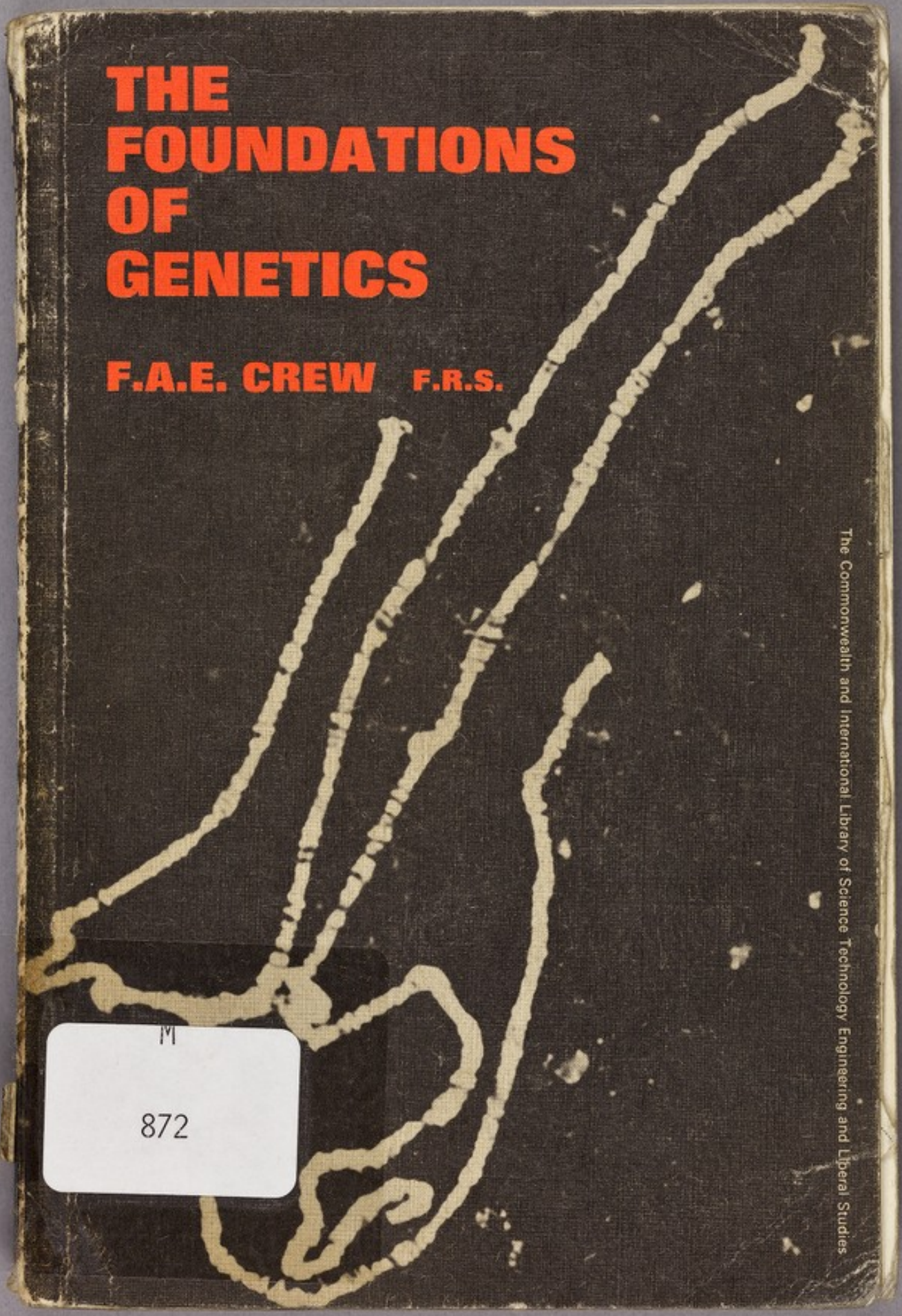
The foundations of genetics / by F.A.E. Crew.

THE FOUNDATIONS OF GENETICS

F.A.E. CREW F.R.S.



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THE FOUNDATIONS OF GENETICS

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"Genetics has become the core science in the biological field ; its basic tenets have profoundly influenced the rate and the direction of the development of all the biological and sociological sciences . . ." In these opening words of his Preface the author makes obvious the important nature of his subject. Beginning with an account of the work of the early hybridizers the book then provides a detailed study of Gregor Mendel, surely one of the most remarkable of men, and of his experiments with the pea, one of the most elegant of enquiries in the history of science. Then follows an outline description of the vast superstructure that was built upon Mendelism, e.g. the Theory of Gene and molecular biology with its genetic code. Finally the ramifications of genetics and the applications of genetics in agriculture and medicine are considered. This book is especially addressed to senior students in schools who are heading towards careers in biological science or technology and to such it should be of considerable interest and value. It should therefore claim its place in school, science and medical libraries.

The author, Professor Emeritus of Public Health and Social Medicine, F.A.E. Crew M.D., D.Sc., Ph.D., LL.D., F.R.C.P.E., F.R.S. (London and Edinburgh), was formerly Professor of Animal Genetics at the University of Edinburgh.

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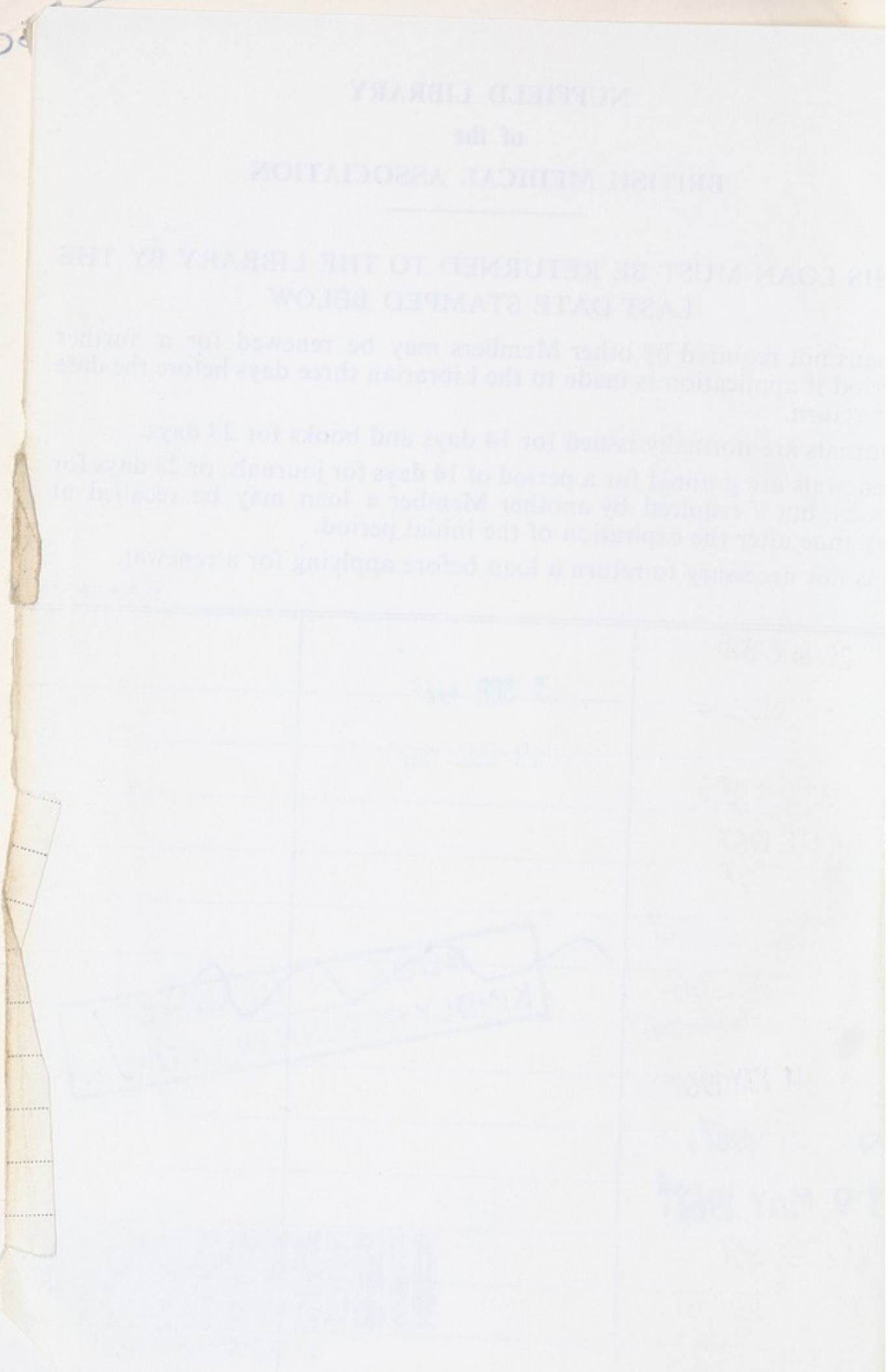

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HE FOUNDATIONS OF GENETICS

The forecourt of the Augustinian monastery of St. Thomas. On the left, the white marble statue of Mendel by the Viennese sculptor Charlemont, a tribute from "the friends of science to the investigator Gregor Mendel". It was unveiled in 1910 when it stood in the Klosterplatz outside the monastery wall. On the right, the sandstone monument erected by the monastery in 1922 on the occasion of the centenary celebrations of Mendel's birth. It stands in the garden plot (120 ft × 20 ft) that was used by Mendel in his pea experiments. The windows on the first floor above the monument and facing the street are those of the apartment occupied by Mendel during these years. On the right of this plot, on the ground-floor, is the room that was the refectory of the monastery and that now is the Mendel Memorial Hall.

THE FOUNDATIONS OF GENETICS

by

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in the University of Edinburgh

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A great man lays upon
posterity the duty of understanding him

JOHN BUCHAN, *Oliver Cromwell*

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PREFACE

GENETICS has become the core science in the biological field; its basic tenets have profoundly influenced the rate and the direction of the development of all the biological and sociological sciences and have found their applications in many different spheres of scientific activity.

The major interest in genetics has been passing from the biological to the molecular level where the basic nature of the living organism is being studied in almost incredible detail by means of the techniques and experimental methods of physics, chemistry and mathematics. For an understanding of the newer molecular genetics an adequate knowledge of what is now called classical genetics is essential.

This book attempts to trace the historical development of genetics, throwing into prominence those contributions to advancing genetical knowledge which can surely claim an exceptional and enduring importance.* It also draws attention to the many and varied spheres of scientific activity in which genetics, in application, has been found to have its fruitful uses.

F. A. E. C.

* These are the scientific papers cited in the footnotes.

ACKNOWLEDGEMENTS

As THE approach in the writing of this book has been the historical, it follows that I have drawn very largely upon the writing of others. I hope that the inclusion of any book or scientific paper in the list of references at the end of this book will be regarded as an acknowledgement of my indebtedness and as a gesture of gratitude to both author and publisher.

I am very grateful to the late Dr. J. Kříženecký, of the section of the Moravian Museum in Brno which is concerned with the collection and conservation of Mendeliana, for the photographs of Gregor Mendel, of his statue and of the monastery in Brno; to Dr. B. M. Slizynski of the Institute of Animal Genetics, Edinburgh University, for the photograph of the giant chromosomes of *Drosophila melanogaster*; to Dr. Marcus Rhoades of the University of Indiana for the photographs of some of the founders of genetics which appeared as frontispieces in the journal *Genetics* and for his permission to reproduce them; to Professor R. C. Punnett and to Professor H. J. Muller of Indiana University for photographs of themselves and to Professor Edward Castle of Harvard University for one of his father, for inclusion in the company of the founders and to Messrs. Oliver & Boyd of Edinburgh for permission to reproduce a number of illustrations in a book written by me and published by them many years ago.

F. A. E. C.

CHAPTER 1

PLANT HYBRIDIZATION BEFORE MENDEL

WHEN, long ago in man's eventful history, the hunter of wild animals and the gatherer of wild plants gave place to the herdsman and to the scatterer of grain, his dependence upon domesticated animals and cultivated plants began. It was inevitable that sooner or later he would seek ways and means of "improving" these animals and plants so that they might more fully satisfy his expanding needs. The accumulated experience of countless generations of husbandmen gradually became fashioned into a traditional craft and out of the breeders' methods of trial and error the art of breeding developed, to be used in the creation of new breeds and varieties attuned to the purposes for which they were being deliberately bred and to the conditions of the environment in which they were to be raised.

When man had gained the mastery over his physical environment and the struggle for existence had become less fierce, the breeder ceased to look upon his animals and plants merely as objects of use and began to look to them for aesthetic satisfaction. He became a "fancier" who exercised the art of breeding in the production of animals and plants remarkable for their beauty or for their quaintness. The great variety of animals and plants of economic importance and their high quality and the great diversity of types of exhibition beasts and birds and flowers and fruits that are to be encountered in the agricultural, poultry, bird and flower shows that figure so large in the life of most countries today bear witness to the astonishing skill that the breeder and the fancier wield. These are the creations of the artist, not of the scientist, for no satisfactory explanation of the successes that these men achieved and of the

failures that sometimes attended their efforts became available before the latter part of the nineteenth century.

It is possible today to examine such records of the past as are available and to conclude that these "improvers" and fanciers used three methods: (i) selection, (ii) breeding from a "sport", an unexpected and novel kind of animal or plant produced by seemingly perfectly "normal" parents, and (iii) hybridization.

Charles Darwin, in his *Origin of Species* (1859), considered this question and concluded that, in the main, the successes were the result of the exercise of "man's power of accumulative selection; nature gives successive variations: man adds them up in certain directions useful to him". By this is meant that the breeder or fancier forms a mental picture of the kind of creature he desires to produce, drawing up a list of the details of its characterization, its size, shape, colour and the like. He thus constructs what he considers to be the ideal animal or plant of a particular kind, his picture of it being a combination of qualities and attributes. These qualities are to be found separately in different individuals, though maybe not very well expressed. His task is that of collecting these qualities and of combining them in one and the same individual. This he does by selecting individuals displaying one or more of these desirable attributes and using them to produce the next generation, discarding all others. He assumes that these qualities are inherited and that "like tends to beget like". Generation after generation he continues to select and breed from his "best", from such individuals as most closely approach his picture of the ideal. For the failures Darwin could find no satisfactory explanation.

That, exceptionally, a new breed or variety had had its origin in a "sport" was well known to Darwin. There was the Ancon breed of sheep of New England, with its long back and its short crooked legs. The mating of a "normal" ram and a "normal" ewe had yielded the first Ancon lamb, a male. Most breeders would surely have got rid of such a monstrosity immediately and quietly, but this lamb was reared. Mated to its mother it sired more Ancons. Further matings revealed that the mating Ancon $\times$ Ancon gave none but Ancons and that a "normal" pair that had produced an Ancon was

likely to produce more, though most of the progeny would be "normals". But for the sudden appearance of such a "sport" and for the mode of transmission of this abnormal characterization from generation to generation Darwin had no satisfactory explanation.

The term hybrid is usually reserved for the definition of the offspring produced by the mating of individuals belonging to different species (Latin, a particular kind), for example, the mule, the product of a horse×ass mating. But horticulturalists give an extended meaning to the term to define the offspring produced by the mating of individuals belonging to different varieties of one and the same species.

It was in 1735 that Linnaeus, a Swedish botanist, in the first edition of his *Systema Naturae*, brought together all that was then known concerning the classification of animals and plants (as John Ray had done before him in 1686) and adopted the binomial system as a universal rule. To every animal or plant two names were given: the first, a generic one, the second a specific one. For example, *Homo* is a generic name; the genus (L. race) *Homo* includes *H. sapiens*, *H. neanderthalensis* and other fossil men. All these possess a large number of characters (details of structure) in common and so are much alike. *Sapiens* and *neanderthalensis* are specific names. These two species, though very much alike, are nevertheless to be distinguished by a number of constant dissimilarities. A species is a group of animals or plants the members of which interbreed freely with one another; there is no barrier of infertility between them, but they do not breed freely, in nature, with members of other species. The members of a species possess a common anatomical architecture that is in harmony with the mode of life that the species follows. Within a species there are commonly many varieties (L. *variare*, to change) all displaying the hallmarks of the species but differing more or less markedly in respect of their characterizations. These varieties preserve their distinctive attributes so long as they are prevented by natural or artificial agencies from mating with other varieties of the same species. The followers of Linnaeus insisted that species were specially created and were fixed and immutable.

Ray, on the other hand, had held the opinion that they were liable to gradual transformation (*Historia Generalis Plantarum*, 1686).

So far as the records tell, the first man to make use of the techniques of hybridization in Britain was Thomas Fairchild who had a nursery in Shoreditch, London. In 1718 he produced a hybrid between the Carnation and the Sweet William. Of this achievement Bradley, Professor of Botany in Cambridge, wrote:

> The Carnation and the Sweet William are in some respects alike, the Farina (L. flour: the pollen) of one will impregnate the other, and the seed, so enlivened, will produce a plant differing from either, as may now be seen in the garden of Mr. Thomas Fairchild, of Hoxton, a plant neither Sweet William nor Carnation but resembling both equally, which was raised from the seed of a Carnation that had been impregnated by the Farina of the Sweet William.

This was an event that initiated a new era in commercial horticulture and the time was to come when hybridization would be the most commonly used method of producing new forms of plants. The facts that Fairchild was a nurseryman and that he was able to make use of the techniques of artificial pollination indicate clearly that by this time much was known about sexuality in the plant and about the essential features of natural fertilization and also that horticulture (L. *hortus*, a garden: *cultura*, culture) was well developed.

The existence of the two contrasted forms of individuals known respectively as male and female in the animal (including man) must have been noted from the very beginnings of human history. The observation that sexual intercourse between male and female commonly preceded the bearing of young by the female must have been made equally early (even though it was not always thought that sexual intercourse and reproduction were causally related). The practice of artificial pollination of the date palm, which must necessarily have stemmed from a recognition of two contrasted forms of tree, was a routine procedure in ancient Assyria (2500–600 B.C.) and in Babylon (1800–500 B.C.). In the thirteenth century the Arab physician Kazwini had written that: "The date has a striking resemblance to man, through the beauty of its erect and slender figure, its division into two sexes, and the property which is peculiar to it, of being fecundated by a sort of union." The most

famous herbalist of the ancient world, Theophrastus, describes how "with dates the males should be brought to the females. For the males make the fruit persist and ripen. . . . When the male is in flower they at once cut off the spathe with the flower and shake the bloom with its flower and dust over the fruit of the female, and if it is thus treated it retains the fruit and does not shed it." It is to be noted that no attempt is made by these writers to generalize the lesson of the date palm and that there was no recognition in those days of the function of the stamen or of the essentially hermaphroditic (Gk. *hermaphroditos*, combining both sexes) structure of the flowers of many common plants.

In the zoological field two observations of the greatest importance had been made. The dictum *omne vivum ex ovo* (everything living comes from an egg), advanced by William Harvey (1578–1657) in his last and posthumous book on the *Generation of Animals*, was the inevitable outcome of the use of a lens, for this enabled him to recognize the essential similarities of the ova of many different forms.

One of the earliest microscopists, Leeuwenhoek, a draper of Delft in the Netherlands, in his *Secrets of Nature* (1695), gives an account of his observation that the seminal fluid (L. *semen*, seed) of the male teemed with wriggling bodies, the spermatozoa (Gk. *sperma*, seed; *zoon*, animal). Though the actual role of the spermatozoon in fertilization was not to be revealed until another two hundred years had passed, the observations of Harvey and of Leeuwenhoek offered a new definition of male and female, the former being an individual that produced spermatozoa and the latter one that elaborated ova and pointed to the fact that both male and female had their parts to play in reproduction.

An event of the greatest importance was the appearance in 1682 of Nehemiah Grew's *Anatomy of Plants*, for in this book was propounded the doctrine that the stamens of the flowering plant were its male organs and the pistil its female organ and that the pollen performed the same function as did the spermatozoon of the animal.

In 1688 a German botanist, Camerarius, Professor of botany in Tubingen University, established Grew's teaching on a firm basis of

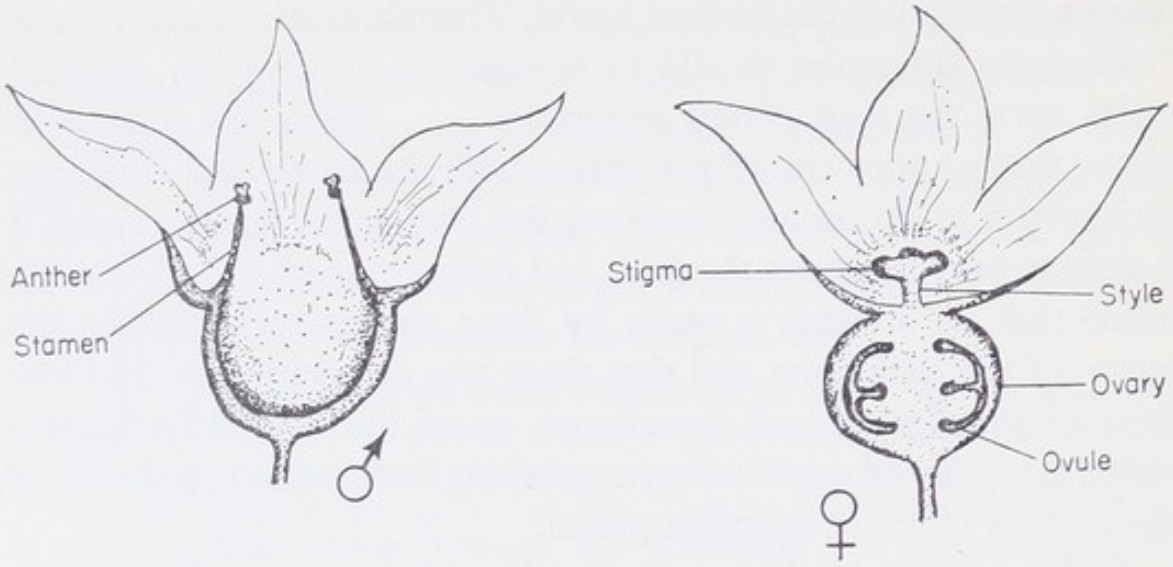


FIG. 1. A plant with separate staminate and pistillate flowers. Such a plant is said to be dioecious (Gk. *dis*, twice; *oikos*, house: two houses; male and female flowers on separate plants). Anther (Gk. *anthos*, flower): the part of the stamen that contains pollen. Ovary (L. *ovarium*, ovary): the enlarged part of the pistil that contains the seed: the seed-vessel of the plant. Stamen (L. warp): the male organ of the plant consisting of stalk and anther. Stigma (Gk. mark): that part of the pistil on to which the pollen falls. Style (Gk. *stylos*, pillar): the slender upper part of the ovary that supports the stigma. The ovary, style and stigma together constitute the pistil (L. *pistillum*, pestle, the seed-bearing organ of the plant).

experimental evidence in his *Letter on the Sex of Plants*. He had observed that a fruit-bearing mulberry tree produced sterile seed vessels. He was puzzled and curious and decided to examine the matter experimentally. For his experimental material he chose the dog's mercury, a common plant which has flowers of different sexes, the male with stamens and no pistil and the female with pistil and no stamens. He planted some seeds and noted that two kinds of plants resulted, some with stamens and no seeds or fruits and others with seeds or fruit but no stamens. When he isolated the fruit-bearing plants from the pollen-bearing, seed vessels still appeared on the former kind but they were sterile (L. *sterilis*, barren, incapable of propagation).

Camerarius went on to investigate the same phenomena in such plants as maize and the castor oil plant in which both stamens and pistil grow on the same plant and found that when the stigma was

removed before the anthers were fully developed, the seed-vessels remained empty and sterile.

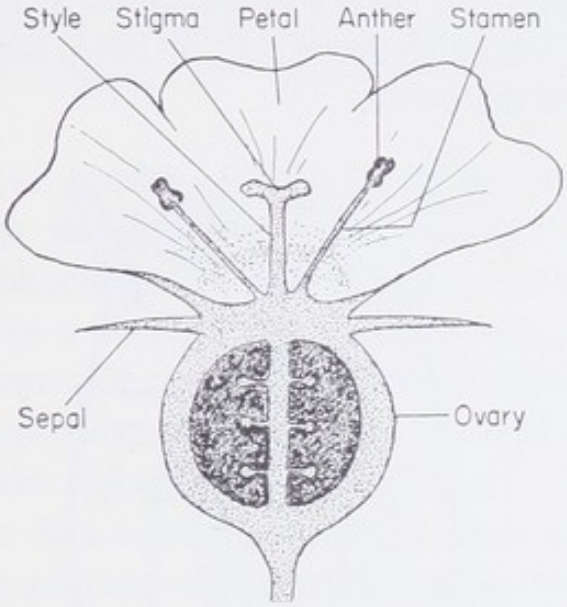


FIG. 2. A plant with a compound ovary or seed-vessel containing many ovules or immature seeds. Above the seed-vessel are the pistil with its stigma (the female organs) and the stamens with the anthers (the male organs). Such a plant is said to be monoecious (Gk. *monos*, single; *oikos*, house: one house; male and female flowers on one and the same plant).

In 1703 Samuel Moreland had contributed a short communication to the Royal Society of London in which he presented the views that "the seeds (of the plant) are at first like unimpregnated ova of animals and that this Farina is a congeries of seminal plants one of which must be conveyed into every ovum before it can become prolific". He acknowledges that Grew was before him in observing that the Farina in some way or other performed the office of the male sperm. In 1716, according to Zirkle, Cotton Mather, in a letter, described the hybridization of different species of Indian corn and of squashes and gourds. But since these were not carefully planned experiments designed to provide an answer to a specific question, no firm conclusions could possibly be drawn from the results obtained.

It was not until the achromatic lens had been developed that Grew's observation could be tested. It was an Italian physicist, Amici,

who, between 1821 and 1830, described the way in which the pollen-grain germinated on the stigma and in which a pollen-tube grew downwards through the tissues of the pistil to reach and enter an ovule. It was he who also described, in 1846, the single egg-cell in the embryo-sac of the ovule.

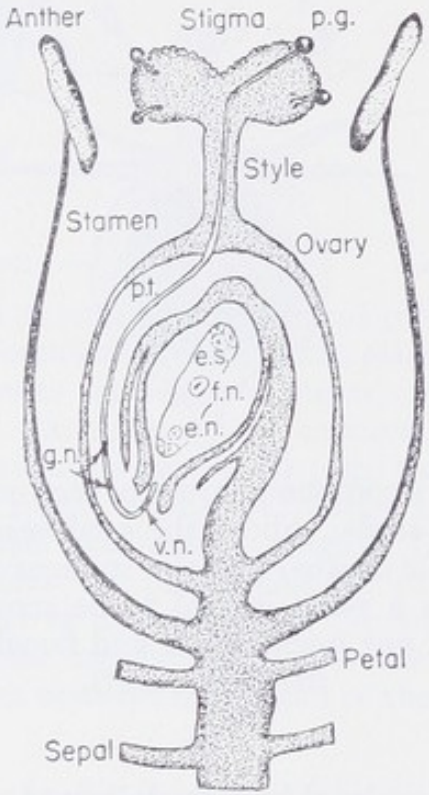


FIG. 3. Fertilization in a flowering plant. Pollen-grains have settled upon the stigma where they germinate. From the pollen-grain the pollen-tube grows down the style to reach the ovule and the embryo-sac. *e.n.*, egg-nucleus. *e.s.*, embryo-sac. *f.n.*, fusion-nucleus. *g.n.*, generative nucleus. *p.g.*, pollen-grain. *p.t.*, pollen-tube. *v.n.*, vegetative nucleus.

But in Camerarius' time and for long afterwards the suggestion that the plant had its origin in the union of one pollen-grain and one ovule was utterly unacceptable for the reason that it was in conflict with the prevailing views concerning the origin of living things and of new forms of living things and concerning the mechanism by means of which offspring came to resemble their parents. The belief in spontaneous generation was widespread, it being held that certain animals arose spontaneously from mud, excrement, refuse and plant juices. The notion of special creation, according to which each

and every species had been suddenly created in a completely finished form by a supernatural power, claimed very many adherents. The time when men would seek for natural causes for biological phenomena was still far in the future and the theory of organic evolution (Charles Darwin's *Origin of Species*, 1859) had yet to be promulgated.

There was but one general picture of the mechanism of organic inheritance. It was thought that in all animals that reproduced through sexual intercourse the resemblance between parent and offspring was due to a nutrient material that was absorbed by the egg or by the embryo (Gk. *embryon*, a young organism in the early stages of its development) from the seminal fluid of the male and from a similar fluid elaborated by the female. In one form or another this notion of a mysterious essence or humour that passed from generation to generation to mould the characterization of the progeny was very widely held right up to Darwin's day.

In his *The Variation of Animals and Plants under Domestication* (1868), Darwin presented the view that every part of the individual produced a germ (L. *germen*, an offshoot, or sprout) of itself. This he called a gemmule. These gemmules passed into the blood-stream to become concentrated in the gametes (Gk. *gametos*, spouse, the marrying cells, the sexual cells, the spermatozoon and the ovum of the animal, which conjugate to give rise to the new individual) that were produced by the individual. Each gemmule reproduced that part of the body that had produced it. Such was the theory of pangenesis (Gk. *pan*, all; *genesis*, descent). Such a theory was attractive in the days when the belief in the inheritance of acquired characters was widespread. Before the nature of reproduction was understood, it was generally thought that the direct effect of an environmental agent upon the body could be passed on to the affected person's offspring. This teaching is usually associated with the name of the French zoologist Lamarck.

When with the development of the microscope and of the achromatic lens the biologist became endowed with great powers of magnification many speculations concerning the nature of objects and events beyond the vision of the naked eye, even when aided by

a lens, were destroyed. For a long time the advancement of biological science had been impeded by the controversy that raged between the "spermatists" and the "ovists". Both these schools of thought taught that the future individual, minute but nevertheless perfect in every detail of its structure and function, lay concealed within the gamete, in the ovum according to the ovists, in the spermatozoon, according to the spermatists, awaiting the opportunity to grow and to be born. It was this disputation that led to the total neglect of Leeuwenhoek's observation of the spermatozoa and of the demonstration around 1790 by the Italian priest Spallanzani (1729–1799) (*Dissertations relative to the Natural History of Animals and Plants*. Modena. English Translation, 1780), that whereas the seminal fluid, filtered through several layers of blotting-paper to retain the actual spermatozoa, did not fertilize frog's eggs, the residue of spermatozoa when suspended in water did so. So completely was the work of these men disregarded that up to the year 1835 or so it was still being debated among leading biologists whether the spermatozoon was a gamete or was a member of a new species of living things. In 1817 the French zoologist Cuvier classified the human spermatozoon, along with creatures that are now known to be the larvae of certain parasitic worms, in a separate genus, *Cercaria*. In 1833 Treviranus compared the spermatozoon to the pollen-grain as Moreland, a hundred years before, had compared the pollen-grain with the sperm, and suggested that they were produced by the tubular walls of the testis just as the pollen-grains were formed from the cells of the anthers. But Owen, the British zoologist, writing in 1835, could still say that it was a matter of doubt whether the spermatozoa should be classified as an independent species.

In 1788, seventy years after Fairchild had produced his Carnation–Sweet William hybrid, there appeared Kölreuter's classical work on plant hybrids and from this time onwards the sudden appearance of a novel form of plant was commonly ascribed to hybridization following chance pollination. Kölreuter was the director of the Grand Duke's garden in Karlsruhe and made a systematic study of the ways in which normal pollination was assured by insect visit,

wind and other agencies. Like Fairchild before him, he observed that both parents contributed to the characterization of the offspring.

In 1809 Thomas Knight, President of the newly formed Horticultural Society of London, presented a communication to the Royal Society of London on the cross-fertilization of apples. His experiments had been undertaken for the purpose of discovering "the best means of forming new varieties that may be found better calculated for the climate of Great Britain than those at present cultivated". Knight did much to improve fruit trees, grapes, currants and strawberries, but these achievements were eclipsed by his experimental work with the garden pea.* The existing knowledge concerning pollination permitted the nurseryman to produce new forms of flowers, vegetables and fruit trees, but when these had been created they had to be propagated by cuttings (roses), grafts (roses, apples, cherries), or by runners (strawberries); they could not be allowed to perpetuate themselves by seed for the reason that the nurseryman did not know how the hybrid could be "fixed", made to "breed true", save by the above-mentioned methods of natural and artificial vegetative propagation (vegetative, L. *vegitare*, to enliven, reproduction by an asexual method). It was recognized that true-breeding forms did turn up occasionally among the later generations of hybrid plants which had perpetuated themselves by seed, but no one knew how to produce such a type deliberately.

In Knight's day there were no fewer than seventeen different true-breeding varieties of the edible pea, *Pisum sativum*, each flower of which has both male and female organs and which is habitually self-fertilized. He chose this plant as his experimental material in his hybridization studies because it had so many true-breeding varieties differing one from the other quite sharply in respect of form, size and colour and also because "the structure of its blossoms, by preventing the ingress of insects and the like, has rendered its varieties remarkably permanent". His experimental work was

* Knight, T. A., An account of some experiments on the fecundation of vegetables, *Phil. Trans. Roy. Soc. London*, **89**, 195–204 (1799).

Knight, T. A., Some remarks on the supposed influence of the pollen in cross-breeding, *Trans. Hort. Soc. London*, **5**, 377–80 (1824).

continued for thirty-six years, from 1787 to 1823. His general method was to pluck off the stamens of all the flowers of a plant and then to dust on to the stigma pollen from the flowers of another plant. He found that when two distinct pure-breeding varieties were crossed in this way, e.g. a white-seeded and a grey-seeded, the seeds of the hybrids so produced were all alike in respect of colour—grey, being the same as one of the parents, no matter which way the cross was made. When he sowed these seeds and raised the plants that arose from them and pollinated the flowers of one plant with the pollen from another plant of the same generation, he found that while most of the pods developed by these plants contained both white and grey seeds, some of them contained only white-coloured seeds and others only grey-coloured seeds. Knight was the first to observe what he called "the splitting of hybrids", the reappearance in the second hybrid generation of the two contrasted characters displayed by the two parental forms.

But Knight's interest in these experiments was focused upon the question as to whether or not superfoetation occurred in plants as well as in animals. In those days, before the essential features of fertilization had become revealed, it was commonly thought that the seminal fluid of the male animal was a general fertilizing material and that the degree to which a child resembled its father was determined by the amount of this fluid that had been involved in its conception. If, for example, a bitch was served in rapid succession by two dogs belonging to two different breeds so that their seminal fluids became mixed within the reproductive passages of the bitch, any one of the puppies, or all of them, could have two fathers and could display a mixture of the characterizations of both of them. Knight deliberately used mixed pollen from two varieties of pea and he regarded the different combinations of the parental characters displayed by the offspring as evidence that such superfoetation had taken place. This term has come to have a different meaning. If a bitch is served in rapid succession by two dogs, the resulting litter can include puppies sired by each of them, but any one puppy has had only one father.

For the sake of clarity it is desirable at this point to introduce a

number of terms that did not come into use until much later. In this experiment which involved white- and grey-coloured seeds, Knight started with a white-seeded pea and a grey-seeded pea and these became the parents of a hybrid. It is both convenient and customary to refer to this parental generation as the First Parental Generation or the P_1. The hybrid individuals produced by these constitute the First Filial Generation or the F_1. The individuals produced by these F_1 individuals constitute the Second Filial Generation or the F_2. This experiment can be described so:

white-seeded	×	grey-seeded	P_1
grey-seeded			F_1
white-seeded	and	grey-seeded	F_2

Of the two characters white seed-colour and grey seed-colour only the latter appeared in the F_1. In the F_2 the white seed-colour reappeared. Knight also back-crossed the F_1 to the P_1 white seed-colour parental type and noted that among the progeny there were both white-seeded and grey-seeded types. Knight was the first to record the phenomena of dominance and recessiveness (it was Mendel who first used these terms in 1865). By dominance (L. *dominans*, ruling) is meant the power of one member of a pair of contrasted characters, such as grey colour and white colour of the seed, to mask, apparently completely, the alternative recessive (L. *recessus*, withdrawn) character in the hybrid.

In 1824 John Goss of Hatherleigh, Devon, reported to the Horticultural Society of London on the sole expression of yellow seed-colour in the F_1 after hybridization of a blue–green seeded pea with a yellow-seeded, followed by the appearance of both yellow and blue–green seeds in the F_2.* Goss noted that of the F_2 greens all were true-breeding, that of the F_2 yellows some were true-breeding while others yielded both yellows and greens. Blue–green and yellow seed-colours constituted another pair of contrasted characters and of them the yellow seed-colour was the dominant member and blue–green the recessive. Alexander Seton (1824)

* Goss, J., On the variation in the colour of peas, occasioned by cross-impregnation, *Trans. Hort. Soc. London*, **5**, 234–5 (1824).

obtained similar results* and these were confirmed by Knight (1824). Sagaret (1826), having listed their contrasted characters,† crossed a canteloup and a melon to find that the characterization of the hybrid was a mixture of the characters of the two parental forms.

Another English hybridizer of this period who claimed his place in the history of horticulture was the Hon. and Very Rev. William Herbert, Dean of Manchester, to whom Darwin made reference. He demonstrated that he could "create" new forms by hybridization within a genus. He was not interested, however, in the mechanisms that were involved in their production.‡

So great was the interest of the horticulturalist in this problem of producing a true-breeding hybrid that could be grown from seed that in 1819 and 1822 the Prussian Academy offered a prize for an answer to the question, "Does hybrid fertilization occur in the plant kingdom?", and in 1830 the Dutch Academy of Haarlem posed the problem: "What does experience teach concerning the production of new species and varieties through the artificial fertilization of flowers of the one with the pollen of the other, and what economic and ornamental plants can be produced and multiplied in this way?" The Dutch prize was offered again in 1836 and Gärtner§ received the reward in the following year, his essay being published in 1848. Gärtner used the garden pea and maize and, like Knight and Goss before him, noted the uniformity of the F_1, the diversity of the F_2 and subsequent hybrid generations and the reappearance of the recessive as well as of the dominant character of the P_1 generation in the F_2 and subsequent generations.

In 1861 the Paris Academy offered a prize for an account of the

* Seton, A., On the variations in the colours of peas from cross-impregnation, *Trans. Hort. Soc. London*, **5**, 236 (1824).

† Sagaret, A., Considérations sur la production des hybrides, *Ann. Sci. Nat.* **8**, 294–313 (1826).

‡ *Herbertia* (The journal of the American Amaryllis Society), 1937, contains a biography of Herbert and a reprint of his paper on crosses and intermixtures in vegetables that had appeared in his *Amaryllidaceae*, 1837. Herbert, W., Hybridization among vegetables, *J. Roy. Hort. Soc.*, November 3, 1847.

§ Gärtner, C. T. von, *Bastarderzeugung*. Stuttgart (1848).

study of plant hybrids: "Étudier les Hybrides végétaux au point de vue de leur fécondité et de la perpetuité de leurs caractères" (Do hybrids which reproduce themselves by their own fecundation sometimes preserve invariable characters for several generations, and are they able to become the types of constant races?)

Among the competitors was the French naturalist Naudin,* whose essay was published in 1864. His experiments were essentially the same as those of Knight, Goss and Gärtner and he obtained precisely similar results. This essay of Naudin's was important, however, for the reason that in it he advanced certain theoretical conclusions of great interest even though they did not rest upon any experimental evidence. He stated that "that which is produced (in the hybrid) is never more than an amalgamation of the forms already existing in the parental types. The hybrid is a composition of borrowed pieces: a sort of living mosaic of which each piece, discernible or not, is ascribable to one or other of the producing species" and "All these facts are naturally explained by the disjunction of the specific essences in the pollen and the ovules of the hybrid. The disjunction takes place in the anther and in the contents of the ovary. Some of the grains of pollen belong totally to the species of the father and others to the species of the mother." Naudin saw the individual as being built up of a large number of component characters and the hybrid as one in which some of the characters had been derived from the father and others from the mother. These characters were based upon, caused by, the action of "essences". In the hybrid, essences derived from father and from mother existed side by side but, for the most part, remained uncontaminated by their association (but contamination could occur and so give rise to blending inheritance). When the pollen or the ovules were formed by the hybrid these essences, paternal and maternal respectively, became separated, disjoined, and the hybrid offspring received some essences from the father and others from the mother and was thus a mosaic. Darwin in a letter to his friend Hooker, Director of Kew Gardens, about Naudin's conclusion, remarks: "I cannot think it will hold.

* Naudin, C., Recherches sur l'hybridité, *Nouvelles Archives du Muséum*, **1** (1864).

The tendency of hybrids to revert to either parent is part of a wider law. . . . Why this should be so God knows. . . ."

In 1865 there appeared Wichura's important work on *Die Bastardbefruchtung im Pflanzenreich* (Hybrid production in the Vegetable Kingdom), in which an account of the author's experiments with the Willow (*Salix*) is given. (To these Mendel referred in his communication to the Brünn Society.) Wichura very nearly reached the conclusions that formed the basis of Mendel's law of segregation.

In 1872 the Horticultural Society published an account of the experimental hybridization work that had been carried out many years before by Laxton,* a horticulturalist of Stamford in Lincolnshire. He had worked with the garden pea and had recorded the dominance of smooth seeds, red blossoms and pigmented seed-coat. He had also noted the possibility of fixing particular combinations of these characters and had given a rough estimate of the numerical proportions of the different types among the generations that he had raised. He had counted the numbers of the dominant and recessive character displaying individuals in the second hybrid and subsequent generations.

In retrospect it seems incredible that Knight, Goss, Gärtner, Naudin, Wichura and Laxton should have failed to recognize the significance of the results they had obtained until it is remembered that in the advancement of scientific knowledge it is customary for a long succession of men to be involved, each man making his own contribution, adding much or little to the sum total, until the last man in the line, standing on the shoulders of his predecessors, suddenly sees, as in a vision, the meaning of the facts that have been established. He is the first of the line whose thoughts are not too greatly entangled in the preferences of the prevailing orthodoxy. It was left to Gregor Mendel to reveal the real significance of the results obtained in this experimentation.

* Laxton, T., Notes on some changes and variations in the offspring of cross-fertilized peas, *J. Roy. Hort. Soc. London*, No. 9, **111** (1872–3).

CHAPTER 2

MENDEL: THE MAN

THE work of certain men of science and their ideas concerning the meaning of the results they obtained led to the framing of generalizations, of scientific "laws", that have revolutionized human thought, changing completely man's concepts concerning the nature of the universe and of himself.

Three outstanding examples of this are: the explanation of the movement of the celestial bodies by Kepler, Copernicus and Newton; Galileo's experiments that inaugurated the age of inductive science;* and Darwin's establishment of the theory of evolution.

To this company of the truly great Mendel belongs. His work, and the theory constructed to explain the results he obtained, changed the basic aspects of practically every science that has been developed in response to the display of man's curiosity and in order that his expanding needs might be satisfied. Discovery of this magnitude seems to be the outcome of the interplay of exceptional intellectual ability on the one hand, and the conditions and circumstances of the time and place on the other, these being such as to encourage the exercise of this ability in particular ways.

Of Mendel as a boy, youth, and young adult, and of the times in which he lived, much can be learnt from the application he submitted for permission to sit the examination for the State Certificate that would qualify him as a high-school teacher of natural science.†

* Induction. The method of reasoning from the particular to the general, the deriving of a general principle or conclusion from a consideration of a number of particular facts.

† Natural science was the term used to define the study and description of nature generally. As it fragmented into botany, zoology, geology, etc., as these special fields enlarged, the term came to be restricted to botany and zoology and became transmuted into natural history.

At this time he was 28 years of age, was a priest (ordained in 1847) and held the position of substitute teacher in the high school in Znaim, a small town near Brünn (now Brno in Czechoslovakia).

> Praiseworthy Imperial and Royal Examination Commission, In accordance with the regulations of the Ministry of Public Worship and Education, the respectfully undersigned submits a brief outline of his life-history.
>
> He was born in the year 1822, in Heinzendorf in Austrian Silesia, where his father was the owner of a small farm. After he had received elementary instruction in the local village school and later at the upper elementary school in Leipnik, he was admitted in the year 1834 to the Imperial Royal Gymnasium (*a high school*) in Troppau. Four years later, as a consequence of a series of disasters, his parents found themselves unable to meet the expenses incurred by the continuation of his studies and it therefore happened that the respectfully undersigned, then only sixteen years old, found himself in the sad position of having to fend for himself. He therefore attended the course of instruction for those intending to be school or private teachers offered by the District Teachers Seminary in Troppau. As he was highly commended in the report of the examination, he succeeded by private tutoring in earning a scanty living during the period of his further study.
>
> When he graduated from the Gymnasium in 1840 he sought the means whereby he might continue his education. He made repeated attempts in Olmütz to earn a living as a private tutor, but all his efforts were fruitless for the reason that he had no influential friends to recommend him. He became so distressed by continued disappointment and so anxious about his future that he fell ill, and was obliged to spend a year in his parents' home convalescing.
>
> At the end of this time the respectfully undersigned fortunately found it possible to earn enough by private teaching to satisfy his most pressing needs. He was therefore able to continue his studies in Olmütz. Overcoming exceedingly great difficulties he managed to complete the required two years of philosophical studies. The respectfully undersigned had come to realize that it was quite impossible for him to endure such exertions any further. He felt himself compelled to seek some position that would free him from the bitter struggle for existence. His circumstances determined his choice of a vocation. He requested and received in 1843 admission to the Augustinian Monastery of St. Thomas in Alt-brünn.
>
> As a consequence of this, his material circumstances underwent a complete change. Now that he enjoyed a modicum of physical comfort, a condition beneficial to any kind of study, the respectfully undersigned regained his courage and his strength, and was therefore able to study the classical subjects prescribed for the year of probation with diligence

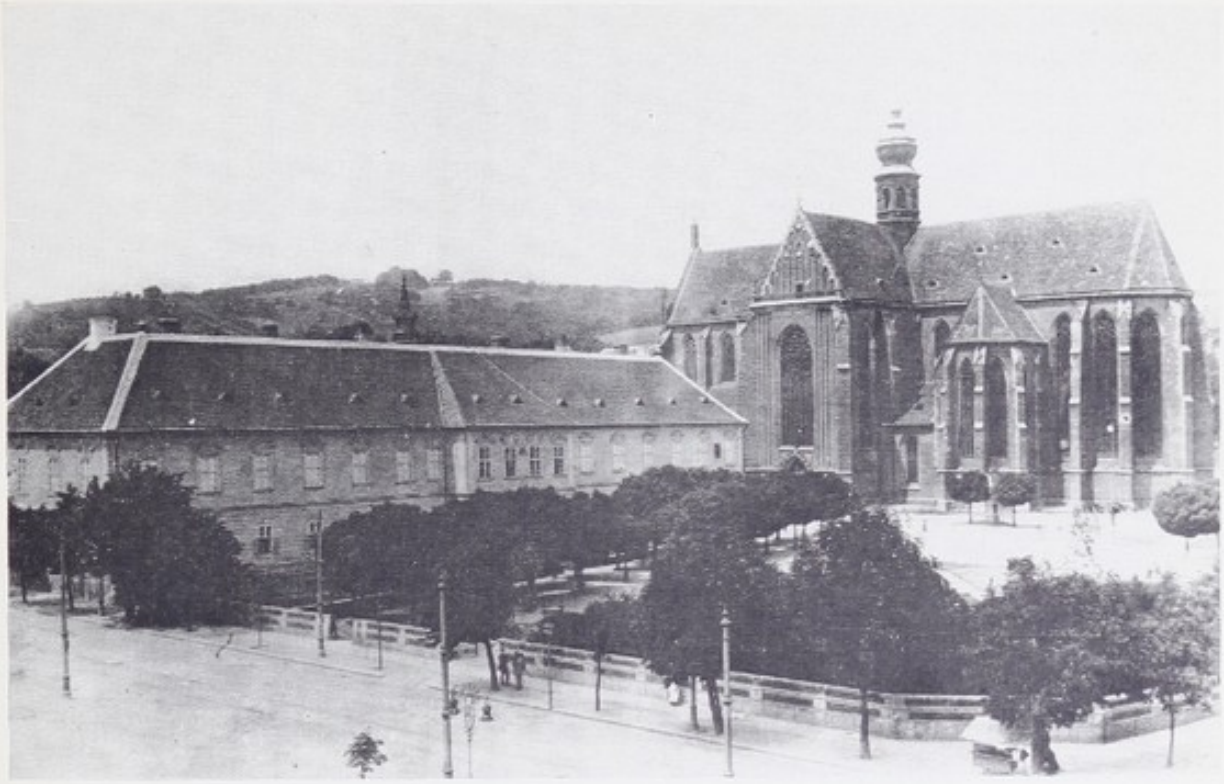


PLATE I

The Augustinian House of St. Thomas (the Königinkloster), Brno. On the right the church; on the left one wing of the cloisters: the other wing runs at right angles to this from the right-hand end. In the angle thus formed is situated the garden plot which Mendel used.

and enjoyment. In his spare hours he busied himself with the small botanical-mineralogical collection that was placed at his disposal in the monastery. His special interest in natural science deepened as the opportunities to become better acquainted with it expanded. Despite the lack of any formal instruction, and despite the fact that self-instruction is perhaps more difficult in this branch of science than in any other, he became engrossed in the study of Nature and made every effort to make good the defects of this method of learning. In the year 1846 he attended courses of instruction in agriculture, pomiculture and viniculture at the Philosophical Academy in Brünn.

After finishing his theological studies in 1848, the respectfully undersigned received permission from his prelate* to prepare himself for the examination leading to the degree of doctor of philosophy. In the following year he was about to present himself for this examination when he was asked to accept the position of substitute teacher in the Imperial Royal Gymnasium in Znaim, and he gladly accepted this invitation. Right from the start he made every effort to present his assigned subjects to his pupils in an easily comprehensible manner. He hopes that his endeavours were not unsuccessful. Certainly during the four years he had spent in earning a living as a private tutor he had learnt a great deal about the needs of pupils and of their variability in respect of capacity to learn.

