, but no one in the scientific community noticed, possibly because no one had taken such a mathematical approach to biology before. When he died, as far as he knew his research and findings would make no difference to the world. However, in the very early 1900s, three scientists investigating the same sorts of processes discovered Mendel's papers, and they became the foundation of a basic building block of biology today.

The Pre-Mendelian Era and Mendelism

Man's curiosity to know about transmission of hereditary characters is as old as humanity itself. From the earliest times it had been noticed that the offspring may resemble their parents, grandparents, or other relations. Many considered heredity to be some sort of a blending process, because of which the offspring showed different of the parental characteristics. The concept of blending inheritance fitted well with ancient thinking as it could explain why some children were more like their parents whereas others were less. As far back as 400 BC an ancient Greek writer suggested the role of environment in producing variations in inheritance. The idea appears similar to the ''Theory of acquired characteristics'' proposed by Lamarck twenty-two centuries later. The earliest indications about the material basis of heredity came from plant breeding procedures.

Mendel's experiments

In 1856 Mendel began his experiments on plant hybridization with garden peas. First of all he concentrated his attention on a single character in his experiments on inheritance. Secondly, he kept accurate pedigree records for each plant. And third, he counted the different kinds of plants resulting from each cross. Fourthly, he analyzed his data mathematically.
The garden pea (Pisum sativum) used in his experiments offers certain advantages: it is an easily growing, naturally self fertilizing plant; it is well suited for artificial cross pollination therefore hybridization (crossing of two different varieties) is easily accomplished; it shows pairs of contrasting characters which do not blend to produce intermediate types. For example tall and dwarf are a pair of contrasting conditions for the character height; similarly round and wrinkled seeds are contrasting forms for the character seed texture. On self pollination each character breeds true. Mendel worked with seven pairs of characters so that he had 14 pure breeding varieties.

Mendel reasoned an organism for genetic experiments should have:

1- a number of different traits that can be studied
2- plant should be self-fertilizing and have a flower structure that limits accidental contact
3- offspring of self-fertilized plants should be fully fertile.

Mendel's work showed:

1- Each parent contributes one factor of each trait shown in offspring.
2- The two members of each pair of factors segregate from each other during gamete formation.
3- The blending theory of inheritance was discounted.
4- Males and females contribute equally to the traits in their offspring.
5- Acquired traits are not inherited.

Mendel laws

The Principle of Segregation: proposes the separation of paired factors during gamete formation, with each gamete receiving one or the other factor, usually not both. Organisms carry two alleles for every trait. These traits separate during the formation of gametes.

Principle of Independent Assortment: that when gametes are formed, alleles assort independently, members of any gene pair segregate from one another independently

Monohybrid cross

Mendel crossed varieties of edible peas which showed differences in morphological characters such as color of flowers (red vs. white), shape of pod (inflated vs. constricted), color of pod (green vs. yellow), texture of seed (round vs. wrinkled), color of cotyledons (yellow vs. green), flower position (axial vs. terminal) and height of plant (tall vs. dwarf). He was dusting the pollen of one variety on the pistil of the other. To prevent self pollination of the female parent, he removed its stamens before the flowers had opened and shed the pollen. After making the cross he would enclose the flowers in bags to protect them from insects and foreign pollen. Mendel's first experiments explain how a single gene segregates in inheritance. When Mendel crossed a true breeding tall plant (female parent) with a true breeding plant of the dwarf variety (male parent), he got tall plants like one parent in the first filial generation designated ***F***1. He used the term ''dominant'' for the ***tall*** character which dominated in the ***F***1 generation, and ''recessive'' for the character of ***dwarfness*** which remained hidden (latent) in the ***F***1 generation. Self fertilization of the ***F***1 hybrids produced the second filial generation ***F***2 consisting of a total of 1064 plants of which 787 were tall and 277 were dwarf. That is tall and dwarf plants appeared in ***F***2 in the proportion which is roughly equal to 3 : 1. When he performed the reciprocal cross by reversing the sexes of the

parents, the same results were obtained showing thereby that it did not matter which plant was used as male or as female parent. Similarly, Mendel crossed pea plants differing in other characters such as color of flowers (red flowered versus white flowered), texture of seed (round versus wrinkled), color of cotyledons (yellow versus green). Such a cross which involves only one character from each parent is called a ***monohybrid cross***. In each case Mendel found one parental character dominating in the F1 hybrid, and after self fertilization in F2 generation both parental characters appeared in the proportion of three-fourths to one-fourth. He performed each experiment on several thousand plants and counted all the plants in F2 progeny which gave an average ratio of 3 : 1.

