Commemoration of the publication of Gregor Mendel's pioneer experiments in genetics / Papers read at the Annual General Meeting, April 23, 1965.

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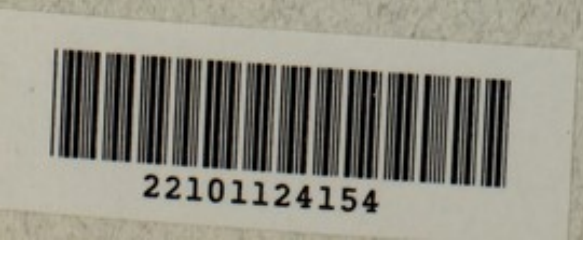

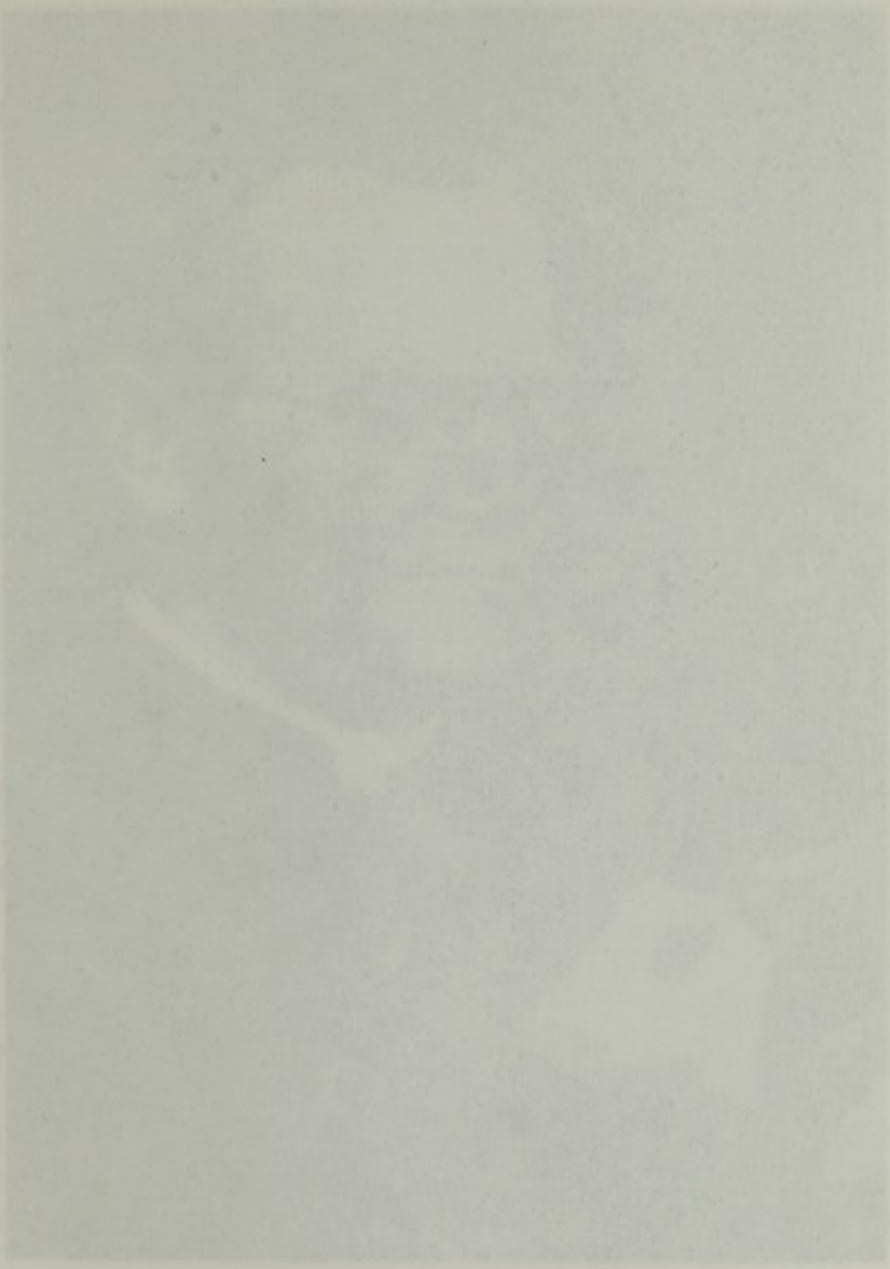

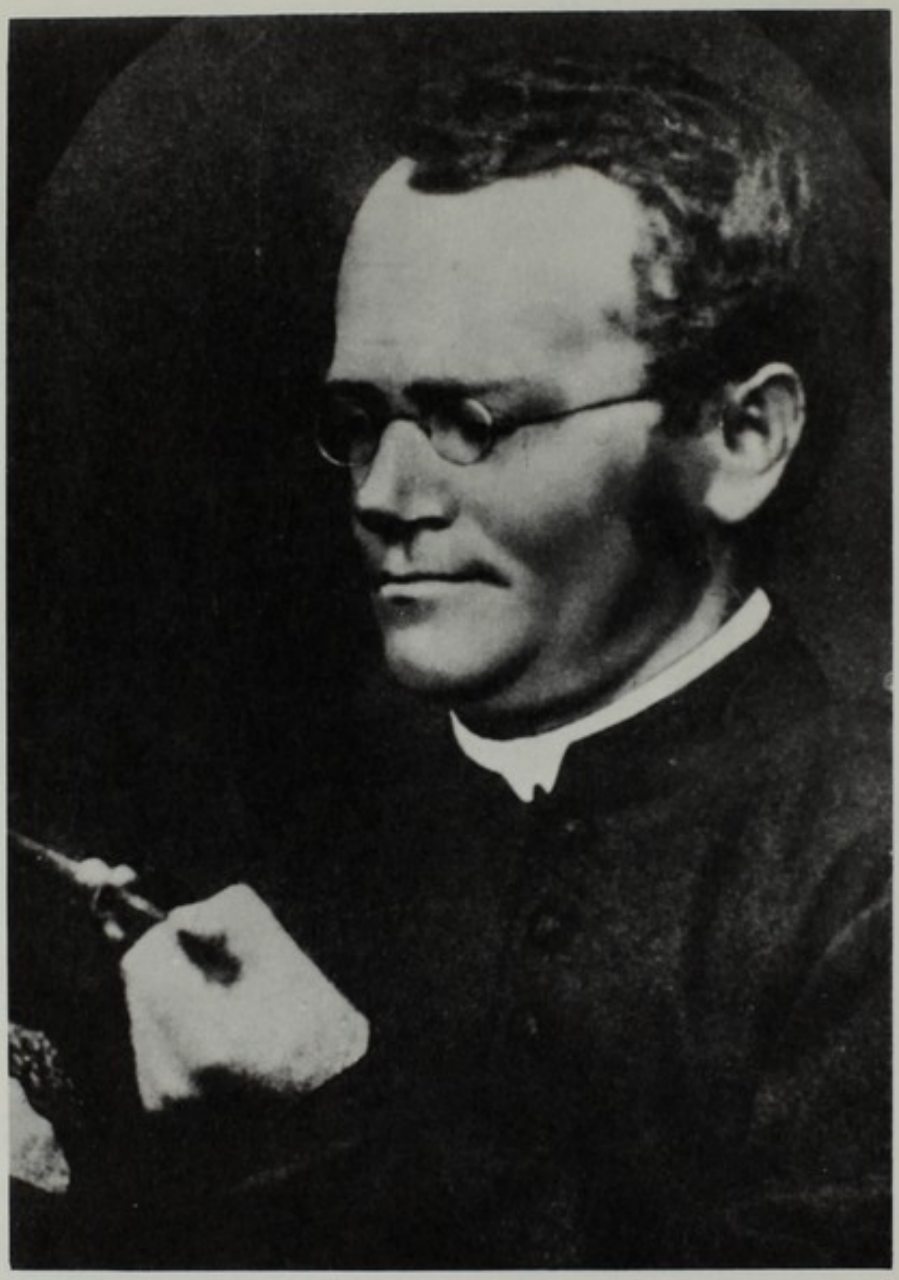

Gregor Mendel. From a portrait group. Mendel Museum, Brno, Czechoslovakia. Courtesy of Dr. E. G. Pringsheim of Göttingen.

COMMEMORATION OF THE PUBLICATION OF GREGOR MENDEL'S PIONEER EXPERIMENTS IN GENETICS

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MENDEL, HIS WORK AND HIS PLACE IN HISTORY

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(Read April 23, 1965, in the Symposium Commemorating the Publication of Gregor Mendel's Pioneer Experiments in Genetics)

For sixty-five years Mendel has been acclaimed by biologists and public alike as one of the most interesting figures in the history of modern science. Now, one hundred years after the presentation of his major work (the single work on which his reputation rests), is a good time to enquire why he occupies the position he does. This will of course raise questions as to what in fact that position is. He is often referred to as the father of genetics. If such a figure of speech is to be used, grandfather would be more appropriate, since a full generation intervened between Mendel's work and the birth of a new branch of science.

The experiments with which he proved the first principles of heredity were carried out between 1856 and 1863. He described them in two communications which he read before the Natural Science Society of Brünn on the evenings of February 8 and March 8, 1865. The lectures were heard by about forty persons. There appears to have been no discussion. Mendel's account was published [1] in the 1865 volume of the proceedings of the Society which appeared in 1866. This journal had a subscription and exchange list of 120 in Europe and the Americas and the author was given 40 reprints for distribution. The published paper was cited in five literature lists—including one in the *Encyclopedia Britannica*—but no attention was paid to the theory until in the spring of 1900 three botanists [2, 3, 4] reported verifications of Mendel's work which amounted to independent rediscovery of his chief principle. His paper was then recognized as the foundation of a new conception of the transmission mechanism of heredity and a new branch of biology began to grow. In 1906 it was given the name of genetics [5] although the central ideas continued for many years to be referred to as Mendelism.

The report of 1865 contained the whole of his results up to that time. The descriptions of the breeding experiments with varieties of the garden pea were factual, concise, and clear. They were explained or interpreted by a new and original theory of inheritance, based on the transmission of elementary units or particles in accordance with some simple rules. The new idea was supported by evidence of a quantitative statistical kind which was also novel. It was derived from the enumeration of large numbers of individually identified descendants of crosses between varieties of peas differing in pairs of sharply contrasting characters. An often quoted sentence from the introduction to his paper was this diagnosis:

> 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 definitely to ascertain their statistical relations.

That was the program which Mendel carried out and he was the first to do it. It opened the way to a solution of the essential problem of hereditary transmission.

The idea at the basis of Mendel's explanation of the results of his breeding experiments turned out to be quite general and provided the elementary principle of heredity in all forms of life from viruses to man. It was that heredity is particulate. Each parent transmits a set of particles to the offspring. In the plants with which Mendel worked and in biparental repro-

[1] Gregor Mendel, "Versuche über Pflanzenhybriden," *Verh. naturforsch, Verein. in Brünn* **4** (1866): pp. 3–47.

[2] Hugo de Vries, "Sur la loi de disjonction des hybrides," *Contes Rendus Acad. Sci. Paris* **130** (26 March 1900): pp. 845–847.

[3] Carl Correns, "G. Mendels Regel über das Verhalten der Nachkommenschaft der Rassenbastarde," *Deutsch. Bot. Ges. Ber.* **18** (1900): pp. 158–168.

[4] E. Von Tschermak, "Uber künstliche Kreuzung bei Pisum sativum," *Deutsch Bot. Ges. Ber.* **18** (1900): pp. 232–239.

[5] William Bateson, "Review of Vorlesungen über Descendenztheorien by J. B. Lotsy," *Nature* **74** (1906) (*cf.* W. Bateson, 1928, p. 442).

duction generally the particles from the opposite parents are members of pairs. For example, from one parent comes a particle representing whiteness of flowers from the other one representing redness. These meet in the offspring but remain distinct. They do not mix or fuse or influence each other. When such an offspring forms its reproductive cells, the members of each pair of particles separate or as we now say segregate. One member enters one cell, the other enters a different cell. The result is that half the cells, say pollen or sperm nuclei, get a particle for whiteness, the other half a particle for redness and similarly for the eggs or ovules. Denoting one kind of particle *A*, the other *a*, sperm are thus 1/2*A* 1/2*a*, eggs 1/2*A* 1/2*a* and when these meet at random in fertilization we have

$1/2a \times 1/2a = 1/4aa$ = white

$1/2a \times 1/2A = 1/4aA$ = hybrid (red)

$1/2A \times 1/2a = 1/4Aa$ = hybrid (red)

$1/2A \times 1/2A = 1/4AA$ = red.

$(A+a)(A+a)$ i.e. $(A+a)^2 = AA+2Aa+aa$

This outcome can also be expressed by multiplication: $(A + a)$ $(A + a)$ etc. This is called Mendel's principle of segregation or separation of intact particles. The particles are now known as genes and have a corporeal existence as deoxyribose nucleic acid but in Mendel's theory they had a purely statistical or symbolic existence. An intact element capable of assuming alternative forms such as *A* and *a* was an assumption required to explain the proportions of individuals with differing forms of a character (such as color) actually counted in the offspring of hybrids.

Elements belonging to different pairs such as *A*, *a* (flower color) and *B*, *b* (tall or dwarf) were found to recombine at random also without influencing each other. Combinations could be predicted by multiplying together the individual binomials, i.e. $(A + a)^2 = AA + 2Aa + aa$; $(B + b)^2 = BB + 2Bb + bb$; $(A + a)^2 \times (B + b)^2$ gave 9 combinations *AABB*, *2AABb* . . . etc. in proportions which were realized in actual counts of the offspring of such double hybrids. This was Mendel's principle of independent assortment, which proved to be of general application when the particles are properties of different linkage groups or chromosomes.

Mendel generalized both of these principles for populations of the kind with which he was dealing, namely hermaphroditic plants reproducing by self-fertilization. The population thus descended from a hybrid *Aa* will, he showed, change in a predictable manner from $AA : 2Aa : aa$ in generation 1 to $(2^n - 1)AA : 2Aa : (2^n - 1)aa$ in generation n. As n becomes large, the population tends to revert to the pure parent forms *AA* and *aa* while the hybrid *Aa* trends toward extinction:

n = 10 *Aa* = about $1/10^3$

n = 20 *Aa* = " $1/2 \times 10^6$.

This laid the basis for the interpretation of the effect of inbreeding as the consequence of Mendelian segregation. It was only a step from this to the generalized Mendelian equilibrium expression for populations mating at random as reached by Pearson, Weinberg, and Hardy.