The respectfully undersigned believes that this is a true summary of his life-history. He learnt during his early years filled with sorrow, that life is a serious affair and that a man must work. Even when he came to enjoy the comforts of a secure economic position the wish to earn his living remained alive within him. The respectfully undersigned would consider himself most fortunate if he could satisfy the praiseworthy Board of Examiners and gain the certificate he now seeks. If he is successful, he will spare no effort to carry out his duties to the satisfaction of all concerned.

Znaim on the 17th April, 1850.

(signed) Gregor Mendel
Subst.Professor. Imp.Roy.Gym.Znaim.

Mendel's four grandparents were all of the local Heinzendorf peasant stock. The family belonged to a small colony of Swabian origin and was not Jewish as the name might seem to suggest; in former times it had been Mandele or Mendele. His father, a peasant farmer who had soldiered during the Napoleonic Wars, held his land by a form of "socage", being required to work three days a week for the lord of the manor of Odrau, a small town in

* A dignitary of the church; an ecclesiastic of the higher order having authority over the lower clergy.

what was then Austrian Silesia. He seems to have been specially interested in fruit growing. His mother was the daughter of a gardener. Johann was the second of their three children and was born on (20 or) 22 July 1822.* When he was a small boy there was no school in Heinzendorf, but his uncle, Anton Schwirtlich, started private classes for those children who could not walk as far as the neighbouring village where there was a school. Later a government school was established in Heinzendorf itself and in it Mendel's formal education continued. The lady of the manor, Countess Waldberg, and the village priest, Johann Schreiber, were both keenly interested in natural history and both had an influence in shaping Mendel's likes.

Thomas Makitta, Mendel's schoolmaster in Heinzendorf (about half-way between Brno and Ostrava), noted the promise shown by his pupil and urged his parents to send him to the church school in Leipnik (about 20 km. away from Heinzendorf) for a year (1833) and thereafter to the secondary school in Troppau (near the Polish border, west of Ostrava and some 70 km. north-east of Leipnik). Mendel spent the years 1834–40 in Troppau and finished with such an excellent scholastic record that it was decided that he should go on to the University of Olmütz (about 25 km. to the west of Leipnik). During the years 1840–3 he attended the courses of instruction in the Philosophical Institute in Olmütz in preparation for entering the university proper.

During the time he spent in Troppau and Olmütz his progress was impeded by bouts of illness and by financial difficulties arising from the disablement of his father. As the result of a serious accident while working for his landlord, his father was obliged to hand over the farm to one of his sons-in-law and thereafter was unable to provide his son with an adequate allowance. Mendel himself, in order that he might earn while learning, took out a course of instruction offered by the District Teachers Seminary in Troppau. In order to help him, his younger sister, Teresie, re-

* The register gives the 20th; Mendel himself always gave the 22nd, for reasons unknown. Heinzendorf is now Hynčice; Leipnik, Lipnik n Benvou; Odrau, Odry; Olmutz, Olomouc; Troppau, Opava; and Znairn, Znojmo.

linquished part of her dowry for his benefit. Mendel repaid this debt in later years by providing for the education of his sister's three sons, two of whom graduated in medicine in Vienna.

On several occasions during this time Mendel suffered from attacks of acute and severe depression; during his first year in Olmütz he became so ill that he was obliged to return to his parents' home for a whole year which meant that, recovering, he had to begin all over again in the Philosophical Institute.

It seemed that these embarrassments must surely bring Mendel's formal education to an abrupt end. It so happened, however, that one of his teachers, Friedrich Franz, came to his aid by writing to the head of the monastery in Alt-Brünn recommending that Mendel should be admitted to the Augustinian Order. His parents agreeing, he was admitted as a novice on 9 October 1843, taking the name Gregorius (Gregor) "in religion". According to his biographer, Iltis, Mendel decided to become a priest because by doing so he could secure the opportunities to pursue his interests in natural science. But van Lierde disagrees, maintaining that he became a priest because the calling greatly appealed to him.

By the regulations of the monastery he was required to take a four-year course at the Brünn Theological College. During the third of these years he was ordained, on 6 August 1847. At this time the Augustinian monastery of St. Thomas in Brünn occupied an important place in the cultural life of Moravia. Its members, a dozen altogether, included scholars of high repute, philosophers, natural scientists, composers and men of letters. No atmosphere could have been more stimulating to a young man of 21 and of the calibre of Mendel.

Following his ordination Mendel served as a parish priest for a time at the Alt-Brünn rectory where his duties included attendance at the St. Ann Hospital. But contact with sickness and suffering affected him too profoundly and Abbot Napp found it necessary to transfer him to the educational side of the monastery's work. He became a (supply) teacher of Latin, Greek, German and Mathematics in the secondary school in Znaim (Znojmo, some 68 km. South-West of Brno, close to the Austrian border on the main

road to Vienna from Praha). There he proved to be exceptionally good at his job.

The monastery of St. Thomas in Brünn nestles at the foot of an isolated hill, the Spielberg, which is crowned with an old fortress. The original monastery buildings date back to 1322, when they housed a nunnery founded by the widow of Wenceslaus, King of Bohemia. For this reason it came to be known as the Königinkloster, "the Queen's Cloister". Little remains of the original structure, the present buildings, church and cloister, dating from 1762. The Order of St. Thomas took the buildings over in 1793. Within the walls of the monastery was a large garden, and it was in a small corner of this that the hybridization experiments that made the name of Mendel famous were carried on. From the time of his novitiate he began to introduce plants into the garden and to watch and record their behaviour under treatment. This monastery was involved in the general dissolution of the religious houses of Czechoslovakia in 1948.

Before Mendel could become a fully accredited teacher he had to gain a University of Vienna certificate by examination. He presented himself for this in 1850. It consisted of written papers and orals in physics, geology and natural history. His performance was unsatisfactory and he failed. It happened, however, that one of his examiners, Professor Kner, submitted the following report concerning him:

> "The result of the oral examination in natural history was more satisfactory in that the candidate showed a greater grasp of the subject and gave evidence of a greater degree of diligence than the written papers had suggested. It was evident that the candidate was devoid of neither talent nor industriousness. It would seem that he had lacked the opportunity for acquiring a comprehensive knowledge of the subject and had not had access to the necessary means of study, so that as yet he cannot be regarded as competent to become a teacher. Nevertheless, it can be expected that if he is given the opportunity for more comprehensive study, together with access to better sources of information, he will quickly be able to fit himself, at least for work as a teacher in the Lower Schools."

It was this assessment of Mendel's worth that persuaded Abbot Napp to send him, at the expense of the monastery, to the University

of Vienna. There he spent the years 1851–3 studying mathematics and natural science. Returning to Brünn he was appointed by the Lord Lieutenant of Moravia to the post of substitute teacher of physics and natural science in the higher secondary school in Brünn in 1854. He continued to hold this post until 1868 when he was elected abbot (or more precisely prälat) in succession to Abbot Napp who had died during the previous year.

In 1856 Mendel presented himself once more for the State Certificate but yet another bout of his peculiar illness, acute depression, overwhelmed him and caused him to retire from the examination. He then relinquished all hope of ever gaining this certificate and began to devote himself more and more to his experimental hybridization work, helped by his colleagues Fathers Winkelmeyer and Lindenthal and by the monastery gardener Josef Maresch.

Mendel interested himself in meteorology and was in charge of one of the meteorological stations in Moravia, maintaining records of sunspots and tornadoes. (Incidentally, this activity can be accepted as evidence of his competence in mathematics.) He had no fewer than fifty hives of bees under observation at one time and had collected queens of all the obtainable "races", European, Egyptian and American. He was an active member of the horticultural section of the Moravian and Silesian Agricultural Society and regularly exhibited at its shows as well as offering prizes for the finest products of hybridization of fruit trees, flowers and vegetables. In 1883, a few months before his death, he was awarded the medal of the Austrian Pomological Society for his exhibit of new sorts of apples and pears. In 1870 he became an active member of the Moravian Bee-keeping Society. These close contacts with "practical" men, horticulturalists and the like, undoubtedly enlarged his knowledge of the animals and plants he used in his own experiments, enabling him to draw upon their great and varied experience. He was not a great traveller, but did visit Italy and France and in 1862 came to London to see the Great Exhibition. He and Darwin never met and the latter knew nothing of the former's work.

It seems that Mendel had hoped that his elevation to prälat would enable him to find better opportunities for the exercise of his

scientific interests, but this was not to be. In 1872 the Government passed a law imposing special taxes upon the property of religious houses. Mendel firmly resisted this enactment and became involved in protracted and unprofitable litigation. From being a cheerful, friendly man he became increasingly suspicious and misanthropic. His health progressively degenerated, he became far too obese and began to suffer from dropsy due to heart and kidney failure (Bright's disease). His last ten years of life were filled with disappointment and bitterness. He died on 6 January 1884.

His biographer, Iltis, records that a few days before he died Mendel drafted his own obituary notice. This is indeed a strange document which reveals Mendel's own estimate of the relative worth of all that he had done.

> "The Augustinian Monastery of St. Thomas at Alt-Brünn in Moravia respectfully and with profound regret informs the public of the death of the Right Reverend Abbot Gregor Joh. Mendel, Mitred Prelate, Companion of the Royal and Imperial Order Of Francis Joseph, emeritus chairman of the Moravian Mortgage Bank, member and one of the founders of the Austrian Meteorological Society, and various other learned and useful organizations, etc. etc. Born in Heinzendorf in Eastern Silesia on July 22nd 1822. After a long, severe and painful illness, having received the Holy Sacrament and having submitted himself to the will of the Most High, he departed this life at half past one in the morning of January 6.
>
> The funeral ceremony will take place at the Monastery church on January 9th at nine in the morning, and thereafter the body of the deceased will be conveyed to the Brünn Central Cemetery for the final rest. R.I.P."
>
> Brünn. Monastery of St. Thomas.
> January 6th, 1884

To every scientist who has grown up in the twentieth century it must seem exceedingly strange that Mendel should have thought that of all his achievements the only ones worthy of placing on record were that he was an abbot with the rank of bishop, that he had received a decoration from the Emperor, that he was regarded as a sound business man and that he was a member of a number of learned and other societies. The omission of any reference to the scientific work that had absorbed his interests between 1856 and 1871 and that was to claim for him a high place among the Immortals

of Science is certainly a reflection of the total neglect of this work by the professional biologists of his day. The reasons for this neglect will be made clear as the story unfolds.

The house in which Mendel was born still stands, though much altered and enlarged. It bears a plaque commemorating this event. Nearby is the village fire-station. It too bears a plaque, unveiled in 1902, which tells of Mendel's munificence. Heinzendorf had been ravaged by fire in 1868. Mendel, now being in a position to do so, immediately came to the help of his relatives and friends and, in addition, donated a sum of 3,000 guilders for the construction and equipment of a small fire-station. On the occasion of the unveiling ceremony Mendel's nephew, Alois Schindler, one of his sister Teresie's sons who had graduated in medicine, delivered the oration telling of Mendel and of his work.

In 1906 an international committee of scientists was formed for the purpose of collecting funds for the provision of a memorial to the founder of the science of genetics, and in 1910 the white marble statue of Mendel was erected in the Klosterplatz in Brünn in spite of the strenuous opposition of those citizens who maintained that it would be an impediment during the time of the local fair. Later, this statute was moved and now stands in the monastery garden which has become a public park. In 1922, on the occasion of the centenary celebration of Mendel's birth, a sandstone monument was erected by the monastery in that part of the garden which Mendel used. Its inscription states that "Mendel has made experiments for his law here". In 1965 when the Mendel Memorial Symposium, organized by the Czechoslovakian Academy of Sciences, was staged to celebrate the centenary of Mendel's communication of the outcome of his experiments with the edible pea to the Brünn Society for the Study of Natural Science, a Mendel Memorial Hall, filled with Mendeliana, was officially opened. The room used to be the refectory of the monastery and its windows look out directly upon the small plot of ground in which Mendel sowed his seeds.

The main points of interest and significance that emerge from this study of Mendel the Man would seem to be the following. He did well at school, where his quality and promise were recognized. His

family was prepared to do everything possible to give him as good an education as was available. He was fortunate in his contacts during his formative years, the village priest in Heinzendorf, the lady of the manor of Odrau, the village schoolmaster in Heinzendorf, the teachers he encountered, the head of the monastery of St. Thomas in Alt-Brünn, an orientalist of repute, all these played their parts in directly or indirectly setting his feet on the path that led to the monastery garden. Only there could he have found the opportunity and the encouragement to pursue his scientific work. It is interesting to speculate concerning what might have happened had Professor Kner, his examiner, not taken the trouble to submit his sympathetic report concerning Mendel when he had failed in his examination.

Though the significance of Mendel's experimental work was not recognized by the scientific world during his own lifetime it seems that Mendel himself had formed a true idea of its quality; it is reported that he had remarked that sooner or later its importance would be appreciated. (Die Zeit wird schon kommen, wo man die Gültigkeit der von mir gefundenen Gesetzen anerkennen wird.) From this reasonable prediction that his time would surely come he must have derived some satisfaction.

In the account of Mendel's hybridization experiments that follows it will be found that in so far as material, methods and results are concerned the difference between Mendel, on the one hand, and Knight, Goss, Seton, Laxton, Gärtner and Naudin, on the other, is very slight indeed. Mendel stands out from the rest because he alone saw that the numerical results which he and the others had obtained were amenable to a very simple and satisfying explanation if they were examined in the light of the fact that in the creation of a new individual of a new generation one pollen grain and one ovule, and nothing else, were involved. Mendel lived in a country where microscopes were widely used and where the cell theory was widely accepted. Mendel used a microscope and he knew that heredity must depend on two gametes. He differed from the rest of the hybridizers in that he was a competent mathematician.

CHAPTER 3

MENDELISM: THE LAW OF SEGREGATION

IN BRÜNN in Mendel's time there was a flourishing scientific society. Among its members, of whom Mendel was one, were several scientists of repute belonging to the different educational institutions in the city. Mendel served for a period as president of this society. At its meetings on 8 February and 8 March 1865 he presented a communication on his experiments in plant hybridization (*Versuche über Pflanzen-Hybriden*). This was published in the Proceedings of the Brünn Society for the Study of Natural Science (*Verhandlungen des naturforschenden Vereines in Brünn* 4, Abhandlungen 1–47) in 1866. From this paper, remarkable for its clarity and incisiveness, the following passages are quoted in order to show what exactly Mendel did and how he interpreted the results he obtained.

Introductory Remarks

Experience of artificial fertilization, such as is effected with ornamental plants, in order to obtain new variations in colour, has led to the experiments which will here be discussed. The striking regularity with which the same hybrid forms always reappeared whenever fertilization took place between the same species induced further experiments to be undertaken, the object of which was to follow up the developments of the hybrids in their progeny.

To this object numerous careful observers, such as Kölreuter, Gärtner, Herbert, Lecoq, Wichura and others, have devoted a part of their lives with inexhaustible perseverance. Gärtner, especially in his work *Die Bastarderzeugung im Pflanzenreiche* (The Production of Hybrids in the Vegetable Kingdom), has recorded very valuable observations; and quite recently Wichura published the results of some profound investigations into the hybrids of the Willow (1865). That, so far, no generally applicable law governing the formation and development of hybrids has been successfully formulated can hardly be wondered at by anyone who is acquainted with the extent of the

task, and can appreciate the difficulties with which experiments of this kind have to contend. A final decision can only be arrived at when we shall have before us the results of detailed experiments made on plants belonging to most diverse orders.

Those who survey the work done in this department will arrive at the conclusion that among all the numerous experiments made, not one has been carried out to such an extent and in such a way as to make it possible to determine the number of different forms under which the offspring of hybrids appear, or to arrange these forms with certainty according to their separate generations, or to ascertain definitely their statistical relations.

It requires indeed some courage to undertake a labour of such far-reaching extent. This appears, however, to be the only right way by which we can finally reach the solution of a question the importance of which cannot be overestimated in connection with the history of the evolution of organic forms.

The paper now presented records the results of such a detailed experiment. This experiment was practically confined to a small plant group, and is now, after eight years' pursuit, concluded in all essentials.

Comments

It is clear that Mendel was well acquainted with the scientific literature relating to hybridization. In work of this kind nothing is of greater importance than the design of the experiment. Mendel's plan differed from those of previous hybridizers in three respects; it was designed so that it would be possible (1) to record the number of the different types of the progeny; (2) to arrange these types with certainty according to their separate generations; and (3) especially to ascertain their statistical relations. Mendel set out to obtain numbers, and intended to study these in an attempt to discover what they and their relationships signified.

Selection of the Experimental Plants

The value and utility of any experiment are determined by the suitability of the material for the purpose for which it is used.

The selection of the plant group which shall serve for experiments of this kind must be made with all possible care if it is desired to avoid from the outset every risk of questionable results.

The experimental plants must necessarily (1) possess constant differentiating characters; and (2) the hybrids of such plants must, during the flowering period, be protected from the influence of all foreign pollen, or be easily capable of such protection.

The hybrids and their offspring should suffer no marked disturbance in their fertility in the successive generations.

At the very onset special attention was devoted to the *Leguminosae*

(e.g. peas and beans) on account of their peculiar floral structure. Experiments which were made with several members of this family led to the result that the genus *Pisum* was found to possess the necessary qualifications.

Some thoroughly distinct forms of this genus possess characters which are constant and easily and certainly recognizable, and when their hybrids are mutually crossed they yield perfectly fertile progeny. Furthermore, a disturbance through foreign pollen cannot easily occur, since the fertilizing organs are closely packed inside the keel and the anther bursts within the bud, so that the stigma becomes covered with pollen even before the flower opens. This circumstance is of especial importance.

As additional advantages worth mentioning, there may be cited the easy culture of these plants in the open ground and in pots, and also their relatively short period of growth. Artificial fertilization is certainly a somewhat elaborate process, but nearly always succeeds.

For this purpose the bud is opened before it is perfectly developed, the keel is removed, and each stamen carefully extracted by means of forceps, after which the stigma can at once be dusted over with the foreign pollen.

In all, thirty-four more or less distinct varieties of Peas were obtained from several seedsmen and subjected to a two years' trial. Of these all save one sample yielded perfectly constant and similar offspring. Twenty-two of these varieties were selected for the experiment. (A small paper in the *Verhandlungen des zoologisch-botanischen Vereins in Wien*, 1854, by Mendel entitled Ueber Bruchus pisi (On the pea weevil) shows that he had begun his breeding experiments with the pea in that year.)

Comment

Mendel's competence as a scientist and experimenter is clearly revealed in the astuteness with which he chose his experimental material. It is to be noted that he spent two years in getting to know this before using it in his experiments.

Division and Arrangement of the Experiments

Numerous experiments have demonstrated that if two plants which differ constantly in one or several characters be crossed, the common characters are transmitted unchanged to the hybrids and their progeny; but each pair of differentiating characters, on the other hand, unite in the hybrid to form a new character, which in the progeny of the hybrid is usually variable. The object of the experiment was to observe these variations in the case of each pair of differentiating characters and to deduce the law according to which they appear in the successive generations. The experiment resolves itself, therefore, into just as many separate experiments as there are constantly differentiating characters presented in the experimental plants.

The various forms of Peas selected for crossing showed differences in the length and colour of the stem; in the size and form of the leaves; the position, colour and size of the flowers; the length of the flower stalk; the colour, form and size of the pods; the form and size of the seeds; and the colour of the seed-coats and of the cotyledons. Some of these characters do not permit of a sharp and certain separation, since the difference is of a "more or less" nature which is often difficult to define. Such characters could not be used for the separate experiments; these could be applied only to characters which stand out clearly and definitely in the plants. Lastly the result must show whether they, in their entirety, observe a regular behaviour in their hybrid unions, and whether from these facts any conclusions can be come to regarding those characters which possess a subordinate significance in the type.

The characters selected for experiment relate to:

1. The shape of the seed—round and full; irregularly angled and wrinkled.
2. The colour of the seed cotyledons—yellow: green.
3. The colour of the seed-coat—white: grey to buff.
4. The shape of the ripe pod—constricted between the seeds: simply inflated.
5. The colour of the unripe pods—light to dark green: yellow.
6. The position of the flowers on the stem—axial: terminal.
7. The length of the stem—long: short (the long being about 5 times as long as the short).
8. The flowering season. (Not completed at the time of the presentation of the paper.)

From a large number of plants of the same variety only the most vigorous were chosen for fertilization.

Furthermore, in all the experiments reciprocal crossings were effected in such a way that each of the two varieties which in one set of fertilizations served as seed-bearer, in the other set was used as the pollen plant.

The plants were grown in garden beds, a few also in pots, and were maintained in their naturally upright position by means of sticks, branches of trees, and strings stretched between them. For each experiment a number of pot plants were placed during the blooming period in a greenhouse, to serve as control plants for the main experiment in the open as regards possible disturbance by insects.

The risk of false impregnation by foreign pollen is, however, a slight one with Pisum, and is quite incapable of disturbing the general result. Among more than 10,000 plants which were carefully examined there were only a very few cases where an indubitable false impregnation had occurred.

Comments

For his study of the mechanism of organic inheritance Mendel

chose seven pairs of contrasted (differentiating) characters, the two members of each pair being sharply distinct and having no grades between them, being examples of *discontinuous* variation. (The other kind of variation, *continuous*, is illustrated by bodily height in man. In any unselected group of a hundred people there will be someone who is the tallest and someone who is the shortest, and between these two there will be a series of intermediate grades.) Mendel made 287 fertilizations on 70 plants in this P_1. His use of control plants kept in a greenhouse is an illustration of the great care he took to avoid error.

The Forms of the Hybrids

Experiments which in previous years were made with ornamental plants have already afforded evidence that the hybrids, as a rule, are not exactly intermediate between the parental species. With some of the more striking characters—those, for example, which relate to the form and size of the leaves, the pubescence of the several parts, etc.,—the intermediate, indeed, is nearly always to be seen; in other cases, however, one of the two parental characters is so preponderant that it is difficult, or quite impossible, to detect the other in the hybrid.

This is precisely the case with the Pea hybrids. In the case of each of the seven crosses the hybrid character resembles that of one of the parental forms so closely that the other escapes observation completely or cannot be detected with certainty. This circumstance is of great importance in the determination and classification of the forms under which the offspring of the hybrids appear. Henceforth, in this paper those characters which are transmitted quite or almost unchanged in the hybridization and therefore in themselves constitute the characters of the hybrid, are termed the *dominant*, and those which become latent in the process *recessive*. The expression recessive has been chosen because the characters thereby designated withdraw or entirely disappear in the hybrids, but nevertheless reappear unchanged in their progeny, as will be demonstrated later on.

It was furthermore shown by the whole of the experiment that it is perfectly immaterial whether the dominant character belongs to the seed-bearer or to the pollen-parent; the form of the hybrid remains identical in both cases. This interesting fact was also emphasized by Gärtner, with the remark that even the most practised expert is not in a position to determine in a hybrid which of the two parental species was the seed or the pollen plant.

Of the differentiating characters which were used in the experiments the following are dominant:

1. Round seed form
2. Yellow cotyledons
4. Simply inflated pod
5. Green ripe pod

3. Grey seed-coat 6. Axial distribution of flowers
7. Tallness (hybrid even taller than tall parent).

Comments

Mendel's choice of the pea and of these seven pairs of contrasted characters was a very fortunate one. Dominance and recessiveness are not displayed by all pairs of characters. For example, red and white coat colours in cattle are characters in the Mendelian sense, so are black and white plumage colours in the domestic fowl. But the cross-bred offspring of a red-coated and a white-coated beast is a roan, and in the Andalusian fowl the mating black by white gives blue offspring.* In these instances the hybrid has a character of its own. Intermediacy of this kind might have complicated things had it cropped up in Mendel's experiments with *Pisum*. However, it did not; of each pair of characters, seven altogether, one was a clear-cut dominant, and so it was that at the time dominance seemed to be an essential feature of the Mendelian scheme.

The First Generation bred from the Hybrids

In this generation there reappear, together with the dominant characters, also the recessive ones with their peculiarities fully developed, and this occurs in the definitely expressed average proportion of three to one, so that among each four plants of this generation three display the dominant character and one the recessive. This relates without exception to all the characters which were investigated in the experiments. Transitional forms were not observed in any experiment.

Structure	Property	Dominant	Recessive	Ratio in F_2
Seed	Form	5,474 Round	1,850 Wrinkled	2·96 : 1
Reserve material in cotyledons	Colour	6,022 Yellow	2,001 Green	3·01 : 1
Seed-coats	Form	882 Inflated	299 Wrinkled	2·95 : 1
Seed-coats	Colour	705 Grey	224 White	3·15 : 1
Unripe pods	Colour	428 Green	152 Yellow	2·82 : 1
Flowers	Position	651 Axial	207 Terminal	3·14 : 1
Stem	Length	787 Tall	277 Short	2·84 : 1
		14,949 Dominants		
			5,010 Recessives	2·98 : 1
			or	3 : 1

* Bateson, W. and Saunders, E. R., *Reports to the Evolution Committee of the Royal Society*, **1** (1902).

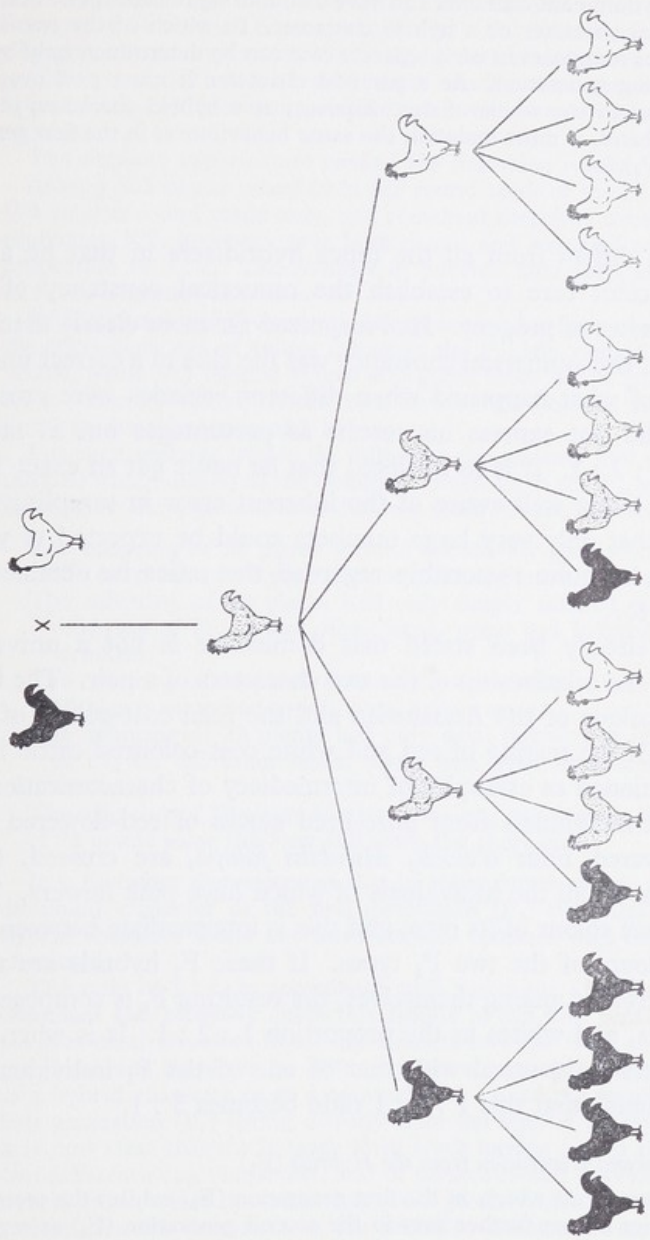


FIG. 4. The unfixable heterozygote. The Blue Andalusian fowl. The mating black × splashed white gives none but blues. Blues mated together produce blacks, blues and splashed whites in the ratio 1 : 2 : 1. Black × black gives none but blacks and splashed white × splashed white none but splashed whites.

The dominant character can have a double significance, viz. that of a parental character or a hybrid character. In which of the two significances it appears in each separate case can be determined only by the following generation. As a parental character it must pass over unchanged to the whole of the offspring; as a hybrid character, on the other hand, it must maintain the same behaviour as in the first generation (F_2).

Comments

Mendel differs from all the other hybridizers in that he alone took sufficient care to establish the numerical constancy of the various classes of progeny. He recognized far more clearly than the others that this numerical constancy was the clue to a correct understanding of what happened when different varieties were crossed. Mendel did not express his results as percentages but as ratios, 3 : 1 or 1 : 2 : 1. It is to be noted that he never got an exact 3 : 1 ratio but, being well aware of the inherent error in sampling and knowing that only very large numbers could be expected to yield this ratio, he quite reasonably regarded the ratios he obtained as being 3 : 1.

It has already been stated that dominance is not a universal feature of the relationship of the two characters of a pair. The blue plumage colour of the Andalusian and the roan coat-colour of the offspring of the mating of red and white coat-coloured cattle have been mentioned as examples of intermediacy of characterization of the F_1. If individuals from pure-bred stocks of red-flowered and white-flowered Four o'clock, *Mirabilis jalapa*, are crossed, they produce an F_1 all the individuals of which have pink flowers. The hybrid has a colour of its own, and this is intermediate between the flower colours of the two P_1 types. If these F_1 hybrids are then selfed or crossed among themselves, the resulting F_2 is composed of reds, pinks, and whites in the proportion 1 : 2 : 1. It is when the F_1 character is identical with that of one of the P_1 individuals—the dominant—that this 1 : 2 : 1 ratio becomes 3 : 1.

The Second Generation from the Hybrids (F_3)

Those forms which in the first generation (F_2) exhibit the recessive character do not further vary in the second generation (F_3) as regards this character; they remain constant in their offspring.

It is otherwise with those that possess the dominant character in the first generation (bred from the hybrids). Of these two-thirds yield offspring which display the dominant and recessive characters in the proportion of 3 : 1 and thereby show exactly the same ratio as the hybrid forms, while only one-third remain with the dominant character constant.

The separate experiments yielded the following results:

Among 565 plants raised from the round seeds of the F_2 generation, 193 yielded round seeds only, and remained therefore constant in this character; 372, however, gave both round and wrinkled seeds, in the proportion of 3 : 1. The number of hybrids, therefore, as compared with the constants is 1·93 to 1.

Of 519 plants which were raised from seeds whose reserve material in the cotyledons was of yellow colour in the F_2, 166 yielded exclusively yellow, while 353 yielded yellow and green seeds in the proportion of 3 : 1. There resulted, therefore, a division into hybrid and constant forms in the proportion of 2·13 : 1.

For each separate trial in the following experiments 100 plants were selected which displayed the dominant character in the F_2, and in order to ascertain the significance of this, ten seeds of each were cultivated.

The offspring of 36 plants yielded exclusively grey seeds, while of the offspring of 64 plants some had grey and some had white.

The offspring of 29 plants had only simply inflated pods; of the offspring of 71, on the other hand, some had inflated and some wrinkled.

The offspring of 40 plants had only green pods; of the offspring of 60 plants some had green, some yellow ones.

The offspring of 33 plants had only axial flowers; of the offspring of 67, on the other hand, some had axial and some terminal flowers.

The offspring of 28 plants inherited the long axis (were tall) and those of 72 plants some the long and some the short axis.

It is therefore demonstrated that of those forms which possess the dominant character in the first generation (F_2) two-thirds have the hybrid character while one-third remains constant with the dominant character.

The ratio of 3 : 1, in accordance with which the distribution of the dominant and recessive characters results in the first generation (F_2), resolves itself therefore in all experiments into the ratio of 2 : 1 : 1 if the dominant character be differentiated according to its significance as a hybrid character or as a parental one. Since the members of the first generation (F_2) spring directly from the seed of the hybrids (F_1), it is now clear that the hybrids form seeds having one or other of the two differentiating characters, and of these one-half develop again the hybrid form, while the other half yield plants which remain constant and receive the dominant or the recessive characters respectively in equal numbers.

Comments

All the pairs of characters studied by Mendel displayed the dominant–recessive relationship. The hybrid in respect of the particular character being considered was indistinguishable from the parent with the dominant character. Yet the F_1 and the P_1 individuals were different. The P_1 with the dominant character was like the F_2 individuals which yielded none but dominants. The F_1 with the dominant character was like the F_2 individuals which yielded both dominants and recessives. Thus animals or plants that look alike can be very different in respect of their factorial constitutions, as revealed during reproduction.

Mendel did not stop at this point. He continued with the round and wrinkled seed and the yellow- and green-coloured reserve material in the cotyledons pairs of characters through six generations, with the grey and white seed-coat colours and the tall and short stem pairs for five generations, and for the rest of the pairs through four generations. The offspring of the hybrid separated in each generation in the ratio 2 : 1 : 1 into hybrids and constant forms.

Fisher (1936) subjected the numerical results obtained by Mendel to rigorous statistical scrutiny and pointed out that because of the smallness of the sample (10 seeds only) the close approximation to the 2 : 1 ratio among the heterozygous and the homozygous dominants is indeed remarkable, too remarkable to be credible. (With numbers of this magnitude a 1·8874 : 1·1126 ratio would have been expected.) Fisher suggests that maybe the gardener or someone else who was helping Mendel, knowing what he wanted and expected, wittingly or unwittingly did what he could to produce it.

It is not improbable, however, that Mendel himself reached conclusions which were not supported by the numerical results of certain of his experiments for the reason that he had already a clear and precise picture of the mechanism which he was manipulating. If organic inheritance was particulate, if pairs of factors in the parents segregated during the production of the germ-cells, if the germ-cells had equal chances of fertilization, and if the hereditary contributions of the two parents were equal, then it was predictable

that the mating Aa × Aa would yield 1 AA : 2 Aa : 1 aa in every 4 on the average. Mendel's experiments were designed to test the validity of his already formed ideas concerning the mechanism of organic inheritance. This is the real purpose of experimentation, to examine the value of an idea first conceived as a piece of abstract and theoretical analysis. Mendel knew what to expect, if his ideas were correct, and he may have presented his results in a way that would best demonstrate his theory to other people. Mendel thought in terms of mathematical symbolization.

Mendel gives a table that shows the numbers, as calculated or as tested experimentally, of the different classes of offspring to be expected in the $F_{2, 3, 4, 5}$ and $_6$ of a monohybrid (involving only one pair of contrasted characters) experiment. Let *D* represent the dominant member of the pair and *d* the recessive.

Generation	*DD*	*Dd*	*dd*	Ratio
F_2	1	2	1	1 : 2 : 1
F_3	6	4	6	3 : 2 : 3
F_4	28	8	28	7 : 2 : 7
F_5	120	16	120	15 : 2 : 15
F_6	496	32	496	31 : 2 : 31
n				$2^n-1 : 2 : 2^n-1$

The Reproductive Cells of the Hybrids

The results of the previously described experiments led to further experiments, the results of which appear fitted to afford some conclusions as regards the composition of the egg and pollen cells of hybrids. An important clue is afforded in *Pisum* by the circumstance that among the progeny of the hybrids constant forms appear, and that this occurs, too, in respect of all combinations of the associated characters. So far as experience goes, we find it in every case confirmed that constant progeny can only be formed when the egg cells and the fertilizing pollen are of like character, so that both are provided with the material for creating quite similar individuals, as is the case with the normal fertilization of pure species. We must therefore regard it as certain that exactly similar factors must be at work also in the production of the constant forms in the hybrid plants. Since the various hybrid forms are produced in *one* plant, or even in *one* flower of a plant, the conclusion appears logical that in the ovaries of the hybrids there are formed as many sorts of egg cells, and in the anthers as many sorts of pollen cells, as there are possible constant combination forms, and that these egg and pollen cells agree in their internal composition with those of the separate forms.

In point of fact it is possible to demonstrate theoretically that this

hypothesis would fully suffice to account for the development of the hybrids in the separate generations, if we might at the same time assume that the various kinds of egg and pollen cells were formed in the hybrids on the average in equal numbers.

Comments

The essence of Mendel's principles of heredity is to be found in the above extract from his paper. Out of the results he had obtained he fashioned an explanation of their meaning. He then designed a number of experiments to test the validity of this hypothesis and the results fully confirmed his theory that "the pea hybrids form egg and pollen cells which in their constitution, represent in equal numbers all constant forms which result from the combination of the characters united in fertilization".

It is convenient at this point to quote from Mendels.

Concluding Remarks

With *Pisum* it was shown by experiment that the hybrids form egg and pollen cells of *different* kinds, and that herein lies the reason of the variability of their offspring. In other hybrids, likewise, whose offspring behave similarly we may assume a like cause; for those, on the other hand, which remain constant the assumption appears justifiable that their reproductive cells are all alike and agree with the foundation-cell (fertilized ovum) of the hybrid. In the opinion of renowned physiologists, for the purpose of propagation one pollen cell and one egg cell unite in Phanerogams into a single cell, which is capable by assimilation and formation of new cells to become an independent organism. This development follows a constant law, which is founded on the material composition and arrangement of the elements which meet in the cell in a vivifying union. If the reproductive cells be of the same kind and agree with the foundation cell (fertilized ovum) of the mother plant, then the development of the new individual will follow the same law which rules the mother plant. If it chance that an egg cell unites with a *dissimilar* pollen cell, we must then assume that between those elements of both cells, which determine opposite characters, some sort of compromise is effected. The resulting compound cell becomes the foundation of the hybrid organism, the development of which necessarily follows a different scheme from that obtaining in each of the two original species. If the compromise is taken to be a complete one, in the sense, namely, that the hybrid embryo is formed from two similar cells, in which the differences are *entirely and permanently accommodated* together, the further result follows that the hybrids, like any other stable plant species, reproduce themselves truly in their offspring. The reproductive cells which are formed in their seed vessels and anthers are of one kind, and agree with the fundamental compound cell (fertilized ovum).

> With regard to those hybrids whose progeny is *variable* we may perhaps assume that between the differentiating elements of the egg and pollen cells there also occurs a compromise, in so far that the formation of a cell as foundation of the hybrid becomes possible; but, nevertheless, the arrangement between the conflicting elements is only temporary and does not endure throughout the life of the hybrid plant. Since in the habit of the plant no changes are perceptible during the whole period of vegetation, we must further assume that it is only possible for the differentiating elements to liberate themselves from the enforced union when the fertilizing cells are developed. In the formation of these cells all existing elements participate in an entirely free and equal arrangement, by which it is only the differentiating ones which mutually separate themselves. In this way the production would be rendered possible of as many sorts of egg and pollen cells as there are combinations possible of the formative elements.

Comments

It is here, especially, that the brilliance of Mendel's mind is revealed. Behind the characters and their mode of inheritance from generation to generation he visualizes the determinants of the characters, factors or elements; he clearly recognizes the states of homo- and heterozygosity (see on) and he postulates the existence of a reduction division during the process of gamete formation and of an element-distributing mechanism remarkably like that which, in the first decade of the present century, was to be built into the chromosome theory of heredity. On the basis of his own observations Mendel formulated a theory of hereditary transmission which time was to prove to be both completely right and of universal application. He produced a theoretical model which predicted with complete accuracy the nature, the properties and the behaviour which the physical hereditary mechanism, at that time totally unknown, must possess. Mendelism is surely one of the most inspired conceptions in the history of science. As in the case of many a man before him and since his time his enduring fame rests upon a single contribution to natural knowledge, but one of supreme importance.

Mendelism can be illustrated by reference to three of Mendel's own experiments, a mono-, a di- and a tri-hybrid.

Consider the characters tall stem and short stem. Each cell of a

pure tall pea has a pair of like factors which are responsible for the difference between it and a short one. Each cell of a short-stemmed pea has a pair of like factors which are responsible for the difference between it and a tall pea. In the formation of the gametes the members of each pair of factors segregate, separate, with the result that each ripe gamete comes to contain one member of each pair. Each gamete produced by a pure tall pea will carry one factor for tallness. Each gamete produced by a short-stemmed pea will carry one factor for shortness.

Since tallness is dominant and shortness recessive, let *T* represent the factor for tallness and *t* that for shortness. If the seed of a tall pea is fertilized by the pollen of a short pea, or *vice versa*, the resulting hybrid (F_1) will have the factorial constitution *Tt* and is a tall plant for the reason that *T* is dominant. At each cell-division of the developing plant the factors segregate so that every cell of the hybrid contains the *Tt* pair of dissimilar factors. When the hybrid proceeds to elaborate its gametes, each of these will contain either the factor *T* or else the factor *t*, and these two forms will occur in equal numbers. There will be *T* and *t* bearing female gametes and *T* and *t* bearing male gametes.

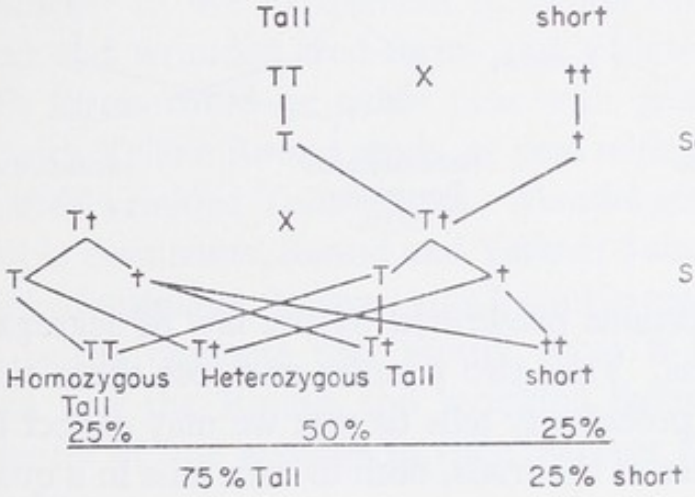
If fertilization is random, then *T* can meet *T* or *t* and *t* can meet *T* or *t* to yield *TT*, *Tt*, *Tt*, and *tt* individuals which will fall into three classes, 25 per cent *TT*, pure talls; 50 per cent hybrid talls, *Tt*; and 25 per cent shorts, *tt*. Characters are not transmitted from parent to offspring; factors that underlie the characters are transmitted. In the case of the *Tt* hybrid one of these factors has come from the maternal parent, the other from the paternal. This association of the dominant and recessive factors leads to no kind or degree of contamination.

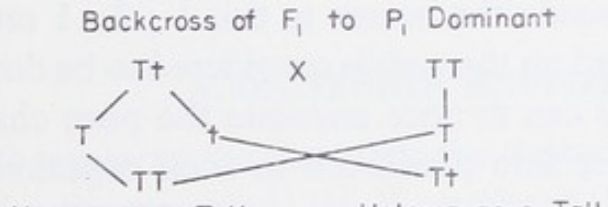
MENDEL'S LAW OF SEGREGATION.* *Hereditary differences are dependent upon separate factors derived from both parents, remaining*

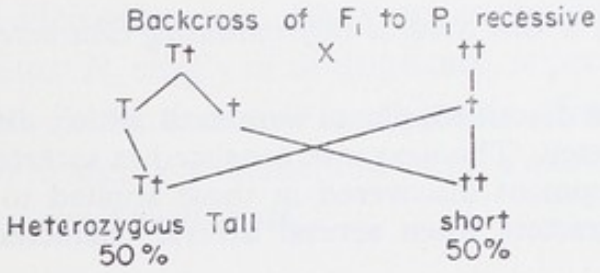
* It was Correns (see on) who thought that Mendel's discovery could be represented by the two "laws of heredity", the law of segregation and the law of free recombination. These abstract laws became the basis of the teaching of the subject and so it was that attention was focused upon ratios and for a while no one asked what exactly was being segregated and recombined.

distinct throughout the entire life-cycle, and finally separating in the formation of the gametes, so that with respect to any single pair of factors one half of the gametes contain the factor derived from one parent and the other half the factor contributed by the other parent. According to Zirkle this phenomenon of segregation was observed and described as long ago as 1597 by Gerard in the tulip though he had no idea of the meaning of what he had observed.

For the sake of convenience two technical terms unknown to Mendel are introduced at this point. An individual that possesses two like factors, e.g. *TT* or *tt*, is said to be a homozygote, to be homozygous in respect of the factor *T* or the factor *t*. The hybrid *Tt* is said to be heterozygous in respect of the factors *T* and *t* (homozygote: Gk. *homos*, same and *zygon*, yoke; heterozygote: Gk. *heteros*, other).

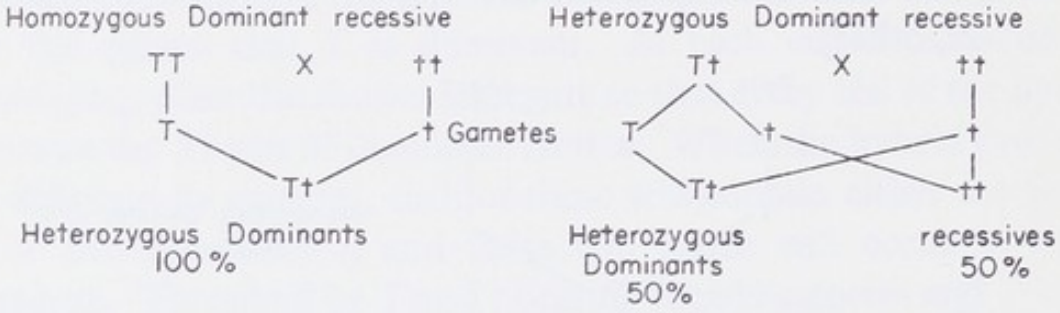






It will be noted that there is no need to apply the term homozygous to the individual displaying the recessive member of a pair of contrasted characters. It is necessarily homozygous for the recessive factor since if the alternative dominant factor were present in the factorial constitution of the individual, the recessive character would not and could not be shown.

Since the display of the recessive member of a pair of characters by an individual is a trustworthy indication of the factorial constitution of that individual, it can be used to determine whether an individual that displays the alternative dominant character is homozygous or heterozygous for the dominant factor.



The numerical proportions prescribed by the law of segregation are statistical predictions. Take two pennies and toss them simultaneously. The law of probability tells us that we may expect both to turn heads in a quarter of the trials, both to turn tails in a quarter of the trials, and for a head and a tail to occur in one half of the trials. The more trials that are made the nearer to this 1 : 2 : 1 ratio will the outcome be. If the head on the coin is considered to be dominant and the tail recessive, one can at once translate the pure chance of the coin-tossing experience into prediction in such experiments as those of Mendel.

The Offspring of Hybrids in Which Several Differentiating Characters are associated

In the experiments above described, plants were used which differed only in one essential character. The next task consisted in ascertaining whether the law of development discovered in these applied to each pair of differentiating characters when several diverse characters are

united in the hybrid by crossing. As regards the form of the hybrids in these cases the experiments showed throughout that this invariably more nearly approaches to that one of the two parental plants which possesses the greater number of dominant characters. Should one of the two parental types possess only dominant characters, then the hybrid is scarcely or not at all distinguishable from it.

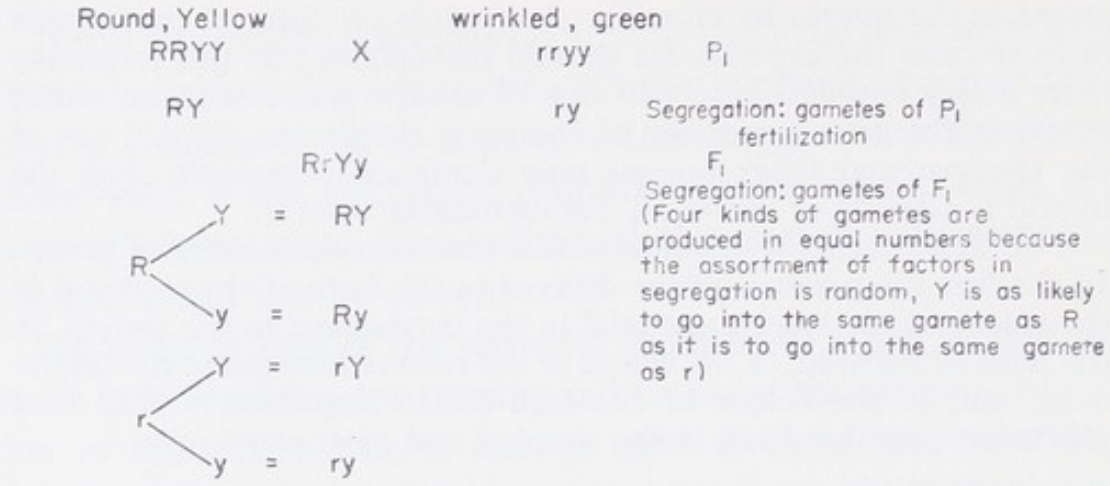
Two experiments were made with a considerable number of plants. In the first the parental plants differed in the form of the seed and in the colour of the reserve material in the cotyledons; in the second, in the form of the seed, in the colour of the reserve material in the cotyledons, and in the colour of the seed-coats. Experiments with seed characters give the result in the simplest and most certain way.

Comments

Mendel's detailed description of these experiments is couched in rather old-fashioned language and is difficult to follow; it is therefore simplified. In the experiment in which the character pairs were Round and wrinkled seed-forms and Yellow and green cotyledons the P_1 forms could be either peas with green wrinkled seeds and peas with Yellow Round seeds, or peas with Round green seeds and peas with wrinkled Yellow seeds. Mendel got in the F_2 in every 16, 9 double dominants, Round and Yellow; 3 single dominants, Round; 3 single dominants, Yellow; and 1 double recessive, wrinkled green. This is the outcome that should occur if the Yellow and green factors and the Round and wrinkled factors behave quite independently of one another in their passage from one generation to the next.

A DI-HYBRID EXPERIMENT

Let *R* represent the factor for the character Round seed-form and *r* that for the wrinkled; let *Y* represent the factor for Yellow and *y* that for green. Let the cross be between a Round Yellow pea and a wrinkled green pea. (Any pea in the factorial constitution of which the factor *R*, singly or in duplicate, is present will have Round seeds; any pea in the factorial constitution of which the factor *Y*, singly or in duplicate, is present will have Yellow seeds because Round and Yellow are Dominants.)