Dominant versus ***Recessive:*** When two pure breeding varieties are crossed, the parental character that expresses itself unchanged in the ***F***1 generation hybrids is ***dominant***: the one that does not appear in ***F***1 but appears in ***F***2 is called recessive. In the above cross three fourths of the ***F***2 progeny show the dominant character and one-fourth the recessive character.

Alleles: Factors which control expressions of a character are said to be alleles. In the cross the character in consideration is height, and factors ***T*** and ***t*** which control tallness and dwarfness are alleles of each other.
Mendel's factors were later replaced by the term '***gene***' by a Danish botanist Johannsen in 1909. The word ***genotype*** refers to the genetic constitution of an individual, whereas ***phenotype*** refers to the external appearance or manifestation of a character.

Summary of Mendel's Results:

1. The F1 offspring showed only one of the two parental traits, and always the same trait.
2. Results were always the same regardless of which parent donated the pollen (was male).
3. The trait not shown in the F1 reappeared in the F2 in about 25% of the offspring.
4. Traits remained unchanged when passed to offspring: they did not blend in any offspring but behaved as separate units.
5. Reciprocal crosses showed each parent made an equal contribution to the offspring.

Mendel's Conclusions:

1. Evidence indicated factors could be hidden or unexpressed, these are the recessive traits.
2. The term phenotype refers to the outward appearance of a trait, while the term genotype is used for the genetic makeup of an organism.
3. Male and female contributed equally to the offspring's genetic makeup: therefore the number of traits was probably two (the simplest solution).
4. Upper case letters are traditionally used to denote dominant traits, lower case letters for recessives.

The Dihybrid Cross

Mendel made crosses between pea plants differing in two characters such as texture of seed and color of cotyledons. Such a cross in which inheritance of ***two*** characters is considered is called a dihybrid cross.

First of all Mendel crossed a pea plant that was breeding true for round seeds with a plant that bred true for wrinkled seeds. The ***F***1 indicated that roundness was dominant over wrinkled texture of seed coat. Similarly, by another cross he could determine that yellow color of cotyledons was dominant over green. He now used as male parent a plant which bred true for both round and yellow characters and crossed it with a female parent that bred true for wrinkled green. As expected from the results of his single crosses, the ***F***1 was round yellow. When he selfed the ***F***1 hybrids, the ***F***2 progeny showed all the parental characters in different combinations with each other. Thus plants with round yellow seeds, round green seeds, wrinkled yellow seeds and wrinkled green seeds all appeared in the ratio 9 : 3 : 3 : 1. Reciprocal cross in which the female parent was round yellow and male parent wrinkled green gave the same results.

P:	Round Yellow	×	Wrinkled Green
	RRYY		***rryy***
Gametes:		***RY ry***	
F1:	Round Yellow	×	Self (Round Yellow)
	RrYy		***RrYy***
Gametes:	***RY, Ry,rY,ry***		***RY, Ry, rY, ry***

	RY	***Ry***	***rY***	***ry***
RY	***RRYY***	***RRYy***	***RrYY***	***RrYy***
Ry	***RRYy***	***RRyy***	***RrYy***	***Rryy***
rY	***RrYY***	***RrYy***	***rrYY***	***rrYy***
ry	***RrYy***	***Rryy***	***rrYy***	***rryy***