From the independent assortment principle Mendel reached the general rule that if n is the number of pairs of differentiating characters, then the number of different combinations will be 3^n, of which 2^n will be constant (homozygous). Thus with only 20 particle differences within a population, an array of over 3 billion (3^{20}) genetically different forms becomes possible and the variety thus generated will tend to be maintained by the equilibrium principle. These were entirely new insights into the nature of the living world. We now recognize that living matter is organized and carries on the activities peculiar to life—reproduction, heredity, diversification, evolution—by means of the units which Mendel recognized. We must realize that it was not only the conception that Mendel provided but the radical proof that such units could explain basic facts of nature which had hitherto lacked explanation.

Since this conception was first proved by Mendel in the case of the transmission mechanism of heredity, some historians of science have represented Mendel as the sole originator of the science of genetics and of the new view of living matter which it has helped to form. Jean Rostand has stated this view most sharply. Speaking of Mendel, he has said (1953),[6] "There is not known another example of a science which sprang full-blown from the brain of the one man (*qui soit toute formeé du cerveau d'un homme*). This kind of exaggeration would be avoided by one who like T. H. Morgan participated most actively in the formulation of the theory of the gene. Morgan, speaking in 1932, said:

> It is the orderly result of disjunction or segregation that is the important feature of Mendel's work: and finally, the clearness with which Mendel stated

[6] Jean Rostand, *Instruire sur l'homme* (Paris, 1953).

and proved the interrelation between character pairs in inheritance, when more than one pair is involved, which places his work distinctly above everything that had gone before. Nevertheless the genial abbot's work was not entirely heavenborn, but had a background of one hundred years of substantial progress that made it possible for his genius to develop to its full measure.[7]

Contributing to the view of Mendel as the unique source of two of the main ideas of modern genetics is the aura of isolation which has clung to him. Even some biologists of today tend to think of him as though he had been a visitor from outer space whose brief transit through European science was unobserved at the time. Indeed his published works cover only a short period, although his scientific activity extended over some twenty years. And he does seem rather an outsider in European botany. One gets this impression from the somewhat patronizing tone of Carl von Nägeli, the authority on hybridization and a leader of botanical research to whom Mendel wrote ten letters. These, published by Correns in 1905,[8] long after Mendel's death in 1882, were composed as scientific reports, explaining, defending, and amplifying the results in his 1866 paper. They reveal a modest, humble person who, while firmly upholding the correctness of the interpretation he had reached, nevertheless recognized that he had not and probably could not convince the one person most competent to understand his work. To contemporary botanists he must have seemed like an amateur, a priest in a provincial monastery, interested in hybridizing and improving garden plants and fruit trees, in beekeeping, meteorological observations and similar occupations. Even after his work had come to recognition he was often referred to as the Abbot of Brünn, as though his scientific work had been a biproduct of a life devoted to other interests. But for fifteen years at least it was the dominant interest.

The older view of Mendel in provincial and ecclesiastical isolation has had to be modified by what we know now about his travels, not only in Austria and Germany, but to Paris and London and several times to Italy and by his participation in the scientific life of Brünn, the capital of Moravia. He was a founding member of the Natural Science Society, was an active member of the Moravian Agricultural Society, the meteorological society and the apicultural society, and sat in the directorate of a deaf mute asylum and of a mortgage bank. And it should not be forgotten that in 1868 at the age of forty-five he was elected the abbot of his monastery and as such became administrator of its properties and its representative *vis-à-vis* city, province, and nation. Much of this happened later in his life. At the time of his greatest research activity, 1855–1866, he was not in a mainstream of science or of affairs. Certainly he seems then to have been in no position to have become the founder of a new branch of science, and is in any case an unlikely figure to occupy such a niche. What he wrote made it quite clear that he never saw himself in such a light and even though he is said to have declared "Mein Zeit wird schon kommen," it is likely that what he meant was that his law "formulated for *Pisum*" would be recognized as well founded.

Much of the impression of Mendel's remoteness may stem simply from our ignorance of his life and this in turn may be due in part to his own reticence. It is not that Mendel is a shadowy figure. What we do know suggests a solid, sturdy figure of flesh and blood, precise, systematic, self-contained and reserved, but not by any means withdrawn, exhibiting the practical good sense of the peasant, as befitted his ancestry and early life. The records bearing on his personal life, diaries, autobiographical writings (except a brief *Lebenslauf* written in his twenty-eighth year), even copies of letters to and from him are few and brief. Hugo Iltis, a successor to Mendel as teacher in Brünn, who published the best biography of Mendel in 1924 [9] was able to interview a few of Mendel's associates and former pupils, and there are some other tangential accounts, but on the whole it is a very sparse, bare record. Oswald Richter, also a Brünn teacher, in papers published between 1925 and 1943,[10,11,12]

[7] T. H. Morgan, "The Rise of Genetics," *Science* **76** (1932) : pp. 261–267 ; 285–288.

[8] Carl Correns, "Gregor Mendels Briefe an Carl Nägeli 1866–1873, *Abh. D. Math. Phys. Klasse d. Königl. Sachs. Ges. d. Wiss.* **29** (1905) : pp. 189–265.

[9] Hugo Iltis, *Gregor Mendel: Leben, Werk und Wirkung* (Berlin, 1924). English Transl. by Eden and Cedar Paul: *Life of Mendel* (New York, 1932).

[10] O. Richter, *Biographisches über Pater Gregor Mendel aus Brünns Archiven*, pp. 261–280, in Ruzicka V. editor: Memorial volume in honor of the 100th birthday of J. G. Mendel (Fr. Borovy, Prague, 1925).

[11] O. Richter, *75 Jahre seit Mendels Grosstat und Mendels Stellungnahme zu Darwins Werken auf Grund seiner Entdeckungen. Verh. naturforsch. Verein. Brünn* **72** (1940) : pp. 110–173.

[12] Oswald Richter, "Johann Gregor Mendel wie er wirklich war. Neue Beitrage zur Biographie des berühmten Biologen aus Brünns Archiven. Herausgegeben mit Unterstutzung des mährischen Landesbehörde, der Landeshauptstadt Brünn und der Deutschen Akademie

has documented and amplified the account of the activities mainly of Mendel's later life, but adds very little to essential knowledge of the man. Ingo Krumbiegel (1957), his latest biographer,[13] has not been able to add much to previous accounts.

As the son of a peasant born in a small Moravian village in 1822 his early education, first in the village school, then successively in primary and secondary schools at greater distances from home, was achieved by sacrifice on the part of his family and hard work on his own part, for in high school he had to earn his own living. But he was an outstanding student in all subjects, and after a final two years at a philosophical institute he was recommended by the professor of physics to the Augustinian monastery at Brünn as an able student and one who would profit by further opportunity for education. Like many another poor boy he became a priest in order to enter a life of study, although there is no evidence that he did not fully accept and live up to his religious vows. After his ordination in 1848 at the age of twenty-six it appeared that he was less fitted for pastoral duties than for teaching, and so he taught as supply or substitute teacher in secondary schools in Moravian towns and finally in Brünn. He failed in an examination for a regular teaching license but one of his examiners recommended that he be given an opportunity for university study to improve his preparation for reexamniation. He was therefore sent by his order for four terms (1851–1853) to the University of Vienna where he studied natural sciences and mathematics. He returned to teaching at Brünn Modern School (Staatsrealschule) and in 1855 again took the examination for teaching license. Again he did not qualify, and it appears that he withdrew from the examination because of illness.[13a] Thereafter he settled down as supply teacher of physics and natural history at the Realschule, where he remained until his election as abbot of the monastery in 1868. It was during these fourteen years that he carried out in the small monastery garden the breeding experiments with peas and with other plants which resulted in proof of the principles which bear his name.

Mendel's later life, which ended in 1882, was saddened by disappointment and defeat. He failed to confirm the principles derived from the pea experiments by arduous work with species and varieties of the hawkweed, *Hieracium*. This was the plant recommended by the eminent authority on hybridization, Carl von Nägeli. After five years of intensive work which had diverted him from other studies and ruined his eyesight, Mendel wrote to Nägeli (July 3, 1870), "On this occasion I cannot resist remarking how striking it is that the hybrids of *Hieracium* show a behavior exactly opposite to those of *Pisum*." [8] This statement, I believe, revealed a disappointment that heralded the end of Mendel's scientific work. No wonder that another experimental geneticist, nearly one-hundred years later, should say (Renner, 1959) "Die Begegnung mit Nägeli ist für Mendel zu einem Verhängnis geworden." [14]

However, it was discovered later that because of its method of reproduction *Hieracium* could provide no test of Mendel's theory. This became clear about 1910 when Swedish investigators [15] showed that species of *Hieracium* produce offspring in part by apogamy, that is by the botanical near-equivalent of parthenogenesis, and in part by normal fertilization, so that crossbred offspring are not always formed after cross-pollination. What defeated Mendel, however, was the fact that in hybrids between species in this genus, the flowers are always apogamous and so the offspring of hybrids are all alike. In the absence of a sexual process no segregation can occur. Mendel suspected some irregularity in the reproduction of *Hieracium* since he had verified his theory by experiments with several other genera. However, he had little time left from his administrative duties and this little he seems to have spent in trying to resolve minor questions of technique with this fractious and unsuitable material. Although he did not admit defeat, one can see now that his last experiments added only to doubt and confusion.

A second disappointment also troubled the last ten years of his life. As administrator of

der Wissenschaften in Prag. Druck von Josef Klar, Brünn," from *Verh. naturforsch. Verein. Brünn* **74** (1943).

[13] Ingo Krumbiegel, *Gregor Mendel und das Schicksal seiner Vererbungsgesetz* (Stuttgart, 1957).

[13a] Jaroslav Krizenecky "Mendels zweite erfolglose Lehramtsprufung in Jahre 1856," *Sudhoffs Arch. f. Geschichte der Medizin und Naturwiss.* **47** (1963): pp. 305–310.

[14] O. Renner, "Botanik" in Geist und Gestalt 2. Band Naturwiss. Biograph., *Beitr. z. Gesch. d. Bayer, Akad. d. Wiss. vornehmlich in 2. Jahrhundert ihres Bestehens* (C. H. Becksche Verlagsbuchhandlung, München, 1959).

[15] Hans Stubbe, *Kurze Geschichte der Genetik bis zur Wiederentdeckung der Vererbungsregeln Gregor Mendels* (Jena, G. Fischer, 1963), p. 108.

the monastery he resisted the Austrian government in its efforts to tax the properties of religious foundations. His refusal to pay caused distraints and sequestrations of monastery properties which he believed had been entrusted to his care. As a man of conscience he took his liberal political views seriously and maintained his defiance of the government decree until his death.

Thus in both his scientific and administrative work he was convinced of the rightness of his views even when these were not accepted by others. The external events of his life which reveal this attitude are matters of record; but we have little record of what he thought. One result of our ignorance of Mendel's personal life is that there is little to deflect our attention from the record on which his reputation rests.

We have to know him from his own writings. He published only four papers—one in 1854 when he was thirty-two years old, on the damage caused in Brünn by the pea beetle *Bruchus pisi*. This tells us that he had become interested in breeding peas. Ten years later came his major paper of 1865 (published 1866) [1] followed by one minor report in 1869 (published 1870) [16] on the failure of his breeding experiments with the hawkweed *Hieracium* to confirm his results with peas. This may well have been responsible for his renunciation of experimental work. At any rate he published nothing further on plant breeding. His last brief paper (presented 1870, published 1871) [17] was the outcome of a long-standing interest in meteorology. It described a tornado which devastated Brünn, October 13, 1870. What was characteristic of Mendel was that the sharp and clear description was accompanied by a new interpretation of the cause of tornadoes as vortices engendered by encounters between conflicting air currents. This paper too seems to have been overlooked by those who many years later developed a similar explanation of the origin of tornadoes. To these four brief papers we must add the ten letters to Nägeli.

This was indeed a modest bibliography for a modern scientist, representing some fifteen years of active devotion to experimental work. But his writings are quite sufficient to reveal a mind of genuine originality and simplicity, one which picked out the main point and explored it with directness and efficiency. In fact only his chief paper is needed to demonstrate these qualities. I venture to say that in clarity and incisiveness this paper has never been surpassed by those which succeeded it as genetics grew.

In judging Mendel's place in history we have to consider first whether he supplied something which was unique. Such a question can properly apply of course only to his own period, for as the history of discovery shows, in time nearly every major idea is rediscovered (Merton, 1961).[18] In the middle of the nineteenth century there is no question that Mendel alone expressed a new and original idea. Its essence was that heredity operates by elements which behave according to definite statistical rules. The main ones were that the transmission mechanism of biological heredity consists of many pairs of alternative characters or elements of which only one member is transmitted by any one reproductive cell; and that in the formation of such cells members of different pairs from the parents enter into all possible combinations with each other. These rules are usually referred to as the principles of segregation and of independent assortment of hereditary elements or genes. The discovery of order where none had been perceived before was of great importance. For the growth of biological ideas, however, the manner of proof was of even greater importance. The rules were demonstrated by simple experiments which anyone could perform. Mendel's paper was throughout an application of inductive reasoning radically applied at a time when general views of biological processes were often reached by deductive processes. Mendel's method of experimental breeding, in which all plants were individually identified and all offspring of deliberately made crosses were classified for each pair of contrasted characters and counted, was simple, but it was original and at that time unique. Moreover the experiments were deliberately designed to test a theory—and this kind of experimental design was new in biology.

One may say that in fact Mendel differed from all his predecessors and contemporaries chiefly in this; that he was looking for a law of a specific kind and designed his experiments to

[16] Gregor Mendel, "Über einige aus Künstlicher Befruchtung gewonnene Hieracium Bastarde," *Verh. naturforsch. Verein. Brünn* **8** (1870): pp. 26–31.

[17] Gregor Mendel, "Die Windhose vom 13 October 1870," *Verh. naturforsch. Verein. Brünn* **14** (1871).

[18] Robert K. Merton, "Singletons and Multiples in Scientific Discovery: A Chapter in the Sociology of Science," *Proc. Amer. Philos. Soc.* **105** (1961): pp. 470–486.

reveal this kind of law. The fact of design itself testifies to the prior existence in Mendel's mind of the idea of transmissible units which could exist in alternative forms, enter into all possible combinations with units belonging to different pairs, and retain their integrity and essential properties in all combinations even when their external effects could not be detected.