Female gametic series

Male gametic series	*RY*	*Ry*	*rY*	*ry*
RY	*RRYY* 1	*RRYy* 2	*RrYY* 3	*RrYy* 4
Ry	*RRYy* 5	*RRyy* 6	*RrYy* 7	*Rryy* 8
rY	*RrYY* 9	*RrYy* 10	*rrYY* 11	*rrYy* 12
ry	*RrYy* 13	*Rryy* 14	*rrYy* 15	*rryy* 16

Fertilization (random)

F_2

	Factorial constitution	Square	Total	
RY (two Dominants) Round and Yellow	*RRYY*	1	1	
	RRYy	2, 5	2	
	RrYY	3, 9	2	
	RrYy	4, 7, 10, 13	4	9
R (one Dominant) Round (and green)	*RRyy*	6	1	
	Rryy	8, 14	2	3
Y (one Dominant) Yellow (and wrinkled)	*rrYY*	11	1	
	rrYy	12, 15	2	3
Neither Dominant wrinkled and green	*rryy*	16	1	1
				16

The segregation of the *R* and *r* pair of factors is quite independent of that of the *Y* and *y* pair. The distribution of the members of the

R and *r* pair is quite independent of that of those of the *Y* and *y* pair. For these reasons every possible combination of the four factors can be expected in the F_2. The 9 : 3 : 3 : 1 ratio results from the combination of two 3 : 1 ratios.

In the F_2 since Round is dominant and wrinkled recessive, three-quarters will be Round and a quarter wrinkled. Of the Rounds, since Yellow is dominant and green recessive, three-quarters will be Yellow and a quarter green.

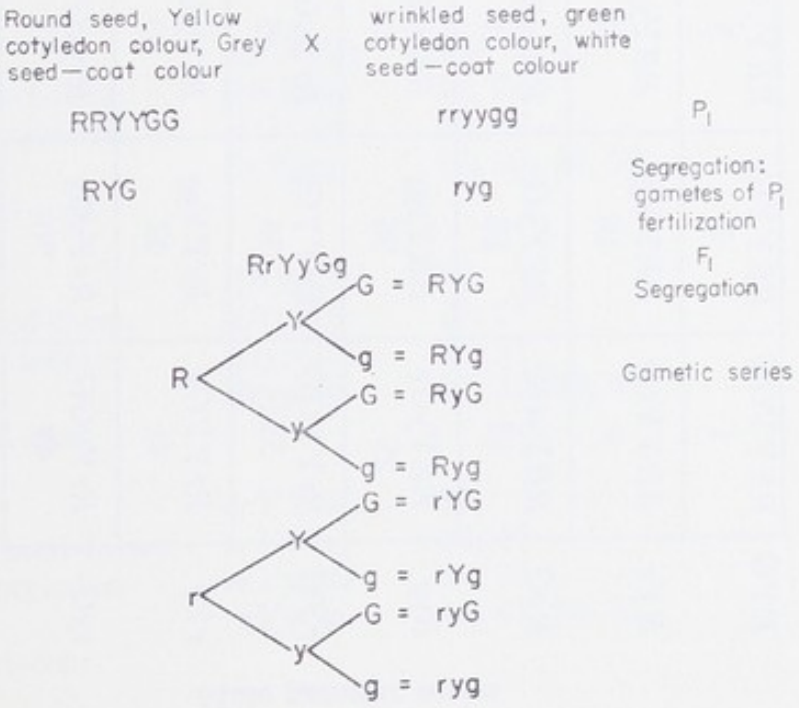
$\frac{3}{4}$ of $\frac{3}{4}$ is $\frac{9}{16}$ Round and Yellow
$\frac{1}{4}$ of $\frac{3}{4}$ $\frac{3}{16}$ Round and green

Of the wrinkled three-quarters will be Yellow and a quarter green

$\frac{3}{4}$ of $\frac{1}{4}$ $\frac{3}{16}$ wrinkled and Yellow
$\frac{1}{4}$ of $\frac{1}{4}$ $\frac{1}{16}$ wrinkled and green.

A TRI-HYBRID EXPERIMENT

The character pairs in Mendel's experiment in which three pairs of contrasted characters were involved were Round and wrinkled seed-form, Yellow and green reserve material in the cotyledons and Grey and white seed-coat. Let *G* and *g* represent the factors corresponding to Grey and white seed-coat colours.



Female gametic series

Male gametic series	*RYG*	*RYg*	*RyG*	*Ryg*	*rYG*	*rYg*	*ryG*	*ryg*
RYG	*RRYYGG* 1	*RRYYGg* 2	*RRYyGG* 3	*RRYyGg* 4	*RrYYGG* 5	*RrYYGg* 6	*RrYyGG* 7	*RrYyGg* 8
RYg	*RRYYGg* 9	*RRYYgg* 10	*RRYygg* 11	*RRYygg* 12	*RrYYGg* 13	*RrYYgg* 14	*RrYyGg* 15	*RrYygg* 16
RyG	*RRYyGG* 17	*RRYyGg* 18	*RRyyGG* 19	*RRyyGg* 20	*RrYyGG* 21	*RrYyGg* 22	*RryyGG* 23	*RryyGg* 24
Ryg	*RRYyGg* 25	*RRYygg* 26	*RRyyGg* 27	*RRyygg* 28	*RrYyGg* 29	*RrYygg* 30	*RryyGg* 31	*Rryygg* 32
rYG	*RrYYGG* 33	*RrYYGg* 34	*RrYyGG* 35	*RrYyGg* 36	*rrYYGG* 37	*rrYYGg* 38	*rrYyGG* 39	*rrYyGg* 40
rYg	*RrYYGg* 41	*RrYYgg* 42	*RrYyGg* 43	*RrYygg* 44	*rrYYGg* 45	*rrYYgg* 46	*rrYyGg* 47	*rrYygg* 48
ryG	*RrYyGG* 49	*RrYyGg* 50	*RryyGG* 51	*RryyGg* 52	*rrYyGG* 53	*rrYyGg* 54	*rryyGG* 55	*rryyGg* 56
ryg	*RrYyGg* 57	*RrYygg* 58	*RryyGg* 59	*Rryygg* 60	*rrYyGg* 61	*rrYygg* 62	*rryyGg* 63	*rryygg* 64

The six factors, being distributed independently, combine to form eight gametes; and of these there will be two series, those from the seed-bearing parent and those from the pollen-producing parent. Fertilization being random, the possible combinations of these gametes will be $8 \times 8 = 64$ as shown in the chess-board scheme (p. 46).

Note that a diagonal running from square 8 to square 57 cuts through all the individuals that are triply heterozygous, *RrYyGg*, and that a diagonal running from square 1 to square 64 cuts through all the individuals that are homozygous, the two members of each pair of factors being alike.

Among these 64 individuals of F_2 there are eight different kinds of peas, the kinds being determined by the number of the dominant factors they possess.

	Factorial constitution	Squares	Total
1. *RYG*			
Round seed-form,	*RRYYGG*	1	1
Yellow cotyledon	*RRYYGg*	2, 9	2
colour,	*RRYyGG*	3, 17	2
Grey seed-coat	*RrYYGG*	5, 33	2
	RRYyGg	4, 11, 18, 25	4
	RrYYGg	6, 13, 34, 41	4
	RrYyGG	7, 21, 35, 49	4
	RrYyGg	8, 15, 22, 29, 36, 45, 50, 57	8
			27
2. *RYg*	*RRYYgg*	10	1
Round seed-form,	*RRYygg*	12, 26	2
Yellow cotyledon	*RrYYgg*	14, 42	2
colour,	*RrYygg*	16, 30, 44, 58	4
white seed-coat			9
3. *RyG*	*RRyyGG*	19	1
Round seed-form,	*RRyyGg*	20, 27	2
green cotyledon	*RryyGG*	25, 51	2
colour,	*RryyGg*	24, 31, 52, 59	4
Grey seed-coat			9
4. *rYG*	*rrYYGG*	37	1
wrinkled seed-form,	*rrYYGg*	38, 45	2
Yellow cotyledon	*rrYyGG*	39, 53	2
colour,	*rrYyGg*	40, 47, 54, 61	4
Grey seed-coat			9

5. *Ryg*			
Round seed-form,	*RRyygg*	28	1
green cotyledon	*Rryygg*	32, 60	2
colour,			—
white seed-coat			3
6. *rYg*			
wrinkled seed-form,			
Yellow cotyledon	*rrYYgg*	46	1
colour,	*rrYygg*	48, 62	2
white seed-coat			—
			3
7. *ryG*			
wrinkled seed-form,			
green cotyledon	*rryyGG*	55	1
colour,	*rryyGg*	56, 63	2
Grey seed-coat			—
			3
8. *ryg*			
wrinkled seed-form,			
green cotyledon	*rryygg*	64	1
colour,			
white seed-coat			
			—
			64
			—

Now that several character-pairs are being considered, it is necessary to make use of a term that will relate to the total characterization of an individual, to one that displays the combination of wrinkled seed-form, green cotyledon colour and white seed-coat, for example. The term used is *phenotype* (Gk. *phainein*, to appear; *typos*, image). Such an individual belongs to the wrinkled seed-form, green cotyledon colour, white seed-coat phenotype, or, the individual's phenotype is wrinkled seed-form, green cotyledon colour and white seed-coat.

It is to be noted that only one individual in each of the phenotypes in the F_2 of a tri-hybrid experiment can be expected to be homozygous for all its factors and will therefore breed true. Thus, no matter how many factors are involved it is always possible to obtain in the F_2 a homozygote possessing any of the possible combinations. But, of course, the chances of getting such a homozygote will be determined by the number of factors that are involved. In a tri-hybrid experiment, such as that being considered, to be at all sure

of getting the triple recessive, *ryg*, the F_2 should consist of at least 292 individuals.

The ratios for more than a tri-hybrid experiment were computed by Mendel. The F_2 of a quadruple hybrid includes 256 possibilities instead of the 64 of the tri-hybrid; the number of possible gametic combinations in the F_2 of a quintuple hybrid is 1024, in that of a sextuple hybrid, 4906, and so on. Manifestly, such numbers are far too large to be dealt with at all easily in experimental breeding work.

Mendel formulated the results he obtained in his di-hybrid and tri-hybrid experiments as a generalization that is sometimes known as his second law—the Law of the Independent Assortment and Recombination of Factors. This law states that *when the gametes are formed the members of the different factor pairs segregate quite independently of each other and that all possible combinations of the factors concerned will be found among the progeny*. But this is not a law in the same sense as his first law, the Law of the Segregation of Factors, because it is not of universal application; there are very many exceptions to the rule that the factors are transmitted independently of each other.

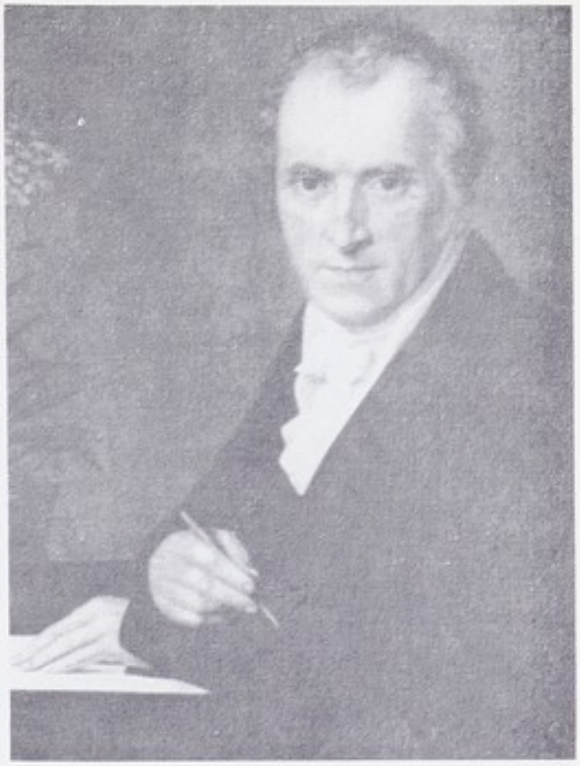
Mendel then designed experiments to discover whether or not what he called the law of development that had emerged from his experiments with the pea applied also and equally to the hybrids of other species and their varieties. He either used, or intended to use, the following: *Hieracium* (Hawkweed), *Geum*, *Circium*, *Linaria* (Toad Flax), *Zea mays* (Maize), *Calceolaria* (Slipper Flower), *Ipomoea* (Morning Glory), *Cheiranthus* (Wallflower), *Antirrhinum* (Snapdragon), *Tropaeoleum* (Canary Creeper), *Veronica* (Speedwell), *Viola* (Tufted Pansy), *Carex*, *Potentilla* (Cinquefoil), *Aquilegia* (Columbine), *Matthiola* (Stock), *Phaseolus*, *Dianthus* (a genus that includes the Carnation and the Sweet William) and *Verbascum* (Mullein).

At the meeting of the Brünn Society on 9 June 1869 he communicated a paper on *Über einige aus kunstlicher Befruchtung gewonnene Hieracium-Bastarde* (On *Hieracium* Hybrids obtained by Artificial Fertilization) and this appeared in the Proceedings in the following

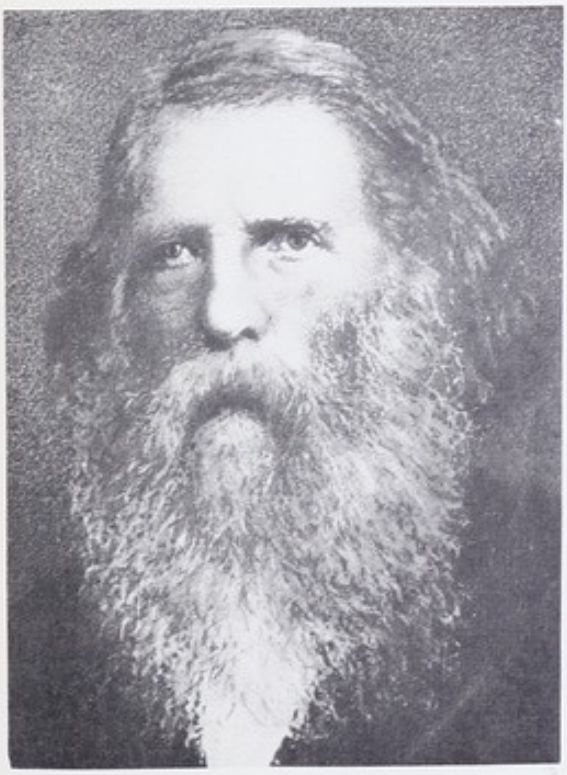
year. *Hieracium*, as is now known, was not a suitable material for experimentation of this kind for it is frequently parthenogenetic (Gk. *parthenos*, virgin; *genesis*, descent; reproduction without fertilization by a male gamete) or apogamous (Gk. *apo*, away; *gamos*, marriage; reproduction without any sexual union). The other plants Mendel used gave results that were in accord with those of the pea experiments.

The Proceedings (*Verhandlungen*) of the Brünn Society were regularly and widely distributed among the libraries of learned societies and academic institutions including the Royal and the Linnean societies of London (about 120 in all). Mendel received forty reprints and distributed them among those botanists whom he thought might be interested. The paper itself was mentioned fifteen times in all in a comprehensive survey of the scientific literature on hybridization by Focke, *Die Pflanzenmischlinge* (Plant Hybrids) (1881). But Focke merely recorded that Mendel's numerous pea experiments had given results similar to those of Knight and that he had found constant numerical relationships among the hybrid types. The paper was included in the bibliography of Bailey's *Plant Breeding* (1894, New York) and in the Royal Society's *Catalogue of Scientific Papers*. Reference to it was made in an article on Hybridism in the ninth edition of the *Encyclopaedia Britannica*, 1881–95. The paper evoked no discussion among the biologists of the time and had it not been for the references to it in the books of Focke and Bailey it might have remained disregarded and unknown for even longer than it did. That Mendel was well acquainted with the current biological literature is revealed by the content of the monastery library. At the time when he was writing his paper he certainly possessed copies of Erasmus Darwin's *Zoonomia* and of Charles Darwin's *Origin of Species* (the 2nd German edition, 1863), the latter with many marginal notes and with much underlining of sentences. After 1865 he had copies of Darwin's *The Variation of Animals and Plants under Domestication*, *The Effects of Cross and Self-fertilization in the Vegetable Kingdom* and *On the Various Contrivances by which Orchids are Fertilized* (German edition). It is of interest to note that at the meeting of the Brünn

J. G. Kölreuter



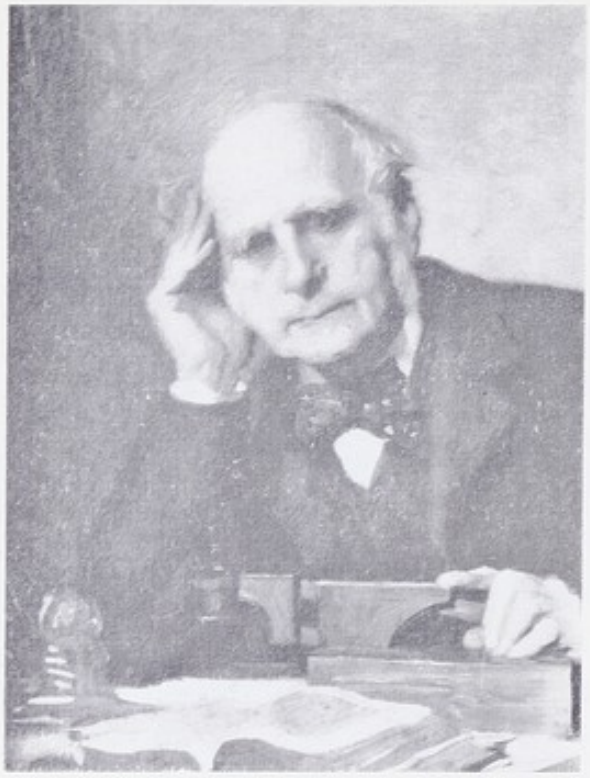
Carl F. von Gärtner



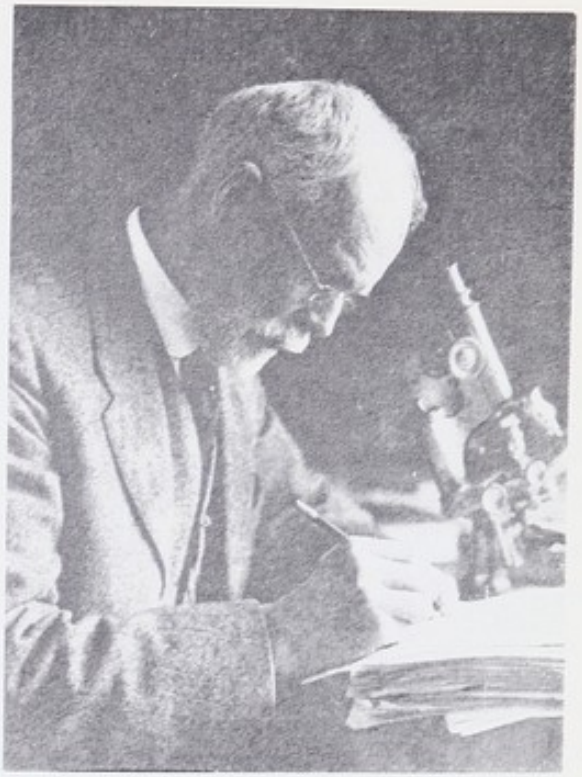
Charles Naudin

August Weismann

PLATE II



Francis Galton



E. B. Wilson

Pierre Louis François
Levegue de Vilmorin

Johann Gregor Mendel

PLATE III

Carl Correns

Hugo de Vries

Erich von Tschermak-Seysenegg

Th. Boveri

PLATE IV

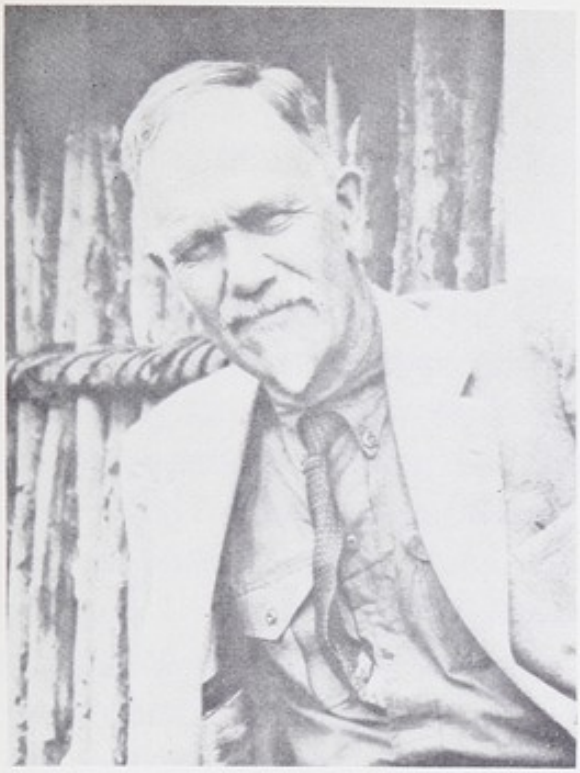
William Bateson

R. C. Punnett

W. Johanssen

W. E. Castle

PLATE V



Charles B. Davenport

Thomas Hunt Morgan

Calvin B. Bridges

H. J. Müller

PLATE VI

Natural Science Society immediately before the one at which Mendel read the first part of his pea paper, there was a discussion of Darwin's theory of evolution. It is probable that at this meeting Mendel was present.

It is probable that Mendel knew Johann Dzierzon, a fellow cleric who was a contemporary of his and who, like Mendel himself, was using the honey bee in experimental breeding work. Dzierzon lived not far away from Brünn. Between 1845 and 1854 he published a series of papers describing his experiments in which he crossed German with Italian bees and found that the unmated hybrid queens produced both German and Italian drones and these in equal numbers, a 1 : 1 ratio. Zirkle (*Genetics in the 20th Century*) suggests that possibly this was the stimulus that alerted Mendel's mind to the importance of ratios.

Letters that still exist reveal that Mendel was in close and constant touch with Professor Nägeli of Munich, consulting him frequently about his problems and his experiments, sending him samples of his pea generations, together with predictions of the ratios of the different types that would appear among the plants grown from the seeds; and receiving from Professor Nägeli copies of his published papers on plant hybridization and *Hieracium* seeds. The correspondence gives the impression that Nägeli, the professional botanist of high repute, regarded Mendel as an over-enthusiastic, uncritical amateur. Extracts from Mendel's letters will serve to indicate the nature of this correspondence.

> The experiments, which were made with different varieties of *Pisum*, resulted in the offspring of the hybrids forming curious series, the members of which, in equal numbers, resembled the two original types. The presence of non-variant intermediate forms, which occurred in each experiment, seems to deserve special attention.
>
> The results which Gärtner obtained in his experiments are known to me. I have repeated his work and have re-examined it carefully to find, if possible, an agreement with those laws of development which I found to be true for my experimental plant. However, try as I would, I was unable to follow his experiments completely, not in a single case. It is very regrettable that this worthy man did not publish a detailed description of his individual experiments, and that he did not diagnose his hybrid types sufficiently, especially those resulting from like fertilizations. Statements like "some individuals showed closer resemblance

to the maternal, others to the paternal type" or "the progeny had reverted to the type of the original maternal ancestor" etc. are too vague to furnish a basis for sound judgment.

I knew that the results I obtained were not easily compatible with our contemporary scientific knowledge and that under the circumstances publication of one such isolated experiment was doubly dangerous; dangerous for the experimenter and for the cause he represented. Thus I made every effort to verify with other plants the results obtained with *Pisum*.

I am not surprised to hear your honour speak of my experiments with mistrustful caution. I would not do otherwise in a similar case.

I attempted to inspire some control experiments, and for that reason discussed the *Pisum* experiments at a meeting of the local natural science society. I encountered, as was to be expected, divided opinion; however, as far as I know, no one undertook to repeat the experiments. When last year I was asked to publish my lecture in the Proceedings of the Society, I agreed to do so, after having re-examined my records for the various years of experimentation and not having been able to find a source of error.

Nägeli had somewhat condescendingly remarked that "it appears to me that the experiments with *Pisum* are far from completion, indeed they are only just beginning". Mendel, despite this haughty criticism, was greatly pleased by the attention that Nägeli gave to him and wrote more fully on two points that were raised by Nägeli, the duration of the true-breeding quality of the different types in the experimental material and the value of the ratios. Mendel defined true-breeding as reproducing offspring like themselves for 4 to 6 successive generations or for as long as they were under observation. As for the ratios he wrote:

My experiments with single characters all lead to the same result; that from the seeds of the hybrids, plants are obtained half of which in turn carry the hybrid character while the other half received the parental characters, the dominant and the recessive, in equal amounts. Thus on the average, among four plants two have the hybrid character, one the dominant parental character and the one the recessive parental character. Therefore 1 DD : 2 Dd : 1 dd is the empirical, simple, developmental series for two differentiating characters. Likewise, it was shown in an empirical manner that, if two or three differentiating characters are combined in the hybrid, the developmental series is a combination of two or three simple series. Up to this point I do not believe that I can be accused of having left the realm of experimentation. If I then extend this combination of simple series to any number of differences between the two parental plants, I have indeed entered the rational

domain. This seems to me to be permissible, however, because I have proved by previous experiment that the development of any two differentiating characteristics proceeds independently of any other differences.

Nägeli had said that, "you should regard the numerical expressions as being only empirical, because they cannot be proved rational".

In one letter Mendel says that he feels himself forced to examine the opinion of Naudin and of Darwin to the effect that a single pollen grain does not suffice for fertilization of the ovule. Naudin maintained that at least three were necessary.

I used *Mirabilis jalapa* for an experimental plant, as Naudin had done; the result of my experiment is, however, completely different. From fertilizations with single pollen-grains, I obtained 18 well-developed seeds and from these an equal number of plants, of which 10 are already in bloom. The majority of the plants are just as vigorous as those derived from free self-fertilization. A few specimens are stunted thus far, but after the success of all the others the cause must lie in the fact that not all pollen-grains are equally capable of fertilization, and that furthermore, in the experiment mentioned, the competition of other pollen-grains was excluded. When several are competing, we can assume that only the strongest ones succeed in effecting fertilization.

Of the experiments of previous years those dealing with *Matthiola annua* and *glabra*, *Zea* and *Mirabilis* were concluded last year. Their hybrids behave exactly like those of *Pisum*. Darwin's statements concerning hybrids of the genera mentioned in the *Variation of Animals and Plants under Domestication*, based on reports of others, need to be corrected in many respects.

Nägeli was himself interested in *Hieracium* hybridization experiments and, for this reason, showed far more interest in Mendel's work with this plant than in that with the pea. The correspondence ceased in 1874 at the time when Mendel became engrossed in his opposition to the tax on religious houses. In the year when Mendel died there was published Professor Carl Nägeli's *Mechanischphysiologische Theorie der Abstammungslehre* (Mechanophysiological Theory of Heredity). In it there is no mention whatsoever of Mendel's work. Yet it includes an account of the reappearance of a typical recessive character in the second hybrid generation of the mating "Common hair-form" × "Angora hair-form" in the cat. It is clear from his discussion of this case that Nägeli's ideas

concerning organic inheritance had remained completely unaffected by anything that Mendel had done or had written.

It is known that the botanist Hoffman of Giessen had read Mendel's *Pisum* paper, for he cited it in his own book *Untersuchungen des Wertes von Spezies und Varietat: Ein Beitrag zur Kritik der Darwinschen Hypothese*, 1869 (Evaluation of Species and Variety; A Contribution to the Criticism of Darwin's Hypothesis). However, all that he gathered from it was that hybrids have a tendency, in later generations, to revert to the parental types. Hoffman gives details of his own *Hieracium* and *Phaseolus* crosses but does not refer to Mendel's work with the same plants.

It is known that a reprint of Mendel's paper was sent to the Viennese botanist Kerner who obtained some of the *Hieracium* hybrids from Mendel. But the paper remained unread for its pages were never cut.

The reason why Mendel's contemporaries failed to grasp the importance of his interpretation of his results was not, as is sometimes suggested, that his paper appeared in an obscure journal with a very limited circulation so that they remained unaware of it. The fact is, the biologists of Mendel's own generation were not ready to entertain such novel ideas, and so these appeared to them to possess no importance. In England, especially, they were interested in the differences that distinguished species and not in differences between varieties of one and the same species. They were absorbed in tracing evolutionary relationships by studies in embryology and comparative anatomy. Though Mendel was satisfied that in the act of fertilization one pollen-grain and one ovule, and no more, were involved, others were not. At this time the nature of the process of fertilization in animals was not understood and the behaviour of the nucleus during cell-division had not been described. The attempts to improve the yield of cereal crops had not yet begun to create a demand for the development of a scientific basis for plant breeding. Time was required for these developments to occur.

Mendel, completing what the horticulturalists and botanists Fairchild, Kölreuter, Knight, Goss, Laxton, Gärtner, Naudin and Wichura had begun, was able to show conclusively that organic

inheritance in the higher, sexually reproducing, plants was particulate, the hereditary determinants behaving as units. He showed that when the hybrid offspring of the same parents of pure descent were crossed with one another it was always possible to reclaim among their progeny individuals that bred true to the parental types; that when the parents differed in respect of several characters, these were combined in various ways in the second hybrid generation and that since some of the individuals displaying each of these combinations were capable of breeding true to type, new combinations of characters could be fixed. He showed also that, when the parents differed from each other in respect of a single character, the inter-crossing of the first generation hybrids produced a second hybrid generation in which a constant proportion of the two parental types could confidently be expected.

CHAPTER 4

THE RE-DISCOVERY OF MENDELISM

MENDEL'S paper on his hybridization experiments with the garden pea, published in 1866, remained unnoticed by the scientific world until 1900. During these intervening thirty-four years many developments in biological science occurred and had prepared the way for the re-discovery of Mendel's law of segregation. In 1866 the eminent German biologist Ernst Haeckel published his *General Morphology* in which he stated that the nucleus was that part of the cell that was responsible for heredity. In the 1870's aniline dyes and oil immersion lenses and condensers were developed and with their aid botanists and zoologists, for example, Weismann, Oscar Hertwig, Strasburger and von Kölliker, in Germany, began to study the chromosomes and their behaviour and observed that in respect of their number there was a constancy that strongly suggested that they formed the basis of heredity and development. In 1883 Wilhelm Roux, in his book *Über die Bedeutung der Kernteilungsfiguren* (The significance of the division of the chromosomes), reasoning from the longitudinal mode of division of these chromosomes, inferred that they must contain qualitatively different hereditary determiners, arranged in a linear order.

The cell, the architectural unit of which the animal and plant is built, consists essentially of a spherical body, the nucleus (L. kernel), lying in a viscous substance, the cytoplasm (Gk. *kytos*, hollow; *plasma*, mould). The nucleus of the resting cell (one that is not dividing) appears in microscopic preparations as a vesicle containing a fine network of delicate threads on which are borne minute masses of chromatin (Gk. *chroma*, colour). At one side of the nucleus is a small area of cytoplasm known as the attraction sphere, the division of which into two heralds the inception of cell-division. As the two

attraction spheres, thus formed, separate, they seem to draw out the surrounding cytoplasm into a spindle of fine fibrils. While this is happening changes are taking place in the nucleus; the tangled skein of fine threads becomes resolved into a number of filaments of definite shape, the chromosomes (Gk. *chroma*, colour: *soma*, body), and these are seen to be splitting along their length. These chromosomes become progressively stouter and more consolidated and arrange themselves on the equator of the spindle. The longitudinal splitting of the chromosomes yields daughter chromosomes and these separate to pass to opposite poles of the spindle. The cell itself begins to divide and the chromosomes begin to spin out again into fine threads to become the nuclei of the two daughter cells so formed. Each of the chromosomes in the nucleus of one cell generation is structurally continuous with a corresponding chromosome in the nucleus of one of the preceding and succeeding cell-generations.

In 1893 there appeared the English edition of the German zoologist August Weismann's *The Germplasm* which gave strong support to Roux's teaching, presenting the view that the mechanism of inheritance was controlled by a special material that was particulate (consisting of a multitude of small parts) and that it was not distributed throughout the entire cell. This hereditary material—germplasm—was carried in the nucleus but not in the whole of it. Only the chromosomes bore the hereditary particles. The hereditary carriers were actually in the chromatin granules which were qualitatively different. They were divided equally whenever the chromosomes split longitudinally. The number of these carriers was constant and characteristic of the species. The number of the hereditary determiners had therefore to be halved in the formation of the egg and the sperm, but their number was restored by the fusion of the nuclei of these two cells during the process of fertilization. The halving of the hereditary particles was effected in one of the peculiar cell-divisions which preceded gametogenesis (the formation of the gametes) where the chromosomes did not split longitudinally though the cell itself divided.

In 1896 in the first edition of his book *The Cell*, the American

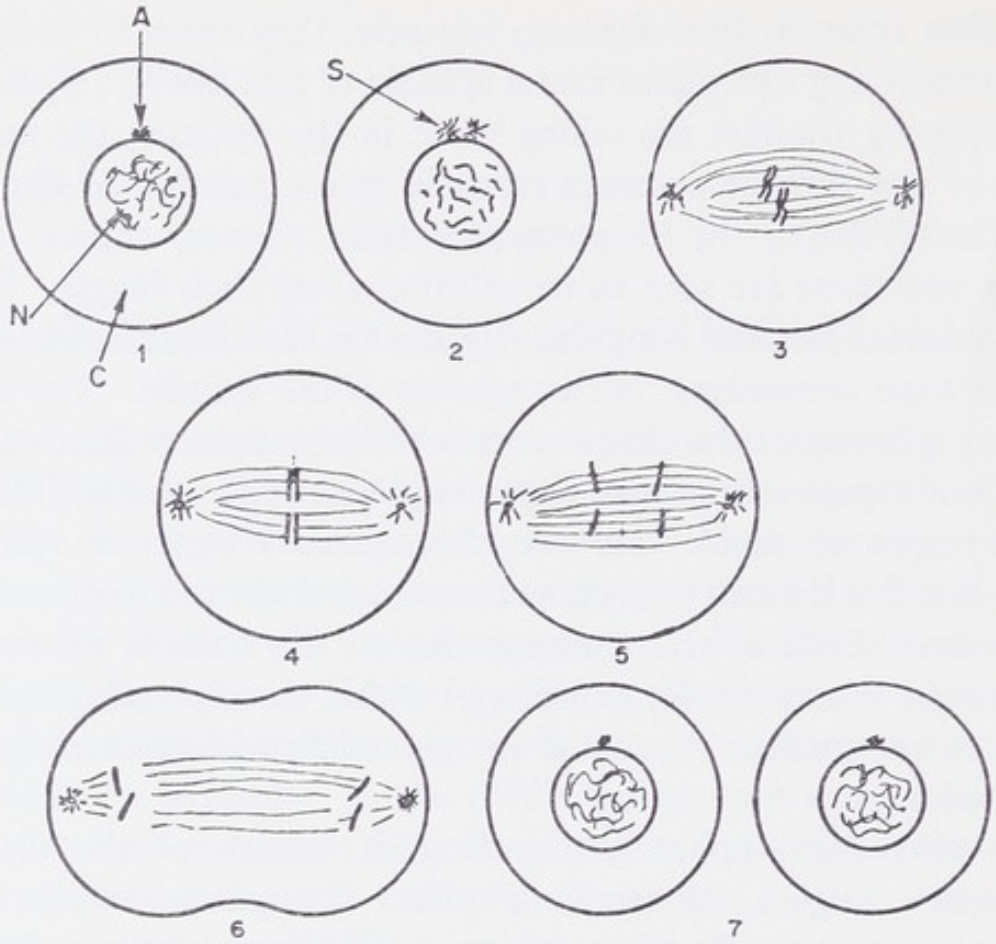


FIG. 5. Mitosis. (For the sake of clarity only one pair of chromosomes is depicted.)

1. The resting cell (before cell-division begins). Within the cell-wall and lying amid the cytoplasm *C* is the nucleus, *N*, the controlling centre of the cell. Enclosed within the nuclear membrane is a skein of fine threads, the chromosomes. Close to the nuclear membrane is the attraction sphere *A* from which, later, the spindle is formed.
2. Cell-division begins, the chromosomes become more consolidated and begin to divide longitudinally while the spindle *S* is formed.
3. The membrane enclosing the nucleus disappears, the spindle extends across the centre of the cell and the chromosomes become shorter and stouter.
4. The chromosomes come to lie along the equator of the cell and the split along their length is completed, each of the chromosomes forming two daughter chromosomes.
5. The daughter chromosomes separate.
6. The cell-body becomes restricted about its middle and so begins to divide into two daughter cells.
7. Cell-division is complete, the daughter chromosomes becoming diffuse as the nuclei of the two daughter cells form to enter into the resting stage.

cytologist Wilson summarized the views of the more progressive biologists of his day in the following words:

> In its physiological aspect therefore inheritance is the recurrence in successive generations of like forms of metabolism and this is effected through the transmission from generation to generation of a specific substance or idioplasm which we have seen reason to identify with chromatin. This remains true however we may conceive the morphological nature of the idioplasm—whether as a microcosm of invisible germs or pangens as conceived by de Vries, Weismann and Hertwig, as a storehouse of specific ferments, as Dreisch suggests, or as a complex molecular substance grouped in micellae, as in Nägeli's hypothesis. It is true, as Verworn insists, that the cytoplasm is essential to inheritance; for without a specifically organized cytoplasm the nucleus is unable to set up specified forms of synthesis. This objection which has already been considered from different points of view, both by de Vries and Dreisch, disappears as soon as we regard egg cytoplasm as itself a product of the nuclear activity; and it is just here that the general role of the nucleus in metabolism is of such vital importance to the theory of inheritance. If the nucleus be the formative centre of the cell, if nutritional substances be elaborated by or under the influence of the nucleus while they are built into the living fabric, then the specific character of the cytoplasm is determined by that of the nucleus, and the contradiction vanishes. In accepting this view we admit that the cytoplasm of the egg is, in a measure, the substratum of inheritance, but it is only so by virtue of its relation to the nucleus which is, so to speak, the ultimate court of appeal. The nucleus cannot operate without a cytoplasmic field in which its peculiar powers may come into play; but this field is created and moulded by itself. Both are necessary to development; the nucleus alone suffices for the inheritance of specific possibilities of development.

While Mendel's paper lay dormant and unnoticed, hybridization experiments, very much like his own, were carried out by Charles Darwin in England, Vilmorin in France, Rumpau in Germany and Bohlin in Sweden.

Darwin was interested in the phenomenon of prepotency in the inheritance of characters (L. *prae*, before; *potens*, powerful: in this context "prepotency" means the same as dominance). In his *Animals and Plants under Domestication* (1868) he gave an account of certain experiments he had carried out with the snapdragon (*Antirrhinum*). One variety of this plant is known as the peloric (Gk. *pelorios*, monstrous; a flower which normally is irregular and becomes regular). He crossed this variety with the

common form both ways, peloric pollen on the common form and common form pollen on the peloric. He raised two beds of seedlings, and observed that not one of these plants was peloric. He carefully examined the ninety plants in the two beds, and noted that the structure of the flowers had not been in the least affected by the cross.

> It must not be supposed that this entire obliteration of the peloric structure in the crossed plants can be accounted for by any incapacity of transmission; for I raised a large bed of plants from the peloric Antirrhinum, artificially fertilized by its own pollen, and sixteen plants, which alone survived the winter, were all as perfectly peloric as the parent plant. Here we have a good instance of the wide difference between the inheritance of a character and the power of transmitting it to crossed offspring.
>
> The crossed plants (F_1) which perfectly resembled the common snapdragon, were allowed to sow themselves; and out of 127 seedlings, 88 proved to be common snapdragons, 2 were in an intermediate condition between the peloric and normal state, and 37 were perfectly peloric, having reverted to the structure of their one grandparent.

It will be noted that the ratio 88 : 37 is not far removed from that of 3 : 1, but it could acquire a meaning only when interpreted in Mendelian terms.

Vilmorin actually got the 3 : 1 ratio. His experiments with *Lupinus* (Lupins) were reported in 1879.* In the F_2 the red and the blue flower colours had appeared in these proportions, but Vilmorin drew no fundamental inference from this observation.

Dr. Wilhelm Rumpau, a prominent German breeder of agricultural plants, in his book *Kreuzungsprodukte landw. Kulturpflanzen* (Hybridization Products of Agricultural Plants) (1891), recorded the constant dominance of certain characters in cereals and leguminosae and cited Focke's *Pflanzenmischlinge* extensively without mentioning Mendel at all. In his book *Svalof* (1886–1946), Professor Åkerman states that a Swedish plant breeder named Pehr Bohlin, in association with Hans Tedin, reported on their extensive crossing experi-

* Vilmorin left copious notes concerning these experiments during the years 1856–60. His son gives an account of this work in: M. H. Vilmorin, *Société Nationale d'Agriculture de France: Note sur une expérience relative à l'étude de l'hérédité dans les végétaux*, Paris, Imprimerie de Madame Bouchard-Huzard, Jules Tremblay, Gendre et Successeur (1879).

Åkerman, A. and Mackey, J. *Svalof* (1886-1946) Lond (1948).

ments with barley, peas and sweet peas during the later years of the nineteenth century at the Agricultural Congress held in Stockholm in 1897. In this report it was stated that "in the F_1 there was no variation while the forms appearing in the F_2 and subsequent generations represented all possible combinations of the parental characteristics and could be predicted with almost mathematical accuracy".

The Dutch botanist, Hugo de Vries, for several years before 1900, had been actively engaged in research which included studies of hybridization. As early as 1898 he had noted in his experiments with *Oenothera* (Evening Primrose) the dominance of one of two contrasted characters, the uniformity of the F_1 and the segregation of the P_1 characters in the F_2 with its 3 : 1 ratio. He obtained the same results in the experiments involving many other plant hybrids. It was when this work was completed and the results were being prepared for publication that Professor de Vries received a letter from his friend Professor Beyerinck of Delft, together with a copy of Mendel's original paper. "I know that you are studying hybrids so perhaps the enclosed report of the year 1865 by a certain Mendel, which I happen to possess, is still of some interest to you." Reading this paper de Vries found that his results, which he thought to be quite new, had been reported thirty-five years before.

He published a preliminary note concerning his experiments and the results he had obtained in the *Comptes Rendus de l'Académie des Sciences, Paris,* on 26 March 1900 under the title *Sur La Loi de Disjonction des Hybrides.* In it de Vries states that:

> The specific characters of organisms are composed of separate units. One is able to study experimentally these units either by the phenomena of variability and mutability or by the production of hybrids. In the latter case one chooses in preference hybrids from parents which are distinguishable from each other by only a single character or by a small number of well-defined characters and for which one considers only one or two of the units and leaves the others aside.
>
> In the hybrid the simple differential character from one of the parents is visible or dominant while the antagonistic character is in the latent condition or recessive. Each pollen grain and each oosphere receives only one of the two antagonistic characters. Pollen and ovule are not hybrid but have the pure character of one of the parents.

Parent with the Dominant Character	Parent with the Recessive Character	Proportion of the F_2 with the Recessive Character
Agrostemma githago	*A. nicaeensis*	24 per 100
Chelidonium majus	*C. laciniatum*	26
Coreopsis tinctoria	*C. brunea*	25
Datura tabula	*D. stramonium*	28
Hyoscyamus niger	*H. pallidus*	26
Lychnis diurna (red)	*L. vespertina* (white)	27
Lychnis vestertina (hairy)	*L. glabra*	28
Oenothera lamarckiana	*Oe. brevistylis*	22
Solanum nigrum	*S. chlorocarpum*	24
Trifolium pratenae	*T. album*	25
Veronica longifolia	*V. alba*	22

> One sees that the proportion of the hybrids with the recessive character is always close to 25 per cent. [By hybrids de Vries here means the F_2, the first generation produced by the F_1 hybrids.] The culture of a further generation permits the study of a distinction among the 75 per 100 individuals presenting the dominant character. The results obtained can be explained if it be assumed that the two antagonistic qualities, dominant and recessive, are distributed mutually exclusively in equal parts to the pollen just as to the ovules.

de Vries goes on to say that there will be 25 per 100 homozygous dominants, 50 per 100 heterozygous dominants and 25 per 100 recessives and that only by raising this further generation can the distinction between the two kinds of individuals displaying the dominant character be made. "The totality of these experiments establishes the law of segregation of hybrids and confirms the principles that I have expressed concerning the specific characters considered as being distinct units."

In this preliminary account of his experimental hybridization work de Vries fails to mention Mendel, but he does so in a more detailed account, *Das Spaltungsgesetz der Bastarde* (The Law of the Segregation of Hybrids), published about the same time (25 April 1900) in the *Berichte Deutschen Botanischen Gesellschaft* (Reports of the German Botanical Society). In this he makes much of the degree of agreement there existed between his results and those of Mendel. In his book on Plant breeding (*Pflanzenzuchtung*) published in 1907, de Vries does not even mention Mendel's name and in the

following year he somewhat brusquely declined to sign a petition for the erection of a Mendel memorial in Brünn.

Professor Correns was a German botanist of high repute who was particularly interested at this time in xenia (Gk. *xenios*, hospitable), the phenomenon in which the pollen seems to affect the tissue of the ovary, the seed or even the fruit, as distinguished from the embryo itself. For example, in the case of the domestic fowl, it has been suggested that the eggs laid by a hen are influenced as to size, shape and colour by the male with which she is mated. He had therefore crossed varieties of peas and maize and observed the regularity with which the parental characters reappeared in the F_2. He had read the section on xenia in Focke's book and had encountered the reference to Mendel and his pea hybrids. He took steps to get hold of Mendel's paper and reading it he, like de Vries, found that his results and his conclusions were not new after all. He had been working with his pea hybrids for four years when in October 1899 the explanation of the 3 : 1 ratio suddenly "like lightning" came to him after a sleepless night. Correns had also observed an intermediacy of characterization in the F_1 in addition to dominance and the existence of characters that passed from generation to generation linked or coupled together as well as those that displayed independent assortment and recombination. With maize he got the 9 : 3 : 3 : 1 ratio in the F_2.

On 21 April 1900 Correns received a reprint of de Vries' *Sur La Loi de Disjonction des Hybrides* and this led him to send on the following day his almost finished paper *Gregor Mendel's Regel über des Verhalten der Nachkommenshaften der Rassenbastarde* (Gregor Mendel's Rule on the Behaviour of the Progenies of Hybrids) to the editor of the *Berichte der Deutschen Botanischen Gessellschaft*. The paper was presented at the meeting of 27 April and appeared in the May issue of the journal. It was Correns who, along with Tschermak, suggested the terms Mendelism and Mendelian laws to define the generalizations framed by Mendel. He writes:

> In noting the regular succession of the phenomena [of hybridization] and finding an explanation for them, I believed myself, as de Vries believes himself, to be an innovator. Subsequently, however, I found

that in Brünn during the sixties Abbot Gregor Mendel, devoting many years to the most extensive experiments on peas, had not only obtained the same results as de Vries and myself, but had actually given the very same explanation, so far as this was possible in the year 1866. This paper of Mendel's to which Focke refers (though without justice to its importance) in his *Pflanzenmischlinge* is among the best works ever written upon the subject of hybrids.

[It is of interest to note that Correns had been a favourite pupil of Nägeli, the man who had done so much to discourage Mendel.]

The Austrian botanist von Tschermak had spent two years working on the commercial seed farms in Stendal and Quedlinburg and had visited Dr. Wilhelm Rumpau, the cereal breeder. Professor Renard of Ghent University, a friend of Tschermak's father, suggested that the young man should spend some time on the fruit and flower farms around that city. But since this activity did not occupy him fully he asked the Director of the Ghent Botanic Garden for permission to begin crossing experiments in the garden in order to study the growth-promoting effects of foreign pollen described by Darwin in his *On the Effects of Cross and Self-pollination in the Plant Kingdom* and also the xenia problem in peas. Receiving permission he began his experiments and the Garden authorities sent the seeds that were harvested to Tschermak in Vienna.

He spent the year 1899 mainly in the private garden of a Viennese banker who encouraged him to continue his pea crosses in pots and also in the garden. At this time Tschermak was waiting for the opening of an experimental station in Esslingen near Gross-Enzerdorf, for he had hopes of obtaining a post on its staff. He was appointed to the staff of this experimental station in 1900 and continued his experiments.

In studying the results of my pea crosses in the autumn of 1899 I discovered the 3 : 1 ratio for yellow and green cotyledons and for smooth and wrinkled seeds as well as the 1 : 1 ratio in backcrosses of the green cotyledon peas with hybrid pollen in the second seed generation of all my experimental crosses.

While recording these results I saw the citation of Mendel in Focke's book and obtained from the University Library the volume of *Naturforschender Verein in Brünn* containing Mendel's paper. There I read, to my great surprise, that Mendel had already carried out such experiments much more extensively, had noted the same regularities and had already given the explanation for the 3 : 1 segregation ratio. This

was the first surprise I encountered during the preparation of my habilitationschrift (a thesis embodying post-graduate research) which I hastened to complete so that I could hand it in to the editors of the institute's journal on January 17th, 1900.

In March Tschermak saw a reprint of de Vries' *Sur La Loi de Disjonction des Hybrides* which, it will be remembered, contained the terms dominant and recessive. Tschermak therefore concluded that, though no acknowledgment was made, de Vries was aware of Mendel's paper and had adopted these terms. "Naturally I hurried to the editor's office on the same day in order to obtain the already corrected thesis for immediate publication. The editor of the *Zeitschrift fur das landw. Versuchswesen in Osterreich* accepted the paper for publication."

In the meantime the fuller and more detailed paper of de Vries appeared in the March issue of the *Berichte der Deutschen Botanischen Gesellschaft*. While reading the proofs of his own paper Tschermak came across Corren's paper *Gregor Mendel's Regel*, etc. in May. He therefore prepared an abstract of his own paper for appearance in the June number of the *Berichte*. He sent reprints of his paper *Über Kunstliche Kreuzung bei Pisum sativum* (On Artificial Crossing in *Pisum sativum*) which had appeared in the *Zeitschrift fur das landw. Versuchswesen* to de Vries and Correns in order to prove that his re-discovery of Mendel had occurred at the same time as theirs. An amicable discussion between Correns and himself at a scientific conference in 1903 removed all possible causes of disagreement and misunderstanding.

Mendel's original paper was republished in *Flora*, 89, 364 (1901).