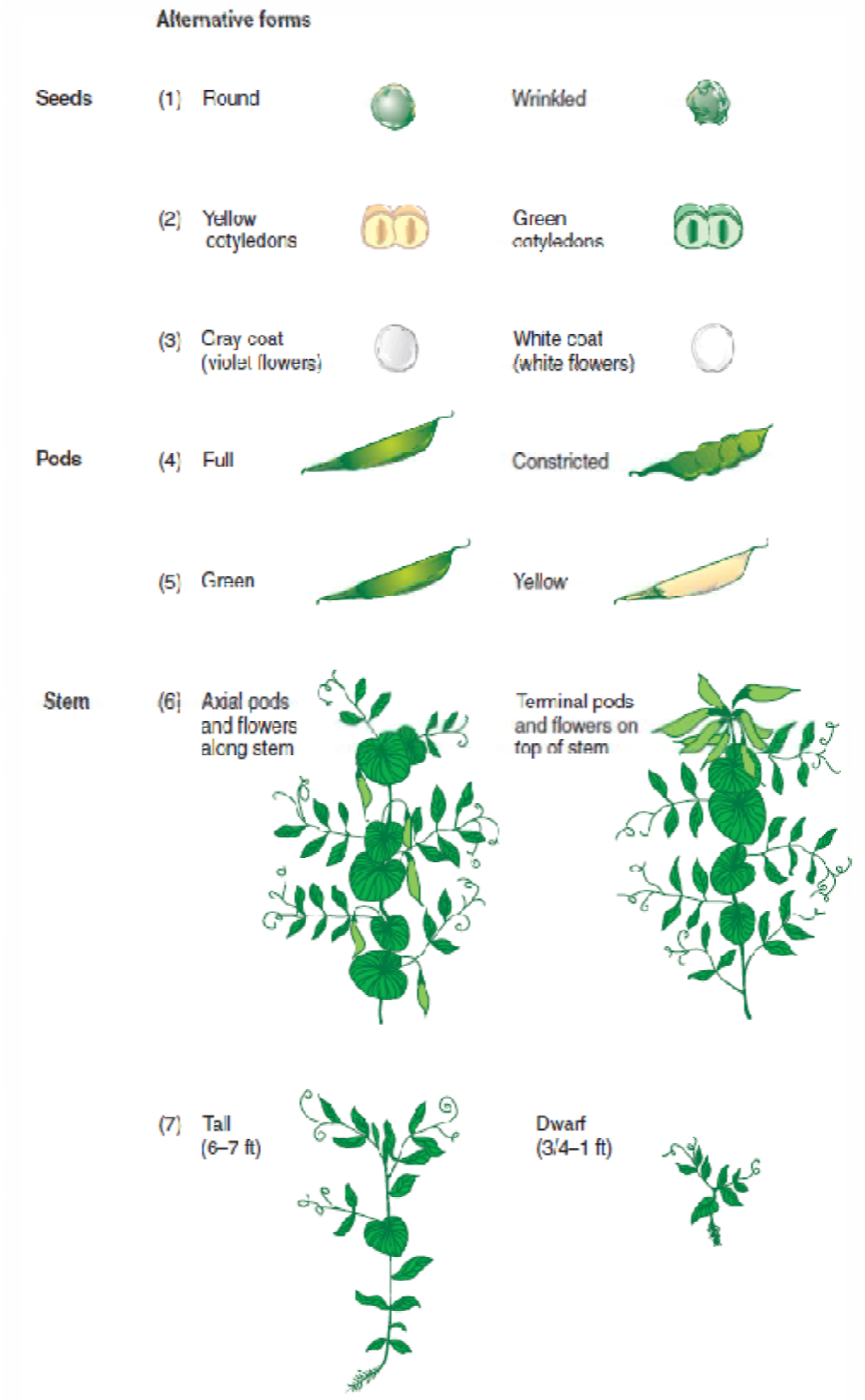


Figure 2.3 Seven characteristics that Mendel observed in peas. Traits in the left column are dominant.

Interaction of genes

The phenotypic ratios obtained by Mendel in garden peas demonstrate that one gene controls one character; of the two alleles of a gene, one allele is ***completely*** dominant over the other. Due to this the heterozygote has a phenotype identical to the homozygous parent. On the contrary, genes were interacting with each other to produce novel phenotypes which did not exhibit dominance relationships observed in Mendel's experiments. In one of the first cases reported, the heterozygote showed a phenotype intermediate between the parental phenotypes. This was termed ***incomplete dominance*** or ***intermediate inheritance.*** In ***codominance*** the heterozygote expresses both the parental phenotypes equally. Sometimes a gene masks the expression of another gene at a different locus. This is known as ***epistasis.*** On still other occasions a gene does not completely mask another gene as in epistasis, but, in some way modifies the effect of the second gene. Known as ***modifying*** genes, such genes either enhance or suppress the expression of a different gene.
Interaction between genes enables some genes to act together to produce an effect that neither gene can produce separately. Such genes are said to be ***complementary.*** There are genes that copy other genes, to produce a similar effect. Thus independent genes that produce the same effect are given the name ***duplicate*** genes. Lastly, but most serious are genes causing death. They are known as ***lethal genes.***

1- Complete dominance

Complete dominance occurs when the phenotype of the heterozygote is completely indistinguishable from that of the dominant homozygote.