One of the most interesting questions bearing on Mendel's originality is whether he had already invented his theory before obtaining the experimental data in his paper, from which the theory is ostensibly derived. There is strong indication in the paper that he knew what numerical results to expect before the progenies of the segregating generations were classified and counted, and that this foreknowledge influenced the outcome of the counting operations. The fact is that the proportions of progeny which Mendel reports agree with those expected from his theory to a degree which cannot be accounted for by luck alone. This was first pointed out by R. A. Fisher (1936),[19] who showed that the overall fit of observation to expectation in Mendel's counts was such that the chance of observing a worse fit (if deviations were due only to accidents of sampling) was only about 1 in 10,000. The fit was thus improbably good and Fisher concluded that there must have been fraud somewhere, possibly on the part of an assistant who knew what the outcome of the counts should be.

In the cases which contributed most to the overall result, however, other explanations are available. An important experiment which Mendel made was to get offspring from those plants in the second generation of a cross of *AA* by *aa* which showed the dominant character *A*. According to his theory, one-third of these should be *AA* and two-thirds *Aa*. He grew one-hundred plants from each of five different F_2 generations, each set involving a different pair of contrasted characters. He classified each plant by planting ten of its seeds. If the ten progeny included both dominant *A* and recessive *aa* types he classified the parent plant as *Aa*; if all ten progeny were *A*, he classified the parent as *AA*. The results were 166*AA* to 334*Aa* plants. This was exactly the 1 : 2 ratio which Mendel said was expected. In fact, as Fisher pointed out, the chance that an *Aa* plant would by chance produce only *A* offspring and thus be classified as *AA* was $(3/4)^{10}$ or 0.0563; hence the actual expectation for *AA* would be increased by 0.0563 to 0.371 instead of 0.333 and similarly 0.629 *Aa* should be expected instead of 0.667. But the observations exactly fitted Mendel's erroneous expectation of 1 : 2.

Dr. Sewall Wright has pointed out to me his view that Mendel, who clearly knew how to compute probabilities, could hardly have been unaware of the likelihood that no recessives would appear in some groups of ten progeny and could have estimated this to be about one in eighteen (0.056). Perhaps he chose the inadequate number ten because of lack of space for growing plants; but perhaps he in fact tested more than ten plants in order to have at least ten left after the inevitable losses. If the average of "at least ten" should be twelve the probability of misclassifying falls from 0.056 to 0.031 and the discrepancy from Mendel's 2 : 1 expectation is not a serious one. It is also possible that for some seed characters he could distinguish *AA* from *Aa* by appearance since he remarks that plants heterozygous for brown seed coat were more spotted than those homozygous for this dominant character.

The most serious evidence of bias in favor of his theory comes from tests of two- and three-factor segregation in which tests of gametic ratios of 1 : 1 : 1 : 1 : gave probabilities of worse fit of only two per thousand. Here in classifying large progenies of plants into four categories, one must be able to see as the tallies grow how the numbers are running. Those who have experience in tallying such outcomes become aware of the danger that unconscious bias in favor of an expected result will creep in and that the count may be stopped at a point which is favorable to the theory. It is now a part of normal operation in genetics deliberately to guard against unconscious bias of this sort. Mendel was the first to make such tallies as tests of a theory of segregation and may well have made unconscious errors. There is no evidence of conscious fraud and he was careful to report wide deviations in some parts of some experiments which he would not have done if bent on fraud.

But the excessive goodness of fit to a theory which runs through his data certainly indicates that he had the theory in mind when the data *as reported* were tallied.

Where did the theory come from? In the paper it is clearly presented as an inference from the numerical data; but this as we have seen can hardly have been the case. He may of course

[19] Ronald A. Fisher, "Has Mendel's Work been Rediscovered?" *Annals of Science* 1 (1936) : pp. 115–137.

have got the idea from trial tests or pilot experiments not reported separately. But this seems unlikely in an investigator who reported results as fully and in as much detail as Mendel.

There are no indications that he had got the essential idea from any of his botanical or horticultural predecessors.[20] Kölreuter and Gärtner, to whom he refers, worked with true species hybrids differing in many variable intergrading characters from which such a rule as Mendel envisaged could not have been derived. Herbert, Lecoq, and Wichura, also cited by Mendel, had not reported their results in such a way that a binary rule like Mendel's could have been inferred from them. The work of those who came closest to Mendel's observations was not mentioned by Mendel. At the time of the formulation of his principles he seems not to have known of the work of Goss or of Seton who in 1822 observed dominance and segregation of seed color in peas, but without numerical observations or interpretation. Charles Naudin, a French contemporary of Mendel, came close (in 1863) to views Mendel reached at the same time but his results were not reported in such a manner that, even had Mendel seen them, they could have served as origin or as tests of a statistical theory.

At present we shall have to assume that Mendel originated the idea of elements which could occur in the alternative states such as he represented symbolically as *A* (round seed form), *a* (wrinkled seed form), etc. His recognition of the binary behavior of such elements, *A* and *a* always splitting in the hybrid *Aa* to enter different gametes of which equal numbers were therefore produced, was clearly evident in his application to them of the binomial principle and the laws of combination based upon the assumption of integral character of elements. This kind of character or behavior had not heretofore been imputed to biological units although it had appeared in the laws of chemical combination based on stable elements.

Barthelmess (1952: p. 76)[21] has made this interesting comment on Mendel's theory:

> This astonishing explanation could have become the basis for resolving the antithesis constancy—changeableness: for it showed that the single traits were in fact constant, and segregated out again unaltered after a cross, while just as truly a change of character occurred in the descendants of a hybrid in which the same single traits appeared in different combinations. Indeed in this way even constant new combinations could arise. "Constant elements, variable combination" was ready to hand as a synthesis—exactly as it had been several decades earlier in chemistry.

This manner of thinking in terms of recombinable elements which was growing in chemistry during Mendel's school days may well have come to his mind again in 1851–1853 when he attended lectures in physics and chemistry at Vienna. It was shortly after this experience, in 1854, that he turned to observations on plants and noted the sharp differentiating characters occurring in different combinations in varieties of peas. Since there was no precedent for such an idea in biology, it is not unreasonable to suggest, as Barthelmess has, that it may have come from chemistry.

There is one aspect of Mendel's scientific culture which has not attracted much attention but which should be considered when seeking sources for his theory. This was his training in and teaching of physics. It was his high school physics teacher, Friedrich Franz, who recommended him to the Monastery of St. Thomas, saying "In my own branch, he is almost the best."[9] This determined the course of his life. When Mendel himself came to teach, it was mathematics and Greek for the first year but thereafter, from 1854 to 1868, he taught physics and natural history. Even though he never qualified for a teaching certificate he appears to have been a successful teacher of physics. It is not clear to what extent his facility with mathematical reasoning which appears in his paper came from his experience in experimental and mathematical physics and there is no evidence to support speculation on this. But mathematics and the physical sciences seem more likely sources than the biological ones for the methods he applied so successfully to the study of inheritance.

From whatever source Mendel got his central theory, it was unique in its time and remained so for thirty-five years. Mendel's scientific character may perhaps be brought into clearer focus by comparing him with some of his contemporaries. Darwin (born 1809) was thirteen years older than Mendel. His work had a scope and a sweep which contrasts sharply with Mendel's concentration on what seemed a restricted and delimited problem, that of the transmission mechanism of heredity. Darwin seldom resorted to counting but when he did, in observing snapdragons of two different colors in the second generation

[20] A careful account of the work of Mendel's predecessors is in: H. F. Roberts, *Plant Hydridization Before Mendel* (Princeton, N. J., 1929), p. 323.

[21] Alfred Barthelmess, *Vererbungswissenschaft*, Orbis Academicus (München, Verlag Karl Albers, 1952).

following a cross, and found a close approach to a 3:1 ratio, then, as Zirkle has noted, "he made nothing of it." He was not looking for statistical explanations of single differences. Darwin, one might say, was concerned with the strategy of evolution, Mendel with one of its tactical problems. But in its more modest way Mendel's penetration to the essential feature of heredity supplied an important clue to understanding the strategy.

An exact contemporary was Francis Galton, born as was Mendel in 1822. Galton was himself the creator of a theory of heredity which for a time shortly after 1900 competed with that of Mendel. He was the founder of biometry, the application of statistical methods to biological variation, but it was variation of the continuous type in which he was interested not the discontinuous or alternate type with which Mendel dealt. He was in most ways in striking antithesis to Mendel—a prolific writer with wide-ranging interests who influenced many phases of nineteenth-century British thought: biology, geography, anthropology, and psychology. In addition he founded the eugenics movement. Through his statistical work and writings on heredity his influence spread to the Continent, and by way of Pearson, Weismann and Johannsen he shortened the period of growing pains in genetics by providing ways of judging quantitative data critically and constructively. One can see now, however, that the residue of ultimate scientific effect from Mendel's single paper is destined to be greater than Galton's greater volume and scope.

It may be more illuminating and useful to compare Mendel with those who, a generation after his work was published, themselves reached a theory like his by similar means. I mean of course those three who in the spring of 1900 independently and in rapid succession announced their "rediscovery" of Mendel's principles and brought Mendel's forgotten work and name into general recognition. De Vries was the first of the three to discover, as he was the first to announce, the principle of segregation. He had been a pure physiologist but the interest which dominated his work from the early 1880's (he was born in 1848) was the nature of the differences between species and especially the manner of origin of the differentiating characters. By 1889 he had developed a general theory of heredity and evolution which he referred to as intracellular pangenesis. Different species, in his view, represented different combinations of relatively few hereditary factors. "These factors," he said in his book of 1889, "are the units which the science of heredity has to work out. Just as physics and chemistry are based on molecules and atoms, even so must the biological sciences penetrate to these units in order to explain by their combinations the appearances of the living world." [22] He began hybridization experiments with the evening primrose, *Oenothera,* in 1890 in an effort to recognize these elementary units. His primary purpose was to determine how new characters arose and this led him to his chief work, the mutation theory. He had obtained F_2 ratios of three dominant to one recessive already in 1892 and by 1900 could report this same behavior of "unit characters" in breeding experiments with fifteen different genera of plants. He introduced his first paper of 1900 by repeating the statement that the specific characters are composed of separate units, and supported the claim by the results of the breeding experiments. One might ask why, if the rule (segregation) had been recognized by him for several years, it had not already been enunciated. The answer I think must be that (1) he had not hitherto regarded it as of decisive importance; (2) he had not seen Mendel's paper. He seems to have first read Mendel's paper early in 1900, for he says that after reading it: *"Thereupon* I published in March 1900----" (Roberts, p. 323).[20] De Vries was primarily interested in unit characters as species components, and not in the discovery of a rule of inheritance as such. He always set more store by his mutation theory, and the rediscovery of Mendel's principles was incidental or accessory to his main purpose.

Correns too discovered Mendel's principles during hybridization experiments directed toward the elucidation in maize of the phenomenon of xenia, that is, the expression in the seed of characters transmitted by the pollen which had fertilized it. By the autumn of 1899 Correns had found both segregation and independent assortment in peas. He recognized both of these principles in October, 1899, and then found Mendel's paper. But Correns too did not feel impelled to publish his results until de Vries's first report reached him on April 21, 1900. By the evening of the next day his own paper was on its way to the journal of the German Botanical Society.[3] He had not until that time considered

[22] Hugo de Vries, *Intracellular Pangenesis* (1889). English translation by C. S. Gager (Chicago, Ill., 1910).

it important to record his observations since (1) they were merely confirmations of Mendel's theory; (2) the intellectual labor of finding such rules had been lightened by Weismann and others so that the discovery of the same theory in the nineties was much less of an accomplishment than Mendel's of thirty years before. Besides, Correns's results differed in some points from Mendel's (lack of dominance in some cases) and other irregularities which turned out to be due to phenomena unsuspected by Mendel—selective fertilization and coupling of different characters. Correns thought these called for further study. The final statement in his paper (added May 16, 1900) was "that Mendel's law of segregation cannot be applied universally."

Correns did much more than rediscover Mendel's principles; he went beyond them in foreseeing some of the exceptions to them out of which additional principles were to arise. He did not consider them as incidental to another interest as de Vries had, nor on the other hand did he think of their discovery as an end in itself. His discovery of the genetic basis of sex-determination and of xenia, his elucidation of selective fertilization, and especially his discovery of cytoplasmic or non-Mendelian heredity, all in the early years of genetics, made him a co-founder fit to rank with Mendel.

Erich von Tschermak had just completed his doctorate in plant physiology when his interest in agriculture and plant breeding led him in 1898 to test, with peas, some of Darwin's ideas on the effects of cross and self-fertilization. He discovered the principle of segregation as a result of observations made for other purposes, found Mendel's account and included a discussion of the new principles in a thesis submitted to the University of Vienna in January, 1900. Then came de Vries's and Correns's papers which led him to hasten the publication of his own and to cause Mendel's paper to be reprinted. He was the first to proclaim the significance of the newly discovered theory for the practice of plant breeding, to which he continued to make contributions throughout his long life.

To these should be added William Bateson as in effect a rediscoverer or even anticipator of Mendel's principles, since in 1899 he called for the kind of statistical study of the offspring of hybrids which led Mendel to his discovery.

Each of the rediscoverers recognized the essential feature of segregation and the existence of stable hereditary units—genes. But for none of them was the departure from the thought of his time so sharp as had been the case with Mendel. Reading their accounts heightens rather than diminishes our respect for Mendel's achievement. It also reminds us that what one good scientist can do, others can too. Mendel now tends to be less isolated upon a pedestal but to stand as first among his peers, even though these belonged to a later generation.

CONCLUSION

Judgments about a scientist's place in history generally have to wait until after a considerable segment of history has happened. This is because the effects of his work depend to a large extent on the state of the science of which they become a part. Like a building undergoing continuous remodeling and new construction, the state of the science is bound to change and with it the part played by individual discoveries. In the case of Mendel, enough history has happened to permit us to see that his work has served as a kind of constructional keystone upon which subsequent developments of genetics have rested. The discovery of the statistical unit of heredity has turned out to be the spearhead of a changing conception of living matter which has penetrated and illuminated all of the major questions of biology. If living activities are based on self-replicating elements which by their stability provide for hereditary succession of metabolic patterns, and by their liability to change provide for plasticity and adaptation to changing conditions, then present function is projected forward and backward—and the dynamism of self-reproduction provides the basis for historical views such as those which have transformed the interpretation of biological evolution.

The idea of the gene, introduced first by Mendel's interpretation, was fruitful and fertile in begetting a succession of theoretical and experimental investigations of increasing degrees of generality and penetration. As the concept of the gene has changed, in somewhat the same way as the concept of the atom has, we have come to see that the idea of an element of living matter was of secondary importance as compared to the revelation of an order accessible to investigation by methods which Mendel introduced.