However, the major textbooks on botany and plant breeding that were published about this time, e.g. those of Strasburger and v. Wettstein, mentioned only the names of de Vries and Correns in this connection and Tschermak found it necessary to protest and to claim his place along with them.

The simultaneous and completely independent arrival by Correns, de Vries and Tschermak at conclusions identical with those reached by Mendel thirty-five years previously and based upon experimentation identical in respect of design with his, is an example of a happen-

ing that is not infrequent in the scientific field. In 1900 the time was "ripe" for the enunciation of Mendel's principles of heredity; in 1865 it was not. In 1865 only the very exceptional man, years ahead of his time, could have thought as Mendel did and acted as he did in the pursuit of his ideas; in 1900 if these three men had not sought answers to the same questions as had intrigued Mendel, others would undoubtedly have done so within a very short time. For example, in Cambridge, Bateson* had been carrying out experiments very similar indeed to those of Mendel which would have shortly led him, almost inevitably, to the same conclusions, for he was examining the very same problems.

* Bateson, W., Hybridization and cross-breeding as a method of scientific investigation, *J. Roy. Hort. Soc.* **24** (1899).

CHAPTER 5

MENDELISM: EXPANSION AND MODIFICATION

As soon as the work of Correns, de Vries and Tschermak became known, a keen interest in problems of heredity was at once awakened and many biologists in many countries began to repeat and to extend Mendel's experiments and to demonstrate that his Law of Segregation applied to all kinds of living things, including man himself. At the same time animal and plant breeders began to turn hopefully to the new and rapidly developing science for help in the solution of their problems. In England, France, Germany and the United States of America, especially, the re-discovery of Mendelism acted as a great stimulus to research relating to heredity, variation and animal and plant breeding.

In the United States, at Cold Spring Harbor, Long Island, New York, a Station for Experimental Evolution was founded and the American Breeders' Association was formed to improve animal and plant stocks, its membership consisting of professional scientists and animal and plant breeders. It was not long before accounts of Mendelian experiments began to appear in the scientific journals, submitted by men who were to be long remembered for the value of their contributions to the development of genetics, A. F. Blakeslee, W. E. Castle, C. B. Davenport, R. A. Emerson, E. M. East, H. D. Goodale, F. E. Lutz, T. H. Morgan, Raymond Pearl, Oscar Riddle, G. H. Shull, W. J. Spillman and A. H. Sturtevant among them.

By 1910 the extraordinary value of *Zea mays* and *Drosophila melanogaster* in genetical studies had become recognized and as a result of the very skilful and extensive use of this material by the American biologists by 1920 the American contributions to genetics

had come to overtop in both volume and importance those coming from all other parts of the world. It was in the early years of the century that Professor W. E. Castle of Harvard University used the fruit-fly *D. melanogaster* in investigations dealing with the effects of inbreeding and of outcrossing. The attention of Professor Thomas Hunt Morgan of Columbia University was attracted to this fly as a laboratory animal. At the meeting of the American Breeders' Association in 1909 Morgan questioned the reality of the existence in the chromosome or elsewhere in the germ cells of the supposed material bodies responsible for the production of mendelizing characters. This is a matter of historical interest, for not so very long afterwards he and his colleagues in the Zoology Department of Columbia University, New York, working with *D. melanogaster*, were to show beyond all possible doubt that the chromosomes were, in fact, the vehicles that carried the material particles that constituted the factors of Mendel.

The American Breeders' Association came to an end in 1909 and was succeeded by the American Genetic Association. Similar scientific societies were formed in many of the European countries and to the subject of Genetics many of the younger biologists were attracted.

In Germany, Holland and Austria respectively, Correns, de Vries and Tschermak continued to be very active, and from France in 1902 came Cuénot's* paper on the inheritance of coat-colour in the mouse, important because it broke new ground.

In England an interesting situation had developed in scientific circles. Following the acceptance of the doctrine of evolution, brought about by natural selection upon a continually varying material, there had come into being a school of biometry which seemed to be turning biology into a branch of mathematics. Francis Galton, a cousin of Charles Darwin, had attempted to give precision to the terms variation and heredity by proposing The Law of Ancestral Heredity which postulated that there was to be discovered a definite degree of resemblance, statistically measurable, in any

* Cuénot, L., La Loi de Mendel et l'hérédité de la pigmentation chez les souris, *Arch. Zool. Exper.* 3 (1902).

familial relationship. Galton* had studied the inheritance of coat-colour in the Basset Hound. In this breed there were two coat-colour patterns, the tri-colour and the non-tricolour, the first consisting of black and yellow markings on a white ground and the second having no black. Galton examined the numbers of these two types in families of various compositions. His figures indicated that there was a close correspondence between the numbers of the two types among the offspring and the numbers of the two types in the pedigrees of the parents. He found that, knowing the ancestral composition of the two parents, it was possible to predict with considerable accuracy the numerical proportions in which the two types would appear among the progeny. On the average the contribution to the progeny of each ancestor was of the order of one-quarter for each of the parents, one-sixteenth for each of the grandparents and one sixty-fourth for each of the great-grandparents and so on, the total heritage being reckoned as unity.

This law supported the orthodox Darwinian position that natural selection worked by the accumulation of small continuous variations. Though Darwin had recognized "sports", instances of discontinuous variation, his chief emphasis was placed upon small variations by the accumulation and mutual supplementation of which, he thought, the major distinction between the species had come about. This view was held by all the botanists and zoologists in Britain, save one, William Bateson, at this time deputy to the Professor of Zoology in the University of Cambridge. Bateson, a fellow of St. John's, Cambridge, had been elected to the Balfour studentship in 1887 and for the next seven years had devoted himself to the patient collection of facts relating to variation in animals and plants, combing through museums, private collections and libraries for examples, attending poultry, flower, cage-bird and other shows and corresponding with and visiting breeders and fanciers, amateur and professional, picking their brains. As his information accumulated he became more and more persuaded that discontinuous variation was far more common than had been supposed and that it had played a far greater role in

* Galton, F., The average contribution of each several ancestor to the total heritage of the offspring, *Proc. Roy. Soc.* **61,** 401 (1897).

providing the raw materials for evolution than had been thought. In 1894 his *Materials for the Study of Variation* was published. It constituted a direct challenge to orthodoxy and was accepted as such by W. F. R. Weldon.

Weldon, a few years senior to Bateson, had been with him at St. John's. They were then great friends. Weldon had become a lecturer in the Zoology Department and had given much help and encouragement to Bateson. Weldon later proceeded to the chair of Zoology first in University College, London, and later at Oxford. He became the champion of the Darwinian continuous variation school and as such came to regard Bateson as the enemy and the friendship that had existed between them dissolved in bitterness. It has to be recorded that the book *Materials for the Study of Variation* met with no success, the professors and lecturers of the day did not introduce their students to it and they themselves regarded its teaching as rank heresy.

The first clash between the antagonists was in 1895 over the question of the origin of the cultivated *Cineraria*, the disputation enlivening the columns of *Nature*. The strict Darwinian held that the different forms had evolved in the hands of the horticulturalist working slowly and consistently towards the ideal that he had in mind from a wild species through the gradual accumulation of small continuous variations. Bateson, the rebel, maintained that many of them had arisen through hybridization between different recognized species. In support of his contention he was able to call upon the results obtained in experiments undertaken by the curator of the Cambridge Botanic Garden. Bateson, realizing that the question would never be settled by argument, turned to experimentation, helped by Miss Saunders, Newnham lecturer in Botany.* Stocks, the sweet pea and poultry were selected as experimental material and hybridization experiments were begun.

Bateson took a great interest in the affairs of the Royal Horticultural Society. This organization convened the first international Conference on Hybridization in July 1899 in London at which

* Bateson, W. and Saunders, E. R., *Reports to the Evolution Committee of the Royal Society*, No. 1 (1902).

Bateson read a paper on "Hybridization and crossbreeding as a method of scientific investigation". This showed clearly the similarity between his ideas, his experimental methods and aims and those of Mendel. A year later, in May 1900, he gave a lecture to this society on "Problems of heredity as a subject for horticultural investigation".* His lecture notes had already been carefully prepared, as was his habit, but in the train on the way to London he read Mendel's paper on the pea. He immediately saw that Mendel's ideas and results provided overwhelming support for his own views concerning the importance of discontinuous variation and therefore incorporated the news of the re-discovery of Mendelism and a critical assessment of its significance into his lecture, sharing with his audience his breathless excitement and unbounded joy. The Society published an English translation of Mendel's pea paper (1901).

Weldon, realizing that Mendel's work constituted a very serious threat to the biometrical school, at once set out to belittle it in a paper, "Mendel's laws of alternative [*sic*] inheritance in peas" in the journal *Biometrika*. In reply Bateson, after having repeated certain of Mendel's experiments, published a small book *Mendel's Principles of Heredity: A Defence with a Translation of Mendel's Original Papers on Hybridisation*, Camb. Univ. Press (1902). Weldon retorted with two papers in *Biometrika*, "On the ambiguity of Mendel's categories" and "Mr. Bateson's revisions of Mendel's theory of heredity". Bateson's reactions to these were described in a letter to the editor of *Nature* for publication. But the editor was "not prepared to continue the discussion on Mendel's Principles and therefore returns herewith the papers recently sent to him by Mr. Bateson".

Since Bateson could not obtain publication in *Biometrika*, now that the columns of *Nature* were closed to him, the only media open to him were the *Cambridge Philosophical Transactions* and the *Reports of the Evolution Committee of the Royal Society*.

In 1894 the Royal Society, at the instigation of Galton, had set up a committee for conducting statistical inquiries into the measur-

* *J. Roy. Hort. Soc.* **25,** Pts. 1 and 2 (1900).

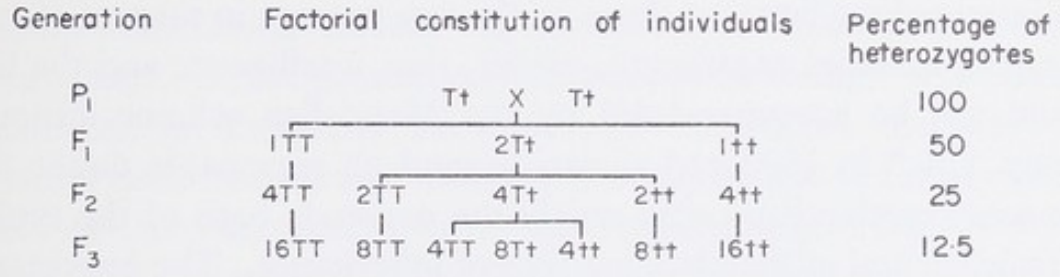
able characteristics of animals and plants. Bateson had been invited to become a member in 1897, but although at this time it seemed likely that an experimental station would be established in connection with the committee, he declined since the committee was concerned with methods of investigation that did not appeal to him. Weldon was a member. Later the committee was reconstituted as the Evolution Committee and the scope of its inquiries was widened. Bateson then became a member, later serving as its secretary. Weldon resigned and with Professor Karl Pearson of University College, London, founded *Biometrika*.

Weldon, following Bateson's example, turned to experimentation. He enlisted the help of a young zoologist named Darbishire who was to work under his direction. A cross was made between the albino and the agouti varieties of the tame mouse and the F_2 gave the 3 : 1 ratio with 75 per cent agoutis and 25 per cent albinos. Then the F_2 agoutis, and those of subsequent generations, were interbred *en masse* and it was observed that the proportion of albinos among the progeny progressively diminished until eventually there were none at all. Weldon held that this completely disproved the Mendelian doctrine. In the columns of *Biometrika* and *Nature* the violent argument between him and Bateson was conducted until the editor of the latter journal again refused to publish any more from Bateson. Bateson was right and Weldon wrong, for the fallacy in the latter's experimentation, as eventually became apparent, was that no distinction was made between the homo- and the heterozygous agoutis. According to Mendelian theory, if in a population containing both kinds mating is random, the homozygous form of the agouti will inevitably become progressively relatively more numerous and the recessive albinos progressively fewer.

Inbreeding, the mating of close relatives, increases homozygosity. With every new generation of continued inbreeding, more and more individuals become more and more homozygous for more and more factors until the population has become broken up into a number of lines, each of which is practically homozygous.

For example, if the heterozygous Tall pea (*Tt*) is self-fertilized it can be expected to produce one homozygous Tall, two heterozygous

Talls and one short plant in every four. If it is assumed that every plant produces the same number of progeny, four in this instance, and that self-fertilization is carried through with each plant in each successive generation, the following scheme shows how two homozygous lines (*TT* and *tt*) emerge while the percentage of the heterozygous individuals decreases from 100 per cent to 12·5 per cent in four generations.



As homozygosity is gradually approached the decrease in heterozygosity from one generation to the next becomes progressively smaller. In the case of less close systems of inbreeding, e.g. brother–sister matings, homozygosity is approached more slowly than with self-fertilization.

In the agouti–albino mouse experiment the albinos were removed in each generation, leaving only the homo- and the heterozygous agoutis. Among the first hybrid generation agoutis there would be 100 per cent heterozygotes; among the second, 75 per cent; among the third 40 per cent and among the fourth 23 per cent and so on. As the heterozygotes agoutis progressively decreased in numbers the numbers of recessive albinos produced would inevitably grow fewer and fewer since their only source was the heterozygous agouti × heterozygous agouti mating.

Galton, as head of the biometrical school in England, had been succeeded by Karl Pearson, professor in University College, London. Because of the conflict between the continuous and the discontinuous variation schools a completely unnecessary disputation arose between the biometricians and the Mendelians. Pearson produced two papers of considerable interest in 1900, "On the inheritance of characters not capable of exact quantitative measurement". Pt. II: "On the inheritance of coat-colour in horses"; and Pt. III: "On the inheritance of eye-colour in man", *Phil. Trans. Roy. Soc.* A,

195, 79, but thereafter (1900–3) spent far too much energy in fruitless debate with Bateson on such topics as heredity, differentiation and the fundamental concepts of biology in the publications of the Royal Society and of *Biometrika*. It was not very long before it came to be accepted that for the study of the inheritance of quantitative characters the tools of biometry were essential.

At this time it was generally accepted that this "blending inheritance" in which the characterization of the offspring tends to be intermediate between those of the two parents in respect of such complex qualities as strength, vigour, size, intelligence and the like, could not be accommodated by the Mendelian scheme although Udny Yule* in 1902 had shown beyond all reasonable doubt that the same mechanism could satisfy the demands both of the typical Mendelian and of the blending type of inheritance. The importance of this paper was not recognized and it was not until the later work of Nilsson-Ehle,† East,‡ Emerson§ and Fisher‖ had shown that blending inheritance was in fact essentially Mendelian and that it was controlled by multiple factors which individually lacked dominance that disputation ceased.

Bateson's experimental work had been partially supported by small grants from the Royal Society and from private sources. His applications for support from the other recognized grant-giving bodies of the time had invariably been unsuccessful. In 1903, however, he was offered £150 per year for two years by a private person who was interested in the work. Bateson promptly invited R. C. Punnett, at that time a demonstrator in the zoology department, to join him. The invitation was accepted but the salary declined. However, Punnett was soon to be elected to the Balfour

* Yule, Udny, Mendel's laws and their probable relations to interracial heredity, *New Phytologist* **1**, 193–207 (1902).

† Nilsson-Ehle, H., Einige ergebnisse von kreuzungen bei hafer und weisen, *Bot. Notizen.* 257–94 (1908).

‡ East, E. M., A Mendelian interpretation of variation that is continuous, *Amer. Nat.* **44**, 65–82 (1910).

§ Emerson, R. A. and East, E. M., The inheritance of quantitative characters in maize, *Neb. Agric. Sta. Rep. Bull.* **2** (1913).

‖ Fisher, R. A., The correlation between relatives on the supposition of Mendelian inheritance, *Proc. Roy. Soc. Edin.* B, **52**, 399–433 (1918).

studentship. The work now became greatly expanded as the Batesonian group enlarged to include, besides Miss Saunders and Punnett, L. Doncaster, Bateson's sister-in-law Miss Durham, R. P. Gregory, C. C. Hurst, a horticulturalist in Leicestershire, Miss Killby, R. H. Lock, Miss Marryat, R. Staples-Brown in Oxfordshire, Miss Sollas and Miss Wheldale, most of whom were to make notable and lasting contributions to the developing science.

In 1904 Bateson was president of the Zoology Section of the British Association for the Advancement of Science, meeting in Cambridge. In his presidential address on Heredity, Variation and Selection, he forcefully presented his considered opinions concerning these matters and was supported by certain of his co-workers who proffered accounts of their own experimentation, Miss Saunders on stocks, Hurst on poultry, Punnett on the comb of the fowl. In the following year Bateson submitted to the Royal Society a paper by Hurst on coat-colour in the horse in which it was stated that chestnut was recessive to both bay and brown. Weldon, having examined the records in the studbook, brought forward several instances where chestnut × chestnut had yielded bays or browns. Hurst maintained that in these instances the recording had been at fault. Bateson thereupon withdrew the paper, studied the studbooks, satisfied himself that Hurst was right and resubmitted the paper which was read at the meeting of the Society on 18 January 1906 when a lively discussion took place in which Bateson took a prominent part.

Weldon died suddenly and unexpectedly in 1906; the long and unhappy disputation came to an end and further and inevitable development in Britain of the science to which Bateson gave the name Genetics (Gk. *genesis*, descent) was thereafter unimpeded. It was in a letter written in April 1905 concerning the title of a professorship relating to heredity and variation, then being considered by the university authorities, that Bateson first suggested Genetics.* A year later, in his inaugural address to the Third International Conference on Hybridization (the Crossbreeding of Genera or Species) held in London, he repeated this suggestion publicly:

* Bateson, Beatrice, *William Bateson, F.R.S., Naturalist*, p. 93.

> I suggest for the consideration of this Congress the term Genetics, which sufficiently indicates that our labours are devoted to the elucidation of the phenomena of heredity and variation: in other words to the physiology of Descent, with implied bearing on the theoretical problems of the evolutionist and systematist, and application to the practical problems of breeders, whether of animals or plants. After more or less indirect wanderings, we have thus a definite aim in view.

It is of interest to note that the first of these international conferences had been held in London in 1899 (The International Conference on Hybridization (the Cross-breeding of Species) and on the Cross-breeding of Varieties); the second in New York in 1902 (the International Conference on Plant-breeding and Hybridization); and the third, the one referred to above, in 1906. This last was the first which had the term Genetics in the title of its proceedings. Since that time, these international congresses have invariably used it and none other. In these changes in the title of these congresses is revealed the historical relationship of plant hybridization and genetics.

The reports to the Evolution Committee of Bateson and his colleagues during the period 1905–8 were all close packed with new knowledge. In the hands of Bateson and Punnett,* the fowl made a number of interesting and important contributions to expanding Mendelism as it did also in the hands of Davenport at Cold Spring Harbor. For example, there are several kinds of comb in the fowl, the single, as that of the Leghorn, the rosecomb of the Wyandotte, the peacomb of the Indian Game and the walnutcomb of the Malay. Rose and single constitute a pair of Mendelian characters, rose being dominant. Peacomb and single constitute another pair of characters, pea being dominant. When individuals with rose and with pea combs are crossed all the offspring have walnut combs and when these walnuts are allowed to produce an F_2, walnuts, roses, peas and singles appear in the proportions 9 : 3 : 3 : 1. Pea and rose must therefore differ from each other in respect of the two factors for this ratio is typical of a di-hybrid experiment. The appearance

* Bateson, W., Saunders, E. R. and Punnett, R. C., Experimental studies in the physiology of heredity: poultry and sweet peas, *Reports to the Evolution Committee of the Royal Society*, Nos. 2, 3 and 4 (1905–8).

of the single comb in the F_2 was somewhat disconcerting for neither of the P_1 individuals had this character. The explanation offered was as follows:

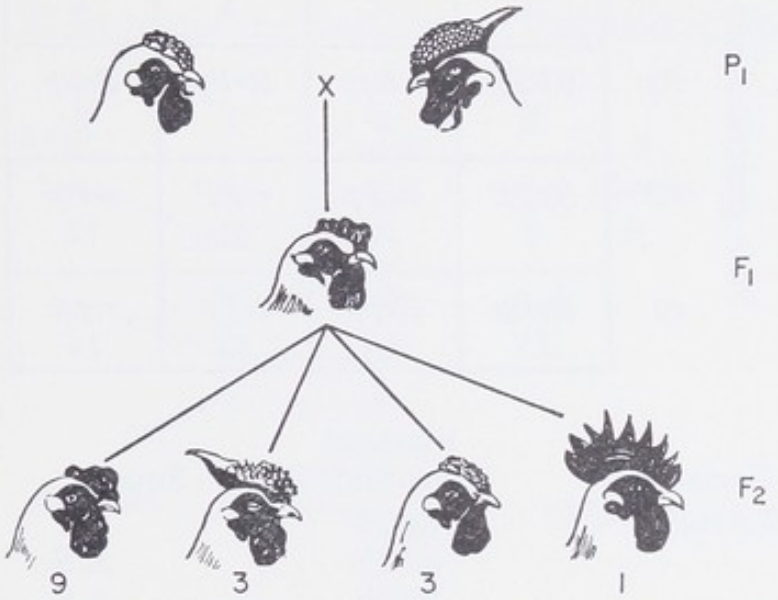
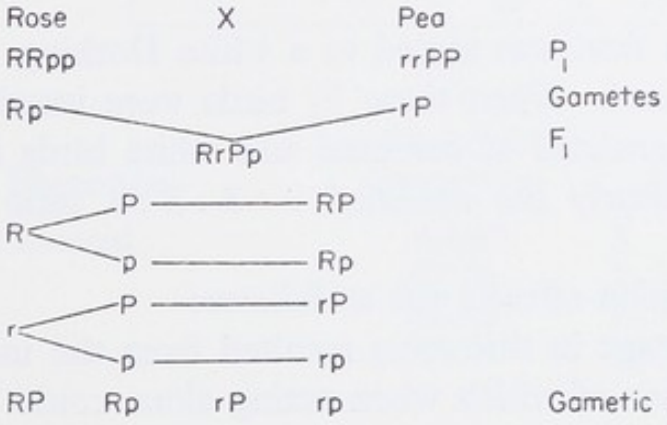


FIG. 6. Peacomb × Rosecomb in the fowl: an instance of factor interaction.

All combs fundamentally are singles, all other kinds are modified singles. The factor *R* is responsible for transforming a single into a rose, the factor *P* is responsible for transforming a single into a pea. The factors *R* and *P* together transform the comb into a walnut (an instance of factor interaction). When neither of these factors is present in the factorial constitution of a fowl its comb is a single.

A homozygous rosecombed bird has the constitution *RRpp* (rose but not pea); a homozygous peacombed bird has the constitution *rrPP* (pea but not rose).



Female gametic series

Male gametic series	*RP*	*Rp*	*rP*	*rp*
RP	*RRPP* 1	*RRPp* 2	*RrPP* 3	*RrPp* 4
Rp	*RRPp* 5	*RRpp* 6	*RrPp* 7	*Rrpp* 8
rP	*RrPP* 9	*RrPp* 10	*rrPP* 11	*rrPp* 12
rp	*RrPp* 13	*Rrpp* 14	*rrPp* 15	*rrpp* 16

F_2

Phenotype	Factorial constitution	Square	Total
RP Walnut	*RRPP*	1	1
	RRPp	2, 5	2
	RrPP	3, 9	2
	RrPp	4, 7, 10, 13	4
			9
R Rose	*RRpp*	6	1
	Rrpp	8, 14	2
			3
P Pea	*rrPP*	11	1
	rrPp	12, 15	2
			3
Neither *R* nor *P* = Single	*rrpp*	16	1
			1

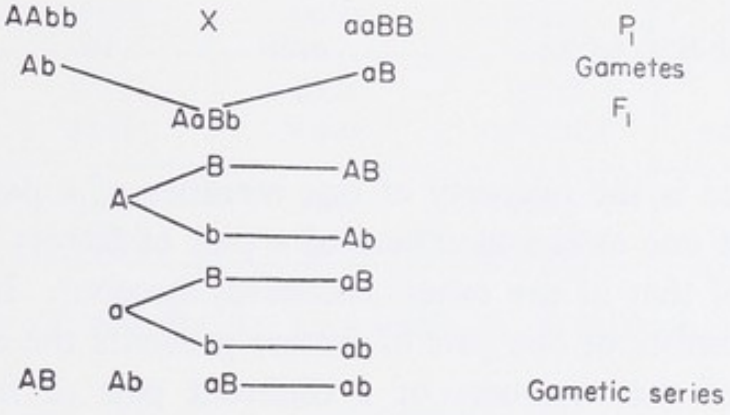
A white Silkie fowl was mated to a white Dorking. All the F_1 birds were coloured. When these F_1 birds were interbred the F_2 thus produced consisted of coloured and white birds in the ratio 9 : 7. This is clearly the modified 9 : 3 : 3 : 1 ratio of the di-hybrid.

The interpretation offered was as follows:

Coloured plumage in this cross resulted from the interaction of two factors neither of which when acting alone could produce its

effect. Each of the two white breeds carried one of these factors and so the cross meant that the complementary factors came together in the F_1.

Let *A* and *B* represent the two factors. The mating was:



Female gametic series

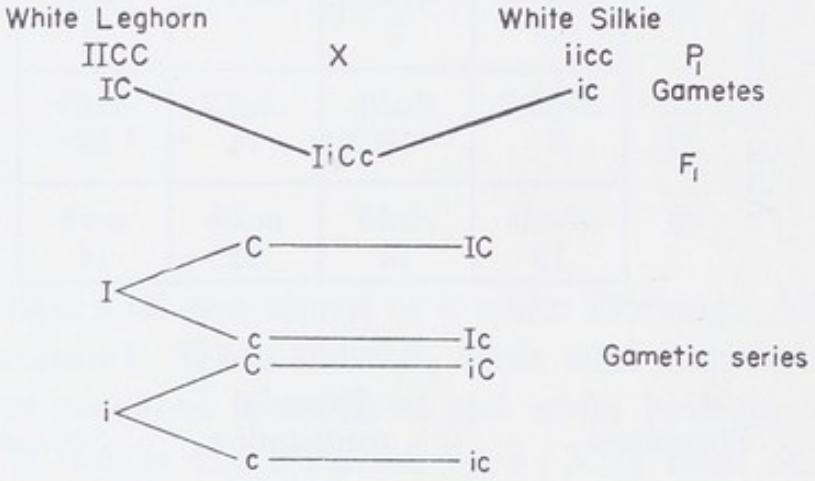
Male gametic series	*AB*	*Ab*	*aB*	*ab*
AB	*AABB* 1	*AABb* 2	*AaBB* 3	*AaBb* 4
Ab	*AABb* 2	*AAbb* 5	*AaBb* 7	*Aabb* 8
aB	*AaBB* 9	*AaBb* 10	*aaBB* 11	*aaBb* 12
ab	*AaBb* 13	*Aabb* 14	*aaBb* 15	*aabb* 16

F_2

Phenotype	Factorial constitution	Squares	Total
A plus *B* = Coloured	*AABB*	1	1
	AABb	2, 5	2
	AaBB	3, 9	2
	AaBb	4, 7, 10, 13	4
			9

A but not *B* = white	*AAbb*	6	1	
	Aabb	8, 14	2	
			3	
B but not *A* = white	*aaBB*	11	1	
	aaBb	12, 15	2	
			3	7
Neither *A* nor *B* = white	*aabb*	16	1	
			1	

Dominance is the property of one member of a pair of factors; the action of one of the members of a pair of factors prevents the expression of that of the other, recessive, member. In certain instances a member of one pair of factors prevents the expression of the action of the members of a different pair of factors. This phenomenon is known as epistasis. For example, the White Leghorn fowl is really a coloured bird, but the action of the factors that produce colour in the plumage is inhibited by that of a dominant factor *I*. The white Silkie, on the other hand, is a coloured bird in which the action of the colour factors is inhibited by a recessive factor *c*. These colour inhibiting factors, one a dominant and the other a recessive, are epistatic to the factors of the two pairs that, were they allowed to do so, would produce coloured birds.



Any bird with the dominant factor *I* will be white. Any bird lacking this factor but possessing the factor *c* in duplicate will be white. A coloured bird must have the constitution *iiCC* or *iiCc*. Of these there are 3 in every 16 on the average; the 13 : 3 ratio is a

Female gametic series

Male gametic series	*IC*	*Ic*	*iC*	*ic*
IC	*IICC* white	*IICc* white	*IiCC* white	*IiCc* white
Ic	*IICc* white	*IIcc* white	*IiCc* white	*Iicc* white
iC	*IiCC* white	*IiCc* white	*iiCC* coloured	*iiCc* coloured
ic	*IiCc* white	*Iicc* white	*iiCc* coloured	*iicc* white

F_2

modification of the 9 : 3 : 3 : 1 due to dominant and recessive epistasis.

Working with the sweet pea Bateson, Saunders and Punnett*

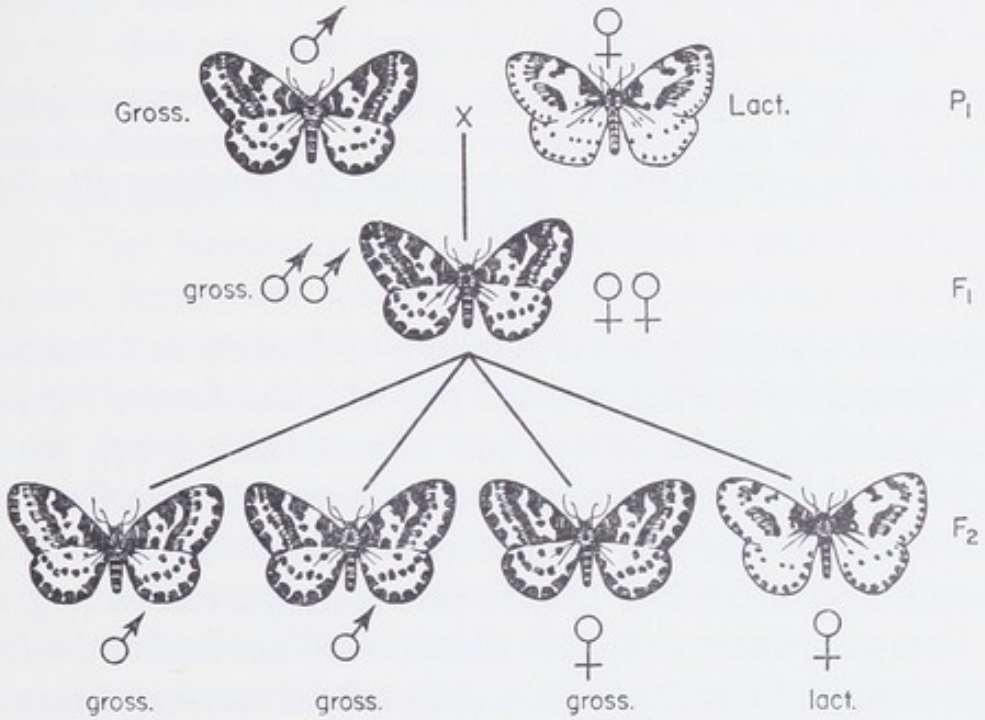


FIG. 7a. Sex-linkage in the currant moth *Abraxas*. The mating *grossulariata* male × *lacticolor* female. The recessive character of the grandmother is displayed by none of her sons or daughters, by none of her grandsons and only by 50 per cent of her grand-daughters. All the *lacticolors* in the F_2 generation are females.

* Bateson, W., Saunders, E. R., and Punnett, R. C., Experimental studies in the physiology of heredity, *Reports to the Evolution Committee of the Royal Society*, No. 3 (1906).

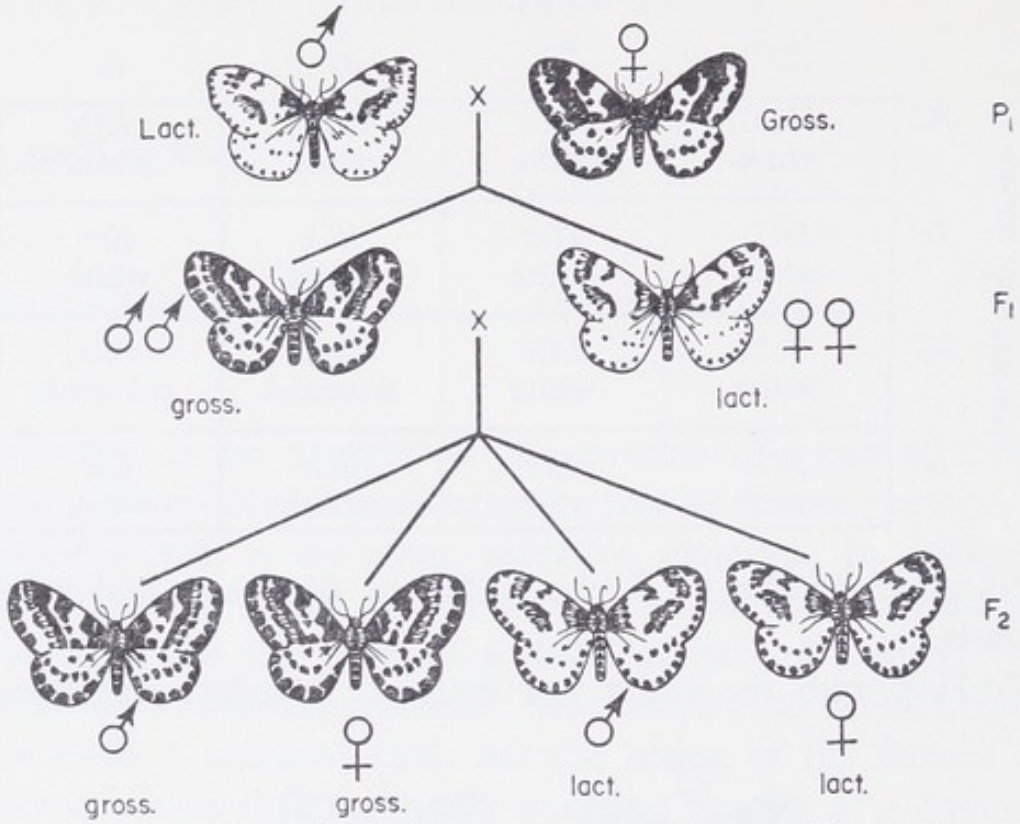


FIG. 7b. Sex-linkage in the currant moth *Abraxas*. The reciprocal cross, *lacticolor* male × *grossulariata* female. Criss-cross inheritance, in the F_1 the sons "take after" their mother, the daughters after their father.

encountered what they called coupling of factors, as Correns had done before them. When a sweet pea with the factors for purple flowers and long pollen-grains was crossed with a pea with the factors for red flowers and round pollen-grains the two factors that entered the cross together, being inherited from one parent, tended to remain together in their transference from generation to generation. Free assortment and recombination did not occur; the factors remained coupled together or linked and the characters corresponding to these linked factors were inherited together.

In 1906 Doncaster and Raynor* recognized the sex-linked mode of inheritance in the moth that they were using as experimental material and two years later the same phenomenon was reported in

* Doncaster, L. and Raynor, G. H., Breeding experiments with Lepidoptera, *Proc. Zool. Soc. London* **1,** 125 (1906).

the canary by Durham and Marryat* and also by Noorduyn† (cinnamon plumage colour). The currant moth *Abraxas grossulariata* has a variety *lacticolor* which has much lighter markings on the wings. When a *lacticolor* female was mated to a *grossulariata* male all the F_1 individuals were *grossulariata* and in the F_2 the ratio of *grossulariata* to *lacticolor* was 3 : 1 but all the *lacticolors* were females. When an F_1 *grossulariata* male was mated to a *lacticolor* female, *grossulariata* males and females and *lacticolor* males and females appeared and the *lacticolor* males were the first that had ever been seen. When a *lacticolor* male was mated to a *grossulariata* female both *grossulariatas* and *lacticolors* appeared among the offspring, but all the *grossulariatas* were males and all the *lacticolors* were females.

Doncaster found that when a *lacticolor* male was mated to a wild *grossulariata* female all the males among the offspring were *grossulariata* and all the females *lacticolor*. So that even in areas where the *lacticolor* form was unknown the females were in reality heterozygous for this character.

The explanation offered at the time was based upon two assumptions: (i) that femaleness and maleness were a pair of Mendelian characters, femaleness being the dominant member, and that the female was a constitutional heterozygote in respect of the factors for these characters, the female being *FM* (where *F* represents the factor for femaleness and *M* that for maleness) and the male *MM*; (ii) that when the two dominant characters, *grossulariata* and femaleness, coexist between them there is mutual repulsion so that into each ovum elaborated by such an individual there will pass one or the other of the two, but not both, factors.

The development of the theory of the gene (see next chapter) soon provided a much simpler explanation. This will be offered later.

It was in 1908, when giving a lecture to the Royal Society of

* Durham, F. M. and Marryat, D. C. E., Inheritance of sex in canaries, *Reports to the Evolution Committee of the Royal Society*, No. 4 (1908).

† Noorduyn, C. L. W., Die Erblichkeit der Farben bei Kanarienvogel (The inheritance of plumage colours in the canary), *Arch. rassen in Gesell. Biol.* **5**, 161 (1908).

Medicine in London, that Punnett was asked why it was that brown eye colour, a dominant Mendelian character, did not become increasingly common in a population. He replied that the numerous heterozygous browns contributed their quota of blue eyes and that this led to an equilibrium. On his return to Cambridge he posed the question to his friend and fellow cricketer, the mathematician G. H. Hardy, who at once gave the answer which later was to become known as the Hardy-Weinberg equilibrium.* (At this time it had been forgotten that Pearson had supplied the answer to this question four years earlier.†)

The tendency towards the establishment of an equilibrium which is inherent in the Mendelian mechanism can be illustrated so.

Let A and a represent a pair of alleles; p the proportion of A genes in the population and q the proportion of a genes. Since a gene is either A or a, $p+q$ must equal 1. Of the male gametes produced by the males in the population p will carry the gene A and q will carry the gene a. Similarly the proportion of female gametes carrying A will be p and that of those carrying a will be q. The random union of the two forms of gametes, male and female, will therefore be as under:

	Male gametes $p_{(A)}$	$q_{(a)}$	Total
Female gametes $p_{(A)}$	$p^2_{(AA)}$	$pq_{(Aa)}$	(p^2+pq)
$q_{(a)}$	$pq_{(Aa)}$	$q^2_{(aa)}$	$(pq+q^2)$
Total	(p^2+pq)	$(pq+q^2)$	1

AA individuals will appear in the population in the proportion p^2, *Aa* individuals in the proportion $2pq$, and *aa* individuals in the proportion q^2.

* Hardy, G. H., Mendelian properties in a mixed population, *Science*, 28 (1908); Weinberg, Über den Nachweis des Verebung beim Menschen, *Jahrb. Vereins Naturf* Wurtemburg, **64,** 368–82 (1908).

† Pearson, K., On a generalized theory of alternative inheritance with special reference to Mendel's law, *Phil. Trans. Roy. Soc.* A, **203,** 53–86 (1904).

The *AA* individuals will produce none but *A* gametes, while half of the gametes produced by the *Aa* individuals will carry *A* and the other half *a*. The proportion of the *A* gametes will therefore be $p^2+\frac{1}{2}\ 2\ pq = p^2+pq = p\ (p+q) = p$, while *a* gametes will be produced in the proportion $q^2+\frac{1}{2}\ 2\ pq = q^2+pq = q(q+p) = q$. This generation will therefore produce *A* and *a* gametes in the ratio $p : q$ and the gene frequencies will be exactly the same as in the previous generation so that *AA*, *Aa* and *aa* individuals will appear in the ratio $p^2 : 2pq : q^2$ as before. Granting that the population is a large one, that in it there is no mutation and that mating is random, the frequencies of the two homozygous classes and of the heterozygous class can be foretold—the heterozygous frequency is equal to twice the square root of the product obtained by multiplying together the frequencies of the two homozygous classes.

Scientific knowledge is verifiable knowledge; the results obtained in a particular experiment by one man will be obtained by others who repeat the experiment with the same material under the same conditions. In his Yellow and green reserve material in cotyledons cross Mendel got 6022 Yellows and 2001 greens in the F_2, numbering 8023; 75·05 and 24·95 per cent respectively. This experiment, being repeated, gave the following results:

	Total number	Yellows	Per-centage	Greens	Per-centage
Correns (1900)	1847	1394	75·47	453	24·53
Tschermak (1900)	4770	3580	75·05	1190	24·95
Hurst (1904)	1755	1310	74·64	445	25·36
Bateson (1905)	15,806	11,902	75·30	3903	24·70
Lock (1905)	1952	1438	73·67	514	26·33
Darbishire (1909)	145,246	109,090	75·09	36,186	24·91
	171,376	128,714	75·10	42,691 (or 3·01 :1)	24·91

It was in 1908 that Bateson was promoted to a readership in Zoology, a post which he held for only a few months, for he was then elected to a newly created chair of Biology in the University of Cambridge (for a period of five years and at a salary of £500). For

his inaugural address he chose *The Methods and Scope of Genetics.** In 1910 he accepted the directorship of the newly founded John Innes Horticultural Institute at Merton, where he was given a free hand to design and plan the gardens and laboratories and to manage and arrange the whole of the work. In 1912 the chair of Biology at Cambridge was permanently endowed and its title changed to Genetics. Bateson was invited to return to Cambridge, but by this time he had cast in his lot permanently with the John Innes and so declined. So it was that Punnett became the first occupant of the first chair of Genetics in Great Britain, and the John Innes one of the world's most productive centres of genetical research.

It will have been noted that the pairs of characters so far considered have been sharply defined alternatives, instances of discontinuous variation. Reference has been made to the other form of variation, the continuous, body height in man being cited as an example. The heights of individuals in an unselected group range from the tallest to the shortest continuously and there is no fixed point at which tallness ends and shortness begins. There are very many characters of this kind, quantitative characters differing from each other by a little more or a little less. Such a character is not based upon a single factor or gene but on several, each of them making its own contribution to the end result and the effects of the genes being additive or cumulative.

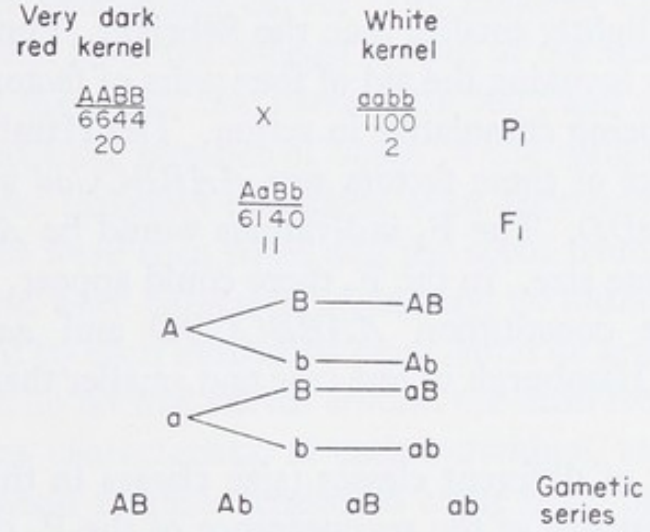
As long ago as 1760 the German botanist Kölreuter, well remembered for his book on plant hybrids, studied the mode of inheritance of a number of quantitative characters in the tobacco plant. He found that the hybrid produced by two parental forms that differed in respect of such a character was more or less intermediate between the two parental forms and that the progeny of such hybrids showed many gradations of the expression of the characters from one extreme to the other. Such "blending inheritance" was assumed to be the rule.

One hundred and fifty years later the American geneticist East repeated Kölreuter's work and it was from this and other related experimentation that the notion of multiple factors or genes grew.

* Cambridge Univ. Press (1908).

This can be illustrated by the work of Nilsson-Ehle,* a Swedish geneticist, on wheat. He crossed two varieties, one which had dark red kernels and the other so pale as to be near white kernels. In the F_1 the colour of the kernels was of a shade that was intermediate between the very dark red and the white. In the F_2 the colour of the kernels ranged from the very dark red of the one P_1 variety through various intermediate shades to the white of the other P_1 variety. One in every 16 F_2 kernels was as dark as the very dark red of the P_1 and 1 in every 16 was as white as the white of the P_1. These results can be explained as follows: two pairs of factors are involved and the factors have different grades of ability to produce red colour in the kernel; let *A* and *a*, *B* and *b* represent the two factor pairs and let the value of these factors be $A = 6$, $B = 4$, $a = 1$ and $b = 0$ in respect of their ability to produce the deep red colour.

The cross was:



This notion of multiple factors involves three reasonable assumptions: (i) that dominance either does not exist or else is incomplete, (ii) that the double dose of the factor has twice the effect of the single dose, and (iii) that the independent yet similar factors are cumulative in operation.

Another example was provided by Punnett's cross between the Golden Hamburgh and the Sebright bantam. The Hamburgh is

* Nilsson-Ehle, H., Kreusungsuntersuchungen an Hafer und Weizen (Hybridization investigations with oats and wheat), *Lunds Univ. Arsskrift*, N.F., Avd. 2, Bd. 5 (1909).

	AB	*Ab*	*aB*	*ab*
AB	*AABB* 20 very dark red	*AABb* 16 dark red	*AaBB* 15 dark red	*AaBb* 11 medium red
Ab	*AABb* 16 dark red	*AAbb* 12 medium red	*AaBb* 11 medium red	*Aabb* 7 light red
aB	*AaBB* 14 dark red	*AaBb* 11 medium red	*aaBB* 10 medium red	*aaBb* 6 light red
ab	*AaBb* 11 medium red	*Aabb* 7 light red	*aaBb* 6 light red	*aabb* 2 near white

much larger than the Sebright. The F_1 was intermediate and in the F_2 there was a range of weight (size) from slightly larger than the Hamburgh to slightly smaller than the Sebright. Punnett explained these results by invoking the aid of four pairs of factors, all affecting body size and being cumulative in action. The Hamburgh's constitution in respect of these factors was *AABBCCdd* and that of the Sebright *aabbccDD*. The F_1 individuals would be *AaBbCcDd* and so of intermediate size. In the F_2 there could appear, though rarely, birds with the constitution *AABBCCDD* and *aabbccdd*, being larger than the Hamburgh in one case and smaller than the Sebright in the other.

The number of different classes (size classes in this case) in the F_2 and the frequency of the reappearance of the P_1 character types indicate the number of factors that are involved.

Proportion of the F_2 as extreme as either of the P_1 individuals	Number of pairs of factors involved
1 in every 4	1
16	2
64	3
256	4
1024	5
4096	6
16,384	7
1,048,576	10

THE PURE LINE

In 1903 there appeared an account of the work of the Danish botanist Johannsen on what he called "pure lines". For his experimental material he had been using the scarlet runner bean and he was interested in the effects of selection. Charles Darwin, when discussing the origin of the breeds and varieties of the domesticated animals and cultivated plants, had concluded, as has already been related, that these had been produced by the breeder by continuous and deliberate selection of small variations in a particular direction and had noted that this procedure was not always successful. It was Johannsen who revealed the reason for this.

He showed that if, for example, 500 beans were taken at random from a much larger quantity and were weighed separately, the curve plotting weight against frequency was in general of the same shape as the ordinary probability curve. The majority of the beans did not diverge much from the average weight of the whole sample (the total weight of the whole 500 divided by 500), and that there was a constantly decreasing number of beans in the weight classes as the upper and lower extremes of weight were approached.

If these seeds were then sown and the seeds from the plants that grew from them were harvested separately, he found that while the beans produced by each individual plant could be grouped according to their weights in normal curves around the most frequent or modal weight that was characteristic of each individual, and while on the whole the heaviest families tended to come from the heavier seeds and the lighter from the lighter, the weight of the parent seed gave only a vague indication of what the modal weight of its progeny might be.

But when the progeny of any one seed were taken and the heaviest and the lightest among them sown he found that the modal weights of the seeds produced by the plants that grew from them were approximately the same. The progeny had a frequency curve of the same maximum, no matter if they were from the heaviest parent seed or the lightest.

A "pure line" consists of the progeny of a single self-fertilized

individual. A "clone" (Gk. *klon*, twig) is a group of individuals produced by a single ancestor by means of asexual reproduction (by continued division of the original individual and its descendants). Within the pure line selection is ineffective. A population, such as that of Johannsen's beans, consists of a number of pure lines and for this reason selection in a population is effective.

The distinction between a pure line and a population of this kind can best be shown by a diagram in which five different pure lines are combined to form a population. The beans that make up a pure line are represented enclosed within an inverted test-tube. All the beans in a test-tube are of the same weight. Tubes in the same vertical line also contain beans of the same weight. It can be seen that a weight-class that is rare in one pure line can be the most common in another. If when selecting a bean one from the extreme left-hand test-tube or from the extreme right-hand one is taken, a pure line is isolated from the population. But if a bean from any of the central tubes should be taken it could belong to one of several pure lines.

In the case of the self-fertilizing bean the factorial constitution of the progeny will be the same as that of the parent. All the progeny will be exactly similar in respect of their factorial constitutions. Yet in respect of the character seed-weight they vary. Such variation must be the result of the differential action of environmental forces, such differences in weight must be acquisitions, modifications and will not be inherited. But differences in respect of weight among the whole 500 beans will be of two kinds, those based on differences in the factorial constitution of the different pure lines within the population and those which are acquisitions.

It was Johannsen who introduced the terms gene, genotype and phenotype,* and who so clearly drew the distinction between genotype and phenotype. The genotype (Gk. *genos*, descent; *typos*, image) is the genetic or factorial constitution of an individual or

* Johannsen, W., *Uber Erblichkeit in Populationen und in reinen Linien* (Heredity in populations and pure lines), Fischer, Jena, 1903.

Johannsen, W., The genotype conception of heredity, *Amer. Naturalist*, **45**, 129–59 (1911).

group; the phenotype is the characterization of the individual or group, the sum total of its characters, inherited and acquired. The phenotype cannot be accepted as a trustworthy indication of the nature of the genotype.