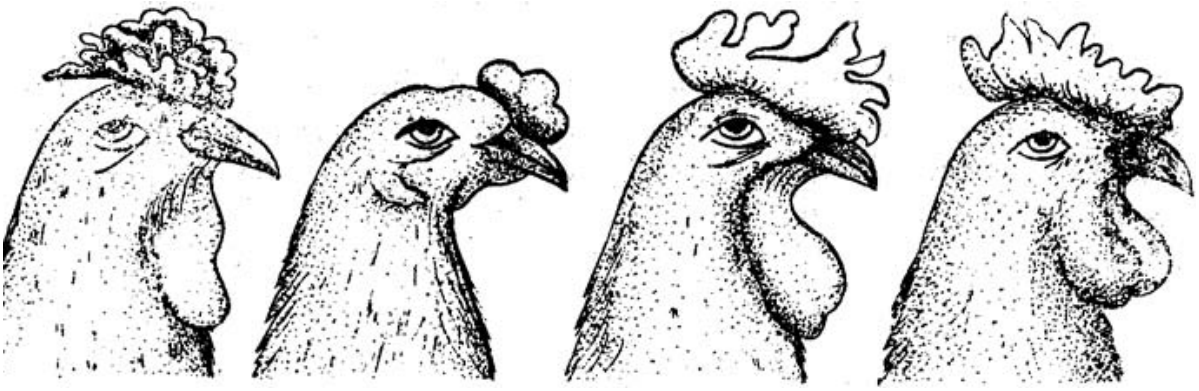
2- incomplete dominance

A monohybrid cross between a red-flowered snapdragon and a white flowered variety does not produce red or white flowered plants in ***F***1 as expected from mendelism. Instead the flowers are pink, ***i.e.*** intermediate between the two parents. This is because neither red flower color nor white is dominant, but each allele has its influence in color development and the hybrid appears pink. If the ***F***1 pink flowers are self-pollinated, the ***F***2 progeny shows red, pink and white flowered plants in the proportion 1: 2: 1. It may be recalled that this is the same genotypic ratio that Mendel obtained in garden peas. The difference is that in the present case the heterozygous progeny is distinct in appearance from the homozygotes.

The name ***intermediate inheritance*** is also given to crosses where ***F***1 hybrids show incomplete or partial dominance with no phenotypic resemblance to either parent.

3- ***codominance***

In 1900 Bateson and his colleagues studied inheritance of comb shape in fowls. There are four types of combs in fowls: rose, pea, walnut and single. Bateson first performed a cross between rose and single. The ***F***1 hens all had a rose comb, and on inbreeding gave rise to an ***F***2 progeny of rose and single in the ratio 3 : 1. The cross indicates that rose and single comb are controlled by a single gene and that rose is dominant over single. In the second cross when chickens with pea comb were mated with single comb, the ***F***1 progeny had pea comb, and ***F***2 had pea and single in the proportion 3 : 1. Obviously, the gene for pea comb is dominant over single. This raises an interesting question—are the genes for rose and pea comb same or different? Bateson then crossed rose and pea. Surprisingly, the ***F***1 birds had an altogether different comb of the walnut type! An ***F***2 progeny raised by inbreeding the walnut type consisted of four types of chickens—walnut, rose, pea and single (Fig.) in the ratio 9 : 3 : 3 : 1. As this ratio is typical for dihybrid inheritance it became clear that rose and pea combs were controlled by two pairs of genes.



Rose pea walnut single

P:	Rose comb	×	Pea comb
	RRpp		***rrPP***
Gametes:		***Rp rP***	
F1:	Walnut	×	Walnut
	RrPp		***RrPp***
Gametes:		***RP, Rp, rP, rp***	

	RP	***Rp***	***rP***	***rp***
RP	***RRPP***	***RRPp***	***RrPP***	***RrPp***
Rp	***RRPp***	***RRpp***	***RrPp***	***Rrpp***
rP	***RrPP***	***RrPp***	***rrPP***	***rrPp***
rp	***RrPp***	***Rrpp***	***rrPp***	***rrpp***

F2:	9 Walnut :	3 Rose :	3 Pea :	1 Single
	RRPP	***RRpp***	***rrPP***	***rrpp***
	RrPP	***Rrpp***	***rrPp***	
	RRPp			
	RrPp			