Mendel's work acted as a catalyst in another way also. A new kind of fervor impelled the rapid development of a new kind of science in the years just following 1900. Much of this was

due to the novelty of the ideas which needed to be tested and extended and refined. But some was due to the circumstances of the original discovery of 1865 and dramatic rediscoveries of 1900. A head of steam had been generated, largely by Weismann's work, in those thirty-five years of neglect, and when it was suddenly released by the rediscoveries it was Mendel who was always the central figure. The contrast between the modern, quantitative order in his paper and the cloistered monk working in isolation in a narrow garden heightened the impression of novelty and tended to give Mendel the aura of a romantic hero.

It is clear now that genetics did not spring full blown from the mind of one man and that others were competent to make, and did make, the essential discovery over again. Mendel however stands as a clear example and guide to a new way of studying a biological problem with sharp, clear experimental design applied to a single question stated with simplicity because it had been reduced to its essentials. The dimension of the problem, which was a limited one as Mendel stated it, was of less importance than sharpness of definition and decisiveness of proof. The latter was Mendel's concern, and from it genetics has continued to draw strength and inspiration; history has now taken care of the dimension.

THE EARLY MENDELIANS

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WHEN Mendel's principles were rediscovered in 1900 their importance was widely recognized, and a whole series of workers began extending and elaborating them. One question that arises is: what was the background of these early workers that led them to appreciate the new approach?

One property was that they were mostly rather young—and they were considered by their older colleagues as what later came to be called "Young Turks." Of the four men who published Mendelian papers in 1900, the oldest were de Vries (fifty-two) and Bateson (thirty-nine). Both of these had been interested in the experimental approach to the study of heredity for some years, and both had views that were unorthodox at the time and that led to their being thought of as mavericks. Of the other two authors who published in 1900, Correns was thirty-six, and Tschermak twenty-nine. Davenport, whose first Mendelian account appeared in 1901, was then thirty-five. Among those who worked actively along Mendelian lines there were several who published results in 1902. Among them may be mentioned Saunders (then thirty-seven), Cuénot (thirty-six), Hurst (thirty-two), Emerson (twenty-nine), Darbishire (twenty-three) and Yule (thirty-one). To this list should be added Garrod (forty-five), who drew Mendelian conclusions from analysis of human pedigrees; and Wilson (forty-six), Boveri (forty), and Sutton (twenty-five) who discussed Mendelism in relation to chromosomes.

In 1903 we have Johannsen, then forty-six, Morgan (thirty-seven) and Castle (thirty-six). In 1904 came Lang (forty-eight), Doncaster (twenty-seven) and Lock (twenty-five), and in 1905 Biffen (thirty-one) and Punnett (thirty), in 1906 Toyama (thirty-nine), and in 1907 Shull (thirty-three), Baur (thirty-two), and East (twenty-eight).

Of the twenty-two workers listed for the period through 1905, only five were over forty—de Vries, Johannsen, Lang, Wilson, and Garrod. Wilson has recorded that his understanding of the relation between chromosomes and Mendelism came about as a result of a summer-long exposure to the ideas of young Sutton, and Garrod's Mendelian interpretation of his results was attributed by him to Bateson. Lang will be discussed below.

It is perhaps significant that the other two (de Vries and Johannsen) were both plant physiologists by training—a background that they shared with Correns and with other more recent geneticists such as Renner. It was evidently this background that gave them an understanding and appreciation of the quantitative, experimental, analytical approach that Mendel first introduced in the study of heredity.

De Vries got part of his training in plant physiology with Julius Sachs; another student of Sachs was Pfeffer, with whom both Johannsen and Correns studied. Both de Vries and Johannsen had already made important contributions to plant physiology—de Vries in connection with the quantitative study of the effects of solutions of various salts on the turgor and plasmolysis of plant cells, and Johannsen on dormancy. De Vries had also published (in 1889) a small book, called *Intracellular Pangenesis,* in which he developed an interesting theory of inheritance which was in some respects similar to that of Mendel.

Both were in the main stream of the biology of their time; but in 1901 de Vries published the first volume of his *Mutation Theory,* in which he seriously questioned the efficacy of selection, and argued that it could produce nothing new. This was a direct challenge to the views of Darwin and of Weismann and most of the others of the period who were interested in such questions. And one of his first and most vocal followers in this respect was Johannsen, beginning in 1903. These two then—the oldest of the active early Mendelians—were recognized as iconoclasts even without their support of the Mendelian ideas.

William Bateson (1861–1926) left a rather full record of how he came to be a geneticist. He was trained at Cambridge, largely in embryology and morphology. In 1883, at the age of twenty-two, he came to this country to study the embryology of *Balanoglossus* in the laboratory of W. K. Brooks at the Johns Hopkins University. Brooks, who was writing a now-forgotten book on heredity, made a great impression on the young Bateson, who wrote in 1910:[1]

> To me the whole province was new. Variation and heredity with us had stood as axioms. For Brooks they were problems. As he talked of them the insistence of these problems became imminent and oppressive. It all sounded rather inchoate and vapourous at first, intangible as compared to the facts of development which we knew well how to pursue, but with the lapse of time the impression became strong that Brooks was on the right line.

In passing it may be noted that Edmund B. Wilson and T. H. Morgan were also trained by Brooks. Through these three men his influence on genetics was very great, even though his own writings on the subject now seem of little interest.

In 1894 Bateson published his *Materials for the Study of Variation*, a book of 598 pages, in which he brought together a large collection of recorded structural variations in animals. This book was a declaration of war against much of the fashionable biology of the time, as may be illustrated by two quotations:

> In these discussions [of phylogeny] we are continually stopped by phrases such as, "if such and such a variation then took place and was favorable," or "we may easily suppose circumstances in which such and such a variation if it occurred might be beneficial," and the like. The whole argument is based on such assumptions as these—assumptions which, were they found in the arguments of Paley or of Butler, we could not too scornfully ridicule. "If," we say with much circumlocution, "the course of Nature followed the lines we have suggested, then, in short, it did." That is the sum of our argument.

On the last two pages of the book is to be found a statement that still has relevance:

> These things [the facts of variation] attract men of two classes, in tastes and temperament distinct, each having little sympathy or even acquaintance with the work of the other. Those of the one class have felt the attraction of the problem. It is the challenge of Nature that calls them to work. But disgusted with the superficiality of "naturalists" they sit down in the laboratory to the solution of the problem, hoping that the closer they look the more truly will they see. For the living things out of doors, they care little. Such work to them is all vague. With the other class it is the living thing that attracts, not the problem. To them the methods of the first class are frigid and narrow. Ignorant of the skill and of the accurate, final knowledge that the other school has bit by bit achieved, achievements that are the real glory of the method, the "naturalists" hear only those theoretical conclusions which the laboratories from time to time ask them to accept. With senses quickened by the range and fresh air of their own work they feel keenly how crude and inadequate are these poor generalities, and for what a small and conventional world they are devised. Disappointed with the results they condemn the methods of the others, knowing nothing of their real strength. So it happens that for them the study of the problems of life and of Species become associated with crudeness and meanness of scope. Beginning as naturalists they end as collectors, despairing of the problem, turning for relief to the tangible business of classification, accounting themselves happy if they can keep their species apart, caring little how they became so, and rarely telling us how they may be brought together. Thus each class misses that which in the other is good.

Here were broadsides against the speculative morphologists, the laboratory men, the field naturalists, and the museum men—and these *were* the biologists of the time. Little wonder that Bateson found academic recognition and advancement slow!

Bateson was early impressed with the importance of breeding experiments in the study of heredity, and began such work in earnest in 1897. Miss Saunders, stimulated by him, had already been carrying on such work at Cambridge, and published in that year an account of experiments with the plant *Biscutella*, using material that had been collected by Bateson, who was already using plants as well as the animal material indicated by his zoological training.

This interest in plants led to two lectures by Bateson before the Royal Horticultural Society, published in 1900. In the first, read 11 July, 1899,[2] appears the statement:

> What we first require is to know what happens when a variety is crossed with its nearest allies. If the result is to have a scientific value, it is almost absolutely necessary that the offspring of such crossing should then be examined statistically. It must be recorded how many of the offspring resembled each parent and how many shewed characters intermediate between those of the parents. If the parents differ in several characters, the offspring must be examined statistically, and marshalled, as it is called, in respect to each of those characters separately.

[1] *Jour. Exper. Zool.* **9** (1910): pp. 5–8.

[2] *Jour. Roy. Hort. Soc.* **24** (1900).

The whole paper makes it clear that here was a man who was ready to appreciate and understand Mendel's approach. The second lecture was delivered 8 May, 1900.[3] On the train going from Cambridge to London to deliver this lecture, Bateson read the account of Mendel by de Vries,[4] and was so deeply impressed with it that he at once incorporated it into his lecture.

Bateson at once became the most active and vocal of the early Mendelians. He built up the first "school" of geneticists at Cambridge (later moved to the John Innes Horticultural Institution near London). Here were Saunders, R. C. Punnett, F. Durham, D. C. E. Marryatt, M. Wheldale (later Mrs. Onslow), and R. P. Gregory. Also associated with this group were C. C. Hurst, L. Doncaster, R. H. Biffen, and others.

Experimental breeding was carried on with stocks, sweet peas, fowls, canaries, mice, rabbits, and many other forms. At this period this laboratory was the principal world center for genetic work. The early exploratory work culminated in Bateson's *Mendel's Principles of Heredity* (1909).

Bateson was a master of the English language, and was also inclined to be rather contentious. During the period in question he engaged in a public quarrel with Weldon and Pearson—the latter also a contentious character who carried on public and acrimonious debates with several other people as well as with Bateson.

It seemed to Bateson that Weldon and Pearson were trying to strangle the new development, and he reacted vigorously. The resulting debate was unfortunate, and certainly did much to delay the use of the powerful methods of statistics in the development of genetics. Perhaps the most important influence in the development of that use was Johannsen, whose *Elemente der exakte Erblichkeitslehre* (1909) was the first serious attempt to apply statistical methods to the Mendelian approach.

Carl Correns (1864–1933) was a student of Mendel's correspondent, Nägeli, and also worked with the plant physiologists, Haberlandt and Pfeffer. He was interested in mosses, and formed a large personal herbarium of this group, from his own field work. He studied the development and growth of cell membranes in algae—a study influenced by Nägeli's micellar theory. He also made physiologically-oriented anatomical studies on several seed-plants, but had to give up microscopical work on account of eye trouble. In 1894 he undertook a study of the phenomenon of xenia, in which the endosperm (especially in maize) shows effects of the pollen parent, though the tissue itself was long thought to be of maternal origin. The double fertilization of the seed plants was worked out by Nawaschin and by Guignard in 1897, and Correns saw that this was in good agreement with his genetic results—as did de Vries, who was also studying the inheritance of maize endosperm characters. In connection with this work Correns also carried out crosses with peas. His paper,[5] giving the results with maize, closes with the statement that the superificially similar phenomena seen in the crossing of green and yellow peas is due to the color being in the cotyledons—i.e., in the developing seedling—"as already correctly pointed out by Darwin and by Mendel." This statement (January, 1900) is the first indication that anyone had understood anything in Mendel's great paper.

The paper in which Correns discussed Mendel's results, later in the same year in the same journal, is the most detailed and convincing of the "rediscovery" papers of that year. He understood the results quite clearly, and his own confirming data were extensive, unambiguous, and included the necessary critical tests. This was characteristic of the man. He made numerous first-rate contributions later, and they consistently show a clear-thinking, careful, and painstaking analytical and experimental approach.

There are three detailed accounts that give a picture of Correns as a biologist and as a man. These are by his student, F. von Wettstein,[6] and by O. Renner.[7] From these accounts it appears that Correns was a reserved type, disinclined to collaborate with others or to engage in controversies—though when occasion called for it he had a sharp pen. His students found him helpful, and a delightful person when once his reserve was broken through, but he did not encourage discussions of his own current work or make use of their assistance in planning or executing it. Like Mendel, he was a "loner"—quite different from the

[3] *Ibid.* **25** (1900).

[4] *Berichte deutsch. botan. Ges.* **18** (1900).

[5] *Ibid.* **17** (1900) : p. 410.

[6] *Zeits. ind. Abst. Vererb.* **76** (1938) : pp. 1–10; *Berichte deutsch. botan. Ges.* **56** (1939) : pp. 140–160.

[7] *Sitzber. Heidelberger Akad. Wissensch.* **1961** : pp. 159–181. This is a comparison of the life and work of Correns and that of Bateson, modeled on the method of Plutarch.

outgoing organizers of collaborating groups, such as Bateson and Morgan.

This is not the place to describe Correns' later contributions to genetics, but it should be pointed out that they were of the first importance in such fields as the relation between genes and chromosomes, non-chromosomal inheritance, pollen competition, self-sterility, and sex determination.

E. von Tschermak [8] (1871–1962) was a grandson of E. Fenzl, under whom Mendel studied systematic botany and microscopy in his student days at Vienna. Tschermak took a Ph. D. at Halle. He was interested in practical plant breeding, and worked at a number of horticultural establishments. He became interested in hybrid vigor, and, following Darwin's example, used crosses of races of garden peas in the study of this phenomenon first at Ghent and then at Vienna. These experiments led to a study of other characters in the hybrids obtained. Thus it happened that he read and appreciated Mendel's paper. At the time Tschermak published his two papers in 1900 he had not had time to carry his experiments beyond F_2 and back-cross generations, so his analysis had to depend on Mendel's results for the critical tests showing that the F_2 ratio is really 1 : 2 : 1 and that both homozygous classes breed true.

His later experiments with stocks, beans, wheat, barley, and rye furnished extensive data confirming the Mendelian principles at a time when such confirmation was important.

It may be noted that several of the other early Mendelians also approached the subject through experience with practical breeding—such men as Biffen, Nilsson-Ehle, Spillman, Emerson, East, and Toyama.

The first American to emphasize the Mendelian approach was C. B. Davenport (1866–1944), who in 1901 published a summary of the papers by de Vries and Correns.[9] Davenport had given a course at Harvard in experimental morphology, taken by W. E. Castle and H. S. Jennings in 1893. This was a result of the growing interest in the use of experimental methods in the analysis of the structure and development of animals, which may be attributed largely to W. Roux, who called it "Entwicklungsmechanik." The subject, embracing primarily the study of regeneration and experimental embryology, was very actively pursued in the 1890's. Several of those who contributed to its development in this period were among the early Mendelians—Davenport, Cuénot, Boveri, Castle, Wilson, Morgan, and others.