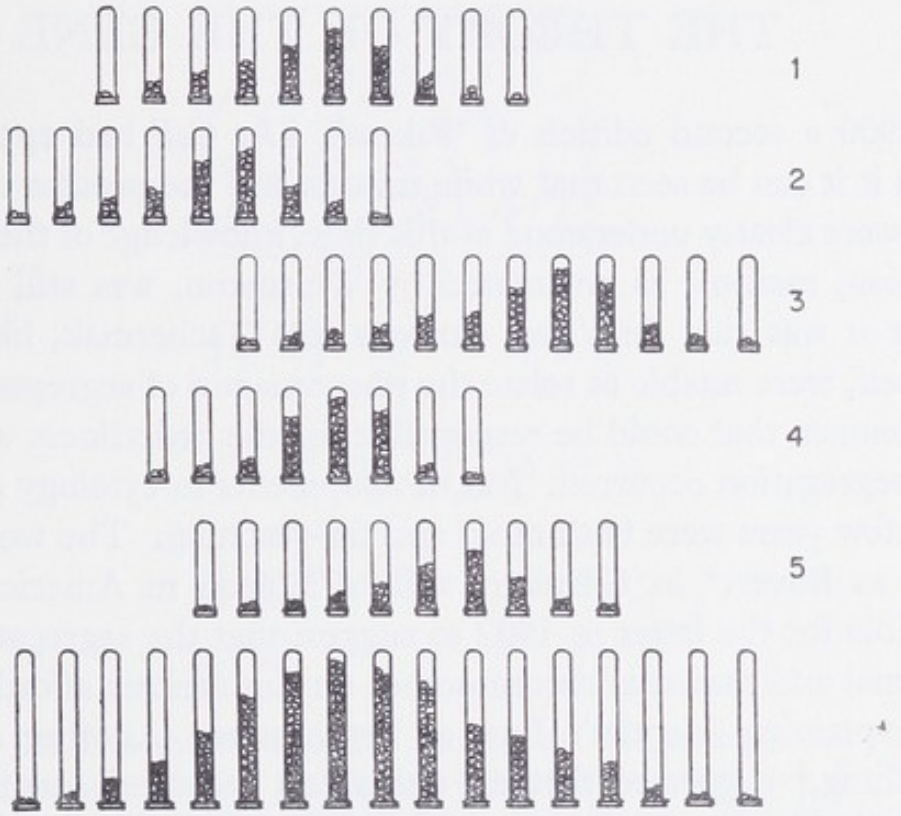


FIG. 8. A population compounded out of five pure lines of beans.

CHAPTER 6

THE THEORY OF THE GENE

In 1900 a second edition of Wilson's *The Cell* had appeared and from it it can be seen that while mitosis and the process of fertilization were clearly understood at this time, knowledge of the reduction division, meiosis, as postulated by Weismann, was still imperfect. Thus it was that de Vries, Correns and Tschermak, like Mendel himself, were unable to relate the phenomenon of segregation to any mechanism that could be responsible for the orderliness with which this segregation occurred. But developments in cytology during the next few years were both rapid and far-reaching. The work of such men as Boveri* in Germany and of Wilson in America made it possible for the latter in 1902 to suggest that the segregation of the paternal and maternal chromosomes during meiosis afforded a basis for explaining Mendel's Law of Segregation. Another American, McClung,† suggested that the characters maleness and femaleness were associated with the distribution from parent to offspring of a particular chromosome, and in 1903 W. S. Sutton,‡ a young American postgraduate student, who later became a surgeon, gave the first satisfactory account of the exact parallelism between the transmission of Mendelian characters from generation to generation and the transmission of the chromosomes from cell-generation to cell-generation. The notion that the hereditary particles were borne by the chromosomes came to be known as the Sutton–Boveri hypothesis.

* Boveri, Th., Befruchtung, *Ergebn. Anat. EntwGesch*, **1**, 386 (1891).

† McClung, C. E., The accessory chromosome—sex determinant?, *Biol. Bull.* **3**, 43–84 (1902).

‡ Sutton, W. S., The chromosomes in heredity, *Biol. Bull.* **4** (1903). "I may finally call attention to the probability that the association of paternal and maternal chromosomes in pairs and their subsequent separation during the reducing division . . . may constitute the physical basis of the Mendelian law of heredity."

It was largely because the development of cytology was actively encouraged by the geneticists of the United States in the first decade of this century that the leadership in the genetical field passed to America.

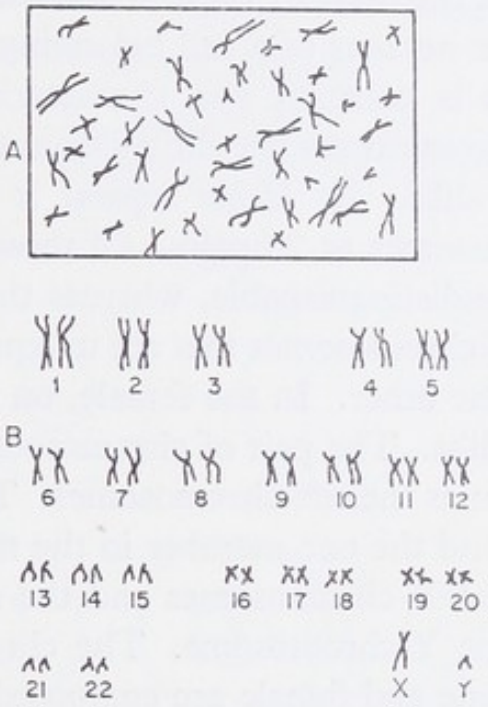


FIG. 9. A. The chromosomes of the normal human male (they are already partially divided into their daughter chromosomes). B. The karyotype of the normal human male (Gk. *karyon*, nucleus; *typos*, image): a systematized array of the chromosomes of a single cell, prepared either by drawing or by photography. It is assumed that this karyotype typifies the chromosome complex of the individual as a whole and also that of the species to which the individual belongs. Suitable material, e.g. blood-film, is exposed to the action of colchicine and hypotonic citrate solution and is then fixed and stained and then squashed in order to disperse the chromosomes. The preparation is then drawn or photographed and greatly enlarged. It can then be seen that the chromosomes differ among themselves in respect of length. They are cut out of the photograph and matched in pairs according to their size. The pairs are then numbered according to their relative length, 1–22, number 1 being the largest, and 22 the smallest. The chromosomes fall into seven size groups: 1–3, 4 and 5, 6–12, 13–15, 16–18, 19 and 20, 21 and 22. Two chromosomes now remain, one of them a large one equal in size to those in the 6–12 class, the other a small one equal in size to numbers 21 and 22. The first of these is the X-chromosome, the other the Y. (In the female there are two Xs and no Y.) This method quickly reveals any deviation from normality in respect of the total number of chromosomes and of the size of each of them.

In the nucleus of the cell the chromosomes are present in the form of pairs, the two members of a pair being alike in respect of size and shape, being homologous (Gk. *homologos*, agreeing). Since the pairs themselves differ in respect of these and certain other qualities it can be shown that the number of pairs and therefore of individual chromosomes in the nucleus of a cell belonging to an individual of a particular species is constant and characteristic of the species. Of these pairs of chromosomes one differs from all the rest in that its members are not alike. In *Homo sapiens* it is established that there are 46 chromosomes or 23 pairs. Of these 22 pairs consist of members that are indistinguishable, whereas the remaining pair in the male consists of chromosomes that are unequal in size, one being much larger than the other. In the female, on the other hand, the two members are alike. The pair of chromosomes that differ in the two sexes are known as the sex-chromosomes. The members of this pair in the female and the one member in the male that is identical with these are called X-chromosomes and the smaller mate of the X in the male is the Y-chromosome. The chromosome pairs that are alike in both male and female are composed of autosomes (Gk. *autos*, self; *soma*, body). The chromosome set of the male of *Homo sapiens* can be represented as XY plus 22 pairs of autosomes; that of the female as XX plus 22 pairs of autosomes.

Weismann's argument that the hereditary determiners must be halved during the formation of the gametes came to be completely confirmed by observations of the behaviour of the chromosomes in the final stages of gametogenesis.

Up to the last cell-division but one in the process of gamete formation the divisions are of the mitotic type, the chromosomes splitting to form daughter chromosomes and these being distributed to the daughter nuclei so that the total number of chromosomes in the mother and the daughter cells remains the same. But in the last division but one the chromosomes do not split but the two members of each pair come to lie side by side on the equator of the spindle. Then the two members of each and every pair move apart and one member of each pair comes to be included in the nucleus of each daughter cell. The number of chromosomes in the nucleus of the

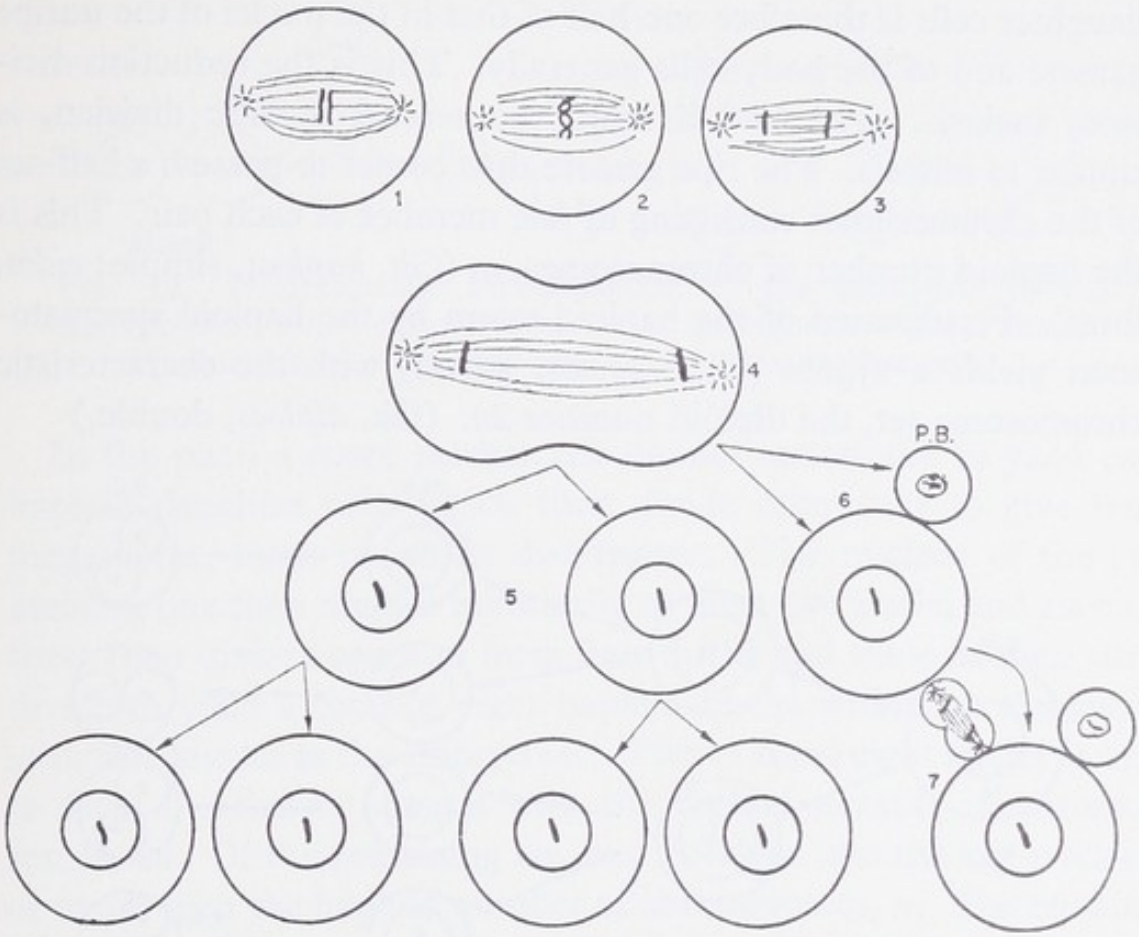


FIG. 10. Meiosis. (For the sake of clarity only one pair of chromosomes is depicted.) The formation of the ripe or mature gamete is the final stage of a long process of cell-division. In this all the divisions save one are of the ordinary mitotic kind (as in Fig. 5). But the last division but one is a reduction division in which there is no longitudinal splitting of the chromosomes before the cell itself divides.

1. Just before this reduction division occurs the two members of each pair of chromosomes move to lie close together.
2. They become closely intertwined.
3. They separate and move to the opposite poles of the cell.
4. The cell-body then begins to divide.
5. Cell-division is completed, one member of each pair of chromosomes passing into each of the nuclei of the two daughter cells. Each daughter cell comes to include one member of each chromosome pair, i.e. a half-set, the haploid number of chromosomes instead of the diploid.

   In the male each of these daughter cells divides again, the division being of the mitotic kind with the longitudinal splitting of the chromosomes. Four functional spermatozoa are thus formed, each with the haploid number of chromosomes.
6. In the female the reduction division yields two daughter cells each with the haploid number of chromosomes. Of these one is destined to become the functional ovum while the other becomes a polar body, an abortive ovum.
7. Each of these divides mitotically, the immature ovum to give rise to a mature ovum and another polar body, the first of the polar bodies to yield two more polar bodies which come to naught.

daughter cells is therefore one-half of that in the nuclei of the unripe gamete and of the body-cells generally. This is the reduction division, meiosis. The last division, the second meiotic division, is similar to mitosis. The ripe gamete thus comes to possess a half-set of the chromosomes consisting of one member of each pair. This is the haploid number of chromosomes, *n*. (Gk. *haploos*, simple; *eidos*, form). Fertilization of the haploid ovum by the haploid spermatozoon yields a zygote (Gk. *zygotos*, yoked) with the characteristic chromosome set, the diploid number *2n*. (Gk. *diploos*, double.)

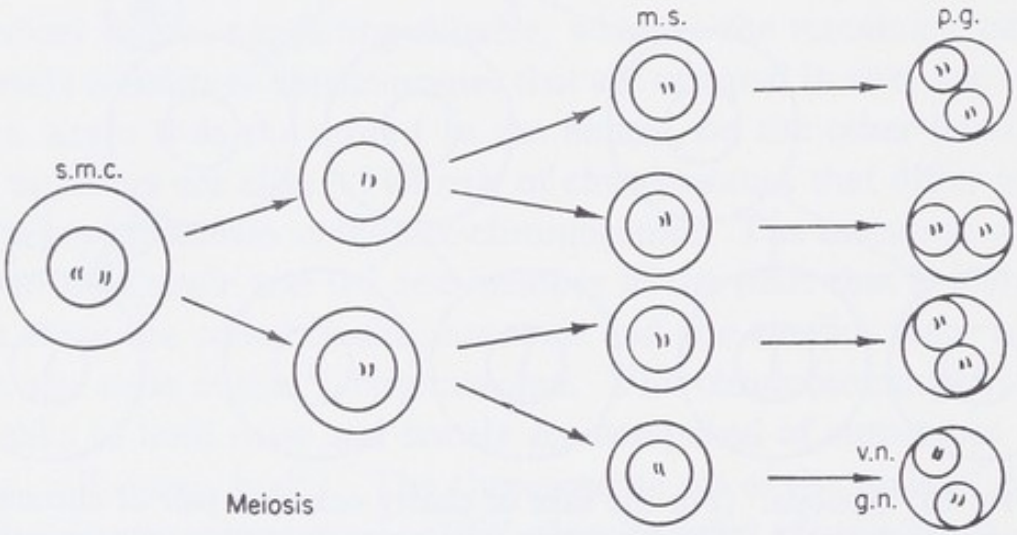


FIG. 11. Diagrammatic representation of the formation of pollen-grains in the stamens of a flower. *g.n.*, generative nucleus. *m.s.*, microspores. *p.g.*, pollen-grains. *s.m.c.*, spore mother-cell. *v.n.*, vegetative nucleus.

In the higher plants the formation of the gamete is a more complicated process than it is in the animal. Reduction divisions occur in both anther and ovule to yield spores, microspores in the anther, megaspores in the ovule, both of which are haploid. In the stamen a spore mother cell divides meiotically to form two daughter cells each with the haploid number of chromosomes. Each of these then divides mitotically so that four microspores arise from each spore mother cell. In each of these microspores the nucleus divides mitotically to yield two nuclei, each of them haploid, but the cell itself does not divide. Each of these cells with two nuclei is a pollen-grain and of the nuclei one is the vegetative or tube nucleus and the other the generative nucleus.

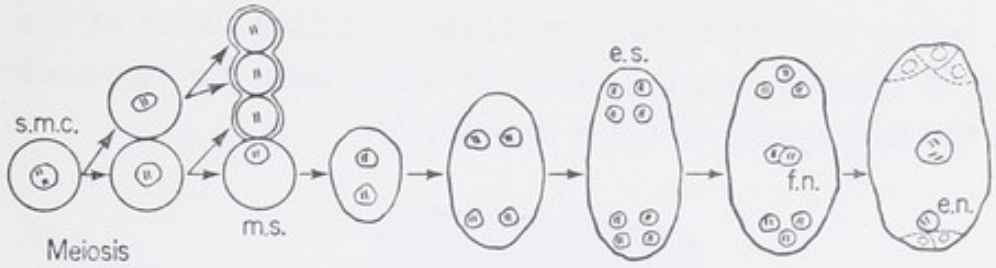


FIG. 12. Diagrammatic representation of the formation of the embryo-sac. *e.n.*, egg-nucleus. *e.s.*, embryo-sac. *f.n.*, fusion-nucleus. *m.s.*, megaspore. *s.m.c.*, spore mother cell.

In the pistil a spore mother cell divides meiotically to yield two haploid daughter cells which then divide mitotically to give four megaspores, three of which disintegrate. The nucleus of the remaining one then divides mitotically to form two nuclei and each of these then divides again to form four nuclei and these in their turn divide to yield a total of eight haploid nuclei within an elongated structure known as the embryo sac. Two of these eight nuclei merge to form the fusion nucleus with the diploid number of chromosomes, $2n$. Of the remaining six, one develops into the egg-nucleus or ovum with the haploid number of chromosomes, n. The remaining five nuclei can be disregarded in so far as this account is concerned.

Prior to fertilization there are the pollen-grains with two nuclei, both haploid, and embryo-sacs each with its two essential nuclei, one of them, the egg-nucleus, haploid and the other, the fusion-nucleus, diploid. When the pollen-grains settle upon the stigma they germinate and from each of them a pollen tube is formed. This grows down into and through the loose tissues of the style on its way to the ovary and as it extends the two nuclei, vegetative and generative, leave the body of the pollen grain and enter the pollen-tube to pass along its length, the vegetative nucleus leading. During its passage down the pollen-tube the generative nucleus divides mitotically into two. The tip of the pollen-tube ultimately reaches a minute opening in the coverings of the ovule to pass through and to burst. The vegetative nucleus, its function finished, then disintegrates and the two generative nuclei enter the embryo-sac, one to fuse with the fusion nucleus to yield the endosperm nucleus

(Gk. *endon*, within; *sperma*, seed, the nutritive tissue of the seed) which is triploid, $3n$, the other to unite with the egg-nucleus to form the new zygote which is diploid, $2n$.

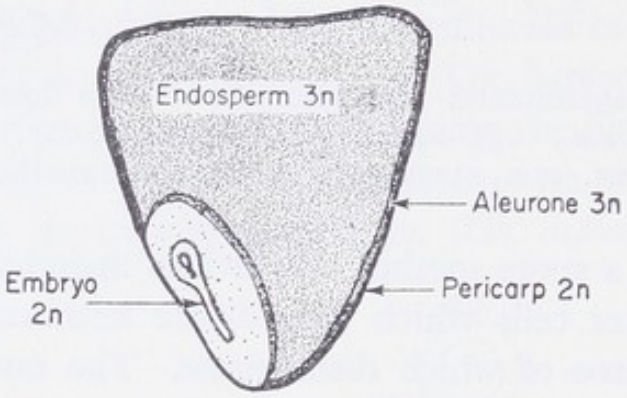


FIG. 13. Diagrammatic representation of a cross-section of a grain of maize showing the different parts that may be affected independently by genes.

On the outside of a grain of maize is the grain coat, the pericarp (Gk. *peri*, around; *karpos*, fruit), which is derived solely from maternal tissue and is therefore $2n$. Within the pericarp is the aleurone layer (Gk. *aleuron*, flour), the layer rich in protein which is $3n$, $2n$ from the female parent and n from the male. Within the aleurone layer is the endosperm, $3n$, and within this is the embryo, $2n$, having received a half-set of chromosomes from each of the parents.

So it is that in a plant such as maize the hereditary characters of the embryo, the endosperm and the pericarp are determined independently. When the seed is planted the embryo uses up the food material of the endosperm and the mature plant is diploid, $2n$.

Up to this point the interest in Mendelism had been focused upon the phenomenon of segregation and upon ratios. Now it was to be directed towards the nature of the units that were segregated and towards the mechanism that was responsible for their distribution. By 1910 it had been shown beyond all reasonable doubt that Mendel's Law of Segregation was of universal application and it had come to be recognized that between the behaviour of Mendel's factors in their transmission from generation to generation and the behaviour of the chromosomes during mitosis and meiosis there was

Giant chromosomes of the salivary glands of
Drosophila melanogaster

PLATE VII

a remarkable correspondence. What was needed at this stage in the development of the science of genetics was an experimental material with the following properties—many discontinuous variations, few chromosomes differing markedly among themselves in respect of size and shape, easily kept under laboratory conditions, prolific and with a short life-cycle. It so happened that the ideal material was already being used, though for non-genetical experiments, in the zoology department of Columbia University, New York. It was *Drosophila melanogaster*, the tiny fruit-fly that Professor Castle of Harvard University had introduced to Professor Thomas Hunt Morgan.

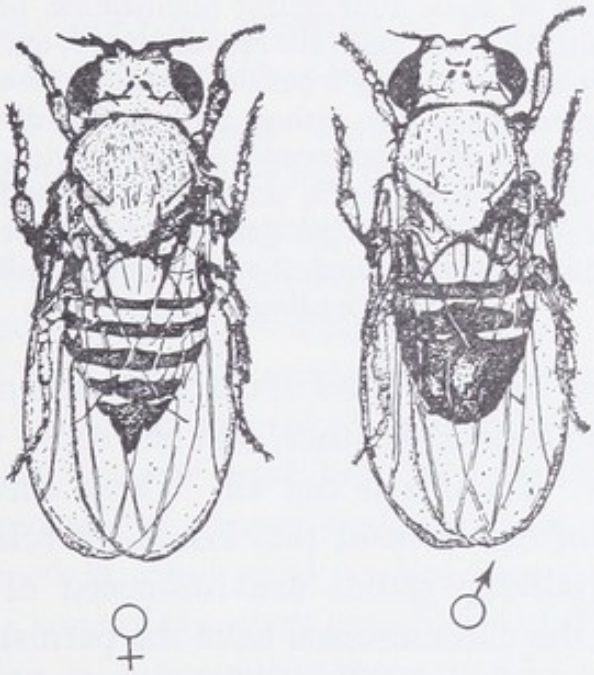


FIG. 14. The fruit-fly *Drosophila melanogaster*. Female on the left; male on the right.

This dipteran (Gk. *dis*, two; *pteron*, wing) can easily be bred in wide-necked half-pint milk bottles stoppered with a plug of cotton-wool. Slabs of fermenting banana provide the food both for the insect and its larvae. The latter hatch out after pupation and the whole cycle occupies about 10 days. A mated pair produces scores of offspring and these can easily be anaesthetized for examination under a low-powered microscope.

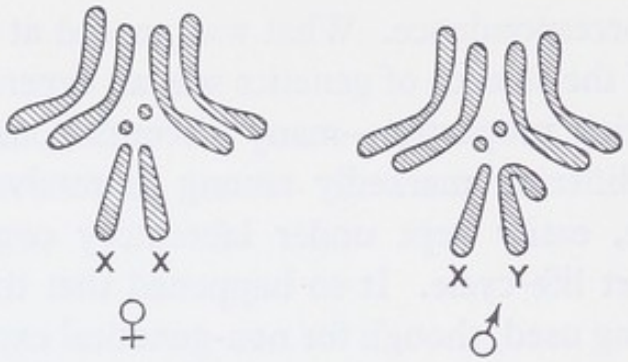


FIG. 15. Conventional diagram of the chromosomes of *Drosophila melanogaster*. The pair at the top right is designated as chromosome II, the pair at the top left as chromosome III and the members of the small dot-like pair in the centre as chromosome IV. In the male the remaining pair consists of dissimilar mates, an X and a Y; in the female the pair consists of two Xs. In the ripe gamete there is one member of each of these four pairs; fertilization of the egg by the sperm means that the four pairs are reconstituted, one member of each pair coming by way of the egg from the mother, the other member by way of the sperm from the father. Since the distribution of the members of one pair of chromosomes is quite independent of that of the members of the other pairs, there are 16 possible combinations of the chromosomes in the ripe gamete and since in fertilization two series of gametes are involved, the number of possible combinations is exceedingly large.

D. melanogaster has four pairs of chromosomes markedly different in size and shape from each other. No one could wish for anything better than this. Yet this is not all. These chromosomes in the salivary glands of the larva of this insect are relatively enormous. The Dipteran salivary glands are composed of cells which are peculiar in that the chromosomes have the permanent form of long paired threads which carry bead-like minute blobs of chromatin along their length. The glands become larger not through an increase in the number of component cells but by the enlargement of the existing cells and as the cells get bigger so also do the chromosomes in the nucleus. Studies of the salivary glands of Diptera had been carried out by Balbiani as long ago as 1881 and by Carnoy in 1884, but their value was not appreciated until Painter* and Heitz and Bauer† called attention to them in 1933.

* Painter, T. S., A new method for the study of chromosome rearrangement and plotting of chromosome maps, *Science* **78** (1933).

† Heitz, E. and Bauer, H., *Ztschr. f. Zellforsch. u. mikr. Anat.* **17,** 62 (1933).

In the space of a few years scores of "sports" made their appearance, an individual or several individuals being found among the progeny of a mated pair which displayed a novel character not possessed by either parent and proving to be a character in the Mendelian sense. It was de Vries who had introduced the term mutation to describe this phenomenon. These sports or mutants (*L. mutare*, to change) provided plentiful pairs of contrasted characters for use in the exploration of the hereditary mechanism. With such material investigations that would have required a century or more with a creature such as the horse or the sheep could be completed within the year. In 1910 Morgan* submitted a paper to the *American Naturalist* in which he expressed the firm view that Mendelian factors could not possibly be carried by the chromosomes, pointing out that were they so carried, characters with their factors in one and the same chromosome would necessarily "Mendelize" together (as Boveri had foretold) and maintaining that this they did not do. But before this paper appeared in print, another which he had subsequently submitted to *Science* was published. In this he presented convincing evidence that the factors for sex-linked characters were certainly carried in the X-chromosome. Thus it was that at the time it seemed that Morgan, who had offered proof that Mendel's factors were borne in the chromosomes, had immediately expressed the view that this could not be so. In 1909 Janssens had noted in cytological studies that the members of a chromosome pair sometimes stuck together, and Morgan made use of this observation to suggest that there could be an actual interchange of material between the members of a pair of chromosomes, crossing-over. At this time Bateson and Punnett, following Boveri, clung to the notion of the individuality of the chromosomes and so were unable to accept Morgan's interpretation. In 1911 Morgan suggested that the closeness of linkage implied nearness in the linear dimension of a chromosome. This led to the mapping of the chromosomes by his colleague Sturtevant.† Then in 1915 came the

* Morgan, T. H., Sex-linked inheritance in *Drosophila*, *Science* **32**, 120–2 (1910); Chromosomes and heredity, *Amer. Nat.* **44**, 449 (1910).

† Sturtevant, A. H., The linear arrangement of six sex-linked factors in *Drosophila* as shown by their mode of association, *J. exp. Zool.* **14** (1913).

Mechanism of Mendelian Heredity by Morgan and his colleagues in which there was offered a comprehensive chromosomal interpretation of the phenomena of organic inheritance. For this, final and conclusive proof was provided by the genetic and cytological work of Bridges,* a member of the Morgan team, on non-disjunction. After Müller,† another member of the Morgan team, had shown in 1927 that exposure of the fly to X-rays greatly speeded up the process of mutation the development of genetics became both widened and quickened. Genetical evidence strongly suggested that not only did such treatment lead to the mutation of a gene, point mutation, but that it also caused deletion, the loss of a segment of a chromosome, and to translocation, the change in position of a segment of a chromosome to another part of the same chromosome or of a different chromosome. Cytological evidence soon became available to support these conclusions.

The teaching of the Columbia school was as follows: The determiners of the hereditary characters are the genes which are resident in the chromosomes, each gene having its own particular place or locus in a particular chromosome so that each chromosome has its own particular series of loci arranged in a linear order in the length of the chromosome. The two members of a pair of chromosomes, save in the case of the sex-chromosomes, have identical series of loci, are homologous. A gene can undergo a change in its internal organization, can mutate, to yield another form of the same gene, an allelomorph or allele of the gene (Gk. *allelon*, another; *morphe*, form). The mutated form of the gene affects the same developmental processes as does the unmutated form, but yields a different end-result, a different character. Mendelian characters are details of structure or of function that are based upon a pair of alleles. Since these alleles are different forms of the same gene they necessarily occupy the same locus, and since this can accommodate but one gene it follows that there can be in a particular locus either the unmutated or the mutated form of a particular gene. In a pair of

* Bridges, C. B., Non-disjunction as proof of the chromosome theory of heredity, *Genetics* **1** (1916).

† Muller, H. J., Artificial transmutation of the gene, *Science* **66** (1927).

homologous chromosomes, therefore, there can be two unmutated genes, one in each chromosome, two mutated genes or one mutated in one chromosome and one unmutated in the other. For reasons of convenience it is customary to speak of alleles as different genes. Homozygous comes to mean possessing two genes of a kind; heterozygous, with two different alleles.

The phenomenon of sex-linkage was first recorded in 1906 in the currant moth *Abraxas* by Doncaster and Raynor. Sex-linked characters, characters whose transmission from generation to generation is manifestly intimately associated with the expression of maleness and femaleness, quickly made their appearance in *Drosophila*. White eye-colour and yellow body-colour were two such. When a white-eyed male was mated to a wild-type Red-eyed female an F_1 of Red-eyed males and females was obtained, and when these were interbred an F_2 consisting of equal numbers of males and females and of three Red-eyed and one white-eyed in every four on the average appeared, and every white-eyed fly was a male. The white-eyed grandfather had passed on his eye-colour character to one-half of his grandsons and to none of his grand-daughters. White-eyed females were obtained by mating the F_1 heterozygous Red-eyed females to white-eyed males. When a white-eyed female was mated to a Red-eyed male all the daughters were Red-eyed and all the sons white-eyed, the sons taking after their mother, the daughters after their father.

The explanation of this form of inheritance in terms of the Chromosome Theory was as follows: *D. melanogaster* has four pairs of chromosomes. In the female the sex-chromosome pair consists of two Xs, in the male of an X and a Y. The latter being considerably smaller than the former cannot include the same series of loci.

Mendel, as is known from his correspondence, had the idea that maleness and femaleness were characters that behaved according to the laws which he had recognized, one of the sexes being a constitutional heterozygote, the other a homozygote. Thus if *A* represented the factor that determined sex, if one sex was *AA* and the other *Aa* the mating of male and female would inevitably produce males and females in equal numbers.

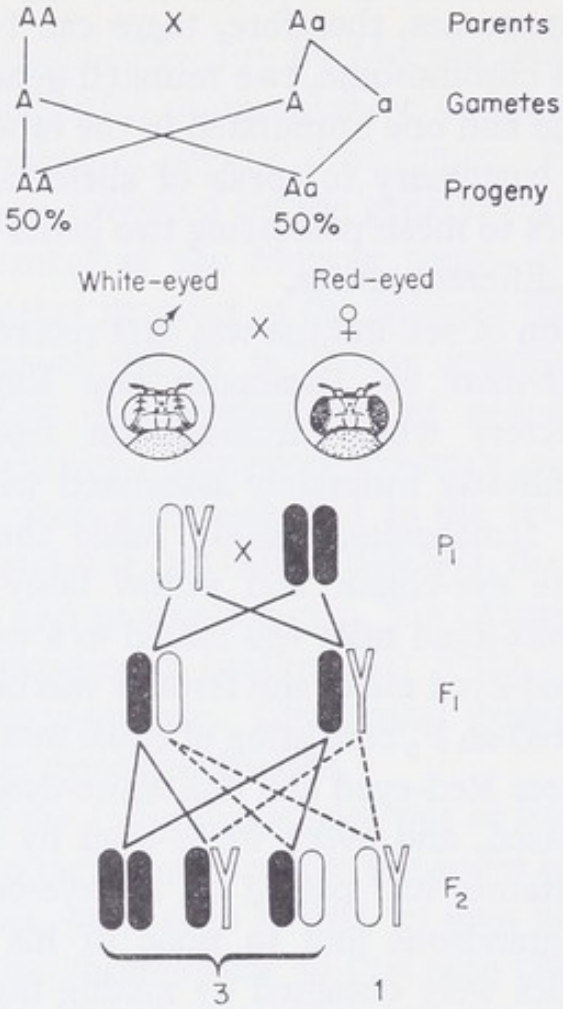


FIG. 16. Sex-linkage in *Drosophila melanogaster*. White-eyed male × Red-eyed female. All the white-eyed flies in the F_2 are males. The recessive character of a grandfather is displayed by none of his sons or daughters, by none of his grand-daughters and only by 50 per cent of his grandsons.

If these hypothetical factors are replaced by the sex-chromosomes the same result is obtained. Characters that are sex-linked, behaving as white-eye above, have their genes in the X-chromosome and there are no loci for them in the Y-chromosome. (Let the use of the bracket indicate that the gene is resident in the X.)

1. The mating: white-eyed male to Red-eyed female

	$(w\mathrm{X})\mathrm{Y}$	×	$(W\mathrm{X})\ (W\mathrm{X})$	P_1
$(w\mathrm{X})$	Y	:	$(W\mathrm{X})$	Gametes
	$(W\mathrm{X})\ (w\mathrm{X})$		$(W\mathrm{X})\mathrm{Y}$	F_1 (all Red-eyed)
$(W\mathrm{X})$	$(w\mathrm{X})$	:	$(W\mathrm{X})$ Y	Gametes
$(W\mathrm{X})W\mathrm{X})$	$(W\mathrm{X})w\mathrm{X})$		$(W\mathrm{X})\mathrm{Y}$ $(w\mathrm{X})\mathrm{Y}$	F_2
homozygous Red-eyed daughters	heterozygous Red-eyed daughters		Red-eyed sons	white-eyed sons

2. The mating: white-eyed male to heterozygous Red-eyed female

$(w\text{X})\text{Y}$		$\times$	$(W\text{X})\,(w\text{X})$		P_1
$(w\text{X})$	Y	:	$(W\text{X})$	$(w\text{X})$	Gametes
$(W\text{X})\,(w\text{X})$	$(w\text{X})\,(w\text{X})$		$(W\text{X})\text{Y}$	$(w\text{X})\text{Y}$	F_1
heterozygous Red-eyed female	white-eyed female		Red-eyed male	white-eyed male	

3. The mating. Red-eyed male to white-eyed female

$(W\text{X})\text{Y}$		$\times$	$(w\text{X})\,(w\text{X})$	P_1
$(W\text{X})$	Y	:	$(w\text{X})$	Gametes
$(W\text{X})\,(w\text{X})$			$(w\text{X})\text{Y}$	F_1
heterozygous Red-eyed daughters			white-eyed sons	

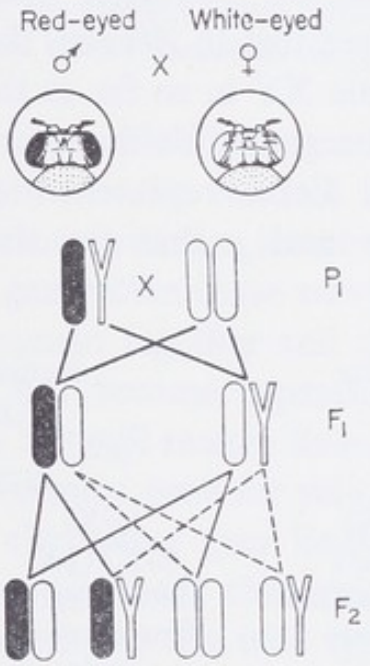


FIG. 17. Sex-linkage in *Drosophila melanogaster*. The reciprocal cross, Red-eyed male × white-eyed female. Criss-cross inheritance in the F_1. The sons "take after" their mother, the daughters after their father. The explanation in terms of the theory of the gene.

A recessive gene in the X-chromosome can find expression in the male for the reason that he has but one X-chromosome, so that there cannot be the dominant allele of the gene in the other X-chromosome, as there can be in the female. Mating 3 above is accepted as the test for sex-linkage (criss-cross inheritance). It is to be noted that in *Drosophila*, as in *Homo sapiens*, it is the male that has the constitution symbolized by XY. In the domestic fowl, on

the other hand, it is the male that has two X-chromosomes and the female only one. The test for sex-linkage in the fowl takes the form of mating a male displaying the recessive member of a pair of sex-linked characters to a female displaying the alternative dominant.

A cock with golden plumage colour (Rhode Island Red)	×	a hen with Silver plumage (Light Sussex)	
(*s*X) (*s*X)		(SX)—	P_1
(*s*X)		(SX) —	Gametes
(SX) (*s*X)		(*s*X)—	F_1
heterozygous Silver males		gold females	

The results obtained by Doncaster and Raynor can easily be explained if it be granted that in *Abraxas* the male has the constitution XX and the female XY in so far as the sex-chromosomes are concerned and that the genes for the characters *grossulariata* and *lacticolor* are X-borne. Let *G* represent the gene for the dominant *grossulariata* character and *g* that for the alternative recesssive *lacticolor*.

1.

Grossulariata male	×	*lacticolor* female		
(*G*X) (*G*X)		(*g*X)Y		P_1
(*G*X)	:	(*g*X)	Y	Gametes
(*G*X) (*g*X)		(*G*X)Y		F_1
(*G*X)	(*g*X)	(*G*X)	Y	Gametes
(*G*X) (*G*X)	(*G*X)Y	(*G*X) (*g*X)	(*g*X)Y	F_2
Homozygous *Grossulariata* male	*Grossulariata* female	Heterozygous *Grossulariata* male	*lacticolor* female	

2.

F_1 *Grossulariata* male	×	*lacticolor* female		
(*G*X) (*g*X)		(*g*X)Y		Back-cross
(*G*X)	(*g*X)	(*g*X)	Y	Gametes
(*G*X) (*g*X)	(*G*X)Y	(*g*X) (*g*X)	(*g*X)Y	
Heterozygous *Grossulariata* male	*Grossulariata* female	*lacticolor* male	*lacticolor* male	

3.

lacticolor male	×	*Grossulariata* female	
(*g*X) (*g*X)		(*G*X)Y	P_1
(*g*X)	:	(*G*X) Y	Gametes
(*G*X) (*g*X)		(*g*X)Y	F_1
Heterozygous *Grossulariata* male		*lacticolor* female	

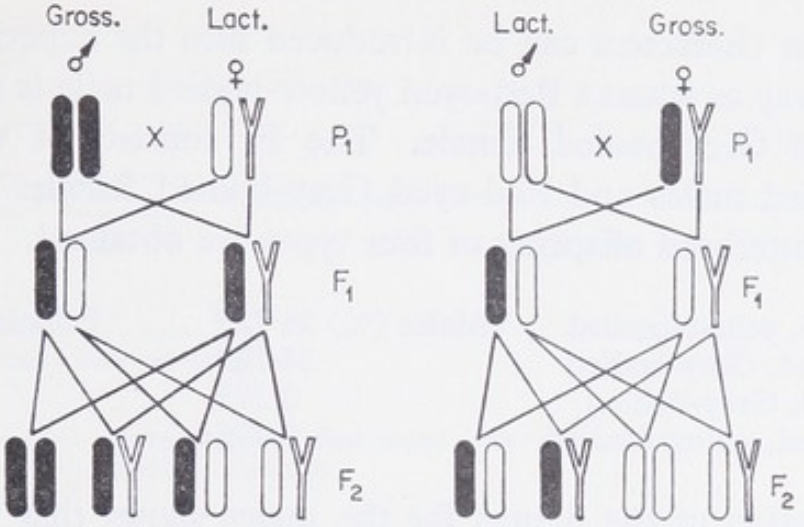


FIG. 18. Sex-linkage in the currant moth *Abraxas*. The explanation in terms of the theory of the gene.

Yellow body-colour in *Drosophila* behaves exactly in the same way as does white-eye. Its gene is also resident in the X-chromosome. So long as the X-chromosome remains intact during its transmission from cell-generation to generation these two genes, being borne in the same vehicle, will remain together and the characters that are based upon them will not become separated as they pass from generation to generation but will remain linked.

Let *y* represent the recessive gene for yellow body-colour and *Y* that for the wild type alternative grey body-colour. (Care is required to distinguish between the Y that represents the Y-chromosome and the *Y* that represents the wild type allele of the yellow gene—the latter is enclosed within a bracket.) When a white-eyed yellow-bodied female is mated to a wild-type Red-eyed Grey-bodied male all the female offspring are all Red-eyed and Grey-bodied while the males are all white-eyed and yellow-bodied. When these are interbred a small but definite proportion of Red-eyed yellows and of white-eyed Greys appear among the offspring.

Red-eyed, Grey-bodied	Males (%) 24·725	Females (%) 24 ·725
white-eyed, yellow-bodied	24·725	24· 725
white-eyed, Grey-bodied	0·275	0·275
Red-eyed, yellow-bodied	0·275	0·275

The two properties, eye-colour and body-colour, are separable although their genes are resident in the same chromosome.

The four characters can be introduced into the experiment in a different way as when a Red-eyed yellow-bodied male is mated to a white-eyed Grey-bodied female. The F_1 consists of white-eyed Grey-bodied males and Red-eyed Grey-bodied females and when these are interbred offspring of four types are obtained.

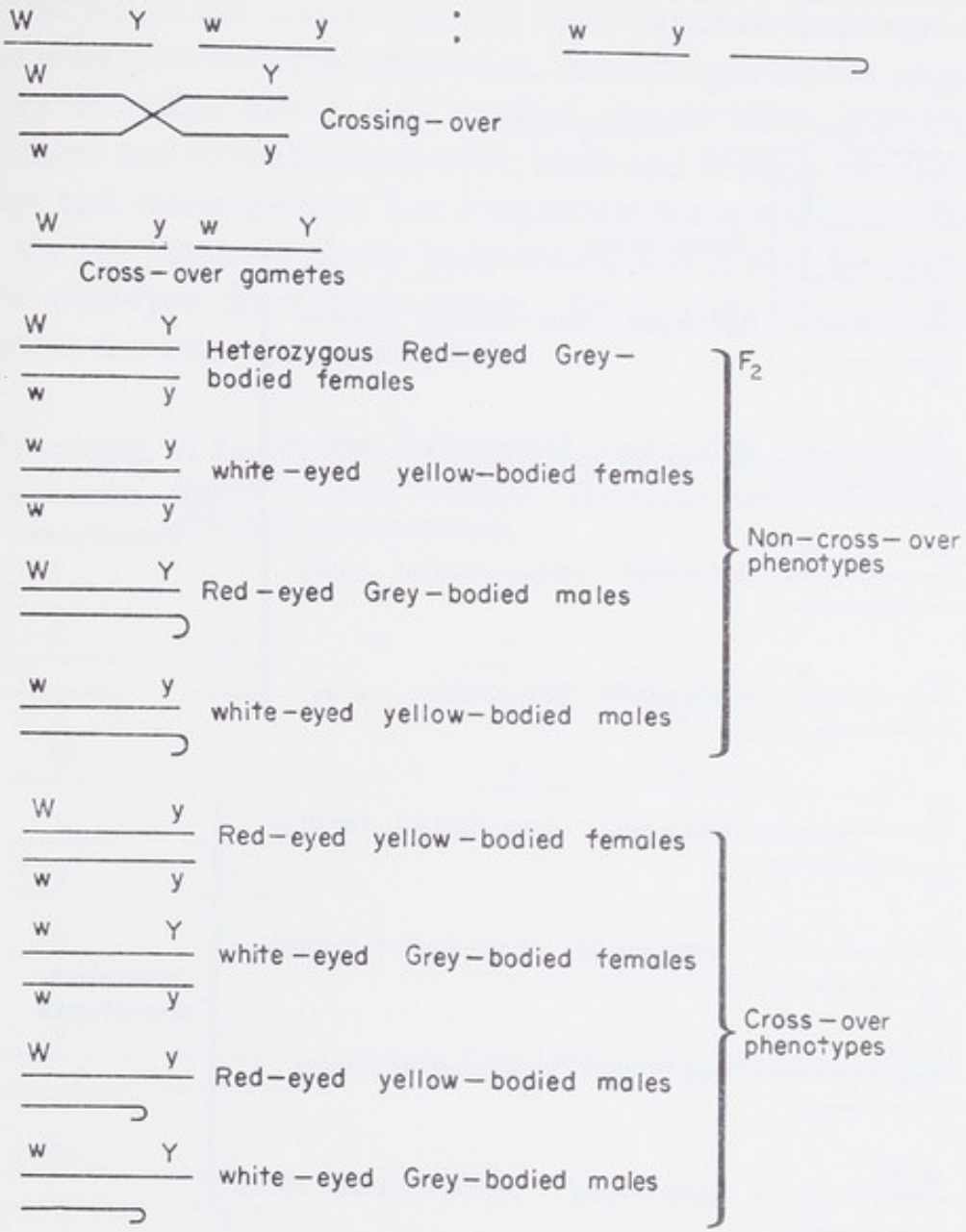
	Males (%)	Females (%)
Red-eyed, yellow-bodied	24·725	
white-eyed, Grey-bodied	24·725	25
Red-eyed, Grey-bodied	0·275	25
white-eyed, yellow-bodied	0·275	

Examination of the figures for the males shows that the extent (1·1 per cent) to which the white and yellow genes become detached when they are introduced from the same parent is numerically equivalent to the extent to which they tend to come together when they are introduced in the first place from different parents. In a fixed proportion of reduction divisions the two loci where the genes white-eye-colour and yellow-body-colour respectively reside become interchanged in the two members of the X-chromosome pair. This is in agreement with cytological observation.

1. The mating. Red-eyed Grey-bodied male to a white-eyed yellow-bodied female.

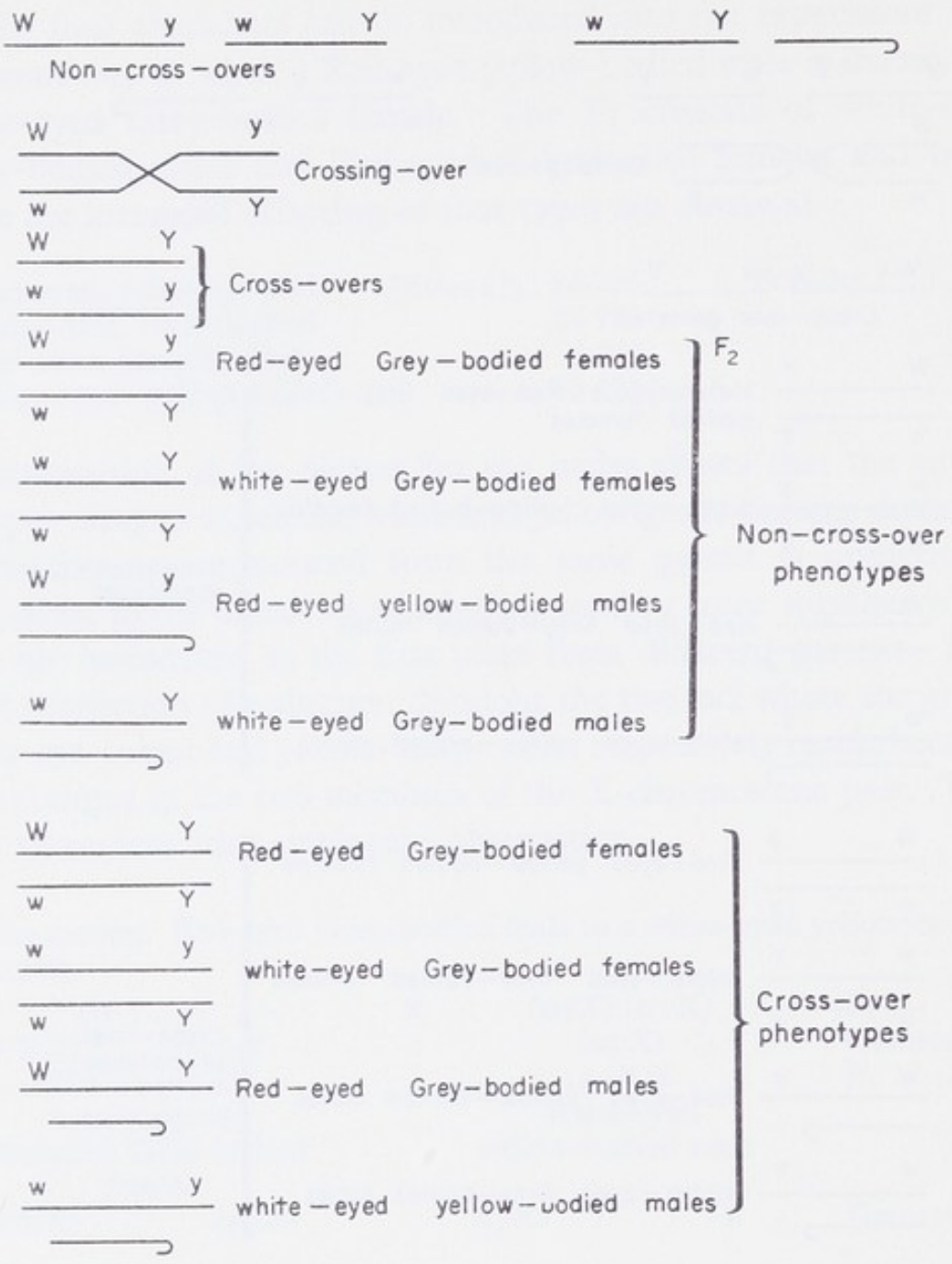
(*WY*X)Y		×	(*wy*X) (*wy*X)	P_1
(*WY*X)	Y	:	(*wy*X)	Gametes
(*WY*X) (*wy*X)			(*wy*X)Y	F_1
heterozygous			white-eyed	
Red-eyed Grey-bodied			yellow-bodied male	
female				
(*WY*X)	(*wy*X)		(*wy*X) Y	Gametes

Let a straight line represent an X-chromosome and a hooked one a Y. Then these gametes can be represented so:



2. The mating. Red-eyed yellow-bodied male to a white-eyed Grey-bodied female.

$(WyX)Y$	×	$(wYX)\,(wYX)$	P_1
(WyX) $\quad$ Y		(wYX)	Gametes
$(WyX)\,(wYX)$		$(wYX)Y$	F_1
Red-eyed Grey-bodied doubly heterozygous females		white-eyed Grey-bodied males	
(WyX) $\quad$ (wYX)		(wYX) $\quad$ Y	Gametes



Another sex-linked character is miniature, the wings are much shortened and do not extend beyond the tip of the abdomen. The percentage of cross-over phenotypes in yellow-miniature matings is 34·3 and that in white miniature matings is 33·2. The difference between 34·3 and 33·2 corresponds to the cross-over percentage in white–yellow matings.