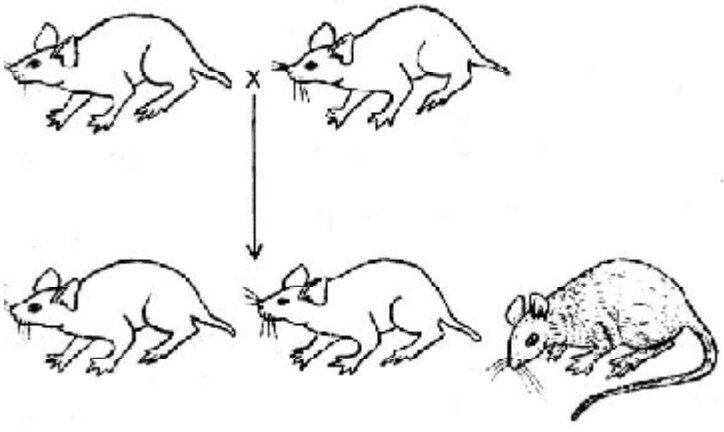
The appearance of walnut comb in ***F***1 of cross between rose and pea shows that both of the independent dominant genes ***P*** and ***R*** are jointly responsible for the walnut comb. When present together in the zygote, ***P*** and ***R*** genes interact to produce the walnut comb. When present alone, they produce rose or pea comb. The recessive alleles of rose and pea combs produce the fourth type of chicken with the single comb.

Lethal Genes

Lethal genes can also alter the basic of Mendelian ratios 9 : 3 : 3 : 1 ratio and lead to death of an organism.

1- Dominant Lethal

The brachyury gene (I) in mouse is lethal in the homozygous state, and when heterozygous the animal survives, but with a short tail. Embryos homozygous for brachyury show a few abnormalities and die in uterus. When two short tail mice heterozygous for brachyury are crossed, the viable offspring produced show a phenotypic ratio of 2 short tail : 1 normal tail (Fig.).



II
Embryo
Aborts

Ii
2 Short tail

ii
1 normal tail

2- Recessive Lethality

The recessive lethal gene remains unnoticed in the population because it does not produce a visible phenotype in the heterozygous state. In fact it may be transmitted through heterozygous carriers for many generations without being detected.

There is a recessive lethal gene in man which causes death of newborn infants by producing internal adhesions of the lungs. A fetus homozygous for this gene completes its embryonic development with the help of oxygen supplied by the maternal blood. But death occurs soon after birth when the lungs fail to function normally. Such a recessive lethal gene is carried in heterozygous individuals without producing harmful effects. It is detected only when two heterozygous persons marry and about one-fourth of their children die after birth, as they receive both recessive alleles from their parents.

3- Sex-Linked Lethals

This is a system in which the lethal gene is carried on the sex chromosome, usually X. In human beings lethal effects among the progeny may be caused accidentally by radiation (X-ray) treatment of the reproductive organs of the parents. According to a study by R. Turpin in France, when women receive X-ray exposures in the abdominal region, recessive lethal mutations are induced in the X chromosome present in the ovum. Such a woman produces more females and very few males in the progeny. If the male parent is exposed to X-rays and dominant lethal mutations are induced on his X chromosome, there will be more boys in the progeny and few females. This is because the single X chromosome is passed to the daughters resulting in their death.

Muscular dystrophy is due to an X-linked recessive gene which shows a visible phenotype many years after birth. Boys having this gene are normal for about 10 years after which there is failure of muscular control and death results.

4- *Conditional Lethals*

Sometimes an organism lives normally under one set of conditions, but when certain changes are introduced in its environment, lethality results. One of the first conditional lethals known was recognized by Dobzhansky in Drosophila pseudoobscura. The flies live normally at a temperature of 16.5°C, but at 25.5°C the flies die.

Early and Late Acting Lethals

The earliest stage at which lethal genes can act is evident from studies on mutations in gametes. Normal gametes are more viable and have better chances of effecting fertilization and producing zygotes. The lethal genes are eventually lost with the death of unfertilized gametes. Such genes are referred to as gametic lethals. The phenomenon by which a certain class of gametes is specifically inhibited from taking part in fertilization has been termed meiotic drive by Sandler and Novitski. There is a gene called segregation distorter (SD) present on the second chromosome of Drosophila. The dominant allele of this gene does not allow gametes to participate in fertilization. Thus only gametes bearing the recessive allele (sd) are able to fertilize eggs and produce viable zygotes.

In human beings the gene described for causing adhesions in lungs expresses lethality soon after birth when the lungs of the newborn infant fail to function normally. In plants most lethal genes are known to act during or after seed germination.