Like most zoologists of the period, Davenport had also done systematic work, in his case on fresh-water Bryozoa. Of the others with this sort of background may be mentioned Cuénot (who was one of the principal authorities on the classification of the Tardigrada), Castle (leeches), Wilson (sea-spiders), and Punnett (the *Balanoglossus* group). This background was not so often found among the early botanical geneticists, though both de Vries and Correns had done some systematic work.

The third important element in Davenport's background was his interest in the statistical approach to the study of variation. He was early associated with K. Pearson, and was one of the three original editors of *Biometrika* in 1901. However, like Bateson and Yule in England, he soon had difficulties with Pearson and never followed his anti-Mendelian lead. It is interesting that at least three of Davenport's students (Jennings, G. H. Shull, and F. E. Lutz) were among the early users of statistical methods in genetics, and that a fourth (Castle) was the first to understand what has come to be known as the Hardy-Weinberg formula (see below).

In 1899 Davenport went to the University of Chicago as instructor in zoology, in the department of C. O. Whitman. He was thus in close contact with two of the most active anti-Mendelians of the period—Pearson and Whitman. He remained firmly pro-Mendelian, and with the establishment of the Station for Experimental Evolution of the Carnegie Institution at Cold Spring Harbor, with Davenport as Director (1904), he began in earnest his genetic work and his support of the staff that he brought together there.

L. Cuénot (1866–1951) was trained, in France, as a zoologist. His early work was in embryology, comparative anatomy, and taxonomy. In 1899 he published [10] the results of an elaborate study on the determination of sex, based on his own experiments published in 1897. The generally accepted view at the time was that nutrition was an important element here, the males resulting from poorer nutrition than the females. Cuénot showed that, in the insects and amphibia that he

[8] Later in life he added another name, so that he appears as "von Tschermak-Seysenegg."

[9] *Biol. Bull.* 2 (1901) : pp. 307–310.

[10] *Bull. Scient. France Belg.* 32 (1899) : pp. 463–534.

studied, the sex of an individual was not affected by its own nourishment during early development, nor by that of its parents. This negative result was important in clearing the way for the solution of the problem that came through chromosome studies (by McClung, Stevens, and Wilson), in the next few years.

The earliest Mendelian results all concerned plants, but Correns suggested in 1901 that the principles probably applied to animals as well, basing this conclusion on observations reported in the older literature. The proof that the principles do in fact apply to animals was produced independently in 1902 by Bateson and by Cuénot. Between 1902 and 1907 Cuénot published a series of five brief notes [11] on the genetics of the coat colors of mice. These accounts did much to clear up the relations involved in the genetic determination of characters for which numerous mutant genes were available. He was the first to understand multiple alleles, he was one of the first to think of gene action in terms of enzymes, and he found the first lethal gene. These achievements have led to an increasing respect for his contributions, but at the time they were not appreciated by his compatriots any more than were those of his contemporaries in their own countries.

One of the younger early Mendelians was G. Udny Yule (1871–1951), who was thirty-one when he published his first account.[12] It appears from this paper that he had been working on parent-offspring correlations in quantitative characters in asexually produced duckweed (*Lemna*) cultures—evidently stimulated by the work of Galton and Pearson. His later work was chiefly statistical in nature; his *Introduction to the Theory of Statistics* (1911) was long a standard text.

Yule's paper of 1902 was an attempt to reconcile Mendelism and the Galton-Pearson "Law of Ancestral Inheritance." He felt that Bateson had been unfair and abusive in his criticism of Weldon and Pearson, and that there need be no conflict between the two views, which dealt with different aspects of the subject. He succeeded in antagonizing both parties, since Pearson in 1904 tried to show that Yule's analysis was incorrect and that the numerical values actually observed for parent-offspring regressions were inconsistent with Mendelism. It is now clear that Yule was right and Pearson was wrong, because the latter assumed complete dominance in each pair of genes.

The Yule paper is remarkable in several respects. It contains the first reasonably clear statement of the multiple-factor interpretation of continuously varying characters, though both Galton and Bateson had insisted that stature must be influenced by many separable elements. Approaches to the interpretation may be found also in Mendel's paper and in Morgan's *Evolution and Adaptation*,[13] but it was Yule who first stated it clearly and explicitly.

Another new idea in Yule's paper is that he raised the question of what will happen if an F_2 population, segregating for a single pair of genes, interbreeds at random. He showed that the proportion of the three types, *AA*, *Aa*, and *aa*, will remain constant under these conditions—i.e., the beginnings of what has come to be known as the Hardy-Weinberg principle, for the special case where the two alleles are equally frequent. He also asked, in effect, what will happen if one eliminates the recessives in each generation, and allows the dominants to interbreed at random? Here he slipped in his analysis, and came up with the wrong answer.

This error was corrected in the next year by Castle.[14] The result was reached by a cumbersome method, and was not stated in simple algebraic terms, but it is clear that Castle understood the principle that any population in which a pair of Mendelian genes is segregating will be stable if random mating occurs, regardless of the relative proportions of *A* and *a*.

Arnold Lang (1855–1916) was a student of Haeckel, and became professor of zoology at Zurich. He was a comparative anatomist, and wrote what was in its time the standard general account of the anatomy of invertebrates. About 1894 he became interested in the reversed asymmetry of the shell and internal organs that occasionally occurs in snails, and bred from reversed examples of Helix. These gave no reversed descendants, but the work led him to undertake experiments on the inheritance of the banding pattern, beginning about 1897. He crossed unbanded snails with five-banded ones, expecting to find in the descendants faint-banded individuals and individuals with some of the five bands missing—types that he knew to exist. Instead he

[11] *Arch. zool. exper. gén.*
[12] *New Phytologist* 1 (1902).
[13] (1903), p. 277.
[14] *Proc. Amer. Acad. Arts and Sci.* 37 (1903): pp. 223–242.

got only unbanded F_1's, and in F_2 recovered both types in the ratio of 3 to 1. These results were very puzzling, especially since he found that the various intermediate types occurring in nature could be obtained in true-breeding lines.

In 1904 he published these results,[15] and gave a Mendelian interpretation. He said in this paper that the Mendelian scheme was well known to botanists, but that most zoologists on the European continent were unaware of it, and that he had not at first read the literature.

T. H. Morgan told me, years later, that Lang was a delightful person and had a wonderful library, for which reasons it was a recognized custom for American zoologists going to Naples to visit him in Zurich. According to this story, Davenport made such a visit, evidently in 1902, in the course of which Lang talked to him about his snail experiments. Davenport recognized the Mendelian nature of the results, and called Lang's attention to the existing literature.

Lang, like Correns, was not a controversial figure. He was, by training and background, a compiler—though he did make real experimental contributions as well—and he began a project of compiling the genetic results obtained with animals. The first volume of this work appeared in 1904, but it then became apparent that this approach was not hopeful because of the very rapid growth of the literature, and the projected later volumes did not appear.

[15] *Festschr. 70 Geburtstag E. Haeckel* (Jena, Fischer, 1940), pp. 437–506.

The backgrounds of the early Mendelians may be roughly summarized as follows:

Plant physiology. De Vries, Correns, Johannsen.

Experimental embryology. Cuénot, Castle, Morgan, Wilson, Boveri.

Statistics. Davenport, Darbishire, Yule.

Cytology. Boveri, Wilson, Sutton.

Taxonomy. Cuénot, Davenport, Wilson, Punnett, Castle.

Medicine. Garrod, Weinberg, Baur.

Agriculture. Tschermak, Biffen, Emerson, Spillman, East, Nilsson-Ehle, Toyama.

Morphology. Correns, Saunders, Lang.

Evolution. De Vries, Bateson.

This listing, which is obviously incomplete, indicates that the new methods appealed to men with a wide variety of backgrounds, but there are several fields of work, now of first-rate importance in relation to genetics, that are conspicuously absent. Notable here are bacteriology, immunology, and biochemistry (except for Garrod). Much of the important work of the past thirty years has come from the relating of these fields to genetics.

MENDELISM, DARWINISM, AND EVOLUTIONISM

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(Read April 23, 1965, in the Symposium Commemorating the Publication of Gregor Mendel's Pioneer Experiments in Genetics)

MENDEL is one of the tragic figures in the history of science. During the autumn of his life he must have felt that his work as a scientist was a dismal failure. It was overlooked and ignored. He could hardly have foreseen that it would be rediscovered and appreciated in 1900, i.e., sixteen years after his death. It was published in an obscure provincial journal, but this was only a partial explanation of its having been disregarded. The scientific literature was then not yet the flood that it has become now. Biologists of 1865 were evidently less well prepared to understand Mendel's insights than were biologists of 1900. There was, however, a biologist living in 1865 to whom the above statement did not apply. This biologist was Darwin. Unluckily for both parties, Darwin did not know about Mendel's discovery. The library of Mendel's Brünn monastery had copies of some books by Darwin with marginal notations in Mendel's handwriting. Mendel failed to send a copy of his publication to Darwin; perhaps by the time he became familiar with Darwin's books he had given up hope of having his contribution understood by anybody.

Mendel was not a great generalizer of masses of heterogeneous data, as Darwin so pre-eminently was. Mendel's genius was in depth rather than in breadth. His place among the greatest of scientists is due to a single published work of modest size. In this work he was able, however, to analyze fully his experimental results, and to apprehend with perfect clarity the causal nexus which these results revealed. A really new discovery in depth is apt to be less easily understood than a discovery in breadth. Darwin, not knowing of Mendel's work, was making some experiments of his own, which led him within an ace of obtaining results paralleling Mendel's. Whether or not he would have analyzed the results as masterfully as Mendel did is a moot point. The late J. B. S. Haldane thought that Mendel's analysis was somehow facilitated by his familiarity with Thomist philosophy. This is an extraordinary compliment for Thomistic philosophy, but I am not convinced that it is warranted.

II

Darwin was certainly aware of the importance of understanding heredity for understanding evolution. In his books, especially in that dealing with domesticated animals and plants, he painstakingly collated every bit of information about heredity that he found in the literature. Evolution is a complement of heredity, or rather a negation of heredity. Heredity tends to make the progeny resemble the parents and other ancestors. Evolution makes the descendants unlike the ancestors. If heredity were always exact, evolution could not happen. An offspring of a pair of parents consists, however, of individuals which differ to some extent from the parents and from each other. This is variation.

Variation is the fountainhead of evolution. Taking variation for granted, Darwin proceeded to describe how natural selection molds it into shapes which make living beings adapted to their environments. He was satisfied that the variation was universal, observable in all organisms. He acknowledged, however, that the origin of variation was unknown. So long as this ignorance was unbroken the theory of evolution was incomplete. One could even say that this theory was a colossus with feet of clay. This was pointed out in 1867 by Fleming Jenkin, an engineer rather than a biologist. Suppose that a light-skinned individual appears in a dark-skinned population. Could the light-skinned variant eventually replace the original form? It seemed that it could not. The new variant, a mutant as we would call it now, is unlikely to arise in many individuals in any one place and at any one time. The mutant will have to mate with an individual of ordinary color. Their children will presumably be intermediate between the parents, and they too will have to marry partners of the usual color. After a few

generations of intermarriage, the mutant will disappear like a drop of a soluble dye in a sea. It will be dissolved in the prevailing norm.

Jenkin's argument tacitly assumes that the heredity of a child is a blend of the parental heredities, and that the components of the blend never regain their purity. This is the vernacular notion, sometimes dignified by the name of "blood theory of heredity," which Darwin and Jenkin, and everybody else in their day, assumed to be correct. Everybody, that is, except Mendel, who showed it to be erroneous. Mendel's paper was, however, reposing on some library shelf which Darwin did not reach. Darwin doubtless felt that the blood theory contained some hidden fallacy, which he was, however, unable to pinpoint. Heslop-Harrison (1958) even argued that Darwin did not really accept the blood theory as valid, because he knew that some hybrids do not show blending but show instead what we at present call Mendelian segregation, i.e., reappearance of individuals resembling the parents of the cross. Darwin did know this, from the literature and from his own experiments. He also knew, however, that in many, in fact in most hybrids, segregation is not easily perceptible. This is called at present polygenic inheritance; it is basically Mendelian but technically difficult to analyze. Darwin's judicious objectivity made in this case a disservice. He drifted towards Lamarckian notions, which happened to be incorrect.

The rediscovery in 1900 of Mendel's forgotten work should have at once laid the ghost of the blood theory of heredity. It was not quite that simple. The early stages of the development of genetics are analyzed for you by Drs. Dunn and Sturtevant. I had the opportunity to discuss the genetics of the orgin of variations before the American Philosophical Society six years ago, when we commemorated the Darwin Centennial (Dobzhansky, 1959). I can limit myself here to only a few remarks concerning these matters.

Some log jams had to be cleared before Darwinism and Mendelism could join forces. For a time, it did not seem unreasonable to entertain a kind of dualistic theory of heredity, assuming that some of the inheritance is transmitted from parents to offspring by miscible "bloods," and other inheritance by immiscible genes. For example, the variation of the eye color in man is nearly (though not quite) discontinuous. Segregation of brown-eyed and blue-eyed types of progeny is observable in many families. On the other hand, the variation of human stature seems to be continuous and the inheritance blending. It took close to thirty years to have almost everybody convinced that continuous variability is fundamentally Mendelian.

Mutation is the source of the hereditary variation which Darwin was looking for. How tantalizingly close he was to its discovery is evident from his following statement:

> All the characters . . . which are transmitted in a perfect state to some of the offspring and not to others, such as distinct colors, nakedness of skin, smoothness of leaves, absence of horns or tail, additional toes, pelorism, dwarfed structure, etc., have all been known to appear suddenly in individual animals and plants. From this fact, and from the several slight, aggregated differences which distinguish domestic races and species from each other, not being liable to this peculiar form of transmission, we may conclude that it is in some way connected with the sudden appearance of the characters in question.

And yet, de Vries, the pioneer student of mutation, contrasted the mutational variability with the ubiquitous continuous hereditary variation, which Darwin believed to represent the raw materials with which natural selection operates.