Ebony body-colour, black body-colour and vestigial wing form are three Mendelian characters in *Drosophila* with their genes

resident in the autosomes. The genes for black body colour and for vestigial wings are resident in the same autosome; the gene for ebony is resident in another autosome. According to the Chromosome Theory therefore ebony and vestigial should show independent assortment and recombination while black and vestigial should show linkage and crossing-over. Let *e* represent the autosomal recessive gene for the character ebony body-colour and *E* that for the alternative wild-type Grey body-colour. Let *v* and *V* and *b* and *B* represent the other two gene pairs.

1. The mating. A doubly heterozygous Grey Longwinged fly to a doubly recessive ebony vestigial. The genes *e* and *v* are resident in different chromosomes.

$$\frac{E}{e}\ \frac{V}{v} \times \frac{e}{e}\ \frac{v}{v}$$

$$\frac{E}{\ }\ \frac{V}{\ } \quad : \quad \frac{e}{\ }\ \frac{v}{\ }$$

Gametes

$$\frac{E}{\ }\ \frac{v}{\ }$$

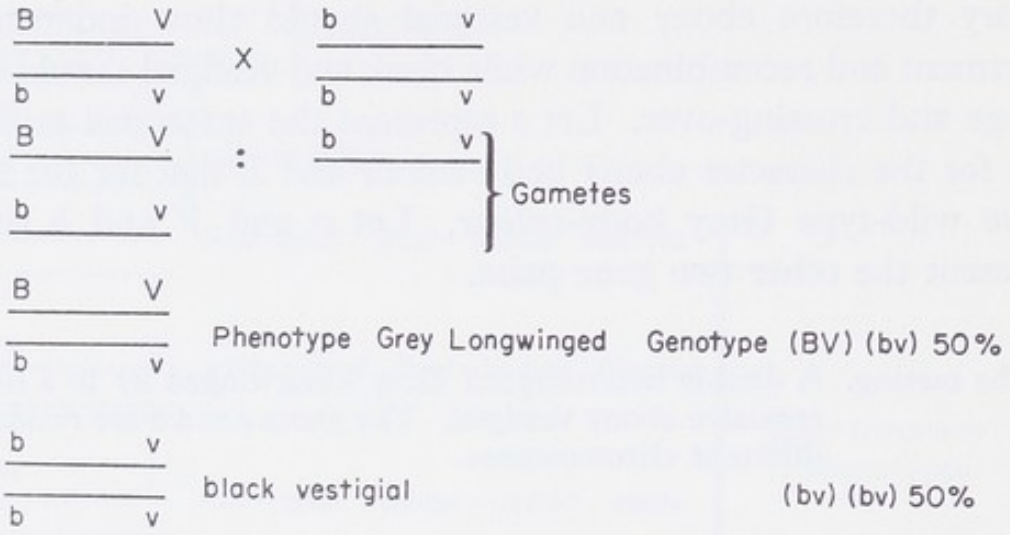
$$\frac{e}{\ }\ \frac{V}{\ }$$

$$\frac{e}{\ }\ \frac{v}{\ }$$

$\frac{E}{e}\ \frac{V}{v}$	Phenotype Grey Longwinged	Genotype	$\frac{EeVv}{25\%}$
$\frac{E}{e}\ \frac{v}{v}$	Grey vestigial		$\frac{Eevv}{25\%}$
$\frac{e}{e}\ \frac{V}{v}$	ebony Longwinged		$\frac{eeVv}{25\%}$
$\frac{e}{e}\ \frac{v}{v}$	ebony vestigial		$\frac{eevv}{25\%}$

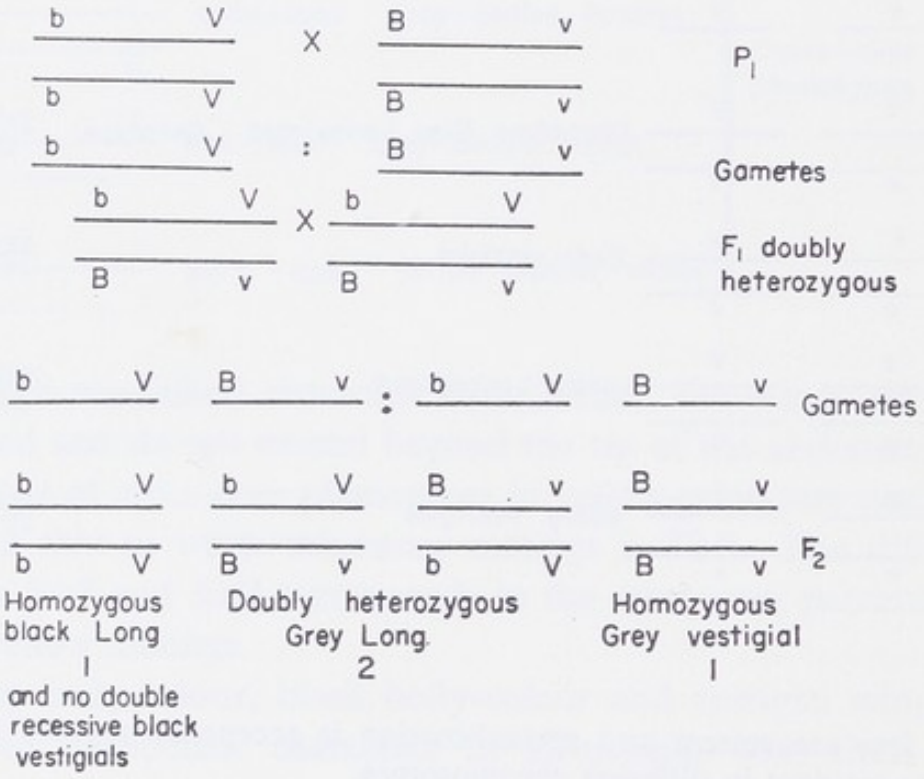
This free assortment and recombination is accepted as proof that the genes are resident in different chromosomes.

2. The mating. A doubly heterozygous Grey Longwinged male fly to a black vestigial female. The genes *b* and *v* are resident in the same chromosome.



The characters Grey and longwinged and the characters black and vestigial went into the experiment together and they came out together; they remained linked. This is accepted as proof that their genes are resident in the same chromosome.

3. The mating. A black Longwinged fly to a Grey vestigial.

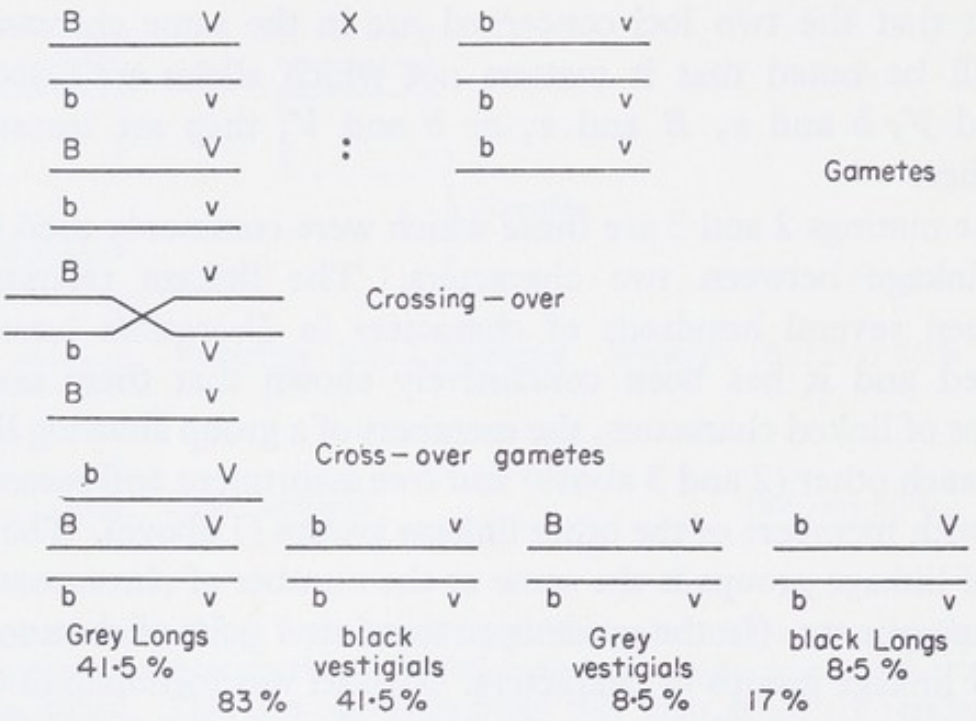


Although four characters, Grey and black body-colour and Longwinged and vestigial wing, are involved in this experiment the ratio obtained in the F_2 is that of a mono-hybrid. The reason for this is that the two loci concerned are in the same chromosome. It will be noted that it matters not which alleles are associated, *B* and *V*, *b* and *v*, *B* and *v*, or *b* and *V*, they are transmitted together.

The matings 2 and 3 are those which were commonly used to test for linkage between two characters. The linkage relationships between several hundreds of characters in *Drosophila* have been studied and it has been conclusively shown that there are four groups of linked characters, the members of a group showing linkage with each other (2 and 3 above) and free assortment and recombination with members of the other linkage groups (1 above). The number of linkage groups is the same as the number of chromosomes in the ripe gamete. (In the garden pea there are 7 pairs of chromosomes and 7 linkage groups of characters. Mendel was fortunate in choosing for his work characters the genes for which lay in different chromosomes.)

If in the mating 2 above the doubly heterozygous Grey Longwinged fly (heterozygous for black and vestigial) had been a female the result would have been different. Instead of the two types Grey Longs and black vestigials appearing in equal numbers there would have been four types as there were in 1 above, but not in equal numbers. There would have been Grey Longs and black vestigials constituting 83 per cent of the offspring (41·5 per cent each) and Grey vestigials and black Longs constituting the remaining 17 per cent. The linkage between the genes black and vestigial (and between their wild-type alleles) broke down in 17 per cent of instances to permit recombination between the four genes. During gametogenesis the members of each pair of chromosomes come together, become closely intertwined and later separate. If when they become intertwined they should stick, break and the broken ends join up again the opportunity for an interchange of material between the two members of the pair of homologous chromosomes would be provided.

4. The mating. A doubly heterozygous Grey Longwinged female fly (heterozygous for the genes black and vestigial) to a doubly recessive black vestigial male.



When such interchange of material occurs between two homologous chromosomes there is no disturbance of linkage relationships, for that which is lost through the joining up of the wrong ends of the broken chromosomes is gained when the reunion takes place. Crossing-over, which does not occur in the male, is followed by discernible effects only when different alleles of the two genes are involved. The fact that the black and vestigial genes (and their alleles) become dissociated in 17 per cent of instances is regarded as an indication of the distance in the length of the chromosome between the two loci concerned. If the chromosomes can break and rejoin with equal ease at all points along their length it is reasonable to assume that the further apart two loci are the greater is the chance that crossing over will occur between them and that, conversely, the nearer they are together the less likely is it that crossing over will occur between them.

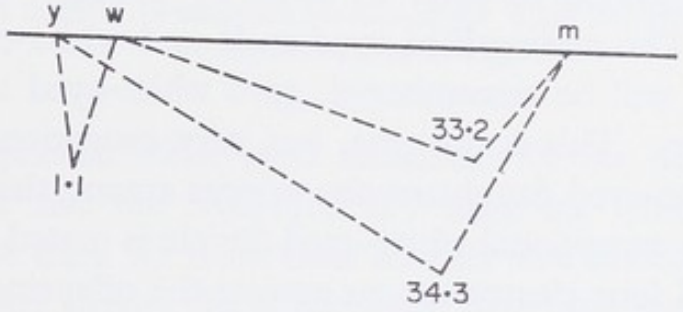
If this be granted it becomes possible to construct a map of the chromosomes showing the relative positions of the various loci in the different chromosomes and the relative distances between them.

If *A*, *B* and *C* form a linear series and if *B* lies between *A* and *C*, then the crossing-over percentage or value (C.O.V.) for *A* and *C* should equal the C.O.V.s for *A* and *B* plus *B* and *C*.

When dealing with the sex-linked characters white eye-colour, yellow body-colour and miniature wing-form, the percentages of the cross-over phenotypes in the different matings were stated to be:

yellow–white	1·1%
white–miniature	33·2%
yellow–miniature	34·3%

These figures can only mean that the three loci yellow, white and miniature are arranged in this order in the length of the X-chromosome and that they are separated one from the other by the following units of distance (1 per cent of crossing-over is taken as one unit of distance).



A crossing-over value of 50 per cent would yield a result that resembled that in 1 above in which there was free assortment and recombination. Loci at the opposite ends of a longish chromosome would seem to be in different chromosomes until other loci between them had been shown by linkage experiments to be in the same chromosome.

Combined genetical and cytological studies of deletions, translocations and other abnormalities in the distribution of the chromosomes made it possible to identify the chromosome and the region of the chromosome that carried the genes for characters whose transmission had been disrupted or altered by such abnormalities in distribution.

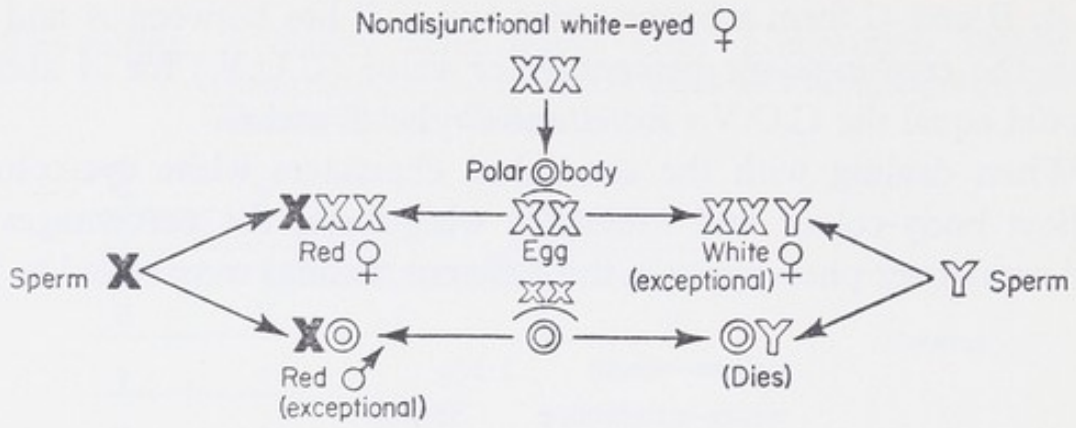


FIG. 19. Primary non-disjunction of the X-chromosomes in a white-eyed female *Drosophila melanogaster*. (Primary is the term used to define the failure of the members of a pair of chromosomes to separate. Secondary non-disjunction is the type of failure to separate that is the consequence of the presence in the chromosome complex of an extra chromosome, as in Fig. 20.)

Conclusive evidence that the genes were resident in the chromosomes was provided as early as 1916 by Bridges' work on non-disjunction. The mating Red-eyed male and white-eyed female of *Drosophila*, it will be remembered, gave white-eyed sons and Red-eyed daughters. This is the rule, but very exceptionally Red-eyed sons and white-eyed daughters also appear among the progeny, and when such an exceptional white-eyed female is mated to a Red-eyed male again all four classes appear among the offspring. Cytological examination of these unexpected white-eyed females reveals that they possess a Y-chromosome in addition to the usual two Xs.

Such an XXY individual could result from the non-disjunction of the two Xs during gametogenesis followed by the fertilization of such an XX ovum by a Y-chromosome-carrying spermatozoon. (It is to be noted that in *Drosophila* the XXY individual is a female; in man the XXY individual is a male.) The XXY female produces four kinds of ova, XX, Y, X, and XY, though not in equal numbers, for the pairing of the two Xs is far more common than is that between an X and the Y. When she is mated to a Red-eyed male, normal in respect of sex-chromosome constitution, these ova will be available for fertilization by X and Y bearing spermatozoa. (Let the solid X indicate that on this chromosome there

is borne the dominant gene for Red-eye; on the X that is not solid there is the recessive gene for white-eye.)

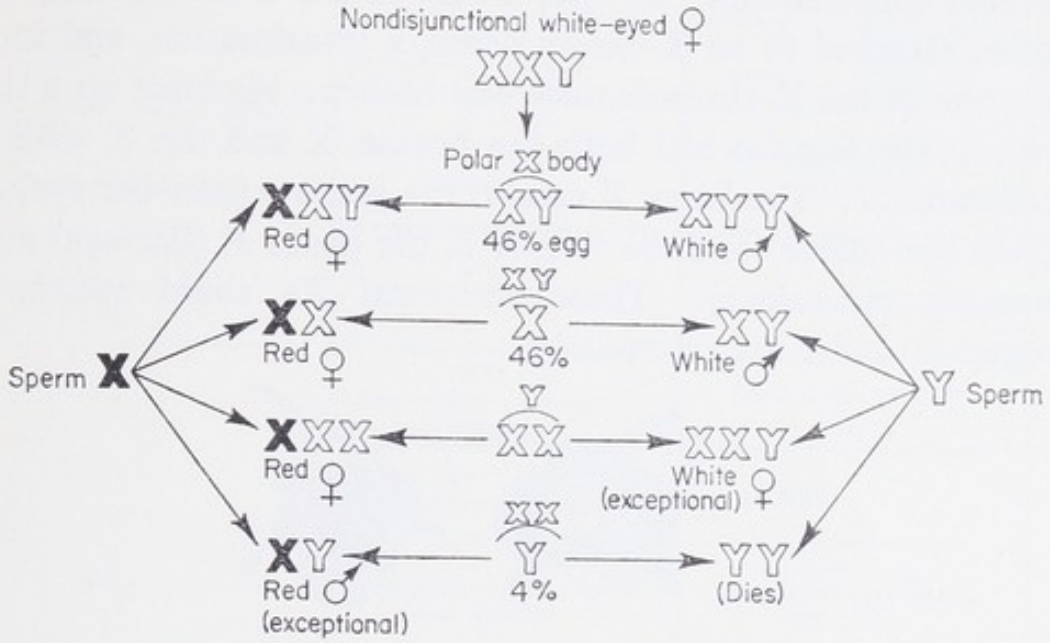


FIG. 20. Secondary non-disjunction of the sex-chromosomes in a white-eyed female *Drosophila melanogaster* with the sex-chromosome constitution XXY.

The exceptional white-eyed daughters of the non-disjunctional XXY female and the Red-eyed XY male are white-eyed because they get both their Xs from their mother and neither of them from their Red-eyed father; the exceptional Red-eyed sons are Red-eyed because they get their Y chromosome from their mother and their single X from their father.

Many instances of non-disjunction of autosomes as well as of the sex-chromosomes and in a wide variety of animals and plants have been recorded and the aberrant behaviour of the chromosome is always correlated with corresponding peculiarities in the behaviour of characters in their transmission from generation to generation.

The proof that crossing-over is due to an interchange of parts between paired chromosomes was provided in 1931 by Stern*

* Stern, C., Zytologisch-genetische untersuchungen als beweiss für die Morgansche theorie des factorenaustausches (Cytological-genetic investigations as proofs of Morgan's crossing-over theory), *Biol. Zentralb.* **51**, 547 (1931).

(*Drosophila*) and Creighton and McClintock* (Maize). Stern discovered two strains of *Drosophila melanogaster* with different chromosomal abnormalities. In one, a part of the Y-chromosome had become attached to an X-chromosome, a translocation, and in the other one of the X-chromosomes was broken. He built up a stock in which the females had both the broken X and the X with the translocated Y. The latter X carried the genes *b* (non-bar eye) and *C* (Red eye-colour) and the former X the genes *B* (Bar-eye) and *c* (carnation eye-colour). These abnormal Xs could readily be recognized under the microscope.

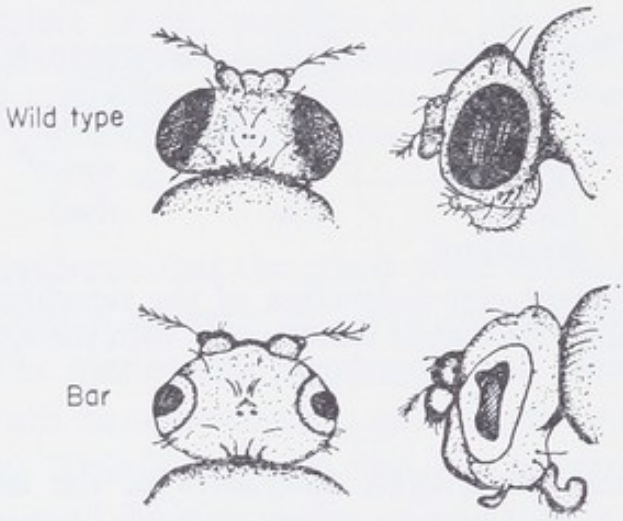
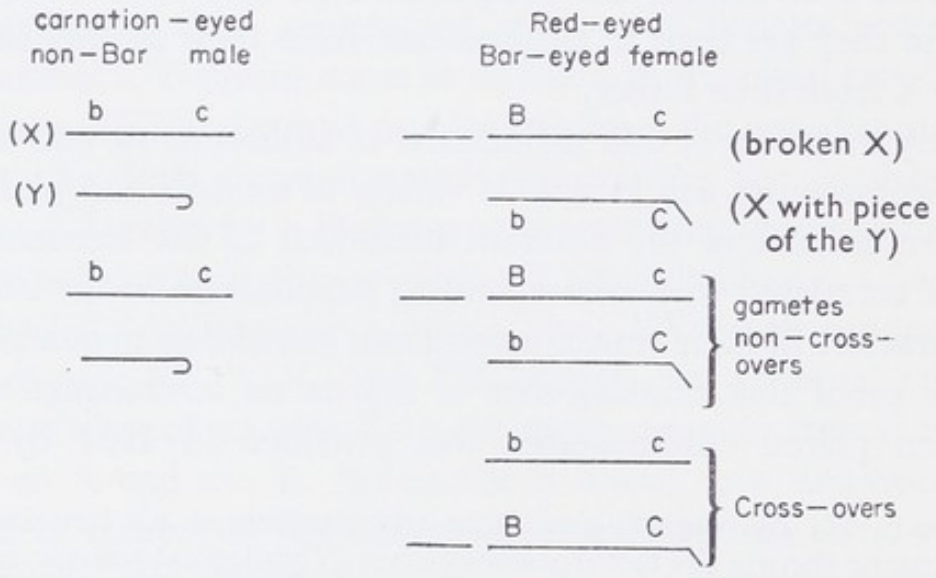
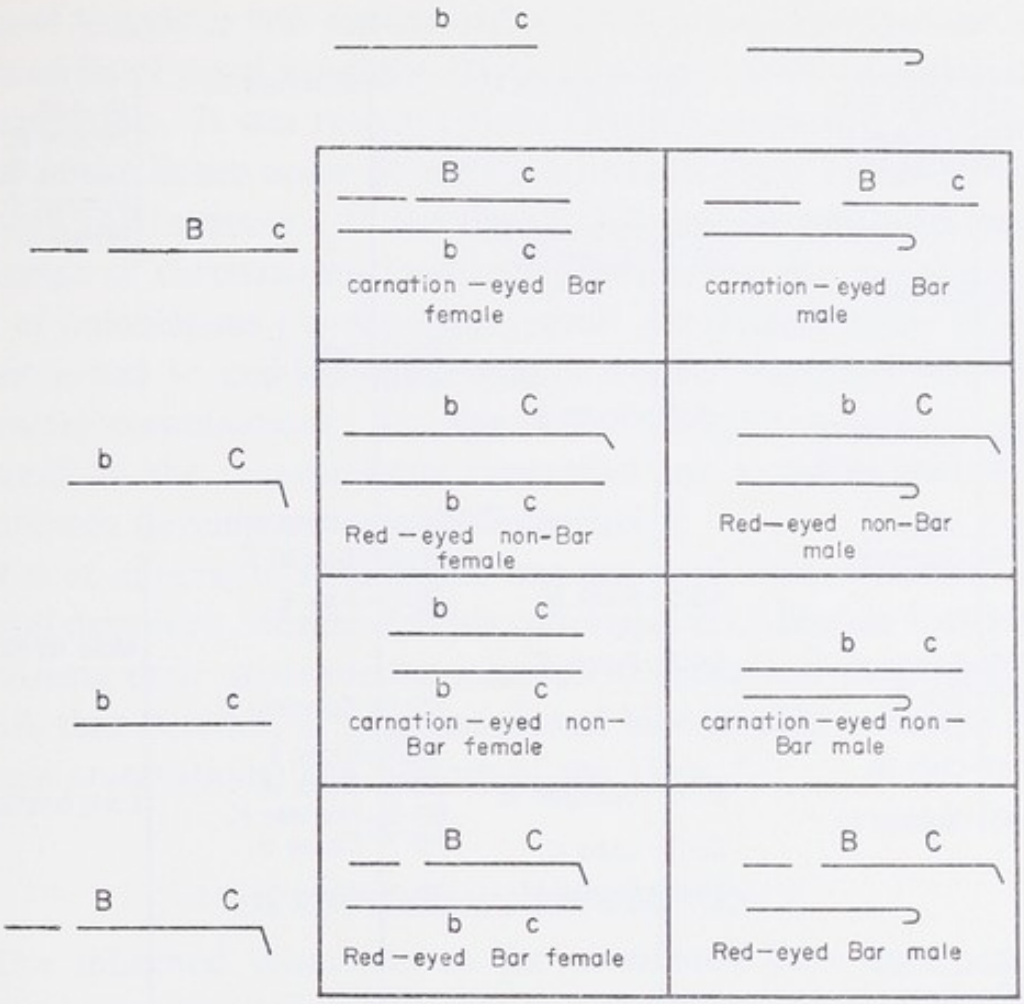


FIG. 21. The Bar-eye character in *Drosophila melanogaster*.



* Creighton, H. and McClintock, B., A correlation of cytological and genetical crossing-over in *Zea mays*, *Proc. Nat. Acad. Sci.* **17** (1931).



The chromosomes of the female offspring were then studied and the cytological results showed quite definitely that the crossing-over of genes was accompanied by chromosomal interchange. In these females one of these Xs always came from the father; this was the normal one and there was always a normal X. The second X came from the mother and she had two kinds to offer, the X with the portion of the Y attached and the broken X. This was so in the non-cross-over classes. In the females of the cross-over classes, however, it was clear that the second X was the result of a chromosomal interchange. In the carnation-eyed non-bar offspring the X was apparently normal, neither broken nor with a translocated Y. In the red-eyed offspring the maternal X was not only broken but one of the broken pieces carried the piece of the Y.

The discovery of experimental material, *Drosophila* and maize in particular, which proved to be ideal from the point of view of the

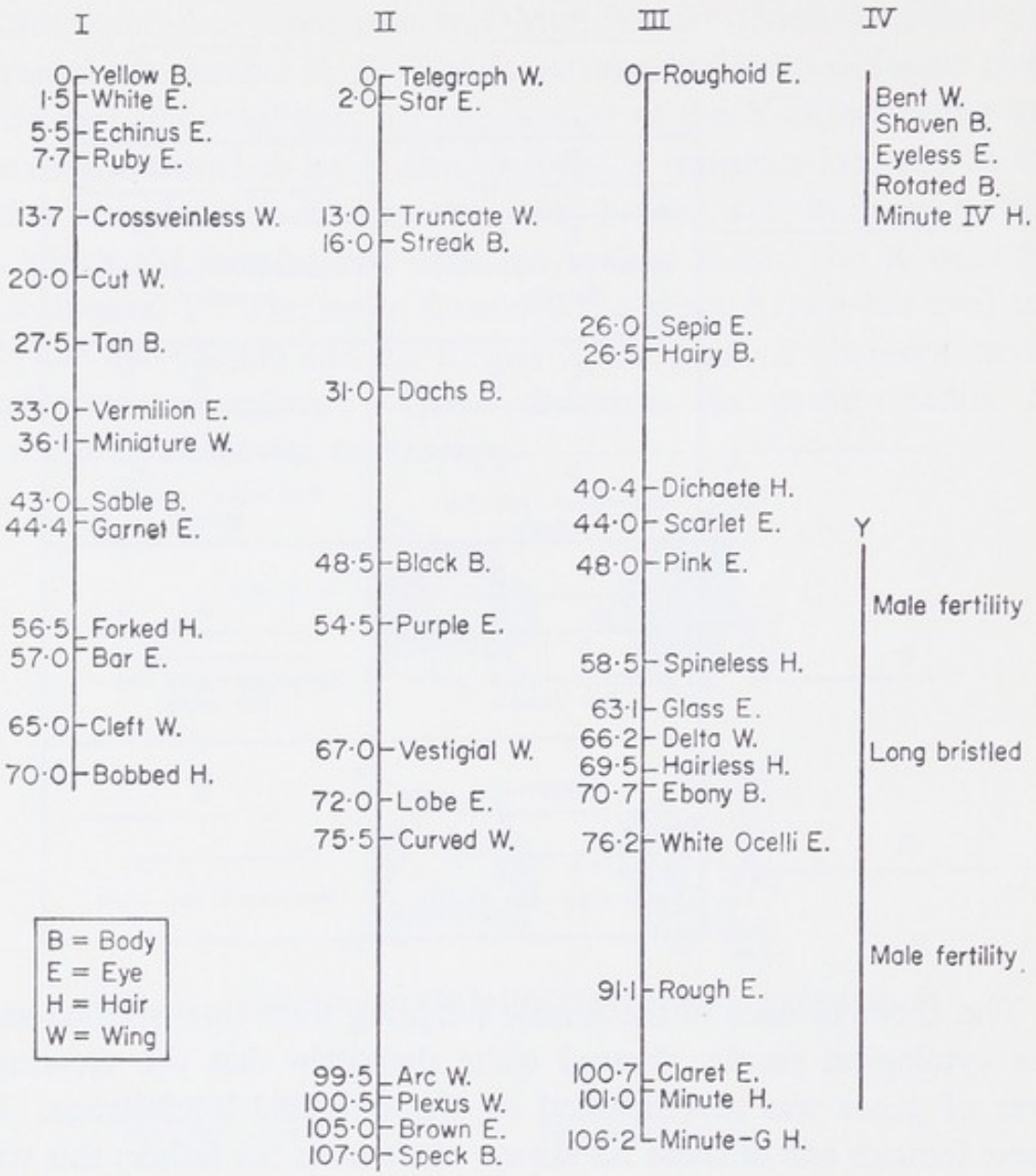


FIG. 22. Linkage-map for *Drosophila melanogaster* showing the relative positions in the chromosomes of a number of genes as determined genetically.

geneticist, was followed by a great burst of fruitful activity and genetics quickly became established as a predictive science dealing with the organization and behaviour of the hereditary material at the biological level. Because of their inherent tendency to mutate the genes were identified and their linear arrangement in the chromosomes of the cell-nucleus was found to be a characteristic feature of all organisms thus far examined. It was recognized that the chromosome was a biological invention that ensured that the linear arrange-

ment of the genes was maintained so long as the chromosome itself retained its physical integrity during its passage from cell-generation to generation. It was recognized too that, exceptionally, rearrangement of the linear order of the genes was brought about by translocation and inversion. It was shown that crossing-over, the mutual exchange of chromosomal material between the two members of a pair of homologous chromosomes, made new combinations of genes possible and so created opportunities for the appearance of novel character combinations. It came to be established that the genic material in the chromosomes controlled the series of events that constitutes development and differentiation.

It is of interest to note that it was not until 1921, when he spent several days with Morgan and his colleagues at Columbia University, discussing their experimental material methods and results in great detail, that Bateson, at long last, found himself able to accept (with certain reservations) the Theory of the Gene.*

CYTOPLASMIC INHERITANCE

The inherited characters so far considered have been such as have obeyed the Mendelian law of segregation, being based upon genes resident in the chromosomes of the nucleus. The vast majority of inherited characters are of this kind, but there are a few that do not show this Mendelian segregation in crosses and which certainly are not so based.

Plastids (Gk. *plastos*, formed; *idion*, dim: cell-bodies other than the nucleus and the attraction sphere) are cytoplasmic structures found in certain cells of plants. They are self-duplicating and are distributed from cell-generation to generation more or less at random to the two daughter cells of the dividing cell. As a rule they produce chlorophyll in the presence of light so that the leaf or stem containing them is green. Exceptionally the plastids lack this ability so that the parts containing them remain white. There can be both chlorophyll-producing and non-chlorophyll-producing plastids in one and the same leaf which is therefore variegated, irregularly

* Bateson, B., *William Bateson, F.R.S., Naturalist*, p. 143.

blotched green and white. Some branches of a plant can be green while others are white. When flowers on a green branch are fertilized with pollen from flowers on a white branch the offspring are all green. When the flowers on a white branch are fertilized with pollen from flowers on a green branch the resulting offspring are all white. So the offspring resemble the mother plant in respect of leaf and stem colour, whichever way the cross is made. Since it is the mother plant that supplies the cytoplasm to the offspring it follows that transmission in such cases is purely cytoplasmic and non-Mendelian. The plastid is a mutable self-duplicating unit that acts as a determiner of a character that is inherited. For this reason it is sometimes called a plastogene. Cytoplasmic inheritance of this kind has been encountered in many plants including maize, sorghum, beans and the four o'clock.

The slipper animalcule *Paramecium aurelia* is a tiny freshwater animal that consists of a single cell. Most of its inherited characters are controlled by genes resident in the chromosomal material of its nucleus, but there is one remarkable attribute that would appear to be cytoplasmically determined. *Paramecium* produces clones by continued cell-division; in addition mating occurs and this is associated with typical Mendelian segregation.

When different clones are kept together it can happen that all the individuals of one clone are killed by a substance that is elaborated by the individuals of the other. This "killer" substance has a twofold basis, a gene *K* resident in the chromosome and what are called kappa particles in the cytoplasm which actually produce the lethal substance. Paramecia with the genotype *kk* are sensitive to this substance and cannot themselves become killers. *KK* and *Kk* are animals which are potential killers but cannot kill unless there are kappa particles in their cytoplasm. These particles are transmitted from cell generation to generation in the cytoplasm.

There are strains of *D. melanogaster* that are hypersensitive to carbon dioxide, being killed by concentrations that have only slight and transitory effects on individuals of other strains. This peculiar property is inherited cytoplasmically.

There are certain strains of mice which are peculiar in that

practically every individual belonging to them sooner or later develops cancer of the mammary gland. There are other strains in which this particular form of disease is extremely rare. Crosses between the two strains gave results that showed quite clearly that the tendency to develop cancer of the mammary gland was inherited from the mother and by way of the milk. What seemed to be an instance of a plasmagene (a character determiner resident in the cytoplasm) came to be thought of as a virus. Between the plasmagene and the virus there are many similarities. Both are self-duplicating and mutable. Both operate only in the presence of certain chromosomal genes. While plasmagenes seem to be normal constituents of the cell viruses are pathogenic invaders transmitted by infection. A plasmagene in one variety of potato behaves exactly like a virus in another. It has been suggested that maybe a virus is a plasmagene in the wrong host and that cancer is sometimes the outcome of mutation in plasmagenes.

CHAPTER 7

THE NATURE OF THE GENE AND THE MODE OF GENIC ACTION

THE study of genetical phenomena at the biological level had revealed much concerning the nature of the gene and concerning the ways in which it exerted its influence upon the processes of development. Since the principles of heredity appeared to be the same in those species in which the fertilized ovum developed within the maternal body and in those in which the male and the female gametes were extruded from the parental bodies thereafter to meet and to give rise to new individuals quite independently of the parents, it was concluded that the hereditary units, the genes, were carried in the gametes since these alone constituted the bridge between the generations. The observed facts concerning reciprocal crosses where the F_1 individuals had the same phenotype, no matter which way the cross was made, was taken to indicate that, in general, the female and the male gamete contributed equally to the transmission of the genes. Since the head of the spermatozoon was practically all nucleus and since this alone took part in fertilization, it was concluded that the nucleus was the essential part of the gamete in so far as the transmission of genes was concerned. Of the constituent parts of the nucleus only the chromatin material was accurately divided at mitosis and segregated during maturation and so it was concluded that the chromatin material, present in the form of chromosomes with a constant and characteristic number and appearance for each species, was the actual hereditary material. Confirmation of this was derived from the study of the exact parallelism that was found to exist between the behaviour of the characters based upon the genes in their transmission from generation to generation and the behaviour of the chromosomes, as seen

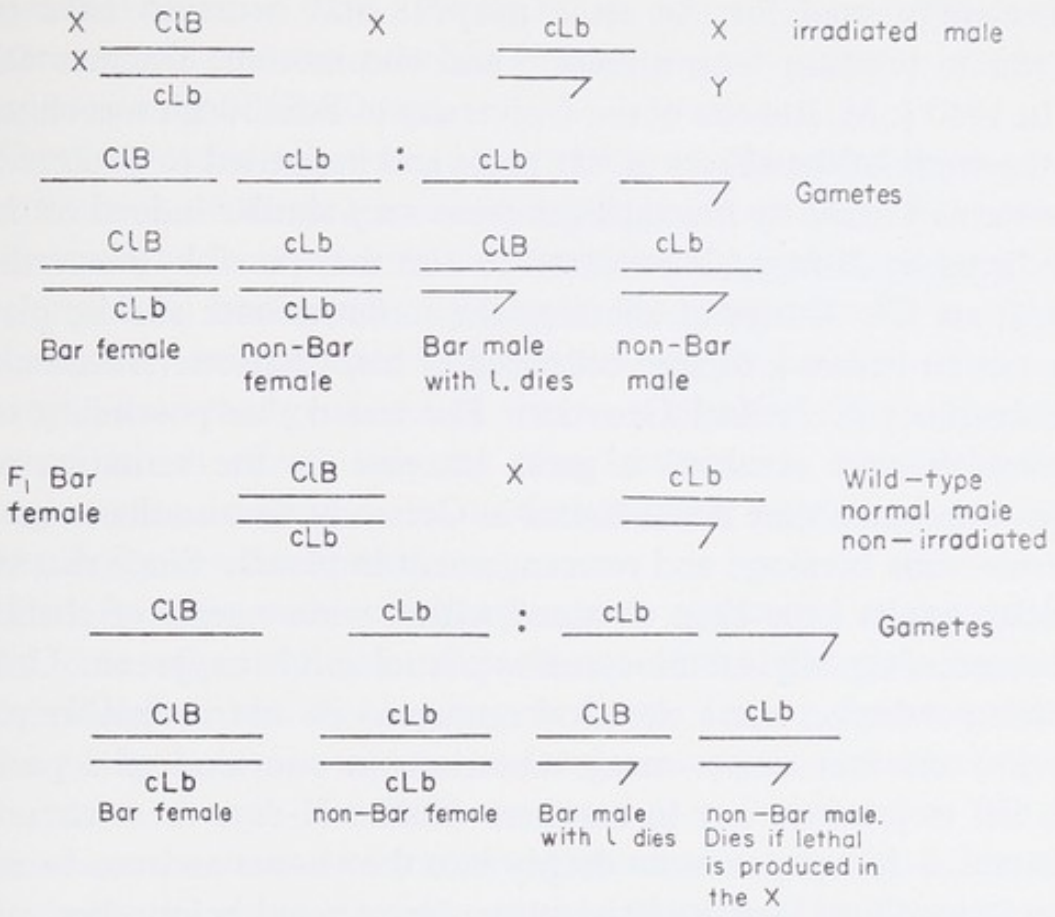
under the microscope. The genes were undoubtedly in the chromosomes.

The genetical evidence indicated clearly that mutation was rare, that the natural mutation rate was low. Müller, for example, had estimated that in *Drosophila*, with its ten generations a year, any particular gene would undergo one mutation while being transmitted through a million generations of individuals, or that in a sample of a million gametes from any single generation only one mutation would be expected in any given locus. It was noted that different genes had different mutation rates, that mutation could occur at any point in the life history of the individual, either in the somatic or in the gametic tissues, but that it occurred most frequently about the time of the maturation of the gametes and that it happened more often in some directions than in others. It was observed that mutation was usually restricted to one gene at a time so that whatever might be the cause of mutation it could not be some gross environmental force which would be expected to affect all genes alike. Of two genes of a pair one could undergo mutation while its mate, exceedingly close to it, could remain unaffected. It came to be recognized that of the mutations that did not affect viability those with slight effects were far more common than those with marked effects and that mutations with lethal effects occurred with much greater frequency than did those which had visible effects. Most mutant genes were found to be recessives. Reverse mutation was encountered, unmutated gene→mutated→original form, so that it could be concluded that mutation was a change in a gene and not the loss of a gene. (In the early days of genetics, Bateson and Punnett had introduced the Presence and Absence Hypothesis to explain the relationship of a pair of Mendelian characters: one of them was based upon a particular factor, the other upon the absence of this.) More than one change could occur in a gene to yield a multiple allelomorphic series, the different members of which usually affected the same character in different degrees but which exceptionally affected different characters. Abundant instances of pleiotropism had been encountered (Gk. *pleion*, more; *trope*, turn; influencing more than one character).

Geneticists had been trying without success to find a method of speeding up this process of mutation using a wide variety of physical and chemical agencies, e.g. variations in food, light, humidity, exposure to radiations, but it was not until Müller* in 1927 devised a special technique using X-rays that a break-through occurred. Than this scheme of Müller's there is nothing cleverer or neater in the whole history of the science. He reasoned that since one allele could mutate while its partner remained unaffected, if the cause was external to the gene itself it must be something as precise in its action as high energy radiation. He decided to look for lethal mutations following irradiation, since in nature these were by far the most common. He therefore deliberately created a stock of *Drosophila* heterozygous for the lethal gene *l*, for the Bar gene *B*, both X-borne, and for an inversion in the X. Crossing-over could occur in females with two normal Xs or with two Xs with the inversion, since in both cases the loci in the two corresponded. But it could not occur in a fly with one normal X and the other with the inversion. The inversion could be used therefore to locate a hidden recessive gene by means of a dominant "marker". The inversion was designated *C* and its normal equivalent *c*. The females of the stock had *ClB* in one X-chromosome and *cLb* in the other. They were viable because the lethal *l* was covered by its dominant allele. These females were mated to (*cLb*)Y males which had been exposed to X-rays. The Bar-eyed female offspring of this mating were (*ClB*)(*cLb*), the first of these X-chromosomes having been received from the mother and the other from the irradiated father. Like their mothers these females were triply heterozygous. They were mated to non-irradiated males (*cLb*)Y and their offspring examined.

Of the males among the offspring half carried the lethal *l* gene and so died. The other half received the X from the irradiated original male and so, if a recessive X-borne lethal gene had resulted from the irradiation these would also have died. Thus if in such a culture there were no males it could be accepted that X-rays had produced a lethal mutation in the X.

* Müller, H. J., Artificial transmutation of the gene, *Science* **66**, 84–7 (1927).



The mutation rate following such irradiation was found to be linearly proportionate to the dosage and independent of the wavelength. It mattered not whether the dosage was given at one time or in small fractions at different times. Such treatment increased the mutation rate as much as 150 times. The mutations so produced were the same as those occurring naturally and most of them were recessives and lethals. Each mutant gene thus produced was thought to be the consequence of a direct hit upon an original gene by a photoelectron. Exposure to X-rays was also followed by fragmentation of the chromosome with consequent deletion, inversion and translocation. The incidence of these increased proportionally to the square of the dosage and spreading the dosage led to a diminution in the rate of such fragmentation.

This method of increasing the mutation-rate has been used extensively since 1927 with both animals and plants and has amply proved its worth in the genetical study of yeasts, moulds and bacteria. Radium, ultraviolet light and high temperature have also been

successfully used for the same purpose and neutrons have been shown to produce both mutation and chromosome fragmentation.

In 1940 J. M. Robson of the University of Edinburgh was engaged in the study of the effects of war gases and happened to observe that the burns caused by mustard-gas were very similar indeed to those produced by X-rays. It occurred to him that possibly mustard-gas might act like X-rays in affecting the mutation-rate and he placed the notion before a former colleague of his, Charlotte Auerbach of the Institute of Animal Genetics. She tested this possibility with *Drosophila* and obtained a great increase in the mutation-rate. About the same time it was found in Germany that urethane caused chromosome breakage and rearrangement in plants. Since that time similar results have been obtained with a wide variety of chemical substances, e.g. allyl isothiocyanate, phenol and benzpyrene. Unlike ionizing radiation these chemical mutagens do not invariably yield results, one that causes many mutations in one kind of organism can fail to produce any in another. Unlike X-rays these chemical substances do not penetrate deeply into the tissues and can become transformed into inert material or can be excreted before they reach the germ-cells. It used to be thought that these mutagens, physical and chemical, acted in an unspecific, random way on chromosomes and genes so that it was impossible to predict what particular mutation or aberration would be produced. But Demerec* and his co-workers in the Carnegie Institute of Washington, working with the bacterium *Escherichia coli*, have succeeded in showing that particular mutagens cause different mutation-rates in specific genes over a wide range of frequencies. Thus, for example, one gene was found to be particularly sensitive to manganous chloride, another to ultra-violet light, another to X-rays and so on. From these experiments it was inferred that the majority of these induced mutations arose through the indirect action of the mutagenic agent. This was thought to induce physiological changes in the treated cells and these in their turn induced mutation. Within limits, therefore, mutation can be directed since different mutagens act on different genes or sub-units

* Demerec, M., Genetic action of mutagens, *Proc. 9th Int. Congr. Genet.*, Pt. I, 201–17 (1954), Suppl. to *Caryologia* 6.

of genes in different ways. It may be, therefore, that with the passing of time it will become possible to exercise a fair degree of control over the process of mutation.

To the geneticist it seemed that the gene controlled the rate and the direction of the processes of development and of differentiation as the embryo evolved into the adult form epigenetically (Gk. *epi*, upon; *genesis*, birth). (By epigenesis is meant that the individual is an entirely new creation and is in no way preformed.) It came to be recognized that genic action was very much like the action of an enzyme which affects the rate of a biochemical reaction without being used up in the process, so that enzymes need to be present in exceedingly small amounts.

The geneticist came to look upon gene replication as the building by a gene of a duplicate of itself out of the materials that were obtainable from the surrounding medium. To him the gene seemed to be a large complex organic molecule occupying a particular place in a series of such molecules arranged in a linear order. He saw spontaneous mutation as a rearrangement of the atoms of the molecule, being the result of random intra- and inter-molecular rearrangement, such accidents tending to happen with a fixed frequency under given conditions.

It is to be noted that although the geneticist had often speculated concerning the ways in which the genes exerted their influence upon the processes of development and differentiation, he had concerned himself, in the main, with the employment of the method Mendel himself had used so successfully—the making of inferences concerning the existence, organization and behaviour of unseen hereditary units from the carefully recorded results of skilfully designed and conducted biological experiments. He was not greatly interested in the nature of genic action and for the most part the characters he studied were not suitable for this kind of inquiry. It was when the geneticist turned his attention to the phenomena of organic inheritance in organisms of relatively very simple organization—moulds, fungi, protozoa, bacteria and viruses—that the interest moved from the character to the chemistry of genic action. The notion that behind the development of a structural character there

was an underlying biochemical character then began to determine the fashion in genetical investigation and soon led to the discovery of the chemical constitution of the genic material and of the molecular events in genic action, in gene replication and in mutation.

It has long been known that the stuff of which the chromosomes were composed is nucleo-protein, protein and nucleic acid. Protein (Gk. *protos*, first) is a complex nitrogenous substance that is characteristic of living matter. Its molecule is a long chain of simpler molecules, amino-acids, of which there are some twenty different kinds altogether. Proteins differ one from another in respect of the kind and variety of amino-acids in them. Most living things need most if not all of these amino-acids if they are to flourish. The higher organisms get those they require from the proteins in the foodstuffs they ingest. Most bacteria can synthesize those they need from the simple inorganic materials in their food. Protein is broken down into its constituent amino-acids and is built up out of amino-acids by the action of enzymes.

The nucleic acid component of the nucleo-protein is deoxyribonucleic acid, DNA, which is built up of nucleotides. A nucleotide consists of three parts, a sugar molecule, a phosphate group and a purine or a pyrimidine base. All the nucleotides of DNA contain the same sugar molecule, deoxyribose, but the bases in different nucleotides are different. Of these bases, made up of rings of carbon and nitrogen atoms, there are four altogether, two of them purines and two pyrimidines. The purines are adenine (A) and guanine (G); the pyrimidines are thymine (T) and cytosine (C). A base is attached to a sugar unit and the units are linked to each other by phosphate, so:

base – – – – – – sugar < phosphate
phosphate
base – – – – – – sugar < phosphate

The number of purines in the DNA of a species is always equal to the number of the pyrimidines (A+G = T+C) and, furthermore, the number of adenines equals the number of thymines and the number of guanines equals that of the cytosines (A = T and G = C).

A different kind of nucleic acid, ribonucleic acid, RNA, is found in the cytoplasm, to a small extent in the chromosome and in certain viruses. RNA differs from DNA in that its nucleotides contain a different sugar, ribose, which differs from deoxyribose by having an additional oxygen atom.

It used to be thought that it was the protein component of the nucleo-protein that was the hereditary material, but studies of the virus and of the bacterium revealed that this was not so and that it was the nucleic acid component that was all important.