Among late acting lethal genes, some clear cut examples can be cited from human diseases. Genes causing muscular dystrophy cause death before or in the second decade of life, before the onset of reproduction. Huntington's chorea on the other hand is fatal when the person is middle-aged, and the gene may have already been passed on to future generations.

Multiple Alleles

After Mendel first advocated the existence of two factors for each character, it was demonstrated in many organisms that a gene consists of a pair of alleles. Each member of the pair of alleles is said to occupy an identical position or locus on each of the two homologous chromosomes in diploid cells of an organism. In Mendel's experiment the gene controlling height of pea plants has both its alleles designated either as T and T or T and t, or t and t. Since there are always only two alleles they can also be denoted as T1 and T2. Similarly the gene determining flower color (R and r) can be denoted by alleles R1 and R2. Sometimes more than two alternative alleles or multiple alleles are present in different individuals of a population. When there are multiple alleles, a gene is denoted by more than two alleles such as T1, T2, T3, T4 and R1, R2, R3, R4, ... and so on. Now there are only two homologous chromosomes in a diploid cell, and at one particular site of a gene or locus, only one allele can be present. Therefore, in one diploid cell only two alleles are present at a particular locus. In other members of the population, due to two or

more mutations, the same locus on two homologous chromosomes could have two different alleles. In this way it is possible to detect a number of alleles for one gene from their different expressions in different individuals. Such a system in which one gene has more than two allelic states at the same locus in different members of the population is known as a multiple allele system.

Blood Groups Alleles in human

The ABO blood group system in human provides an excellent illustration of a multiple allelic system. Typically, we teach with genes for which only two alleles are known, but many genes have more than two different alleles--thus, "multiple" alleles.

One such gene which is of great interest to humans is the ABO blood group gene. This particular gene has three alleles, rather than two. Of course, each of us has only two sets of chromosomes, so any each individual has only two of these alleles at once. But the presence of three different alleles means that there are six possible genotypes, rather than the three possible for the more familiar two-allele situation.

For the ABO gene, the three alleles are the I^A, I^B and i alleles. We typically call these alleles "A," "B," and "O," but of course our rules for assigning symbols to alleles demand that all three be represented by some version of the same symbol. In this case, that common symbol is the letter "I," which stands for "immunoglobin."

By now, the concept of dominance should be familiar to you. Of course, things get a bit more complicated when there are three alleles instead of just two. As the symbols above should suggest, the i allele (the "O" allele) is recessive to both the I^A and I^B alleles (the "A" and "B" alleles). The I^A and I^B show co-dominance. This means that in an individual who is heterozygous for these two alleles, the phenotypes of both alleles are completely expressed, thus producing blood type AB.

Thus we have the following:

Genotype	Phenotype
ii	Type O
I^AI^A or I^Ai	Type A
I^BI^B or I^Bi	Type B
I^AI^B	Type AB

The other aspect of blood type which is of most interest to us is the Rh factor. Genetically, this is much simpler than the ABo system. It has only two alleles, one dominant (Rh-positive) and one recessive (Rh-negative).
Our blood type is part of the marvelous protective machinery in our bodies called the Immune System.
Our immune system's task is to identify and destroy biological materials which are foreign to our own bodies. In order to perform this task, of course, your immune system needs to know how to distinguish between what belongs to you and what is foreign. This isn't the easiest of tasks, as you are made out of precisely the same materials that would compose any living invader. So a vital part of your immune system is the tagging of your own cells and tissues, so your antibodies won't destroy your own cells.
Blood type is part of this much larger self-tagging system aspect of your immune system. "Blood Type A" actually means "blood cells tagged with antigen A." Antigen A is a specific protein marker found on the surfaces of all Type A blood cells. And the task of the I^A allele is to cause the creation and attachment of this specific kind of antigen. The I^B allele causes the creation and attachment of a different protein marker, the B antigen.
Knowing this about blood type can also explain to you why the I^A and I^B alleles are co-dominant, and why the i allele is recessive. The I^AI^B genotype results in both A and B antigens on the cell surfaces. The i allele causes no antigen to be produced, and is thus a "silent" allele.
There are also natural antibodies in the blood so that persons with type A blood have anti-B antibodies, and B group persons have anti-A antibodies. Blood of AB type does not have antibodies in its plasma. Persons with O type blood have both anti-A and B antibodies and are often called universal donors as they can donate blood to persons of A, B and AB types.