De Vries dealt with mutations so sharply distinct from the parental form that he believed them to be new biological species. Mutationism was construed not as an integral part of, but as an alternative to Darwinism and Mendelism. The work of T. H. Morgan and his school at last resolved the puzzle. Mutations come, so to speak, in all sizes, from so drastic ones that the mutants are inviable, to so slight ones that a very keen eye or a statistical refinement is needed to detect them at all. No matter how drastic a mutation may be, it does not create a new species (except for the special case of doubling the chromosome complement in some otherwise sterile hybrids between distinct species). All the numerous mutants observed in *Drosophila* flies still belong to the same species in which they have arisen. Mutants do, however, possess all the characteristics which seem requisite in the materials from which natural selection could compound species differences. They are hereditary variants that cannot be swamped by blending with the ancestral form, but they can become more and more frequent if they are favored by natural selection and can eventually replace the ancestral form. Hardy and Weinberg showed independently, both in 1908, that the Mendelian mechanism tends to preserve the variant genes in the population, from one generation to the next, with constant frequencies, unless they are either eliminated or multiplied by natural selection.

The stage was now set for further advances. Chetverikov in 1926 had sketched the outlines of what has more recently come to be called the biological, or synthetic, theory of evolution (an English translation of Chetverikov's classic was published in the *Proceedings* of the American Philosophical Society in 1961). Fisher (1930), Wright (1931), and Haldane (1932), largely independently of each other and unacquainted with Chetverikov's contribution, gave more rigorous mathematical formulations of the basic tenets of the theory. This was unprecedented in biology—a theory was deduced mathematically from a single fundamental premise—Mendel's law of segregation. Some additions and elaborations, but no basic changes were made in this deductive theory for about thirty years. The mathematical theory has, however, far outstripped its biological foundation—again for the first time in the history of biology. Significant developments since Haldane-Wright-Fisher halcyon days were generalizing works which examined the factual data accumulated in several biological disciplines, and found that those data make sense in the light of the deductive theory. Mayr, Simpson, Rensch, Schmalhausen, Stebbins, Darlington, White, Ford, and Grant are the outstanding names among the founders of the modern biological theory of evolution. This theory has also been named "synthetic." It is synthetic, in the sense that it embodies a synthesis of data from biology as a whole. The word "synthetic" may, however, also mean artificial or factitious, as contrasted with genuine, and this makes the designation "biological" preferable in my opinion.

III

In Mendelian terms, the process of organic evolution can be described as a sequence of substitutions in consecutive generations of some genes for others. Genes, let it be noted, are carried mostly, though not exclusively, in the chromosomes, and a definition of evolution must accordingly be framed to include the chromosomal and the cytoplasmic heredity. This definition is satisfactory as far as it goes, but it does not go far enough. It describes adequately only the elementary components, and not the way the components compose the evolution. The definition is reductionist, and it needs a compositionist counterpart, to use the expression suggested by Simpson (1964*a*). For evolution is not only substitution of independent components; it is also integration of the components to form adaptively coherent systems. My favorite analogy is that genes act not like solo players but more like members of a symphony orchestra.

The origin of strains of bacteria resistant to antibiotics can serve as a paradigm of elementary evolutionary events which are experimentally reproducible. The origin of insect populations resistant to pesticides is less easily reproducible but equally clear. What is involved is adaptation of organisms to man-made environmental factors. Antibiotic-resistant bacteria and insecticide-resistant insects can live in environments in which bacteria and insects ordinarily do not live. The adaptation occurs through a mutation-selection mechanism. Mutation is a change in a gene, or in a chromosome which carries the genes. It is adaptively ambiguous; i.e., mutations arise regardless of whether they will be useful or harmful to their carriers, and a great majority of mutations are in fact harmful. Mutation is not evolution, but, as pointed out above, it supplies the raw materials from which evolution can be built in response to challenges of the environment. The builder is natural selection.

Mutant bacteria resistant to antibiotics, and insects resistant to insecticides, arise in the species whose genes are capable of producing these mutants, irrespective of whether antibiotics or insecticides are present or absent in the environment. A bacterial culture containing many millions or billions of cells, or an insect population of many millions of individuals, would usually include a few resistant variants. Resistant variants have no advantage, and they are likely to be at a disadvantage in survival and reproduction, in environments free of antibiotics or insecticides. Natural selection not only does not increase their frequencies in the bacterial cultures of the insect populations, but keeps the frequencies down. The situation changes when the antibiotics or insecticides arrive on the scene. What was disadvantageous becomes advantageous, and it may be the only form able to survive. The nonresistant forms fail to be perpetuated, and the resistant ones take their place. The speed of the replacement depends, of course, on how great the respective advantages and disadvantages are. It may be that, at high concentrations of an antibiotic or an insecticide, only the resistants survive and all the sensitives are killed. The change is accomplished in one generation. On the other hand, one form may produce 100 offspring in an environment in which the other produces only 99. The replace-

ment by natural selection will then take many generations. It is nevertheless important to know that, given enough time, natural selection will be effective even when operating with small fitness differences.

Another kind of experimentally reproducible genetic changes should be mentioned. A form of natural selection, called balancing selection is particularly important in higher organisms. It leads not to replacement of one gene by another but rather to maintenance of both. Contrary to what some geneticists liked to think, natural selection does not usually establish some kind of an optimum genetic endowment shared by all members of a species, but rather sustains a genetic diversity. The population becomes polymorphic, consisting of two or more genetically distinct kinds of individuals. Human populations, like those of most sexually reproducing organisms, are highly polymorphic; so much so, that no two individuals, identical twins excepted, are at all likely to have the same genotypes, complements of genes.

The two most interesting kinds of balancing selection are the heterotic and the diversifying. Heterotic selection occurs when the heterozygote, the genotype having two variants of the same gene or gene complex, enjoys hybrid vigor, heterosis, compared to the homozygotes, carrying the same gene in double dose. Diversifying selection depends on the complexity of the environment. Suppose, for example, that there are two kinds of food available, and two genotypes, one of which thrives better on one and the other on the other food. In human societies there may be different occupations or professions which are most congenial to, or which can be performed most successfully by, carriers of different genotypes. Natural selection will, then, tend to make each kind of genotype reach a frequency in the population conforming to the prevalence of the respective foods or opportunities.

In many species of *Drosophila* flies, the populations in their natural habitats are polymorphic for the structure of their chromosomes. Some individuals have chromosomes differing from others by inversions of blocks of genes. The chromosomal variants interbreed freely. The chromosomal polymorphism is maintained by heterotic balancing selection. The highest fitness is found in flies which have the two chromosomes of a pair different in structure (heterozygotes), while flies with pairs of similar chromosomes (homozygotes) are inferior in fitness. The exciting thing is that the selection pressures acting on these naturally occurring variants are so great that the natural selection can be reproduced and measured in the laboratory. We can make experimental populations, maintained in special cages made of wood or of plastic, and observe the chromosomal variants change in frequencies from generation to generation, until they reach stable equilibria. The selection is not only strong, but exquisitely responsive to environmental changes. Two chromosomes found in the populations of *Drosophila pseudoobscura* in the western United States give a heterozygote which has a fitness more than twice that of one of the homozygotes, in the experimental populations kept at 25°C and fed on a certain food. Lowering the temperature by only 9 degrees, to 16°, makes these heterozygotes and homozygotes identical in fitness, within the limits of precision of the experimental technique. Altering the food on which the populations are kept also produces considerable changes in fitness relationships.

IV

Natural selection is often compared, especially in popular writings, to a sieve. It retains the useful genetic variants, and lets the harmful ones become lost. So crude a mechanical analogy is of limited usefulness. It does fit the simplest situations, like the selection of antibiotic-resistant and insecticide-resistant strains, or the elimination of hereditary diseases and malformations which many mutations produce. These elementary processes are repeatable, predictable, and reversible, at least in principle. Provided that mutations resistant to streptomycin are produced in a species of bacteria, exposing to streptomycin a number of bacterial cells large enough to contain at least one mutant makes it very probable that a streptomycin-resistant strain will be obtained. Conversely, placing a streptomycin-resistant strain on a nutrient medium without streptomycin encourages the selection of mutants reverting to the original form.

The sieve analogy is less appropriate to describe balancing natural selection. Here the "sieve" would have to be so contrived that it will retain genetic variants when they are rare and remove them when they become frequent. Adaptation to heterogeneous environments is most readily achieved by genetic diversity. Genetic diversity, polymorphism, raises a new problem, to which the sieve analogy is irrelevant. This is mutual

adjustment, coadaptation, of constituents of a genetic system. Let me reiterate that the analogy most appropriate to describe the gene action in ontogeny, the development of an individual, is a symphony orchestra. The ontogeny, from fertilization to birth, adulthood, and death, is not a sequence of independent gene effects following each other, but a marvelously well-integrated system of feedbacks. To be adapted to an external environment, the components of a genotype must be internally coadapted, i.e., must fit harmoniously together. A gene, *A*, may interact favorably with *B* but not with *C*; natural selection will favor *A* if it arises in a genotype containing *B*, and will discriminate against *A* if it arises with *C*.

This has important consequences. Evolutionary changes depend on the changes that preceded them, and condition the changes that follow them. The role of the environment in evolution is now seen in a new light. In the origin of antibiotic-resistant strains the environment is the determining factor. In the presence of an antibiotic, the bacteria must either become resistant or be destroyed. Even here, it appears that the organism has a certain amount of "freedom"—there are several genes, any one of which may mutate to produce a resistance. With genetically more complex changes, the environment can only be described as presenting challenges, to which the organism may respond by any one of the many possible adaptive reconstructions. Which response will actually be given depends on the genetic materials which will happen to be available when and where the challenge is to be met.

Another consequence is the so-called "law" of irreversibility of evolution. As pointed out above, the elementary evolutionary events, sometimes called microevolutionary, such as the mutation-selection episodes yielding the antibiotic-resistant bacterial strains, are reversible. Not so with macroevolutionary processes. The changes which led to the origin of mankind from its pre-human ancestors are irreversible. The reason is that the series of consecutive changes which took place in, presumably, thousands of genes are infinitely unlikely to be retraced in the same sequence in which they occurred before. By the same token, they are unlikely to be re-enacted. Microevolution is repeatable; macroevolution is unrepeatable. In recent years this matter has been debated in connection with the speculations concerning the likelihood of existence elsewhere in the universe of living beings, including humanoids resembling those on earth. Dobzhansky (1960) and Simpson (1964*a*) have discussed the problem in more detail. Very briefly, even assuming that some sort of life arose in many places in the cosmos, it seems highly improbable that it would evolve into anything resembling the creatures met with on earth. Those who hold the contrary opinion, usually argue that the adaptive features of the living beings fit remarkably the demands of the environment. This is true, but beside the point. The problem of becoming adapted to a given environment can be "solved" in evolution usually in many different ways. It cannot be lightly assumed that whenever a "solution" is possible it will in fact be achieved. Microevolution is deterministic, macroevolution is creative. The results of a creative process are uncertain—it may succeed or fail.

Experimental evidence bearing on macroevolution must, of necessity, be indirect. We cannot re-enact the evolution of the horses during the Tertiary, or the emergence of the land-dwelling from the water-dwelling vertebrate animals. At best, experiments can be made on complex kinds of microevolutionary changes, for which I have suggested the designation "mesoevolution" (Dobzhansky, 1954). Two examples of such experiments can be briefly reviewed here. In both of them the chromosomal variants of *Drosophila pseudoobscura* are utilized as materials. As mentioned above, these variants are maintained in natural populations of this fly by the heterotic balancing selection. Now, the cultures in which the flies are kept in laboratories have environments obviously not identical with the natural ones. The laboratory flies are maintained either in culture bottles, or in the population cages mentioned above. Natural selection taking place in these highly artificial, or if you wish unnatural, conditions makes the flies progressively more fit to live in the respective laboratory environments, the culture bottles or the population cages.

Suppose, then, that one has strains of two chromosomal variants, *A* and *B*, which have lived for a series of generations in culture bottles, and other strains which lived in population cages. Strickberger (1963) made two kinds of experimental population cages; in the first kind, the *A* parents were from bottles and *B* from cages, and in the second *A* from cages and *B* from bottles. The equilibrium frequencies which the chromosomes *A* and *B* attained in the experimental populations were different; *A* chromosomes were less frequent, and *B* more frequent, in the first than in the second kind of population. The

difference persisted generation after generation. The chromosomes had their histories, as it were, inscribed in their genes.

The evolutionary histories of natural populations which live in territories with different climatic and other conditions are also "inscribed" in their genes, in the sense that such populations become different races, each adapted to its environment. The chromosomal types, which we have denoted above as *A* and *B*, often occur in the populations of different territories. Experimental laboratory populations containing *A* and *B* may be arranged in two ways. In experimental populations of geographically uniform origin the chromosomes *A* and *B* are descended from wild ancestors collected in the same locality; in populations of geographically mixed origins the chromosomes *A* come from one locality and *B* from another. Dobzhansky and Pavlovsky (1953) and Dobzhansky and Spassky (1962) found an interesting difference between the behavior of the populations of uniform and of mixed origins. The results obtained in populations of geographically uniform origin are repeatable and predictable; if one arranges several replicate populations with flies from the same cultures, and keeps them in the same controlled environment, all the populations reach, within the limits of experimental errors, the same equilibrium frequencies of the chromosomal forms. Scientists take it almost for granted that well-executed experiments should be repeatable; if a repetition fails to yield the same result as obtained formerly, one looks for undetected flaws in the experimental procedure. And yet, replicate experimental populations of geographically mixed origins often reach quite diverse equilibrium frequencies of the chromosomal forms.

This, at first sight, complex and confusing situation has a simple explanation. Assume that two geographic areas are inhabited by populations differing in n genes. Mendelian segregation and recombination in the progenies of hybrids between such populations may produce as many as 3^n different genotypes. If n is in tens, not to speak of hundreds, the numbers of potentially possible genotypes become vastly greater than the numbers of individuals in any experimental or natural populations. In other words, many potentially possible genotypes will not in fact be formed. Consider now the situation presented by several replicate experimental populations. The genotypes which will arise will usually not be the same in any two populations. How will natural selection act in these circumstances? It will encourage the propagation of whatever favorable genotypes will happen to present in any given population. Replicate populations give therefore dissimilar and diverging results. We observe, in miniature, what we called above the creativity of the evolutionary process. The "problem" of becoming adapted to a given environment may be solved in a variety of ways.

V

According to Wald (1963), "living organisms are the greatly magnified expressions of the molecules that compose them." This trenchant aphorism is, of course, a restatement of the organism-the-machine theory of Descartes. But as Wald himself said on another occasion (Wald, 1958),

> Confronting any phenomenon in living organisms, the biologist has always to ask three kinds of questions, each independent of the others: the question of mechanism (how does it work?), the question of adaptation (what does it do for the organism?), the twin questions of embryogeny and evolution (how did it come about?).