The viruses (L. poisonous liquid) belong to the no-man's-land that lies between the living and the non-living. They display many of the properties that are characteristic of the living organism, but they cannot metabolize foodstuffs, they cannot break down ingested foodstuffs into their simpler elements and out of these build the materials they require. They can thrive and reproduce themselves only when they are within a living host cell. They are exceedingly minute, none but the largest of them could be made visible by magnification until the coming of the electron microscope. Like the chromosomes they consist of nucleo-protein, some with DNA as their nucleic acid component, others with RNA instead.

Viruses are known to be the causal agents of many diseases in man and other animals and in plants. In man, for example, they cause chicken pox, the common cold, influenza, measles, mumps, poliomyelitis, rabies, shingles and smallpox. When a virus makes its way into a cell it takes over the direction of the cell's activities, causing it to manufacture the kind of protein that it, the virus, requires for its own well-being rather than the kind that the host cell needs and that is characteristic of the cells in the body of the host. Within the living cell the virus reproduces its own kind and when the cell is destroyed, lysed (Gk. *lysis*, loosing, causing dissolution), the new virus particles escape to attack and destroy other cells. From a particular virus new strains with different properties arise and thereafter "breed true".

It is now thirty years since the virus that causes mosaic disease in the tobacco plant was first obtained in a crystalline-like form, free from all substances save protein and nucleic acid. It was found

possible to separate the protein from the nucleic acid and to apply each of these components of the nucleo-protein separately to the tobacco leaf. The protein component did not give rise to mosaic disease whereas the nucleic acid component did. Furthermore, infection with the nucleic acid of one strain of the virus always yielded new virus particles of this particular strain, and when the nucleic acid component from one strain was mixed with the protein component from another strain the new virus particles that were produced in the infected plant had the protein and the nucleic acid components of the strain from which the nucleic acid that had been used to infect the plant had been derived.

In this virus the nucleic acid component of the nucleo-protein is RNA, whereas that of the gene is DNA. However, it is clear that in mosaic disease of the tobacco plant it is the nucleic acid component that determines what kind of protein the host cell shall produce.

Some viruses attack and destroy bacteria. There are the bacteriophages (Gk. *bakterion*, a small rod; *phagein*, to devour). Their nucleo-protein is DNA. Different strains of a particular phage exist and each of them, entering a bacterium, compels its host to manufacture the particular form of protein that it requires. The different strains of a phage arise from a pre-existing strain by a process that is not to be distinguished from gene-mutation. The typical bacteriophage has a rounded "head" and a long thin "tail". The head consists almost entirely of DNA though there is a small quantity of protein present as well. The tail consists solely of protein. When a phage attacks a bacterium, it attaches itself thereto by the tip of its tail and this proceeds to make a hole in the wall of the bacterium. The contents of the head are then injected into the bacterium through the length of the tail. Since that which is injected is almost exclusively nucleic acid, DNA, it follows that it is this component of the nucleo-protein that directs the activities of the host bacterium.

Genetical studies of the bacteriophage have revealed that it possesses genes that are arranged in a linear order in a chromosome. Between the chromosomes of two different strains of phage crossing-

over occurs so that new combinations of genes come into existence. Certain regions of the chromosome of the phage have actually been mapped.

A bacterium, a single-celled organism, contains several "nuclear bodies" which carry the hereditary material. Lederberg and Tatum* were able to show that this material was present in the form of genes aligned in a single chromosome and that a mixture of different bacteria with different inherited properties could give rise to strains in which properties characteristic of the different strains were recombined. The chromosome of many species of bacteria has already been mapped.

The bacterium, like the chromosome and the virus, consists of nucleo-protein. Its nucleic acid component is DNA. It has been shown that when this DNA is separated from the protein component and brought into association with other bacteria these assume the characteristics of the kind to which this DNA belonged. DNA can penetrate into a living bacterium and take charge of its activities in such a way that the transformed bacteria produce offspring in the likeness of the kind from which the DNA is derived. It would seem to be proven, therefore, that the gene of the bacterium consists of pure DNA. It would seem likely, therefore, that the gene of the higher organisms are similarly constituted.

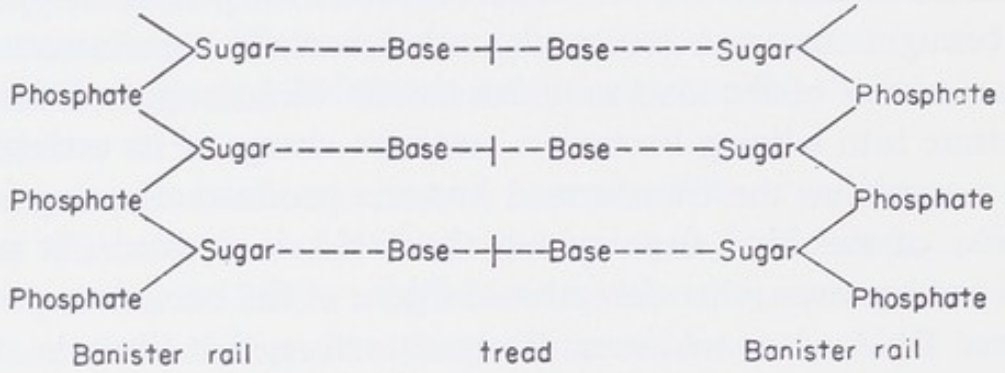
In 1952 Brown and Todd put forward a general theory of the chemical nature of the nucleic acids, making both DNA and RNA polydiesters of phosphoric acid in which the individual nucleotides are linked in a regular fashion. Then the physicists took over. When X-rays pass through a substance such as nucleic acid they are scattered by its atoms and from the pattern that the scattered beams form on the X-ray plate the crystallographer can infer the relative positions of these atoms to each other. The crystallographic studies of Wilkins of King's College, London, of DNA yielded an X-ray diffraction picture of its constitution. Watson, a young American biologist, and Crick,† an English physicist who turned to biology,

* Lederberg, J. and Tatum, E. L., Gene recombination in *Escherichia coli*, *Nature* **158** (1946).

† Watson, J. D. and Crick, F. H. C., Molecular structure of nucleic acids: a structure for DNA, *Nature* **171** (1953).

working together in Cambridge (England), in interpreting this picture, produced in 1953 a model of the DNA molecule which not only explained the very peculiar quantitative relationship of the purine and pyrimidine bases but also gave a simple explanation of the ability of this material to replicate itself.

They saw the DNA molecule as two strands wound spirally round each other, the diameter of the windings remaining the same throughout the molecule. The whole structure had the form of a double helix (Gk. spiral) not unlike a spiral staircase with the banister rails consisting of continuous chains of sugar and phosphate and with each of the treads consisting of a pair of bases. If a section of this staircase could be unwound and flattened it would appears so:



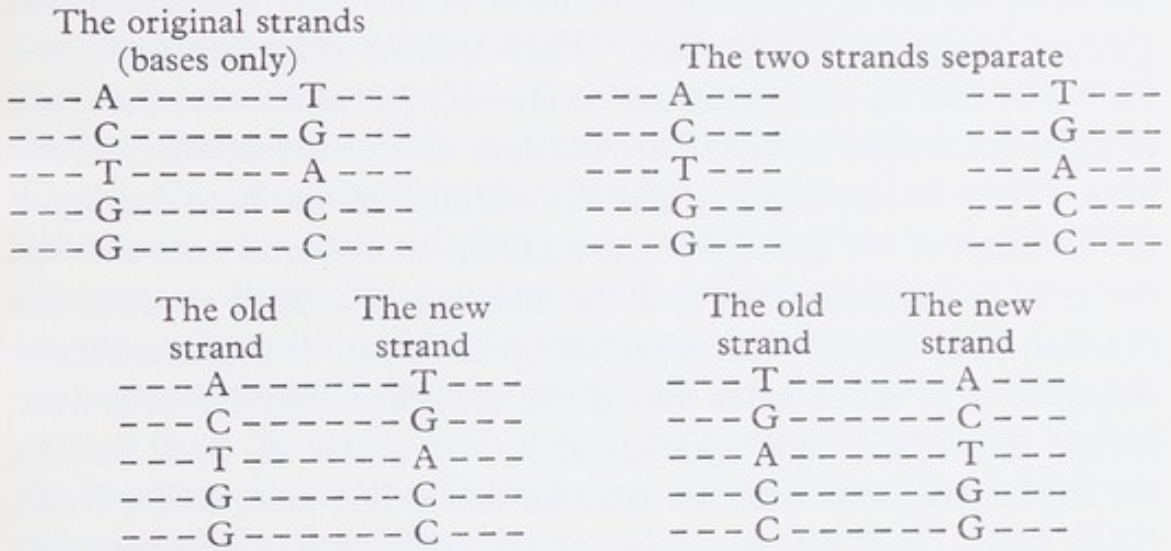
Each base is securely attached to its banister rail but the joint between the bases at the centre of the tread is a loose one.

Of the two kinds of bases, the purines and the pyrimidines, the former are much larger than the latter. Since the X-ray diffraction picture shows that the diameter of the double helix does not vary, it follows that a purine base must always be paired with a pyrimidine one. Furthermore, when the chemical configuration of these bases is taken into account it is found that in order to fit into the available space the purine adenine must always be paired with the pyrimidine thymine and guanine with cytosine. This being so it follows that the sequences of the bases in the two strands must always be complementary to each other, if there is adenine in the one there will be thymine in its partner and so on.

The way in which these strands (and therefore the genes and the chromosomes) reproduce, replicate, themselves is thought to be as

follows: the two strands uncoil and separate (coming apart between the two bases in the tread). When the strands are free the base sequences are exposed to the surrounding medium, the cytoplasm, which contains many chemical substances including those out of which DNA can be synthesized. From this store each base in the strand attracts to itself those units which together form the complementary base (thymine if the old base is adenine). The new bases then become joined with each other by sugar-phosphate links and the new strand, thus formed, joins with the old original strand to form a double helix. Each daughter strand therefore is composed of one of the original strands together with a new one and has the same sequence of bases as did the original strand.

For example:



It is thought that gene differs from gene (and allele from allele) in respect of the sequence of the bases in the DNA chain and that the nature of the chemical "message" emitted by the gene is determined by this sequence. These messages are picked up by messengers which consist of RNA. These messengers pass into the cytoplasm to attach themselves to the ribosomes, minute particles of RNA and upon these ribosomes, according to the instructions conveyed by the messengers, the amino-acids are assembled. The RNA seems to act as a kind of template (a pattern in wood or metal used as a guide in the making of mouldings) on which enzymes and other proteins are formed from the surrounding medium.

In several countries and especially in the United States of America a great concentration of talent and technique is now being focused upon the method by means of which the messages sent out from the bases are deciphered and translated into specific biochemical processes, upon the way in which genes control development. The tempo of the work continues to rise, for the subject is now one of the chief points of expansion in biological science. For the present it is very difficult to find one's way through the labyrinth of elegant experimentation and exciting theorizing, for no sooner has one surprising advance been made than it is succeeded by another even more surprising. It must suffice to outline the "triplet code" that has been put forward by Crick and his colleagues.

This suggests that the basic unit of DNA which "codes" one of the amino-acids is a sequence of three of the four bases, adenine, guanine, thymine and cytosine. They studied gene mutations in a virus that attacks the bacterium *Escherichia coli* and found that each of these mutations involved the addition or else the deletion of one base. They found, further, that the addition of one base destroyed the function of the gene, that the addition of a second base still left the gene functionless, but that the addition of a third restored the function of the gene. This astonishing result can be explained if the sequence is of three bases and if the sequence starts from a fixed point. If the bases are represented by the letters A, B, C and D, the triplet ABC would be the code for one amino-acid, BCD, DAB, CAB, BAD, CAD and so on for others. The code is read from left to right. If the sequence is CAB, BAD, DAB, CAD, for example, and if an additional base becomes added, call this X, this becoming inserted at the end of the first of the triplets, this would give CAB, XBA, DDA, BCA, . . . and all the amino-acids apart from the first would be incorrectly coded. The same result would be obtained if a second X becomes inserted immediately after the first, CAB, XXB, ADD, ABC, . . . But if three bases are added, the third immediately following the second, the result would be CAB, XXX, BAD, DAB, CAD, . . . and only one amino-acid in the whole chain would be incorrectly coded, which might allow normal functioning of the protein synthesized. Such a sequence of three bases is the least

that could code the twenty amino-acids that are to be found in proteins.

A hundred years ago Mendel concluded that the phenomena of organic inheritance were to be explained by the orderly distribution of elements or factors which by their action gave rise to the characters that were displayed by the plants he studied. Today the chemical nature of these factors is known; the chromosomal gene has been shown to consist of a linear array of nucleotides, the linearity being a consequence of the geometry of the nucleic acid molecule which is a linear polymer. It has been demonstrated that this linear array is rigorously maintained when the gene is replicated. Nucleic acids have been identified as the carriers of genetic information in viruses and bacteria and of these nucleic acids deoxyribonucleic acid has been shown to be the most important, though ribonucleic acid is known to be involved in the synthesis of proteins and to constitute the messenger system that carries, in code, the information by means of which the amino-acids are polymerized in proper sequence. Benzer* has shown that in the bacteriophages of the bacterium *E. coli*, the gene itself is divisible into "cistrons", "recons" and "mutons", sub-units of function, recombination and mutation. The way in which the gene imposes its will upon the cell is now very largely understood and it can be assumed with confidence that the sequence hypothesis will be supported by the evidence that will emerge from the work that is now in progress in laboratories all over the world and that it will be found to apply equally to all living things, including man himself.

No wonder then, that in the genetical field today there is much excitement: no wonder that the names of so many of those whose work has contributed notably to the development of this science are to be found among the Nobel laureates of recent years—T. H. Morgan (1933), H. J. Müller (1946), G. W. Beadle, E. L. Tatum and J. Lederberg (1958), S. Ochoa, A. Kornberg (1959) and M. H. F. Wilkins, F. H. C. Crick and J. D. Watson (1962), two of these British, all the rest American. (And in 1965, three Frenchmen—F. Jacob, A. Lwoff and J. Monod.)

* Benzer, S., Fine structure of a genetic region in bacteriophage, *Proc. Nat. Acad. Sci.* **41** (1955).

CHAPTER 8

RAMIFICATIONS OF GENETICS

THE ramifications of classical genetics, the superstructure that was built upon the foundations of Mendelism, can best be illustrated by reference to the fields of interest and activity in the titles of which the term appears. Animal genetics, biochemical genetics, biometrical genetics, cytogenetics, developmental genetics (epigenetics), evolutionary genetics, human genetics, medical (clinical) genetics, microbial genetics, pharmacogenetics, physiological genetics, plant genetics, population genetics and radiation genetics are all active spheres of research in many countries and many of them are names of university departments, research institutes and research units. The subject of genetics claims its place in the courses of instruction that lead to degrees and diplomas in agriculture, anthropology, botany, medicine, sociology, veterinary medicine and zoology. A brief glimpse at certain of these branches of genetics and of the contributions which genetics has made to other sciences must suffice to illustrate the truly astonishing developments that have taken place during the last fifty years.

ANIMAL GENETICS AND ANIMAL BREEDING

The greatest effect of the development of genetics upon the breeding of animals of economic importance has been the replacement of phenotypic selection by genotypic. Selection based upon the appearance of the character or characters of importance, selection of those animals that most closely approached the ideal, as parents of the next generation had often been successful though failures were far from uncommon. Many fine-looking animals had failed to produce offspring "as good as" themselves. This was particularly so in so far as "production" characters such as milk or egg produc-

tion were concerned. The reason for this was, of course, that, as Johannsen had showed, the phenotype is not a trustworthy indication of the genotypic constitution, is not a guide to the transmitting ability of the individual. Nor can the pedigree be relied upon, for not all the individuals in a "line" are of equal quality, for the reason that there is a plentiful genetic diversity among animals that are closely related, much heterozygosity, so that segregation and recombination occur to yield dissimilarity in characterization.

The modern genetic type of selection is based upon the idea that the best way of judging the qualities of parents is by assessing the qualities of their offspring. Individuals are selected as parents only if they produce offspring of the desired type. This type of selection is known as the progeny test or progeny selection. In the fowl both males and females are selected for further breeding on the egg-production of their daughters. In cattle a dairy sire is chosen on the records of his first six daughters.

Genetics also provided an explanation of the varied results that had followed the practice of inbreeding, the mating of closely related individuals. The belief that inbreeding is a hazardous proceeding is still common among breeders. This belief has some basis in fact, for there are many records that show that inbreeding has led to the development of degeneracy in the stock. But this is not always so and it is undoubtedly the case that inbreeding has played a prominent role in the production of the modern breeds of livestock.

Genetics has shown that inbreeding increases homozygosity in the population, isolating pure lines, bringing to light characters that are based on recessive genes. In every individual of a population that has not been consistently inbred there will be many recessive genes in the single dose and many of these will relate to characters that are disadvantageous or unwanted. Under a system of random mating these recessive genes are carried along in the heterozygous state from generation to generation. But under any system of inbreeding the heterozygotes in a population become less frequent and the homozygotes more frequent. Since many of these genes affect such quantitative characters as fertility, viability and vigour, the population as a whole can display a tendency to degenerate.

But other recessive genes relate to advantageous characters and homozygosity brings these to light. The effects of inbreeding are determined by the numbers and nature of the recessive genes in the heterozygous state in the genotype of the original population. It will bring to light both advantageous and disadvantageous characters based upon recessive genes. In laboratory animals such as the rat and guinea pig inbreeding has been practised to produce lines in which the animals are remarkably uniform in respect of characterization, anatomical and physiological. The offspring of a single mated pair are taken and divided into a number of pairs, each consisting of a brother and a sister, to form the origins of a number of lines. Generation after generation within each line brother is mated to sister. After a few generations some of these lines come to an end through sterility, and some produce large numbers of individuals with various defects and derangements. But other lines flourish and after about twenty generations or so they can be distinguished one from the other by a number of true-breeding differences. Line comes to differ from line, but within the line the individuals are remarkably alike. In a few of the surviving lines such qualities as fertility, viability and general vigour are greater in degree than they were in the original stock. This experience shows that inbreeding must be associated with the most careful selection.

Genetics has also proffered an explanation for hybrid vigour. Breeders have long been aware that the hybrid is often remarkable for its vigour which far exceeds that of either of its parents. Crossbred cattle are deliberately produced for the meat market as are also crossbred pigs. The mule is hardier than either the horse or the donkey and has for long been deliberately produced because of its valued qualities. When individuals belonging to two different inbred lines of the rat or the guinea pig are mated, they sometimes produce offspring remarkable for their vigour. It would seem that there are many genes that correspond to vigour (physical strength, luxuriant growth, lots of energy), each one of them dominant to its allele which corresponds to lack of vigour. These dominant genes would seem to be scattered on various chromosomes and to be incorporated into various linkage groups. Any inbred line is apt

to have these dominant genes in a homozygous condition but also to have the recessive alleles of many of them also in a homozygous condition. Crosses between inbred lines may bring all the dominant genes together in the hybrid if each inbred line carries the dominant vigour genes the other one lacks. If this is not so then the hybrid will not display heterosis (Gk. *heteros*, other), which is another name for hybrid vigour. Another suggested genetical explanation of heterosis is that certain genes in the heterozygous state yield a greater degree of vigour than either allele does in the homozygous state, that hybrid vigour results from heterozygosis.

Any of the animals that are of economic importance or that are bred by the fancier could be used to illustrate the extent to which genetic tenets have been applied to animal breeding; a vast literature relating to this subject now exists. It must suffice to make use of one, the fowl. The deliberate production of "hybrid" chickens on a vast industrial scale by using as parents individuals of two highly inbred strains of the same breed is nowadays a commonplace procedure.

The explanation of sex-linkage soon led to its commercial exploitation. Reference has already been made to the sex-linked plumage colour characters, Silver and gold, in the fowl. The mating gold cock (e.g. Rhode Island Red) mated to Silver hens (e.g. Light Sussex) produces chicks of two colours, those with yellowish white down and those with a warm golden down, the first of these are males and the second are females and the sex can be identified on hatching by reference to the down colour. Punnett and Pease (1930)* developed what is called an autosexing breed, one in which male and female are to be distinguished on hatching by differences in down colour. They used the Barred Rock, a silver, barred breed and the Golden Campine, a gold, barred breed. In the Barred Rock the white bar that runs across the feather is wider in the male so that he is paler than the female. In the day-old chick there is a white patch on the top of the head; it tends to be larger in the male. The reasons for this sex-dimorphism are that the barring gene *B* is

* Punnett, R. C. and Pease, M. S., Genetic studies in poultry, VIII. On a case of sex-linkage within a breed, *J. Genetics*, **22**, 395–7 (1930).

X-borne and that the male has two X-chromosomes, the female only one. The barring in the Campine is caused by an autosomal recessive gene, *ab*. Barred Rock was mated to Golden Campine and the offspring backcrossed to the Campine for several generations. The (*B*X)(*B*X) males could be identified by their pale blotchy down. These were then mated to their barred sisters (*B*X) to yield the Golden Cambar, rather like the Golden Campine but possessing the *B* gene of the Barred Rock, the cocks being paler than the hen and the male day-old chick having a pale blotchy down while the female has a warmer ground colour with irregular stripes on the back and dark spots on the head. Using similar procedures other autosexing breeds were synthesized, a gold series, the Buffbar (Buff Orpington), Brussbar (Brown Sussex), Dorbar (Dorking), Legbar (Brown Leghorn) and a silver series, Silver Cambar (Silver Campine) and Silver Dorbar.

The breeds used in the production of these autosexing breeds were not such as had been bred for utility purposes and so the new synthetic breeds cannot as yet compete in respect of productivity with those that are used by the commercial poultryman. But there is no reason to think that continued selection will not remove this disqualification.

Because the fowl exists in a large number of "breeds" and varieties, differing markedly one from another, because it matures and reproduces itself rapidly and has large numbers of offspring, and because it is easily kept, it has been much used for genetical investigation so that much concerning its inherited characters is known. It is not only an animal of considerable economic importance, it is also a favourite of the fancier who, exercising his art, has produced many varieties remarkable for their beauty or for their quaintness. All that is known concerning the genetics of the fowl is contained in a book with that title by Hutt. The fowl has 39 pairs of chromosomes. Of these the X (two in the male and one in the female) and five of the autosomal pairs are relatively large while all the rest are very small. The Y-chromosome has not been identified; if there is a Y, which is by no means improbable, it is one of the very small chromosomes. With so many chromosomes and therefore with so many

linkage groups, to establish the linkage relationships of genes must be very difficult save in the case of those of the sex-linked characters. Thus far the six linkage groups have been described, that of the eleven X-borne genes being the largest. Altogether about 80 pairs of Mendelian characters have been identified, some of them being of considerable economic importance. Several lethal genes have been detected; they so affect the processes of development that the resulting characterization is incompatible with continued life and the affected individuals die usually before hatching. There is also an interesting multiple allelomorphic series of genes which affect the rate of feathering.

A breed consists of a group of animals which have a few striking characters—the trademarks of the breed, e.g. plumage colour, combform—each based upon a single gene, and a number of quantitative characters such as body size or egg-yield, based upon multiple genes, in common. Their creation is made possible by the occurrence of mutation.

The state of the existing knowledge of the genetics of an animal of economic importance or of one that is prized by the fancier is determined by many factors, the more important of which have already been mentioned in connection with the fowl. Far more is known of the genetics of the rabbit, or the hamster, for example, small, quickly maturing and reproducing, giving large numbers of offspring, easily and cheaply kept and with many mutant genes, than of the genetics of the horse, the pig, the sheep or of cattle. The fancier tends to cherish any variant that appears in his stock for the reason that it might prove to be the origin of a new variety; the commercial breeder tends to get rid of any variant for the reason that what he seeks is high-grade uniformity. Thus it is that the animals that are the favourite of the fancier and that can be used as experimental material in scientific laboratories have contributed more to genetical knowledge than have the animals of the farm.

BIOCHEMICAL GENETICS

In 1908 Garrod, an English physician, gave a series of lectures entitled *Inborn Errors of Metabolism* to a London medical society

and in them he described a number of illnesses in children which behaved as though they were caused by a Mendelian recessive factor. Each of these conditions seemed to be due to an inborn inability on the part of the individual to carry out one of the usual chemical processes that in their sum constitute metabolism (Gk. *metabole*, change). It was known that many of these chemical processes either did not take place at all or else proceeded exceedingly slowly unless a special enzyme was present and active. Garrod reasoned that in each of the conditions he was describing a particular enzyme was lacking with the result that certain chemical substances which, in its presence, would have undergone further change, accumulated in the body and were excreted in the urine.

One of his examples was a rare condition known as alkaptonuria. In the affected individual the urine turns black on standing due to the presence in it of homogentisic acid (alkapton). Garrod suggested that this was a normal stage in the breakdown of two of the amino-acids found in protein-containing foodstuffs, phenylalanine and tyrosine. If an individual with alkaptonuria is given a large dose of either phenylalanine or tyrosine he excretes them in the form of homogentisic acid. In the normal person this homogentisic acid is broken down further into carbon dioxide and water and is not excreted as such. Garrod therefore argued that the alkaptonuric individual lacked the particular enzyme that was responsible for the conversion of homogentisic acid into carbon dioxide and water.

In 1934 a second autosomal recessive gene was found by a Norwegian doctor, Fölling, to intervene in the same chain of metabolic reactions. The gene for alkaptonuria in the homozygous state causes blackened and hardened cartilage, but this second gene, the gene for phenylketonuria, is the cause of an extreme form of mental deficiency. The urine of these individuals contains large amounts of a chemical known as phenylpyruvic acid and gives a green colour when mixed with a solution of ferric chloride.

The different steps in the breakdown of phenylalanine are as follows:

to tyrosine—to parahydroxyphenylpyruvic acid—to homo-

gentisic acid—to maleylaceto-acetic acid—to fumarylaceto-acetic acid—to fumaric acid and aceto-acetic acid—to carbon dioxide and water.

Each of these steps requires the presence of a specific enzyme and in the normal individual all are present and active. The phenylketonuric child cannot break down phenylpyruvic acid into para-hydroxyphenylpyruvic acid for the reason that in him the requisite enzyme is missing. Thus it is that phenylpyruvic acid accumulates in the body and is ultimately excreted in the urine. It has been shown beyond all doubt by Fölling and by Penrose that this condition is the outcome of the activity of a single autosomal recessive gene.

Lipid and carbohydrate metabolisms, like amino-acid metabolism, are also affected by mutant genes that are related to the production of specific enzymes. In a disease called Tay-Sach's disease and characterized by profound physical and mental disturbances, the cause is the absence of a particular enzyme that is necessary for the oxidation of the lipid sphyngomyelin and this absence is due to the action of an autosomal recessive gene in the homozygous state.

The most direct evidence of the interconnection between genes and enzymes emerged from the brilliant genetical and biochemical work of Lindegren,* Dodge,† Beadle and Tatum‡ on fungi and yeasts. The fungus *Neurospora crassa* normally grows as a spreading mycelium (Gk. *mykes*, fungus), a network of hyphae (Gk. *hyphe*, web), or strands which contain many nuclei in a common cytoplasm. All these nuclei are haploid (7 chromosomes). Vegetative or asexual reproduction occurs by growth of the hyphae and repeated mitotic division; it occurs also by the formation of asexual spores called conidia (Gk. *konis*, dust: *idion*, dim) which are also haploid. Sexual reproduction also occurs, two haploid nuclei fuse through the union

* Lindegren, C. C., *The yeast cell; its genetics and cytology*, St Louis (1949).

† Dodge, B. O., The mechanisms of sexual reproduction in *Neurospora*, *Mycologia*, **27**, 418 (1935).

‡ Beadle, C. W. and Tatum, E. L., Genetic control of biochemical reactions in *Neurospora*, *Proc. Nat. Acad. Sci.* **27** (1941).

of two opposite mating types. These two mating types cannot be distinguished morphologically (Gk. *morphe*, form) but can be shown to differ by the fact that when two strains of opposite mating types are grown together characteristic sexual spores, ascospores (Gk. *ascos*, a bladder or bag), are formed, whereas when the strains are of the same mating type these spores are not formed.

In the sexual form of reproduction a cell is formed which contains two haploid nuclei, one from each of the two strains. These nuclei fuse to yield a diploid cell. The fusion nucleus then divides meiotically to give rise to eight haploid ascospores in a sac-like structure known as an ascus. These ascospores can be isolated and cultured separately.

Neurospora can live and thrive on a watery medium containing sucrose, nitrate, minerals and biotin, one of the B series of vitamins. From this minimal medium the fungus can synthesize at least twenty amino-acids and everything else it requires.

The uninucleate haploid ascospores were irradiated and then plated out on an enriched medium—the minimal medium to which had been added all the vitamins and amino-acids known to be required by the fungus. From the resultant colonies small samples were transplanted on to the minimal medium. Some of them were found to be no longer capable of thriving on this though they did well on the enriched medium. Each of these strains was found to require one substance to be added to the minimal medium; some needed arginine, others tryptophan, others niacin and so on. Irradiation had resulted in the formation of strains with altered nutritional characteristics, lacking the ability to form some particular essential substance.

When, for example, a niacin-requiring strain was crossed with a "normal" strain the eight ascospores of a single ascus were isolated and grown separately. When they were germinated on a medium containing niacin, all the eight formed colonies. If samples of these, inocula, were then transferred to a medium that lacked niacin, four of them flourished and four failed to grow. Half the spores were niacin-dependent and half were not, so that the trait segregated as for a single gene difference. Mutation due to irradiation had re-

sulted in the loss of the ability to carry out a particular and essential biochemical reaction.

From such studies of the control of metabolic processes and of development in mould, yeasts and bacteria, a unified set of principles involving genetics, embryology and biochemistry has been evolved.

CYTOGENETICS

When once the parallelism between the behaviour of the inherited characters, as they passed from generation to generation, and the behaviour of the chromosomes during cell-division and gametogenesis, had been noted, it was inevitable that nuclear or chromosomal cytology would pursue a very rapid development, since it was to the cytologist that the geneticist had to turn for the testing of many of his hypotheses. For example, genetic linkage was first observed by Bateson and Punnett in the sweet pea in 1906. Its significance was not recognized, however, until some four years later, when many instances of the phenomenon were encountered by Morgan and his colleagues in *Drosophila melanogaster*. The notion that genes that were linked must be resident in the same chromosome then took shape. Genetic support for this notion was quickly forthcoming. The break-down of linkage—crossing-over—demanded that there should be an actual interchange of chromosomal material between the two members of a pair of homologous chromosomes. In 1931 clear cytological proof of such an interchange was forthcoming (Stern in *Drosophila*; Creighton and McClintock in maize).

As early as 1909 Janssens,* a Jesuit professor at Louvain University, had reasoned that such interchange did take place. It will be remembered that during the maturation of the gametes the two members of each pair of chromosomes come to lie closely applied side by side. Each chromosome then splits so that for the time being there are four closely associated threads (chromatids). This association of the four chromatids is known as a tetrad (Gk. *tetras*, four). The two members of the pair of chromosomes then separate, each

* Janssens, F. A., *La Cellule* **25**, 389 (1909).

of them being double because of the split. When separating they do not come apart evenly, but stick together at a number of points to give the appearance of a series of crosses. Each of these crosses is called a chiasma (Gk. a cross). Janssens held that these chiasmata were trustworthy indications of an actual interchange of material between two chromatids belonging to different members of the pair of chromosomes. Janssens had realized that there was to be found "une plus large application cytologique de la théorie de Mendel".

It came to be generally accepted by cytologists that these chiasmata were associated with cytological crossing-over, but concerning the actual nature of this association two differing schools have evolved, one holding that the chiasma is the result of cytological crossing-over, the other that it is the chiasma that is the cause of the crossing-over.

The discovery in 1927 by Müller that X-rays could produce both gene mutations and structural arrangements of the chromosomes opened up vast new fields in both genetics and cytology. For example, exceptionally, the expected does not appear, Mendelian ratios are disturbed, linkage relationships are altered or the phenotype of an individual is very unusual. Cytology has been able to provide satisfying explanations for such aberrations. The case of the white-eyed *Drosophila* female that disobeyed the rules of sex-linked inheritance has already been cited. Non-disjunction, due to a cytological mishap, was shown to be the cause. Such aberrant behaviour of the chromosomes is invariably associated with corresponding peculiarities in the behaviour of the genes and of the characters that rest upon them. Darlington, for example, has shown that the varieties of the cultivated cherry differ one from the other in having an extra chromosome of one or another of the chromosome pairs. Non-disjunction can therefore give rise to important, economically valuable variations which in the case of the cherry can be perpetuated by grafting.

It is not uncommon for translocation—a piece of one chromosome becoming broken off and attached to another chromosome, often of a different pair—to be detected genetically before it is ob-

served under the microscope. For example, Müller* found in a strain of *Drosophila* the genes from scarlet to roughoid which normally reside in the IIIrd chromosome, to be linked with genes in the IInd linkage group. The genetic evidence indicated quite clearly that a large block of genes of the IIIrd group had somehow or other become part of the IInd group. Painter, examining the material cytologically, found that one of the IIIrd pair of chromosomes was much shorter than usual and that one of the IInd pair was correspondingly much longer.

Sometimes a broken-off piece of a chromosome does not become attached to another chromosome but remains free and is often lost during cell-division. If such a deletion is not too extensive the individual may live. For example, Gates† got a waltzing mouse female in a cross between a waltzing mouse (*vv*) and a normal non-waltzing mouse (*VV*). He concluded that somehow or other the dominant allele *V* for normal gait had got itself lost in this particular mouse which should have been *Vv* in genetic constitution. Cytological examination showed that one of the chromosomes was only about a quarter the size of its mate.

A section of a chromosome can become reversed with respect to the rest of the chromosome to form an inversion. This cytological mishap is, as a rule, recognized by the reversal of the usual linkage relations of a group of genes. Only very rarely can it be detected cytologically, save in the forms with giant chromosomes.

The extent to which the development of the science of genetics has depended upon the choice of *D. melanogaster* by Morgan and his colleagues as their experimental material cannot possibly be exaggerated. In the whole history of science there can have been nothing more fortunate. This small fly first of all proved to be the ideal laboratory creature for genetical studies; it then proved to be an equally ideal material for the linking up of genetical and cytological discoveries, having only four pair of chromosomes and

* Müller, H. J. and Painter, T. S., The cytological expression of changes in gene alignment in *Drosophila*, *Arnes. Naturalist*, **63**, 193 (1929).

† Gates, W. H., A case of non-disjunction in the mouse, *Genetics*, **12**, 295 (1927).

these readily distinguished one from the other. Then, in 1933, it proffered the giant chromosomes in its salivary gland cells, 100 to 200 times longer than those of the somatic cells and gametes and from 1000 to 2000, or even more, times larger in volume.

These larval salivary glands are a pair of club-shaped organs attached by a common duct to the insect's pharynx, and near the mouth of the larva. Each consists of about a hundred cells. They are dissected out in a saline solution, placed upon a microscope slide and stained with a drop of acetocarmine. A coverglass is then placed over the preparation and pressure is applied to it to disintegrate the cell and nuclear membranes. The chromosomes then float free. Under the microscope it can be seen that the chromatin material consists of six ribbon-like elements, all of them being attached to a dark-staining body, the chromocentre. The elements are banded, being built up of alternating bands of dark-staining chromatin and of light or non-staining material. The order and arrangement of the bands, some 5000 altogether in *D. melanogaster*, are identical for any of the elements observed in different cells or in different individuals.

Each of the elements consists of the two members of a pair of homologous chromosomes, a fine dividing line can be detected throughout the entire length of the element and the two chromosomes are closely applied each to the other, band by band. Each of the chromosomes consists of a number of strands all with exactly the same bands in exactly the same order. As the cells of the salivary glands grow without dividing and their nuclei become enlarged, the chromosomes split repeatedly along their lengths but the resulting new chromosomes do not separate from those that gave them origin. This process being repeated time after time, bundles of replicas of the two original chromosomes are formed to give the appearance of single strands.

Four of these elements are the "right" and the "left" limbs of chromosomes II and III. One of the remaining elements, a very short one, is the IVth pair and the last of them, attached by its end to the chromocentre, is the pair of Xs in the female. In the male the Y-chromosome is completely incorporated in the chromocentre.

It can easily be seen that these elements are not of uniform thick-

ness, for along their lengths, here and there, are local swellings, "puffs" or bulbs and also constrictions. The bands themselves vary greatly in thickness and depth of staining and the distances between any two of them also vary considerably. It is possible, therefore, to recognize the different chromosomes under the microscope and the different regions of one and the same chromosome and to relate different bands in a particular chromosome to particular loci in the genetic map of this chromosome.

Whether the bands or the material between them are the genes, whether or not the genes are discrete bodies within the chromosome or merely points of chemical linkage in complex protein molecules are questions that still await final answer. Translocations, inversions, deletions and duplications (identical series of bands in the same chromosomes or in different chromosomes) can be identified by the arrangement of the bands, the puffs and the constrictions.

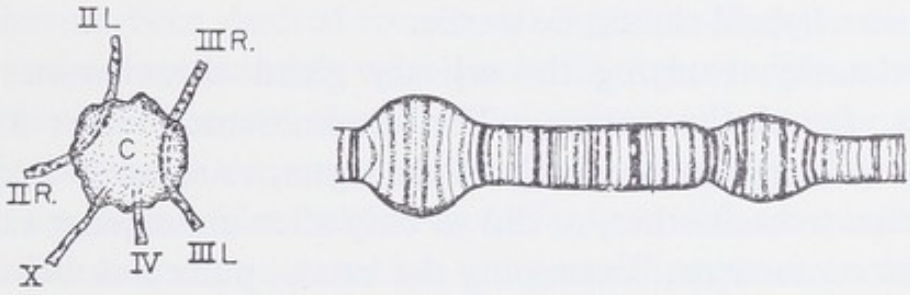


FIG. 23. Diagrammatic representation of a section of a giant chromosome of the salivary gland of *Drosophila melanogaster* showing bands, puffs and waists. *c.* the chromocentre. IIR, IIL, IIIR, IIIL, the right and left limbs of chromosomes II and III. IV, the fourth chromosome.

The contributions of cytology to an understanding of the mechanism and processes of evolution have been of immense importance. As early as 1905 the American cytologist McClung was speaking of the value of comparison of karyotypes in related species, of comparisons between the karyotypes of individuals showing unusual characterizations and those of "normal" phenotypes, and of the experimental alteration of the karyotype. Since then all these methods have been extensively used to determine the degree of relatedness of different species and varieties. For example, the genus *Drosophila*

includes many species with chromosome numbers ranging from three to seven pairs. It seems that all these species have arisen through the fusion of chromosomes in a primitive karyotype that consisted of six pairs, five of them rod-like and the sixth dot-like and that inversion, deletion, duplication and translocation have been the means whereby this variation in chromosome number has been brought about.

Two of these species are so very much alike phenotypically that it is exceedingly difficult to distinguish between them. Each has five pairs of chromosomes and the karyotypes are so very much alike that they would appear to be identical. Yet *D. pseudo-obscura* and *D. miranda* are classified as different species for the sufficient reason that though they can be hybridized the hybrid progeny are sterile. Because they are so much alike it is reasonable to assume that they must be correspondingly alike in respect of their genotypes. Yet if they are alike genotypically it becomes difficult to understand why the species hybrid should be sterile.

Dobzhansky, studying the salivary gland chromosomes of the hybrids, found the reason. The chromosomes either failed to synapse (Gk. *synapsis*, union), to conjugate, to come to lie in close apposition to each other, or did so only after undergoing extremely complex contortions. Examining the bands, puffs and waists of the regions involved in this abnormal pairing, he was able to show that the two species differed extensively in respect of inversions and translocations and that though the two possessed the same genes the spatial relations of these in the two species were very different. From this and similar observations it can be concluded that evolution can be a consequence of chromosomal aberrations. If a population of organisms becomes divided into isolated groups, if different types of chromosomal aberration occur in the different groups, and if these possess a selective value, then the groups will ultimately come to differ so greatly in their karyotypes that hybrids between them will no longer be capable of elaborating functional gametes and in this way new species can come into existence.

POLYPLOIDY

(Gk. *polys*, many; *aploos*, onefold; *eidos*, form; reduplication of the chromosome complement.)

In plants about half the species examined have chromosome numbers that are multiples of that of one member of the series. For example, the three species of wheat, *Triticum monococcus*, *T. durium* and *T. spelta*, have 7, 14 and 21 chromosomes respectively (the haploid numbers). Among potato species there is a series 24, 36, 48, 60 and 72; among chrysanthemums one that ranges from a basic 9 through 18, 27, 36, 45, 54, 72 to 90; among rose species a series 14, 28, 42, 56; among tulips one of 24, 36, 48 and 60. It is accepted that the higher numbers have arisen by chromosome duplication, by polyploidy, taking the form of a division of the chromosomes without any division of the cell itself during gametogenesis. The cultivated tobacco plant *Nicotiana tabacum* has 24 chromosomes, twelve of them having been derived from a wild species *N. sylvestris* and the other twelve from another wild species *N. tomentosiformis*. It seems probable therefore that the cultivated tobacco plant arose from the doubling of the chromosome number in a sterile hybrid between the two wild species. The einkorn type of wheat with a haploid number of seven chromosomes gave rise, it is generally agreed, to the emmer types with fourteen chromosomes by polyploidy following hybridization, and another hybridization with a related species of grass followed by chromosome duplication gave the species with the haploid number twenty-one.

Though polyploidy has been recorded in a variety of animal species, e.g. *Paramecium*, the earwig, the butterfly, the newt, the evidence is not completely convincing. Certainly no such series as the above have been encountered. There is no reason to think that polyploidy has played a role in the evolution of animal species.

To the list of the methods used for the creation of new breeds and varieties of domesticated animals and cultivated plants can now be added the artificial induction of polyploidy by treating the seed or the bud of the plant with colchicine. Polyploidy has been induced in the mouse, the rabbit and the pig by the same means.

Polyploids that arise through the duplication of the chromosomes within one and the same species are known as autopolyploids (Gk. *autos*, self) as contrasted with allopolyploids (Gk. *allos*, other) which have their origin in the hybridization of two species or genera with subsequent duplication of each of the two chromosome complements. Autopolyploids among garden plants, flowers, vegetables, crop plants and trees, including fruit trees, whether naturally occurring or artificially produced, are usually larger in all their parts than the corresponding diploid forms.

Polyploidy can lead to serious difficulty during the formation of the gametes and during fertilization. The essential features of gametogenesis are the pairing or conjugation of the two members of each pair of homologous chromosomes, their separation without any longitudinal splitting and their passage into the nuclei of the two daughter cells, each of which comes to include one member of each pair of chromosomes. The essential feature of fertilization is the reconstruction of the chromosome complement by the coming together of two half-sets of chromosomes identical in respect of loci. In the autopolyploid the loci are the same, but the number of the chromosomes is abnormal and can lead to failure in pairing and in the distribution of the chromosomes to the nuclei of the daughter cells. Some gametes can come to have an excess number of chromosomes while others can be deficient for certain of them. Fertilization involving such gametes can prove to be fruitless or can result in the appearance of zygotes that are weakly or inviable.

In the allopolyploid the number of the chromosomes provided by the two parents belonging to different species or genera can be the same but the genes they carry are different. The radish and the cabbage both have nine chromosomes in the haploid set. Crossing the two yields a vigorous hybrid which is almost sterile. Most of the gametes it elaborates are useless. The reason for this is that the two sets of nine chromosomes fail to pair and so they are distributed at random to the nuclei of the daughter cells each of which receives a mixture of radish and cabbage chromosomes. Occasionally, when the seeds of this hybrid are planted, reasonably fertile plants are obtained. They turn out to be tetraploids that have arisen from two

diploid gametes. In the tetraploid cell there is therefore a complete set of radish chromosomes and a complete set of cabbage chromosomes so that pairing is possible and diploid gametes can be produced. The new plant differs from both parental forms in its characterization.

For such a tetraploid species hybrid to breed true it must have the chromosomes of each kind in even numbers so that regular segregation can occur. Triploids, pentaploids and other odd numbered types cannot breed true by sexual reproduction; that is why triploid and pentaploid tulips are multiplied by vegetative methods.

When polyploids are involved the ratios of the different phenotypes in the F_2 and similar generations can be greatly disturbed. It can happen that a dominant gene fails to gain expression in the presence of two or more of its recessive alleles.

While plants in general seem to be well able to withstand large-scale changes in the numerical proportions of the genes in their genotypes, animals apparently cannot. Possibly the genic balance is more delicately poised in the animal than in the plant with the result that any considerable disturbance of it, by polyploidy, for example, leads to a serious impairment of viability.

HUMAN GENETICS

Though it had long been recognized that many human traits were faithfully transmitted from parent to offspring in an orderly fashion, it was not until after the rediscovery of Mendelism in 1900 that it became possible to describe the transmission of a human "character" as an instance of Mendelian inheritance. It was Farabee* in the United States of America who in 1905 recorded the incidence of brachydactyly (Gk. *brachys*, short; *daktylos*, finger) in five generations of a Pennsylvanian family and showed that its mode of inheritance was that of a typical dominant based upon a single factor. In the same year Nettleship† in England published records of the

* Farabee, W. C., Inheritance of digital malformations in Man, *Papers of Peabody Mus. of Amer. Arch. and Ethn. Harvard Univ.* **III**, 3, 69 (1905).

† Nettleship, E., On heredity in the various forms of cataract, *Rep. Roy. Lon. Ophth. Hosp.* **16**, 1 (1905).

inheritance of cataract and of colour-blindness. In 1907 Davenport, head of the Station for Experimental Evolution at Cold Spring Harbor in the United States, described the mode of inheritance of eye-colour in man and Nettleship, in England, reported upon the transmission of congenital stationary night-blindness. In 1908 there was an outpouring of new knowledge concerning human heredity, both in Britain and in America (see the bibliography in Bateson's *Mendel's Principles of Heredity*) and it became abundantly clear that the same laws of organic inheritance applied to man as to other organisms. Since that time human genetics has developed with ever-increasing speed as the usefulness of such knowledge gained appreciation in anthropological, educational, medical and sociological circles.

Because gross defects and derangements are far more easily recognized and traced than is "normality", and because they are of interest to medicine, they have been extensively studied. It was from such studies that the discipline of medical (clinical) genetics developed. From studies of the incidence of such abnormal characters in a population and of the frequency of the genes that correspond to them came the need for the development of (human) population genetics with its novel and sophisticated statistical techniques. Variations in respect of such qualities as intelligence, body-build and stature, instances of continuous variation, being of interest to the anthropologist, the educationist and the medical man alike, have been the subjects of much investigation during which new biometrical techniques were devised to add to the development of biometrical genetics. Human genetics, as this developed, inevitably led to a reconsideration of the aims of eugenics.

Though man and other animal types have much in common, he is unique. He, like the rest, is the product of the evolutionary process, of natural selection—the differential reproduction of biologically advantageous combinations of mutant genes leading to the persistence, improvement and multiplication of dominant types, each of these achieving a highly successful level of organization. Thus came into being biological man. But his evolution did not end at this point. He developed mechanisms for the transmission of

experience, of ideas and of attitudes from individual to individual, from generation to generation. He invented an aggregate life and devised societies and communities. He gained an ever-expanding control over his physical environment and over its living and non-living contents. He began to replace the forces of natural selection with psychological and sociological selective agencies of his own choosing. He began to shape himself, to take charge of his own terrestrial destiny and to use science and technology as instruments of social policy.

So it is that in the establishment of some of the most valued of the attributes of socialized man, of man as *socius* (L. companion), his cultural inheritance alone is operative and in that of many others this plays a more prominent role than does his genetic endowment. This being so, the investigation of the relative roles of "nature" and of "nurture" in the determination of man's intellectual and emotional attributes, normal and abnormal, is rendered difficult. In such investigations much profitable use has been made of twins, following Galton's lead.

Of twins there are two distinct kinds, identical and fraternal. The first kind are always of the same sex and resemble each other far more closely than do fraternal twins or ordinary brothers and sisters. This is not surprising for they are, in fact, one and the same individual in duplicate, arising from one and the same fertilized ovum (monozygotic) and being therefore genetically identical. They have their origin in the early splitting of the embryo into two, each of the two resulting portions developing into a zygote. The other kind, fraternal twins, on the other hand, are dizygotic, resulting from the synchronous fertilization of two separate ova by two separate spermatozoa. They can be of the same or of different sexes and are no more alike than are ordinary brothers and sisters born at different times, being more or less genetically different owing to the heterozygosity of the parents.

Twins can be reared together or apart. Identical twins exposed to the same environment and to different environments; fraternal twins exposed to the same experience and to different experiences; ordinary brothers and sisters reared together and reared apart,

children reared by their own parents and by foster parents, can be studied and the effects of genetic similarity and dissimilarity and of environmental similarity and dissimilarity roughly measured. Identical twins are never exactly alike and such dissimilarity in respect of physical, intellectual or emotional attributes as is displayed by them must be due to differences in experience, to environmental and not to genetic factors. If fraternal twins show a greater degree of discordance than identicals, the excess must be due to genetic differences.

In respect of characters that are genetically based and are not discernibly affected in their expression by environmental factors, the resemblance between identical twins is very nearly complete. The resemblance between fraternal twins in respect of such characters is much less. In respect of characters that are wholly environmental in origin, identical twins resemble each other no more than do fraternal twins. In so far as characters with a combined genetico-environmental origin are concerned the resemblance of identical twins is incomplete but still notably greater than that of fraternal twins.

In this field of human genetics there are two questions that attract a great deal of interest and that have attached to themselves a great deal of prejudice. Individuals differ in respect of general intelligence as measured by the intelligence-test score; is this variation due to variation in respect of genetic endowment? Are some individuals, by virtue of their hereditary endowment, more intelligent than others; in so far as general intelligence is concerned are they "superior"? And are some "races", some ethnic groups, some geographical varieties of mankind, naturally more intelligent than others?

Extensive studies of twins and of adopted children have given results which suggest that much of the variation in general intelligence among schoolchildren is the expression of genetic variation, but that an appreciable amount is due to variation in educational experience and in home background. About 50 per cent of the variation is of genetic origin, it is thought. The character "general intelligence" would seem to be based upon a number of genes,

without dominance and with many modifying factors, both genetic and environmental.