The first kind of questions call for Cartesian, reductionist; the other kinds for Darwinian, compositionist, answers (Dobzhansky, 1964; Simpson, 1964*b*). Organisms do not arise by accidental conflux of molecules. The creatures that are alive today are the products of unbroken sequences of patternings of molecular components; these sequences extend back to the origin of life, two or more billion years ago. Every generation involves formation and dissolution of a pattern, but the consecutive patterns are not independent. They are products of accumulation and storage of genetic information. Natural selection is a cybernetic process which transfers the information concerning the state of the environment to the genotype.

Already Darwin grappled with the difficulty that the formation in evolution of complex organs, such as the vertebrate eye, seems an improbable event. A few years ago, one of the outstanding living mathematicians sent me a long and closely argued private letter, in which he urged that a combination of many gene mutations adding up to such an organ is so absurdly improbable that we have to suppose that organic evolution is guided by a deity. I cannot gainsay his mathematics, but biological mathematics is at best only as valid as the biological assumptions on which they rest. The assumption implied in his argument was

that, in order that an organ be formed, numerous mutants must arise and all come together in one place at the same time. This is, indeed, too far-fetched to credit. But it is the assumption that is at fault. Natural selection was working in a long succession of generations; it was not aiming to build the organ or the body which we now observe in a state of relative perfection; it was acting to modify the structures and the functions of a succession of ancestral organs and bodies in accord with the challenges coming from the ancestral environments.

The argument is out of focus also in another way. It tries to envisage the evolutionary development, the phylogeny, as though it were an individual development, an ontogeny. An individual begins as a single cell, a fertilized ovum, and proceeds to develop through a complex series of maneuvers. Body structures and functions that are formed fit together as if planned by some foresight for the purpose of making a body which can live in a certain environment. Ontogeny seems to be attracted by its end rather than impelled by its beginning. This is an astounding thing for a pile of molecules to do, and Sinnott (1950–1957) sees himself forced to assume that the development is governed by a psyche, a new name for the old vital force. This misrepresents both the ontogeny and the phylogeny.

Individual development is understandable only as part of the phylogenetic development of the species, not the other way around. The ontogeny follows a certain course, because it is a part of a cyclic (more precisely, a spiral) sequence of the developments of the ancestors. Organs in a developing individual are formed for future uses, because in evolution they were formed for contemporaneous utility. The development of an individual may be said to end in death; a better way of understanding it is to say that it continues in the progeny. It is a part of the process of the storage of genetic information which continues through time. Ontogeny may be likened to building an automobile or some other complex machine on an assembly line. The automobile is not being used while on the assembly line, it is being prepared for future uses. Phylogeny is more like the gradual derivation of the present automobile models from the primitive ones, and eventually from coaches, chariots, and pushcarts. Natural selection performs the role of the engineer—it devises both the ways to improve the models and the techniques of manufacturing them.

VI

In discovering the genes, Mendel has, without knowing this, furnished the keystone of the arch which Darwin was building. With "blood" heredity, biological evolution would, at best, be exceedingly slow and inefficient; with gene heredity, evolutionary mechanisms are comprehensible. In turn, the theory of biological evolution is the keystone of the evolutionary world view. However, it is useful to be reminded that the cosmic and the cultural evolution theories were arrived at before the biological one. The nebular hypothesis of Kant (1755), Herschel (1791) and Laplace (1796) antedates the biological theory of Lamarck (1809), and the uniformitarian geology of Hutton (1795) and Lyell (1830) comes before *The Origin of Species* of Darwin (1859). The rise of the evolutionary view of man is less easy to date. Condorcet's (1793) inspired vision of the ten periods of historical development of mankind was clearly evolutionistic. Herder's *Ideas of the Philosophy of the History of Humanity* (1784) leads the way to the evolutionary speculations of Fichte (1806) and to Hegel's *Philosophy of History* (1837).

Evolutionist world views consider the inorganic, the organic or biological, and the human or cultural evolutions as integral parts of a universal evolutionary development. On the other hand, some people have objected that biological evolution is an extension of the inorganic, and human evolution an extension of the biological, only in a chronological sense. Is it legitimate to use the word "evolution" for such disparate processes? I believe that it is legitimate, and yet the objection contains a kernel of truth and deserves consideration. The elementary components of the biological evolution are mutations, changes in the hereditary materials. Mutation presupposes heredity, and heredity is self-reproduction, or self-copying, of certain molecular patterns, which exist only in living systems, and which are, in fact, the chief characteristics of life. These carriers of genetic information are the nucleic acids and, secondarily, proteins. Furthermore, the process of mutation supplies only the genetic raw materials, from which evolutionary developments may or may not be constructed by natural selection, Mendelian recombination, and other processes.

Natural selection is predicated on mutation and self-reproduction, and hence on life. To apply the term "mutation" on the human level to novel

ideas and inventions, is to use a vivid but rather misleading analogy. The same must be said concerning "natural selection" of physico-chemical processes in the inorganic nature, which supposedly led to the origin of life on earth. To have natural selection, life must already be present, because natural selection is differential reproduction, and reproduction is a basic characteristic of life. Culture is learned behavior which is shared by members of a human group. In nonhuman animals only barest traces of such behavior can be found. Culture is not inherited biologically through some special genes; it is learned, i.e., acquired, by every individual in every generation. Acquired biological traits are not inherited; all the so-called cultural inheritance is, on the contrary, acquired.

Inorganic, organic, and human evolutions occur in different dimensions, or on different levels, of the evolutionary development of the universe. The changes in the organic evolution are more rapid than in the inorganic. Nevertheless, the inorganic evolution did not come to a halt with the appearance of life; organic evolution is superimposed on the inorganic. Biological evolution of mankind is slower than the cultural evolution; nevertheless, biological changes did not cease when culture emerged; cultural evolution is superimposed on the biological and the inorganic. The evolutionary changes in the different dimensions are connected by feedback relationships.

The attainment of a new level or dimension is, however, a critical event in the evolutionary history. I propose to call it evolutionary transcendence. The word "transcendence" is obviously not used here in the sense of philosophical transcendentalism. I am using it in the same sense as Hallowell (1960): "The psychological basis of culture lies not only in a capacity for highly complex forms of learning but in a capacity for transcending what is learned, a potentiality for innovation, creativity, reorganization and change." Erich Fromm (1959) wrote that man "is driven by the urge to transcend the role of the creature," and that "he transcends the separateness of his individual existence by becoming part of somebody or something bigger than himself."

Dubos (1962) said that "what is still so completely mysterious as to acquire for many human beings a mystical quality, is that life should have emerged from matter, and that mankind should have ever started on the road which so clearly is taking it farther and farther away from its brutish origin." This is just as mysterious, but I hope no more so, as is the ability of life to continue amidst hostile environments. Cosmic evolution went beyond the range of inorganic processes when it produced life. The origin of man was a transcendence of biological evolution, because it opened up a new range of potentialities, of processes and events, which occur exclusively in man or under the influence of man. These fateful transcendences are not, however, beyond hope of understanding. They may be envisaged as extreme cases of evolutionary innovation, lesser examples of which are also known. A quantitative difference may, to be sure, be large enough to appear as a qualitative one. The origin of terrestrial vertebrates from fishlike ancestors opened up a new realm of adaptive radiations in the terrestrial environments, which was closed to water-dwelling creatures. The result was what Simpson (1953) has called "quantum evolution," an abrupt change in the ways of life as well as in the body structures. Domestication of fire and the invention of agriculture were among the momentous happenings which opened new paths for human evolution. In a still more limited compass, the highest fulfillment of an individual human life is self-transcendence.

Rough stone tools have been found in association with australopithecine remains both in east-central and in South Africa. *Homo erectus* in China is the oldest known user of fire. The Neanderthalians were burying their dead. These are evidences of humanization. Some animals, birds, and even insects are known occasionally to use objects as tools, but intentional manufacture of a tool is a sign of a psychic organization known to exist in man alone. All animals die, but man alone knows that he will die; a burial is a sign of a death awareness, and probably of the existence of ultimate concern. The ancestors of man began to transcend their animality perhaps as early as 1,700,000 years ago. The process is under way in ourselves. Nobody has characterized this process more clearly than Bidney (1953):

> Man is a self-reflecting animal in that he alone has the ability to objectify himself, to stand apart from himself, as it were, and to consider the kind of being he is and what it is that he wants to do and to become. Other animals may be conscious of their affects and the objects perceived; man alone is capable of reflection, of self-consciousness, of thinking of himself as an object.

And according to Hallowell (1959):

> The great novelty, then, in the behavioral evolution of the primates, was not simply the development of a cultural mode of adaptation as such. It was, rather, the psychological restructuralization that not only made this new mode of existence possible but provided the psychological basis for cultural re-adaptation and change.

To an orthodox reductionist, the concept of evolution transcendence may sound faintly vitalistic. A similar view has, however, been arrived at by the simon-pure dialectical materialists in Russia. Despite his Marxist jargon, Present (1964) states it fairly clearly as follows:

> Wherever it arose, the human society must have come from the zoological world, and it was work, the process of production, that made man human. However, what has removed people from the animal way of life and gave a specificity to their (new) life, became the essence and the basis of the history that ensued. . . . Likewise, in the realm of living nature, what removed the novel form of material motion from its nonliving prehistory, necessarily became its essence, its fundamental basis.

Reductionism is not wrong, but it tells only a part of the story. Where man is concerned, it is only a small part. Reductionism must go hand in hand with compositionism, Cartesian with Darwinian inquiry and discovery.

VII

Mendel, a peasant's son, found an opportunity for his intellectual pursuits only behind a monastery's walls; Darwin, a wealthy English country squire, made the study room in his house his laboratory. Neither of them was a professional scientist, and unknown to each other (Mendel read some of Darwin's books probably after his own biological work was finished), they collaborated to lay the foundations for an evolutionary world view. The universe, life, a man, are evolving products of evolutionary developments.

It is often alleged that Darwin's evolution theory has rendered complete man's alienation from the world which he inhabits. Copernicus and Galileo showed that man is not the center of the world, and that the earth is but a speck of dust in the cosmic spaces. Before Darwin, man was believed to be only slightly "lower than the angels," Darwin showed that he is only slightly higher than brute animals. And animals are, to consistently reductionist biologists, automata only slightly more complicated than watches, and perhaps less complicated than some electronic computers. All this misses the main point. Evolution means that, whether one considers the present state of the world and of man satisfactory or otherwise, it is not necessarily fixed and unchangeable forever. It is at least thinkable that man may recast the whole situation in a direction which he believes to be good, even though a long time and much effort may be needed to accomplish the reform. Evolutionist world views range from deeply pessimistic to brightly optimistic ones.

To Sir Julian Huxley, H. J. Muller, Sir Charles Galton Darwin, and others, mankind is headed for biological twilight, unless something is very quickly done to rescue it. And what will a world without man be worth? The development of culture and civilization has brought about an unpremeditated reversal of the trend of the biological evolution from beneficial to nefarious. Mankind evolved as it did because natural selection fostered improvements of the genetic basis for intelligence, group solidarity, cooperation, and, so it is believed, for human ethical values. Civilization has tended increasingly to frustrate and pervert the action of natural selection. Many kinds of hereditary infirmities and weaknesses are cured or relieved by ministrations of the medical arts; the carriers of genetic defects are helped to survive and to reproduce, thus increasing the incidence of the same defects in future generations. Living in dense populations, particularly in crowded cities, may have also more subtle but sinister effects. When nuclear families and even individuals must be sufficient unto themselves, instead of mutual help being enjoined on all by custom, natural selection which in the past favored altruism may now favor selfishness.

The way out is an eugenic selection of desirable types. One must begin, with all deliberate haste, to collect and preserve in deep-frozen condition the semen of eugenically approved donors, particularly of great and illustrious men. This will be utilized for artificial insemination of numerous women. Eventually techniques should be developed to obtain and preserve also the egg cells of superior women. Even more ambitious methods may be possible in the future. Sir Charles Galton Darwin thinks, however, that the willingness of people to regulate their procreative activities taking in consideration the common good is itself a genetic trait. If so, those who fail to heed such considerations will outbreed those who do, and their uncooperativeness will grow more and more frequent in future generations. A human flood,

rising higher and higher, will overwhelm a multitudinous but degenerate mankind. The "next million years" will see the eclipse of the human species.

The evolutionary world view of Teilhard de Chardin is in a different key.[1] Its consideration must, unfortunately, begin with a refutation of the author's statement in the first paragraph of the Preface to his most widely read book (1959: p. 29): "If this book is to be properly understood, it must be read not as a work on metaphysics, still less as a sort of theological essay, but purely and simply as a scientific treatise." Read as a scientific treatise, it is equivocal, as has been pointed out by scientific reviewers, sometimes in needlessly scathing ways. Teilhard was a Christian mystic, who happened to be also a scientist, a metaphysician, and a poet. This can be seen in his other books (e.g., Teilhard de Chardin, 1960, 1964), which expound the same evolutionary world view as *The Phenomenon of Man*, without claiming to be purely and simply scientific treatises. However, it is sheer misunderstanding to see in Teilhard's writings attempts to derive his religious beliefs from, or to prove them by, his science. What he is trying to do is rather to include his science in his total world view, which is basically a religious one. Such an attempt is of interest to scientists. We have heard a great deal in recent years about the divorce of the two, or several, "cultures," about science being a "glorious entertainment," etc. Teilhard attempts to effect a reunion.

Teilhard's basic insight is that the cosmic, biological, and human evolutions are not only components but are developmental stages of a single process of universal evolution. This single process has a discernible direction. It has advanced from matter, to life, to thought. Teilhard's extrapolation anticipates further advances, to the coming "mega-synthesis" and to the "Omega point." A difficulty arises because of his unfortunate use of the word "orthogenesis" to describe the directionality of the organic evolution. The directionality is indisputable. We do not know what the primordial life was like, but it must assuredly have been represented by some very simple forms. More complex organisms developed later. Land plants appeared in the Silurian period, land animals in the Devonian, first mammals in late Triassic and early Jurassic, first primates in Paleocene, hominids in late Pliocene or early Pleistocene. However, orthogenesis was not simply a word describing the fact of directionality, but a now almost defunct hypothesis pretending to explain the causation of this directionality. It postulated that evolutionary changes are the unfolding or manifestation of preexisting rudiments. Evolutionary changes are predetermined, in the same way that ontogenetic changes, from embryo to adult to death, are predetermined. The comparison between ontogeny and phylogeny is, to believers in orthogenesis, more than a simple analogy. It is envisaged as a causal similarity.