During the evolution of man there has undoubtedly been a steady selection for general intelligence; the increase in brain size and the progressive improvement in the techniques of tool and weapon making testify to this. But such progress took place some thousands of years ago and there is no indisputable evidence that there has been a rise in the level of average intelligence in historical times. Since different ethnic groups of mankind have had very different histories and have developed in isolation, geographical, social, cultural, it can safely be assumed that selective forces for intelligence have differed in different parts of the world and that there have been differences in the distribution of the genes concerned with intelligence in the different ethnic groups, just as there have developed differences in respect of the blood groups. Such evidence that exists at present strongly suggests that any differences there may be in average intellectual ability on the part of different "races" are small compared with the variation that is to be encountered within each race, for every race so far studied has been found to include both very backward and very intelligent individuals.

It is of interest to note that a beginning has been made to the mapping of the human chromosomes. Some thirty X-borne genes have been identified and the spatial relationships of certain of these have been determined. As would be expected, since there are twenty-two autosomes, it is but rarely that it can be shown that two autosomal genes are resident in the same chromosome.

EUGENICS

Francis Galton, a cousin of Charles Darwin, was born in 1822 (as was also Gregor Mendel). He became greatly impressed by the argument presented in the *Origin of Species* (1859) and developed the view that the substitution of social control for natural selection in guiding human evolution was "the logical application of the doctrine of evolution to the human race". His developing views upon this subject were first presented in a paper in 1865 (the year in which Mendel communicated the results of his hybridization

work with the pea to the Brünn Society). Galton had satisfied himself that mental traits were inherited (*Hereditary Genius*, 1869; *Inquiries into Human Faculty*, 1883) and had devised statistical methods for the study of inheritance which led to his *Law of Ancestral Heredity* (1897). This, as has already been stated, while describing certain resemblances in respect of graded or continuous characters between parents and offspring, did not provide any explanation or general principle.

By 1883 Galton's ideas had been given the name eugenics (Gk. *eu*, well; *genos*, birth: well-born), the science dealing with all influences that improve the inborn qualities of a race, also with those that develop them to the utmost advantage, but had not attracted much attention. In 1901 he gave a lecture to the Royal Anthropological Society on "The possible improvement of the human breed under existing conditions of law and sentiment", and by this time there were many who were ready to accept his teaching. In 1904, in response to his advocacy, a fellowship in eugenics was established in University College, London, and this led to the formation of the Galton Laboratory of National Eugenics in 1907 in the college, of the Eugenics Education Society in 1908 and of the Eugenics Record Office in the U.S.A. in 1910. During the next decade the eugenics movement attracted many adherents, especially in the U.S.A. and in Germany.

In the United Kingdom the development of human genetics, part of the foundation upon which eugenics had to be built, was greatly impeded by the disputation between the Mendelians led by Bateson, and the biometricians (who also happened to be the leading eugenists) led by Weldon and Karl Pearson. This development was also greatly impeded by the extravagance of those who chose to disregard Galton's own definition of eugenics as a science and to think of it as a social movement or as an instrument which could be profitably used in the exercise of prejudice. As early as 1908 Galton found it necessary to call attention to the "danger to which these (eugenic) societies will be liable arises from inadequate knowledge joined to great zeal of some of the most active among their probable members. It may be said without mincing words, with regard to much that

has already been published, that the subject of eugenics is particularly attractive to 'cranks' ".

The methods of genetic improvement advocated by some of the early eugenists centred around the application of conscious and deliberate selection to human reproduction; those with superior genetic endowment were to be encouraged to reproduce their kind while those with inferior genotypes were to be discouraged or even prevented. Such a policy involved value judgments and invited violent disagreement concerning the definitions of superior and inferior. In the case of natural selection the "superior" genotype is that which yields a characterization that is best adapted to the conditions of the environment; the fittest are those which beget most offspring that survive to reach maturity and reproduce in their turn. The breeder of domesticated animals and cultivated plants, practising artificial selection, is concerned with three interrelated considerations: (i) the conditions of the habitat (husbandry); (ii) the destiny of the animal or plant being bred, the special purpose for which it is being produced—meat, wool or egg production, abundance and quality of fruit or flowers, beauty of form or colouration, etc.; and (iii) the characterization of the stock. Knowing the environment and the destiny his task is that of producing a characterization that is in harmony with these.

The physical, climatic and social features of man's environment can be defined and much can be done to harmonize these with man's needs, but concerning man's destiny there has always been great uncertainty. The characterization of the "ideal" human being has always varied with time and place. Moreover, many of the details of this characterization are undoubtedly acquisitions and are not the expression of the genotype. Galton was not unaware of this, for he stated that "man is so educable an animal that it is difficult to distinguish between that part of his character which has been acquired through education and that which was in the original grain of his constitution". In his last public lecture on "Probability, the basis of eugenics", he presented the view that for the time being research in the field of human genetics was the most urgent need and that the social application of knowledge thus gained was for the somewhat

remote future. But dissension between the Galton Laboratory and the Eugenics Education Society continued and Galton found it necessary to make it known that the two bodies were quite distinct, the function of the Laboratory being that of investigating without bias data that might throw light on eugenical problems, while that of the Society was to popularize the results of such investigations. The staff of the Laboratory was interested in science; the members of the Society were concerned with social and political questions. Time came when this division of interest and activity was recognized and when a harmonious relationship between the Laboratory and the Society was established.

In the United States of America it happened that the first of the eugenists were Mendelians. Unfortunately, in their enthusiasm they came to regard such complicated conditions and habits as mental deficiency and vagrancy as simple Mendelian recessive characters and in so doing brought the whole eugenics movement into disrepute. However, the damage was not permanent, for the science of genetics developed with amazing speed in the U.S.A. during the next two decades, and as it grew the extravagances in human genetics were eliminated.

In Germany a Society for Race Hygiene was founded in 1902; in 1909 this became the Society for Race Hygiene and Eugenics, it being agreed by Galton that the two terms were really synonymous. This was an unfortunate decision, for race hygiene was closely associated with anthropometrical anthropology and through this with the pseudo-science of political anthropology invented by the French diplomat and author Gobineau (*Essai sur l'Inégalité des Races Humaines*) and expanded by his disciple Houston Chamberlain, an Englishman by birth and a German by naturalization (*The Foundations of the Nineteenth Century* and *The Aryan Philosophy of Life*). Inevitably, therefore, eugenics, and indirectly genetics, became heavily involved in politics and was grossly misused to support the racial doctrines and policies of the Nazis. As a result of this the development of the science of human genetics was delayed for a generation in a country in which in the first quarter of this century genetical research of the highest quality had been exceedingly active and productive.

In Russia also genetics was to become too greatly entangled in politics. As early as 1866 Florinsky had enunciated ideas very similar indeed to those of Galton, but it was not until 1919 that a department of eugenics was created in the Institute of Experimental Biology in Moscow. Shortly afterwards a Eugenics Bureau was formed in Leningrad and in 1920 a Eugenics Society was founded. In 1923 a Russian journal of eugenics appeared. Then both eugenics and genetics fell into disrepute and were ultimately suppressed. The communist is a dyed-in-the-wool environmentalist and ardently believes that the best way to improve mankind is to improve his habitat. There is, of course, no doubt whatsoever that improvements in nutrition, in education, in environmental sanitation, in human interrelationships, for example, can lead to considerable improvement in the quality and efficiency of a human population, but to such improvement there is a limit and when this has been reached there still remains much to be done to decrease the frequency of undesirable genes in that population.

Today in the U.S.A. and in the United Kingdom there are people of eminence who advocate controlled human breeding in attempts to raise the level of the quality of a population. The central idea is that first suggested by Serebrovsky in 1929 (*Antropogenika Mediko-biologcheskii Zhurnal* **5**) and advocated by Brewer in 1935 (*Eugenics Review* **27**) and known as eutelegenesis (Gk. *eu*, well; *tele*, afar; *genesis*, descent; artificial insemination). This idea has been developed by the Nobel Laureate H. J. Müller, in America ("The guidance of human evolution", *Perspectives in Biology and Medicine* **3**, 1959) and by Julian Huxley in the United Kingdom ("Eugenics in evolutionary perspective", *Eugenics Review* **54**, 1962.) Taking full advantage of the developing techniques of tissue culture, refrigeration and ectogenesis (Gk. *ectos*, outside; *genos*, birth: embryonic development outside the maternal organism; development in an artificial environment), the testicular material of outstanding men of admirable quality would be preserved and used for the fertilization of women or of their ova, and the ova of outstanding women would be implanted in other women. Though it is possible that a method such as this, devised for the deliberate improvement of the species,

will be employed in the future, the time for its application has certainly not yet arrived. For the present it has to be recognized that any over-enthusiastic advocacy of such a positive eugenical measure must inevitably result in the loss of public confidence in human genetics as a basis for social and political action. Much more research and much more education are needed before the geneticist can subscribe wholeheartedly to such a policy and before the general public can be expected to comprehend all that is involved.

Though no two individuals are likely to have the same image of the ideal human being, most people would surely agree that in a human population variety in respect of characterization is most desirable and that among the attributes that such an ideal person would display would be robust health, abundant energy, mental stability, a high level of general intelligence, creativeness, inventiveness, imagination, perseverance, kindness, compassion, tolerance and co-operativeness. Though many of these qualities are largely acquisitions, in most if not in all of them there is a genetic element. It will be generally agreed that those married couples which display such qualities should be encouraged to have families larger than the average and that such as exhibit their opposites should be encouraged to have families smaller than the average. There are those who are incapable of making decisions of this magnitude because of their infirmity, e.g. the idiot, the imbecile and the high-grade mentally defective, and for them in certain countries compulsory sterilization is the policy that has been adopted.

That man is gradually taking control of his own further terrestrial evolution, substituting some form of artificial selection for natural selection, is certainly true. He has been and is very active in improving his environment, physical and social. He will continue to take such steps as seem reasonable and desirable to alter the frequencies of genes in the population in the interests of future generations. To many people at the present time it seems morally wrong to make use of such methods as the sterilization of the "unfit". But in the future this may not be so. Even if the moral aspects of such a procedure are disregarded there are many matters that need to be considered when such measures are discussed; the mode of inherit-

ance of the undesirable character, an autosomal dominant, a recessive or a sex-linked recessive, since this profoundly affects the efficacy of the policy, the lethality or otherwise of the characterization produced, the curability or otherwise of the condition, e.g. diabetes, harelip and cleft palate, juvenile cataract are all genetically determined but can successfully be treated; the incidence of fresh mutation which means that no gene can be permanently eliminated; the ease with which, in the case of a recessive gene, the heterozygote can be identified, since these greatly outnumber the homozygotes who display the characters so that if the former cannot be identified, non-propagation on the part of all afflicted individuals will not prevent the passage of the gene in question from one generation to its successor, and the relative fertility of the diseased category, e.g. idiots practically never and imbeciles only occasionally have offspring, while high-grade mentally defectives, greatly outnumbering the idiots and imbeciles, seem to be rather less fecund than those members of the population with greater intelligence.

In a world that is being fashioned by man making full use of science and technology there is little room for the dullard and the moron. If social progress is to continue it is imperative that the general level of intelligence in the population shall be raised. Among the measures that will be adopted will be those that have for their object the increase of the frequency of the genes that lie at the roots of general intelligence and of decreasing that of those that in their action produce the dullard and the moron.

At this time it is reasonable to think that in the future it may become possible to induce mutations at will in any desired direction, to convert an undesirable gene into its desirable allele and to evoke new mutations that will provide characterizations that are in harmony with novel conditions.

Though Mendel cherished the hope that the time would come when the value of his scientific work would be recognized, he could not possibly have foreseen, even in his most unrestrained imaginings, that it would lead to developments such as these.

MEDICAL (CLINICAL) GENETICS

Clinical medicine (Gk. *kline*, a bed; *medicus*, healing) is the application of the knowledge derived from the medical sciences, the sciences upon which medicine is built (together with a number of acquired skills), to the problems of health and disease in the individual. There is also the medicine of the group, of the population as a whole, of the community. Medical genetics is genetics applied in the medicine of the individual. Population genetics has much to contribute to the medicine of the group. Since clinical medicine is almost exclusively concerned with the recognition, treatment and attempted cure of disease, if follows that medical (clinical) genetics is almost exclusively the genetics of the abnormal, of the pathological (Gk. *pathos*, suffering; *logos*, discourse), of defect and derangement.

In so far as aetiology (Gk. *aitia*, cause; *logos*, discourse) is concerned, disease can be considered as being of three kinds, that in which the cause, as far as can be discerned, is solely genetic; that in which, as far as can be discerned, the cause is solely environmental, external to the individual; and that in which genetic and environmental forces combine to evoke the reaction that is disease. The last of these is by far the most common.

The number of abnormal characters, structural and functional, that are known to be either wholly or partly genetic in origin runs into many hundreds. The genetic basis and the mode of inheritance of very many of these are well known, but in the case of many others these still remain more or less unclear for the reason that a sufficient number of family histories including them is not yet available. It is impossible to make use of the experimental method in human genetics. It is necessary to wait until the appropriate matings happen and until a sufficient number of offspring of such matings present themselves. A number of inherited conditions can be successfully treated medically so that individuals carrying the responsible genes do not display the corresponding characters. When the cause of a defect or derangement is a combined genetico-environmental one, if the environmental element is brought under control, the genetic

element remains unrevealed. For reasons such as these the study of heredity in man is often difficult.

Among the greatest triumphs of modern scientific medicine is the conquest of the diseases caused by insanitation and privation, by faulty habits and ignorance, and of the infectious diseases, the causes of which are micro-organisms present in the environment of man. As the incidence of such diseases has declined, that of diseases of genetic origin, wholly or partly, has gained in prominence. For example, in 1922 in England and Wales, of the total blindness among schoolchildren, it was estimated that 37 per cent was genetically caused, the remaining 63 per cent being of environment origin. In 1954 it was discovered that 68 per cent of this blindness was genetically caused, the cause being the individual, the genotype, while only 32 per cent was of environmental origin. During this period the total incidence of blindness among schoolchildren had been halved.

The contributions of genetics to clinical medicine have taken the forms of (i) genetic prognosis (Gk. *prognostikos* from *pro*, before, and *gignosko*, to know) and genetic counselling, (ii) diagnosis on the basis of the family history, (iii) preventive measures against certain diseases on the basis of the known genetic background, and (iv) expert evidence in medico-legal cases based upon such characters as the blood groups.

It is becoming increasingly common for married couples who have produced a child displaying a grievous defect or derangement to seek advice concerning the possibility that any subsequent child born to them might be similarly abnormal. Sometimes betrothed couples, knowing that in the pedigree of one of them there is a record of some serious abnormality, seek advice concerning the possibility that one of them is carrying the responsible gene and might transmit it to any offspring that they might have. It has become necessary, therefore, for the family doctor to acquaint himself with the elements of genetics or to inform himself as to where genetic advice of the kind required can be obtained. Such advice is given in terms of odds.

The risks to be weighed by the seekers after advice in the case of a simply inherited defect or derangement (based upon a single

gene, dominant, recessive or sex-linked recessive, the expression being unaffected, as far as can be discerned, by any environmental factor and always being complete) are, in general, serious, 1 in 2 for any child of a parent with a dominant condition such as achondroplasia: 1 in 4 for any subsequent child of a couple who have already produced one with a recessive condition such as juvenile amaurotic idiocy; 1 in 2 for any male child of a couple who have produced a child with a sex-linked recessive abnormality such as haemophilia; 1 in 2 that a daughter of such a couple will be a carrier (a heterozygote). When the aetiological basis is more complicated, being genetico-environmental or multifactorial, the risks, in general, are much less. For example, the risk of a subsequent child following the birth of one with anencephaly or spina bifida is about 1 in 25; that for a subsequent child following the birth of one with low-grade mental deficiency of the ordinary undifferentiated type is about 1 in 30 and about 1 in 40 for epilepsy. Anything more than 1 in 10 is usually regarded as a risk not worth taking.

The role of genetics in diagnosis can be illustrated by reference to a strange condition known as ectodermal dysplasia, an inherited condition of the skin in which there is a complete absence of sweat glands and a deficiency of hair and teeth. It is based upon an autosomal dominant gene. Until an examination of the family history is made, the nature of this abnormal condition is likely to remain very puzzling.

The contributions of genetics to preventive medicine can be illustrated by reference to haemolytic icterus, a disease in which the spleen becomes greatly enlarged and withholds red blood-corpuscles from the circulation, gradually destroying them. Jaundice and severe anaemia result, to lead to death. The treatment is removal of the spleen. The cause of this disease is an autosomal dominant gene and so the chances that the offspring of an affected person will possess the gene are 1 in 2. Since it is possible to detect the earliest signs of the disease by an examination of the blood, the possessor of the gene can be identified before the disease has assumed serious dimensions and the spleen can be removed before any irreparable damage has been done.

The power of medicine to prevent and to cure disease was greatly enlarged by the discovery of the blood groups. For an understanding of the nature of these an elementary knowledge of antigens and antibodies is necessary. After a person has suffered and has recovered from certain diseases such as measles, it is most unlikely that he will ever again contract the disease for the reason that he has developed an acquired immunity. The causal organism, a virus in the case of measles, is largely composed of protein and this, to the person attacked, is a "foreign" protein, differing from that of which his own cells and tissues are composed. This foreign protein acts as an antigen (Gk. *anti*, against; *genos*, birth), a substance that causes a series of physiologico-chemical reactions on the part of the host's body, resulting in the formation of antibodies (Gk. *anti*, against; Anglo-Saxon, *bodig*, body). The interaction of antigen and antibody can be of several kinds. If the foreign protein, the antigen, is in the form of cells, e.g. bacteria or red blood-corpuscles, the antibody can cause them to disintegrate; the antibody is then called a lysin (Gk. *lysis*, loosing) and the reaction lysis, e.g. bacteriolysis or haemolysis. Or, the antibody can cause the cells to clump together, to agglutinate, when the antibody is called an agglutinogen. If the antigen is in the form of a toxin (Gk. *toxicon*, poison) the antibody can neutralize it and is therefore called an antitoxin. If the antigen is in solution the antibody can cause it to settle out of the solution and is therefore called a precipitin. An antibody is highly specific, reacting with one and only one particular antigen.

It is because of this antigen–antibody reaction that skin grafting from one person to another is unsuccessful, save when the two are identical twins, who are genetically one and the same person in duplicate. The proteins in human blood corpuscles act as an antigen, but the specificity of the blood proteins is not nearly so pronounced as is that of the cells of the skin and so the transfusion of whole blood from one person to another is possible.

Blood is composed of cells and fluid. The cells are of two kinds, the red which contain haemoglobin (the oxygen-carrying pigment) and the white. The fluid, the plasma (Gk. form) contains a considerable variety of chemicals in solution and is the means whereby

salts, food, hormones and the antibodies which confer immunity are transported throughout the body.

It was in the year 1900 that it was first observed that when the red blood-corpuscles of certain individuals were mixed with the serum (L. whey, the watery fluid that separates from the blood-cells when blood coagulates) of certain other individuals they became clumped together, agglutinated, a typical antigen-antibody reaction.

It was discovered that human beings could be divided into four classes or groups according to whether their red blood-corpuscles carried one or other of the antigens called A and B, both of them or neither of them. It was found further that in the serum of the individual there were antibodies to the antigens that were not present in the red blood-cells.

Blood group	Protein of the red blood-corpuscles	Antibody in the serum
A	antigen A	anti-B
B	B	anti-A
AB	A and B	neither
O (neither A nor B)	neither A nor B	both anti-A and anti-B

For successful transfusion the donor has to be so chosen that his blood is not clotted by the antibodies present in the serum of the recipient. A drop of the donor's blood is mixed with serum known to contain either antibody A or antibody B. If the red blood-corpuscles of the donor are agglutinated the reaction is said to be positive.

		Reaction with anti-A serum: negative	Reaction with anti-A serum: positive
Reaction with anti-B serum	negative	Group O	A
	positive	B	AB

An AB group individual can safely receive blood from donors of all groups; an O group recipient can receive blood from an O donor and none other; an A recipient can receive blood from an A or an O group donor and a B group recipient from a B or an O donor.

The ABO blood groups are characters based upon three alleles of one and the same gene called the *L* gene in honour of Landsteiner.

The gene mutated more than once to produce three forms of itself and since the three genes L^A, L^B and l are members of a multiple allelomorphic series and therefore occupy the same locus, any two of them can be present in the genotype of any one individual. The possible genotypes for the four blood groups are:

Group O	Genotype $l\,l$
A	L^AL^A or L^Al
B	L^BL^B or L^Bl
AB	L^AL^B

l is recessive to both L^A and L^B and so cannot be recognized in the presence of either L^A or L^B.

This ABO series has proved its usefulness in the medico-legal field in cases of disputed paternity. The consequences of the differences in the genotypes of the four blood groups are clear. An O group individual can occur among the offspring produced by the mating of an individual with the genotype L^Al with another with the genotype L^Bl, but no O group individual could possibly have had a parent with the genotype L^AL^B nor could an AB group individual have resulted from the mating of two ll individuals (see p. 172).

Another multiple allelomorphic series of inestimable value in the medical field is the Rhesus factor. When rabbits were injected with blood from a Rhesus monkey their blood-serum was found to contain an antibody which combined with the red blood-corpuscles of about 85 per cent of the human subjects in the experimental group; in the remaining 15 per cent there was no such reaction. An individual whose blood reacts with the antibody against Rhesus blood is said to be Rhesus positive, Rh+; one whose blood does not, Rhesus negative, Rh—. It seems that the red blood-corpuscles of a Rh+ individual carry an antigen so much alike to the antigen on the Rhesus blood-cells that the antibody cannot distinguish between them. The red blood-corpuscles of the Rh— individual lack this antigen.

When a Rh— individual is given a transfusion with blood from a Rh+ donor he elaborates antibodies against this "foreign" antigen. After several such transfusions the reaction may be a very severe

Mother's group

Father's group	O (Genotype *ll*)	A (Genotype L^AL^A or L^Al)	B (Genotype L^BL^B or L^Bl)	AB (Genotype L^AL^B)
O (*ll*)	O (*ll*)	O (*ll*) or A (L^Al)	O (*ll*) or B (L^Bl)	A (L^Al) or B (L^Bl)
A (L^AL^A) (L^Al)	O (*ll*) or A (L^Al)	O (*ll*) or A (L^AL^A) (L^Al)	O (*ll*) or A (L^Al) or B (L^Bl) or AB (L^AL^B)	A (L^AL^A) (L^Al) or B (L^Bl) or AB (L^AL^B)
B (L^BL^B) (L^Bl)	O(*ll*) or B (L^Bl)	O (*ll*) or A (L^Al) or B (L^Bl) or AB (L^AL^B)	O (*ll*) or B (L^BL^B) (L^Bl)	A (L^Al) or B (L^BL^B) (L^Bl) or AB (L^AL^B)
AB (L^AL^B)	A (L^Al) or B (L^Bl)	A (L^AL^A) (L^Al) or B (L^Bl) or AB (L^AL^B)	A (L^Al) or B (L^BL^B) (L^Bl) or AB (L^AL^B)	A (L^AL^A) or B (L^BL^B) or AB (L^AL^B)

Children's group

Blood groups	
Parents	Offspring
O × O	none but O
O × A	O or A
O × B	O or B
O × AB	A or B
A × O	O or A
A × A	O or A
A × B	O or A or B or AB
A × AB	A or B or AB

Blood groups	
Parents	Offspring
B × O	O or B
B × A	O or A or B or AB
B × B	O or B
B × AB	A or B or AB
AB × O	A or B
AB × A	A or B or AB
AB × B	A or B or AB
AB × AB	A or B or AB

one as the recipient's red blood-cells are destroyed. No such antibodies are elaborated by the Rh+ individual who is transfused with Rh+ blood since in this case the Rh antigen is not a "foreign" antigen.

But of even greater importance is the fact that this Rhesus discovery furnished the explanation for what had been a most serious and mysterious disease, haemolytic disease of the newborn, erythroblastosis foetalis. About once in two hundred pregnancies in Europe and North America, the newborn infant suffers from severe jaundice and anaemia which, not so long ago, was usually fatal in the majority of cases. It was known to affect several children in the same family and this seemed to point to a hereditary basis, though the mode of the action of the gene or genes concerned was not straightforward. The explanation was found when it was established that in almost every case the mother was Rh— and the infant Rh+ and that the mother's blood contained the anti-Rhesus antibody. No such antibody was found in the blood of a Rh— woman who had never been pregnant or who had given birth only to Rh— children. It was therefore concluded that the Rh— woman reacts to the Rh+ foetus as she would to the transfusion of Rh+ blood, elaborating antibodies against the Rh antigen. As after blood transfusion, the level of antibodies takes time to build up so that first-born children very rarely suffer from the disease. But in the second or third pregnancy of a Rh— mother with a Rh+ child, her antibodies may get into the circulatory system of the foetus and destroy its red blood cells to cause jaundice and anaemia.

Genetic studies of the family histories of large numbers of these babies showed that either a number of alleles or, alternatively, a number of closely linked genes were involved. Considered as an immunological rather than as a genetic problem the situation can be described as follows. Rh+ is dominant and Rh— recessive. The recessive genotype will be rh.rh but the dominant can be either homozygous Rh.Rh or a heterozygote Rh.rh. If the father is Rh.Rh. he will transmit the Rh gene to every one of his offspring, but if he is Rh.rh. half his offspring by a rh.rh mother will be Rh.rh. and the other 50 per cent rh.rh. If a child of a rh.rh mother is Rh+ it

must have received the Rh gene from its father. In Britain about 13 per cent of marriages are between a Rh— woman and a Rh+ man. In Japan Rh— individuals are exceedingly rare.

The grouping of the bloods of potential parents has become a routine procedure and special attention is focused upon a Rh— woman with a Rh+ husband. Should their child be Rh+ and show signs of developing the disease, its blood can be replaced with blood known to be free of the Rh antibodies. Similar gene-controlled incompatibilities between the blood groups of mother and offspring are known in the rabbit, dog and horse.

One of the most remarkable stories in medical, population and pharmaco-genetics is that recorded by Dean* concerning the incidence of porphyria variegata among the Dutch and Bantu of South Africa. This condition is based upon a dominant autosomal gene. The majority of those who possess this gene display little or no evidence of its presence, but some do show skin blemishes and suffer from bouts of acute abdominal pain. It is another example of an inborn error of metabolism and porphyrin can be detected by suitable tests in the urine and faeces.

But when the "silent" carriers of this gene are given barbiturates, sedatives, tranquillizers, or thiopentone anaesthetics or hypnotics, they become acutely ill, hysterical, complain of acute pain for which no cause is to be found, pass port-wine coloured urine, become paralysed and often die. So common is this gene in the Dutch population of South Africa that it has become the rule in some of the hospitals to test the stools for porphyrin by screening with ultraviolet light before an anaesthetic is given.

Dean was able to trace this gene in the pedigrees of affected individuals and to show that some 8000 individuals in the white and coloured populations must have inherited it from either one Gerrit Jansz who in 1688 was a settler in the Cape or from his wife, a young girl, Ariaantje Jacobs, who was one of eight sent out from an orphanage in Rotterdam to provide wives for the Dutch South African farmers.

* Dean, G., *The Porphyrias* (Pitman Medical Publishing Co., London, 1963).

In 1658 there were forty original Dutch settlers in the Cape of Good Hope. Of the 3 million whites in South Africa today 1 million carry the names of these first forty, a 12,000-fold increase in three hundred years. The porphyria gene was caught up in this amazing multiplication process to cause much trouble when the barbiturates arrived. Because it was not uncommon in the early days for the settlers to mate with their slaves and their servants, the gene, which is exceedingly rare in other parts of the world, was passed to the Bantu.

It has been estimated that every individual in a population such as that of the United Kingdom carries in a single dose from three to eight recessive genes that correspond to abnormal characters of a pathological kind. Most people happen to marry someone who is heterozygous for a different set of harmful genes and even if two people each heterozygous for the same undesirable gene do marry and produce a child, the chance that it will be a homozygote in respect of the gene in question is not more than 1 in 4. So that unless a person marries a close blood relative, e.g. a first cousin, the chances of producing a defective child are small.

In certain diseases it is possible to identify the heterozygote. For example, nephrogenic diabetes insipidus is caused by a sex-linked recessive gene. It is a serious disease and can be the cause of death in the very young. Early diagnosis and treatment can usually ensure relatively normal development. When a male child with this disease is born to a "normal" father and a "carrier" mother, the risk that a subsequent male child will be likewise affected is 1 in 2. Tests are now available which can detect the heterozygotes among the affected infant's female relatives so that everybody concerned can be forewarned.

There is an autosomal recessive gene that in the single dose causes thalassaemia minor, an abnormal but not serious condition of the blood, and in the double dose a more severe degree of abnormality which amounts to a diseased state, thalassaemia major or Cooley's disease. In certain areas of northern Italy about 1 person in every 5–10 is heterozygous for this gene, and has thalassaemia minor. Random mating among them yields about 1 child in every 100

suffering from thalassaemia major. Since it is easily possible, by examining the blood of a person, to detect whether or not he or she is a heterozygote, it becomes possible to know when two such heterozygotes are marrying and to advise them as to the possibilities of their producing a child with Cooley's disease.

The gene which, when present in duplicate, is responsible for sickle-cell anaemia produces a much milder but, nevertheless, recognizable form of sickling (a deformity of the red blood-cells) in the heterozygote. It was observed that the homozygote was rare in the areas where the heterozygote was most common and this for the reason that the homozygote seldom lived long enough to reach maturity. It was then noted that the heterozygote was common in highly malarious regions and rare in those areas where malaria did not occur. It was concluded, therefore, that this sickling gene in some way protected the heterozygote against malaria. The gene in the double dose causes profound anaemia; in the single dose it seems to make the blood uncongenial to the malaria parasite. This is an instance of what is known as pleiotropy, a gene producing more than one effect. In the early days of genetics it was thought that a particular factor produced one character, but it soon became clear that this was not so but that every gene produced a variety of effects, taking part in the fashioning of several characters.

The development of new cytological techniques that made it possible to obtain clear pictures of the karyotype, and therefore to recognize abnormalities in respect of chromosome number and the size and shape of individual chromosomes, brought in its train the ability to associate such abnormality with particular defects and derangements. An example of this is mongolism or Down's syndrome, a serious disease which is encountered in about two in every thousand live-born babies in Europe and North America. About a hundred years ago this disease was recognized by an English physician, Langdon Down. Because the affected child's features somewhat resembled those of the Mongolian geographical variety of mankind, small slanting eye-openings with a persistent fold of skin over the inner edge, he called it mongolism. But since the main stigmata of the disease are a grade of mental defect and congenital

malformation of the heart it is now commonly accepted that it is far better to call it Down's syndrome.

The cause of the disease has been shown to be trisomy of chromosome 21, this particular chromosome being present in triplicate and the total number of chromosomes being 47. The addition of this minute chromosome is sufficient to disturb the balance of the genes to such an extent that the phenotype is rendered grossly abnormal. In some instances of the disease the extra chromosome is attached to one of the others, being a translocation, so that the total number of chromosomes seems to be the normal 46. Unless a translocation is involved the risk of producing a second mongol is very low, little if at all greater than that for any other woman of the same age. But it seems that while translocation, carrying a high risk of recurrence, is a rare event in elderly mothers of such abnormal children, it may not be infrequent in younger mothers who have already produced a mongol child. An examination of such a woman's karyotype could reveal the existence of such a translocation and thus indicate the extent of the risk.

Twin studies have their important uses in the medical field. In many diseases of great social importance such as certain of the mental disorders, cancer and tuberculosis, the cause is multiple, genetic factors interacting with environmental ones and it is necessary to disentangle the two kinds. In tuberculosis there is infection by the tubercle bacillus, but the outcome of this infection is determined very largely by environmental factors such as malnutrition, insanitation and overcrowding. There is a proneness to succumb to the infection, a predisposition, a susceptibility to contract the disease on the part of certain individuals and a resistance to the attack of the organism on the part of others. Such susceptibility, such resistance would seem to be genetic in origin for twin studies have shown that if one identical twin has active tuberculosis of the lungs the other twin is very likely to suffer from the same condition whereas this is not so in the case of fraternal twins. Even when the sharing of a common experience by twins is allowed for it still seems certain that genetic factors are involved.

PLANT GENETICS AND PLANT BREEDING

In applying the principles of genetics to achieve his aims the plant breeder is greatly advantaged as compared with the breeder of domesticated animals. Plants are relatively cheap and to discard a whole year's crop is not disastrous. Most plants mature within a year or two and produce, in great numbers, seeds which can be stored for future use. But, like the animal breeder, he looks for desirable genes, combines them in his stock and attempts to fix them in a homozygous state.

Cultivated plants can roughly be divided into three kinds; those which habitually are self-fertilized, those which habitually are cross-fertilized, and those which are propagated vegetatively by tubers, cuttings, grafts and the like. The chief cereal crops, excluding maize, are self-fertilized so that in them recessive genes, arising by mutation, quickly come to light in a homozygous form. Wheat breeding, therefore, comes to be essentially a process of inbreeding and the isolation of pure lines.

Even when self-fertilization is the rule it is always possible to cross-fertilize in order to combine the desirable qualities of two different varieties or species. For example, the hard spring wheat Marquis was produced by crossing Red Fife and Hard Red Calcutta wheats. Marquis wheat is susceptible to rust disease whereas Juroslav emmer is rust resistant. Biffen of Cambridge had shown, as early as 1905, that susceptibility and resistance to rust disease constituted a pair of Mendelian characters, resistance being the recessive member. The American wheat breeders built upon this discovery to create a hard spring wheat, resistant to rust disease.

With the habitually cross-fertilized plant it is necessary to ensure that the stock, when this has been brought into being by the collection of desirable genes, is systematically inbred so as to preserve its characterization. Inbreeding in this case is not without its risks, for it can bring to light in the homozygous state recessive genes that correspond to disadvantageous characters and these may be so numerous as to make their elimination exceedingly difficult. The

most important crop plant of this kind is maize which occurs in several varieties of the same species. Because it is a dioecious plant with a large number of inherited characters and has only ten pairs of chromosomes and because it is of such great economic importance, maize has been used extensively in genetical studies. Its chromosomes have been mapped and the spatial relations of some 500 genes have been determined genetically.

As a direct consequence of the impact of genetics upon plant breeding practices, the whole system of maize growing has become transformed. Inbred lines of maize tend to display a marked loss of vigour. But when two such inbred lines are "hybridized" the progeny exhibit a remarkable luxuriance of growth and productivity. It came to be customary for four inbred lines of maize to be maintained (call them A, B, C and D). Lines A and B and lines C and D are grown in alternate rows, the male flowers of lines A and C being removed before maturity. The cobs are harvested and are all AB and CD hybrids with low yields. In the following year these AB and CD seeds are sown in alternate rows and the plants produced by these are remarkable for their high yields. The seeds produced by these plants are not used for further sowing and each year the farmer obtains fresh hybrid seed.

This hybrid corn is the outstanding success in the field of applied genetics. It had its origin in the experiments of the American geneticist Shull* who was trying to produce pure lines of maize by self-fertilization. He noticed that crosses between closely inbred lines in which the plants themselves were small, weak and of low yield gave plants that were superior to their parents and to the stocks with which the experiments had started. From this observation emerged the suggestion that inbred lines should be systematically maintained for the sole purpose of producing hybrid progeny. This suggestion was accepted by those concerned and the results were truly spectacular. By 1947 the increased yield of maize in the United States resulting from the use of hybrid corn was estimated to be in the neighbourhood of 800 million bushels. This practice has

* Shull, G. H., The composition of a field of maize, *Proc. American Breeders Association*, **4** (1908); ibid. **5** (1909).

been adopted in many other countries and has done much to hold in check the widespread threat of malnutrition and famine.

Most of the common fruits, the sugar-cane and the potato are examples of the third kind of plant, those that are usually propagated vegetatively, but in all of them the possibility of sexual reproduction exists and new varieties of potatoes, for example, are usually produced in this way. The seeds of the plant, which are borne in the small berries that develop from fertilized flowers, when planted, give rise to plants bearing tubers which can then be used to propagate the stock without further recourse to sexual reproduction. Vegetative propagation means that the descendants of a given plant form a clone and that in the absence of mutation or chromosome fragmentation they remain fixed and identical in genetic constitution. Such plants can be grown as a crop even when they are sterile. Some of the best known apples, bananas and many citrus fruits are practically sterile, having no "pips", and all are propagated vegetatively.

Hybridization is used as much as ever before for the production of new varieties of plants, and to the modern hybridizer genetics has given both an understanding of what he does and has amplified his power to achieve his aims. It has placed in his hands the tools of irradiation and of induced polyploidy by the use of colchicine which can be used for the production of mutation and chromosome aberration and thus for the creation of new forms.

It has to be recorded that it was in this sphere of plant-breeding that a violent controversy developed between the geneticists and the agronomists, led by Lysenko, in the U.S.S.R. The latter, practical plant-breeders and agriculturalists, while granting that chromosomes and genes played a part in organic inheritance, maintained that there were other and more important mechanisms concerned and that, under certain conditions, acquired characters were inherited. They cited instances of "vegetative hybridism" to support their claims. It is well known that when one plant is grafted on to another, the scion, the one that is grafted, sometimes shows characters that are the direct result of the influence of the stock, the plant that received the graft. But the Lysenko school, named after the Russian plant-breeder Michurin, claimed that this influence of the

stock extended to the progeny of the scion. It claimed also that it was possible, by manipulating the environment, to transform winter wheat into summer wheat and vice versa. Lysenko severely criticized Mendel's use of mathematics to explain his results and maintained that the ratios he obtained were meaningless.

The validity of such claims and contentions might easily have been put to the test of critical experiment and all differences ironed out had not political considerations become attached to the argument. The Michurin school received full support from the rulers of the country and the further development of orthodox genetics, which up to that time had proceeded apace, was halted.

It had not been forgotten in Russia that in Germany in the 1930's, Mendelism, with its concept of inborn differences, had been used as a basis for the doctrine of ineradicable human inequality and that this had provided the Nazis with a sufficient reason for bitter racial discrimination. So it was that for a considerable period of time the genetics that flourished in the United States of America and in western Europe was looked upon as a prop for imperialism and colonialism. It is reported (February 1965) from Moscow that Lysenko has been dismissed from his post as head of the Soviet Institute of Genetics, being held responsible for the backward state of Soviet genetics and being charged with having used administrative measures to establish mistaken views. If this is true it becomes possible to expect that in the near future Russian contributions to advancing genetics will come to be as numerous and as noteworthy as they were in the 1920s.

RADIATION GENETICS

The radiations of radio-active substances are ionizing, ejecting electrons from the atoms through which they pass and leaving these positively charged. They also cause excitation, raising an electron in an atom or molecule to a state of higher energy. X-rays, neutrons and protons are ionizing but ultraviolet is not, though it does cause excitation. Ionizing radiation is high energy radiation that is capable of penetrating deeply into living tissues and is massively destructive, particularly of cells that are undergoing division. It is mutagenic.

The physical environment in which man lives is being constantly bombarded by a certain amount of background radiation from naturally occurring radioactive elements and from outer space; but the amount of this is not nearly enough to account for the spontaneous mutation rate which must result largely from other causes such as the natural inter- and intra-molecular motions of living matter.

Many people are engaged today in work that involves radioactive substances and radiations, but the methods of protection that have been devised are such that no detectable increase in mutation is likely to result always granting that adequate care is taken to ensure that excessive doses are never received.

In recent years much nuclear energy has been released during the testing of atomic bombs with the result that the background radiation has been considerably increased. A proportion of the stupendous energy released from nuclear fission and fusion is in the form of high energy ionizing radiation and of radioactive isotypes of elements such as strontium and carbon. It is established that a correlation exists between exposure to such radiation and the development of malignant disease, such as leukaemia (a malignant disease affecting the white blood-corpuscles), and also between such exposure and a shortening of the life span. Radioactive strontium-90 is formed as a consequence of the explosion of a hydrogen bomb and this replaces calcium in bone. Washed down from the ionosphere it is widely distributed over the earth's surface by rain and snow and from the soil it is ingested by the growing plant. Thence it enters the grazing animal and appears in its milk. Taken into the human body it forms centres of radioactivity in the bones, especially in those of growing children, and these can give rise to cancer of the bone and to a variety of other pathological conditions.

As yet there is no clear-cut answer to the questions as to how much strontium-90 can be tolerated in the human diet or how large an increase in the total amount of strontium-90 can be absorbed without having seriously deleterious effects on the population as a whole. But no one can deny that there exists sufficient reason for anxiety.

The other effect of such radiation is not upon the individual exposed to it but upon his germ-cells and therefore upon future generations. That such radiation increases the mutation-rate is beyond dispute. Since a fairly large proportion of mutations are either lethal in their effects or else definitely disadvantageous, it is reasonable to assume that as the background radiation increases, the average dose received by individuals exposed to it also increases as does also the number of disadvantageous mutations affecting the gametes. In the case of the relatively rare dominant mutation the effect would be revealed in the offspring of the individuals who were exposed to the radiation, but in the case of the much more common recessive mutations several generations of the descendants of those who were exposed would have to be studied before it could be decided that no such recessive mutations had been caused.

The evidence concerning the production of lethal and disadvantageous mutations affecting the progeny of those who were exposed to the effects of the bombs dropped on Hiroshima and Nagasaki is not conclusive; no substantial rise in their incidence has so far been recorded. But the anxiety that these events evoked is not yet dispelled.

GENETICS AND EVOLUTION THEORY

Darwin's theory of evolution postulated that both the "fit" and the "unfit", the "useful" and the "useless", are to be found in every population and that the unfit and the useless are eliminated therefrom by the struggle for existence so that only the fit and the useful flourish. Darwin was the first to suppose that organisms exhibit evolutionary change for the reason that they become adapted in respect of their characterizations, through natural selection, to live in different environments. Organic diversity is the response of the living organism to diversity of environments. Darwin explained evolution as the consequence of natural selection acting upon naturally occurring variants which arise by chance and which can be of all kinds; natural selection is the force that channels them into the path of evolutionary progress. Among the naturally occurring variants in any population there can be one that is best adapted to

the conditions and circumstances of the kind of life the organism leads: this one will have more offspring than will such as are ill-adapted. If the characters that endow the organism with this advantage are inherited they will reappear in the offspring and with the variant characterization will have become that which is typical of the population as a whole. Variation of this kind can ensure the continuance of a species should the environmental conditions change and also can provide new characterizations that, though out of harmony with one kind of environment, may be well suited to another.

Darwin thought that evolution depended upon the origin of new forms which differed from pre-existing forms by small continuous differences in no constant or predictable direction. When the new and the old forms were crossed blending inheritance occurred. To the variations as they appeared direction was given by the forces of natural selection which favoured some and eliminated others. In this way selection, adaptive selection, was given to the variations after they had appeared. Lamarck, on the other hand, held that direction was given to variations before they had appeared, adaptation being direct and acquired characters being inherited, changes in the phenotype, due to changes in the environment, determining corresponding changes in the genotype. Darwin came to see that spontaneous variation with blending inheritance could not give direction to evolutionary change and so to his theory of natural selection he added the doctrine of pangenesis.

At the beginning of the present century these views constituted orthodoxy in the biological sciences. It has been recorded how, in England, Bateson, who had satisfied himself that large, spectacular discontinuous variations had contributed largely to evolutionary progress, had become a saltationist (L. *saltans* from *salio*, to leap) and was looking for a saltationist interpretation of evolution. This he had found in Mendelism and this is the reason why Mendelism came to mean so much to him. It was not until it came to be recognized that both kinds of variation, the continuous and the discontinuous, had played their parts and that there was no essential difference between them, both having a genetic basis, that disputa-

tion between the naturalists and biometricians on the one hand and the Mendelians on the other ceased. Baur in Germany and East in America did much to demonstrate the importance of the small continuous variation and biometrical tools for the study of quantitative characters were quickly fashioned.

Mendel was well aware of Darwin's views and shared them. As de Beer (1965) has shown, Mendel's paper contains many paragraphs that indicate perfectly clearly that they refer to *The Origin of Species*. The reason why Mendel did not refer to Darwin by name would seem to be that he was obliged to be careful not to offend the authorities in Austria-Hungary. At this time it was dangerous to entertain liberal views or to welcome unorthodox ideas. It seems certain that it was for such political reasons that Mendel made no direct reference to Darwin.

It appears from his scientific papers and from his correspondence with Nägeli that he recognized the flaw in Darwin's argument—the lack of any satisfactory explanation of the origin of heritable variations and of any adequate theory of organic inheritance. He saw, too, that his own researches provided that which was lacking in Darwin's theory—the means whereby a sufficient supply of heritable variations was provided by segregation and recombination of factors. Mendelian genetics provided exactly the mechanism required to explain how evolution by natural selection works, a mechanism capable of yielding either great heritable diversity through mutation, segregation, recombination and crossing-over, or, on the other hand, great heritable stability for the reason that mutation is rare, because there is no contamination of factors and because crossing-over can be minimized.

Mendel showed that what was inherited from parents to offspring was an aggregate of factors (genes) which retained their identity, segregated and recombined. By his work the notion of pangenesis was destroyed and that of the inheritance of acquired characters rendered unacceptable. With the development of genetics it became clear that the ultimate source of heritable variation was mutation, by which is meant point mutation, an alteration in the internal organization of a gene which yields a corresponding alteration in the

characterization. (Mutation is the term originally used by de Vries to describe the very large and striking variations that had occurred in the evening primrose. It is now known that most of these inherited changes were not gene-mutations but recombinations.)

Different genes have different mutation rates. Each individual gene mutates only very rarely, but as the total number of cells and of cell-generations in most organisms is very large, the overall mutation frequency per generation may be very considerable. In animals generally naturally occurring mutation rates range between 1 in 10,000 to 1 in 100,000. In man the mutation rate for most of his genes would seem to be of the order of 1 in 100,000, though a fresh mutation yielding the gene for haemophilia occurs about once in 50,000, so that it is to be expected that in a human population 1 in every 50,000 gametes will be carrying this gene. Cell-division in a bacterium can occur once every 2 hours or so and in the higher organisms the production of spermatozoa or of pollen-grains by continued cell-division is prodigious. The sum total of all the mutations that have occurred must be vast, for evolution has been proceeding for millions of years.

Recombination has been the main source of variants in the higher organisms. Independent assortment, linkage and crossing-over can, as has been shown, yield a very wide variety of phenotypes. In a species with a great number of genes, each of which can exist in two or more forms, there is hardly a limit to the number of possible combinations of genes in the genotype. Sex would seem to be a biological invention that makes it possible for mutant genes that have appeared in different individuals at different times to become combined in one and the same genotype. Sex, the division of a species into two distinct and complementary forms, known respectively as male and female, and the sexual form of reproduction, involving the mating of male and female, constitutes a mechanism for the wide dispersal of mutant genes in a population for ensuring the recombination of genes.

Whenever there is a variety of genotypes within a population the forces of selection operate and as a result of a differential reproductive rate or of a differential viability, or of both, some will flourish while

others will not. When mutations occur they may be eliminated from the population or they may spread through the population at the expense of their respective alleles. A population, "race", ethnic group, will in time come to differ from all others by the frequency with which certain genes are to be encountered in its genetic constitution. Though it is possible that a particular gene might not be represented at all in a particular population, it is probable that such an event is very rare indeed. Most of the known genes that are to be found in man are represented to some extent in all populations, races, ethnic groups so far studied. These differ not in respect of genes but of gene frequencies. Evolution has largely depended upon extensive shifts in gene frequencies. Factors other than the intensity of selection that affect such frequency are the incidence of mutation, the incidence of migration, and of mobility within the population, the system of mating and the total size of the population.

The frequency of genes and the control of this frequency by mutation, selection and random event constitute the subject-matter of population genetics which has two roots, the mathematical represented by the work of Fisher (1930), Sewall Wright (1931) and Haldane (1932), and the evolutionist, represented by that of Dobzhansky (1951) and of Goldschmidt (1955).

The effects of migration and mobility within the population upon gene frequency are to be seen in the present-day distribution of the ABO blood-group genes, which shows an interesting gradient (genocline) from east to west. It is accepted that studies of such gene diffusion are of considerable value in tracing connections between different populations.

In the British Isles there is a high frequency of gene l and a low frequency of gene L^A in the Celtic-speaking areas and a high frequency of L^A and a low frequency of l in the English-speaking areas. In south-east England the frequency of L^A is similar to its frequency in west and central Europe generally. l has a high frequency in the Basque-speaking areas of France and Spain, among the Berbers of North Africa and the peoples of the western Caucasus in Asia. The frequency of the gene L^B rises more or less progressively from 10 to

15 per cent in eastern Germany, eastern Czechoslovakia and Yugoslavia, to 15–20 per cent in European Russia, eastern Finland and the Middle East, to 20–25 per cent in Asia. The highest L^A frequencies are found in southern Norway, southern and central Finland, Portugal and western Spain, areas along the Franco-German frontier, Switzerland, Romania, Bulgaria and Turkey.

The general picture is of an Asiatic people with a high L^B frequency pushing westwards as far as central Germany, the frequency becoming progressively lower towards the periphery of the area; of a solid mass of peoples with a high L^A frequency stretching right across Europe from Scandinavia to Spain, Italy and Greece, and of a people with a high l frequency being pushed to the very edges of the European region, to the extreme north-west, into North Africa, the Mediterranean islands and to the Caucasus area. This distribution is accepted as evidence of the multiplication and westward migration of a central Asian people with a high L^B frequency into areas in which the indigenous peoples did not possess this gene. It is established that such invasions of the Huns, Avars and other Mongoloid peoples did occur. In so far as the British Isles are concerned, it is established that Iron Age and Anglo-Saxon immigrants into eastern and southern England partly displaced to the north and west earlier inhabitants who were descendants of New Stone Age immigrants from North Africa and the Iberian Peninsula, together with even earlier peoples. It is now generally accepted that similarity in respect of blood-group is a trustworthy indication of ethnic (Gk. *ethnos*, nation) relatedness.

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To a large extent this book is a distillate of the books and scientific papers listed below. To them the attention of any reader who seeks fuller and more detailed information than is given herein is directed.

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