This is inconsistent with Teilhard's basic view that the organic as well as human evolution proceeds by "groping" (*tâtonnement*). Groping is "pervading everything so as to try everything, and trying everything so as to find everything." Ontogeny and orthogenesis do not try anything, because they move in a straight line toward a predetermined end result. The "grouping" leads to a succession of "layers" (*nappes*), of progressively more complex levels of organization of matter, of life, and of thought. This is neither orthogenesis nor vitalism. Mendelian recombination of genes is the way, on the biological level, of "pervading everything so as to try everything," i.e., to try out as many genotypes as can be formed. Teilhard did not know that the numbers of potentially possible genotypes are far greater than the numbers of individuals in which they can be realized and exposed to natural selection. "Trying everything so as to find everything" is a splendid metaphorical description of the operation of natural selection.

Teilhard was sceptical concerning the competence of natural selection to arrive at evolutionary "inventions." This seemed to him relying too much on "chance." He did not realize that natural selection is not building perfect organisms out of piles of unrelated genes; selection acts on a succession of parental and descendant generations modifying the organisms to fit their environments. Any orthogenetic theory of evolution postulates preformation; all that happens was bound to happen; man and animal and tree were equally present in the primordial life, and it just took time to have them gradually emerge from their hidden to their manifest state. This is completely contrary to Teilhard's basic philosophy of universal evolution being a creative

[1] In the Introduction to the English translation of Teilhard's *The Phenomenon of Man* (1959), Sir Julian Huxley claims that Teilhard's ideas are mostly similar to those published earlier by himself. This is true only in so far as both authors are, of course, evolutionists. Beyond this, their ways of thinking are almost at polar opposites.

process, not just an unveiling of what was there all the time in a concealed state. Creation implies the risk of miscreation, and Teilhard envisaged the possibility of the evolution being a failure: "There is a danger that the elements of the world might refuse to serve the world—because they think; or more precisely that the world should refuse itself when perceiving itself through reflection." Having been a palenotologist, Teilhard was familiar with the phenomenon of extinction of phyletic lines. Believers in orthogenesis assume that the cause of extinction is a "senescence" of the phyletic line, predetermined by the organization of the latter in much the same way as the senescence and death of an individual organism. Predetermination is foreign to Teilhard's thinking. If all that happens in evolution is a long strip-tease act, all evolution becomes meaningless. Why should there be such a delay in reaching the state of final perfection? This, together with the problem of the existence of evil in the world, would vitiate any attempt to build a theodicy, an understanding of the meaning of God's creative activity, which is in the center of Teilhard's whole thought. Evolution is meaningful only if it involves creativity and freedom. Extinction is comprehensible because evolution is, to use Teilhard's metaphor, "groping" in the dark, among dangers and pitfalls. Extinction is a consequence of becoming irrevocably adapted to environments which do not last.

Despite the dangers and pitfalls, evolution has been, on the whole, a success rather than a failure. It has achieved the two great transcendences, the origin of life and the origin of man. In this article, which has attempted to trace the directions in which Mendel's work has led evolutionary biology, it would be out of place to discuss Teilhard's extrapolations that the evolution will eventually reach the transcendences of the "mega-synthesis" and the "Omega." It is perhaps appropriate to conclude in Teilhard's words:

> The outcome of the world, the gates of the future, the entry into the super-human—these are not thrown open to a few of the privileged, nor to one chosen people to the exclusion of all others. They will open to an advance of *all together*, in a direction in which *all together* can join and find fulfillment in a spiritual renovation of the earth. . . .[2]

[2] Somewhat similar ideas were a part of the creed of the Tientai (Tendai) sect of Buddhism, which arose in China in the sixth century A.D. One of the tenets of this sect was that all human souls, and even all that exists, will eventually rise to the dignity of Buddha himself (*cf.* Anesaki, 1963).

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MENDEL AND HUMAN GENETICS

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(Read April 23, 1965, in the Symposium Commemorating the Publication of Gregor Mendel's Pioneer Experiments in Genetics)

MENDEL left no records concerning studies in human genetics. His biographer Iltis, however, states that Mendel had shown persistently great interest in hereditary phenomena in man and in anthropological and medical problems. He studied the records of old Brünn families for aspects of inheritance and, in his own kindred, made careful observations of peculiarities in hair form, hair color, and body size in successive generations. Regularly he took measures of body dimensions of his growing nephews and he often attended autopsies in a hospital. Had Mendel's time not gradually been completely absorbed by his duties as abbot of his monastery, it might be surmised that he would have reported on his observations on man, expanded them and, with the insight gained from his experiments on peas, been able to clarify problems of human inheritance in such a way as to be counted a direct founder of human genetics. But it hardly changes the situation that Mendel did not make a specific contribution to that field. His basic discoveries in plants could be applied to man without requiring new insights.

Human genetics had a slow growth. This has been ascribed to the difficulties which man with his long life span, his small families, and the absence of scientifically controlled matings offers to genetic analysis. It has also been ascribed to the dampening effect on *bona fide* research which resulted from class and race prejudice within the eugenics movement Undoubtedly both of these aspects had some influence, but perhaps most important was the fact that for decades the best minds working in genetics were interested in the general phenomena of inheritance, not in their expression in specific species. "If you want to study the genetics of rabbits," it has been said informally some forty years ago, "study rabbits. If you want to study genetics, study *Drosophila*!" Replace the word *Drosophila* for a still earlier period by pea (*Pisum*), fowl, sweet pea (*Lathyrus*), or gypsy moth (*Lymantria*), and by bread mold (*Neurospora*), colon bacterium (*Escherichia*), or bacteriophage for a subsequent one, and it becomes understandable why human genetics remained peripheral to the center of genetic advance.

Beyond such influences on the development of a field, its history may depend on extrinsic phenomena, such as the state which related areas have attained. Mendel's paper can serve as an illustration. The reason that it remained without influence for thirty-five years and then, on its "rediscovery," was immediately recognized in its importance, depended primarily on what had happened during the intervening period. This period had included the discovery of chromosomes and their behavior in cell division and gametogenesis, an intensive study of biological variation, and the formulation, by Weismann, of a conceptual framework for a theory of heredity, development, and evolution. The time was ripe for Mendelism.

One additional element should be mentioned which influences the growth of knowledge. This is the limitation of individuals and communication between individuals which leads them to recognize only slowly the significance of new findings, whether made by others or by themselves. The development of human genetics furnishes examples for such delays, as will be shown in the following pages.

There are many interweaving threads in human genetics. A few main strands will be followed here in artificial separation from one another. The discussion will halt at the time when human genetics became of age, at the end of the period between the two World Wars.

PEDIGREE ANALYSIS

Careful descriptions of pedigrees and the establishment of empirical rules of inheritance of specific traits preceded the recognition of Mendel's work (fig. 1, center). Already the Talmud gave evidence of knowledge concerning the mode

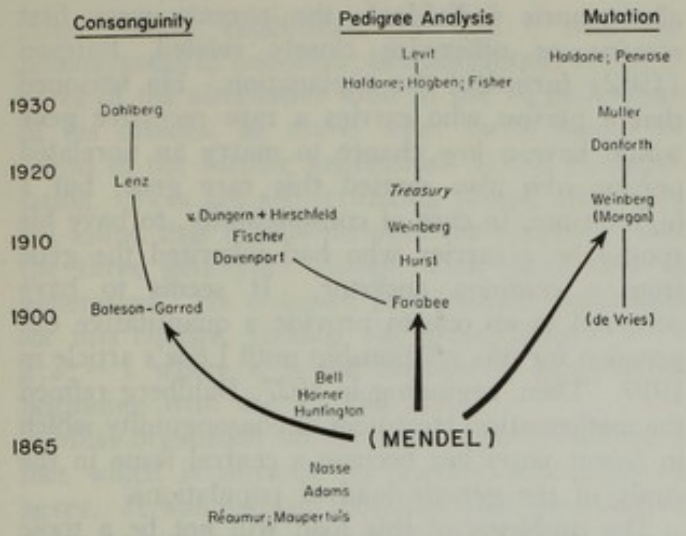

FIG. 1. Trends in the history of human genetics: pedigree analysis, consanguinity, and mutation. In this figure as well as in the similar figures 3 and 4, the selection of names of investigators does not lack arbitrariness. While the inclusion of persons can probably be defended in most cases, absence of names can often be excused only by the attempt not to overload these schematic presentations. Names in parentheses refer to individuals not directly concerned with human studies. The word "Treasury," in italics, refers to a specific serial publication (see Bibliography under K. Pearson, ed.).

of transmission of hemophilia,[1] and Nasse, in 1820, gave a specific formulation of it. Maupertuis and Réaumur, in the middle of the eighteenth century, each described in admirable detail a pedigree of polydactyly.[2] The discovery of red-green color blindness in an English boy (Whisson 1779) was accompanied by the realization of its occurrence in other members of his family and of its hereditary nature. This was followed by other studies of "Daltonian" color blindness and, one hundred years later, by Horner's codification of the empirical facts of transmission. In 1814 the physician Joseph Adams wrote a penetrating *Treatise on the Supposed Hereditary Properties of Diseases,* in which the modern reader can discern many of the features of both general and specifically human genetics now familiar to us. Sedgwick, in 1861, assembled extensive data "On Sexual Limitation in Hereditary Disease," and Huntington, in 1872, accurately described the mode of transmission of a hereditary chorea which now carries his name.

[1] See M. Fischer, "Zur Geschichte der Bluterkrankheit." *Eugenik* 2 (1932): 119–120.

[2] B. Glass, "Maupertuis, Pioneer of Genetics and Evolution." pp. 51–83 in *Forerunners of Darwin: 1745–1859,* B. Glass, O. Temkin and W. L. Straus, Jr., eds. (Johns Hopkins Press, 1959).

In an impressive memoir, "Upon the Formation of a Deaf Variety of the Human Race," Alexander Graham Bell, in 1883, showed the hereditary basis of many instances of deafness and emphasized the fact of preferential marriages between deaf mutes. All these studies, however, remained separate and mostly without further consequences. Even when the rules of inheritance of a trait were clearly described, no underlying causes were recognized, so that the level of the discussions rose only slightly above that of casuistics. This became different as soon as Mendel's work was rediscovered. When Garrod began to study the biochemistry of alkaptonuria and became aware of its familial occurrence, Bateson suggested that it might well be a recessive Mendelian trait (1902). A year later Farabee (1903*a*), described a Negro kindred with several occurrences of albinism as evidence for the recessive nature of this trait. During the winter of 1901–1902 Farabee had attended Castle's lectures on inheritance at Harvard University in which the latter interpreted albinism in mice as being due to a recessive allele. In 1903 (*b*) Farabee filed his doctoral dissertation, which contains a description of a large Pennsylvania kindred with brachydactyly and demonstrated convincingly that the trait followed the transmission of a dominant gene (or "character" as it still was called). Ever since, in a steady stream, innumerable pedigrees have been published, largely concerned with abnormal and medically significant traits. Variations within the normal range were likewise interpreted in Mendelian manner, eye and hair colors being the first two examples (G. C. and C. B. Davenport, 1907, 1910; Hurst 1908). A third example concerns the human A-B-O blood groups which were discovered by Landsteiner (1900, 1901). Their inherited nature was recognized by von Dungern and Hirschfeld, and a two gene-pair hypothesis was proposed. We shall return to this topic. Mendelian segregation became also apparent in racial crosses as for various anthropological traits in the Rehoboth hybrids between Caucasians and Hottentots in South Africa (Fischer), and, for skin color, in the Negro-Caucasian hybrids of Jamaica (Davenport, 1913). This was of general significance since the belief in a non-Mendelian "blending" inheritance in racial mixtures had been particularly strong.

The recording of a single pedigree or a few pedigrees for a given trait was expanded into

monographic treatments of all its known incidences. Pearson's monumental *Monograph on Albinism* (1911–1913) and the series of many volumes entitled *The Treasury of Human Inheritance* which was founded by him in 1912 and still continues publication, as well as Cockayne's *Inherited Abnormalities of the Skin and its Appendages*, furnished abundant data not only for the conclusions of their authors but also for independent investigators in need of facts.

The enthusiasm of many workers was both a boon and a danger in the early days of genetics. Hurst, for instance, the student of eye-color inheritance, was "a tireless worker and full of ideas, but over-apt to find the 3:1 ratio in everything he touched" (Punnett, 1950). Only gradually did a truly critical attitude toward pedigree studies evolve. The first one who saw the methodological problems posed by analyses of pedigrees was the physician Wilhelm Weinberg. Beginning in 1908 with a paper on the demonstration of inheritance in man, and particularly in a publication of 1912 on methods and sources of error in studies directed toward Mendelian proportions in man (1912*a*), he devised means of correcting for various types of ascertainment. The fact which had concerned Bateson (1909) and for which Garrod showed an intuitive though not explicit understanding, namely that the fraction of albinos in segregating sibships from normal parents is higher than the fraction ¼ expected from $Aa \times Aa$ crosses, became comprehensible as the necessary deviation from Mendelian expectation when it remained uncorrected for biases introduced by family selection. Little further progress in this area was made for twenty years; then Hogben (1931), Haldane (1932*a*), Fisher (1934), and others began to apply their rigorous minds to the problems of pedigree analysis. During this period also it was recognized generally that the manifestation of many genotypes varies from person to person. The bearing of incomplete penetrance on the problem of dominance in man underwent an important analysis by Levit (1936).

The knowledge of Mendelism early made possible a new interpretation of the effects of consanguinity (fig. 1, left). This age-long problem had been actively followed in the nineteenth century, with the pioneering inquiry by Bemiss (1858) deserving specific mention. Again, the facts gained remained without a rational foundation. When, however, Garrod (1901) noticed that in three out of four sibships containing alkaptonuric individuals the parents were first cousins or otherwise closely related, Bateson (1902) furnished the explanation. He reasoned that a person who carries a rare recessive gene would have a low chance to marry an unrelated person who also carried this rare gene, but a high chance, in case of consanguinity, to have his spouse be a carrier who had inherited the gene from a common ancestor. It seems to have occurred to no one to provide a quantitative expression for this relationship until Lenz's article in 1919. Then, beginning in 1927, Dahlberg refined the mathematical treatment of consanguinity which in recent years has become a central issue in the study of the genetic load of populations.

The problems of this load will not be a topic of this account, but a brief reference is indicated to the mutations which compose a highly important part of it (fig. 1, right). Mendel did not make a direct contribution to the problem of the origin of different varieties of a gene, of its alleles. On the other hand, de Vries was led to his rediscovery of Mendel's paper by his earlier studies of genetic changes in the evening primrose. Morgan, of course, who first discovered as well as analyzed mutations in *Drosophila*, came to genetics via Mendel and de Vries. The epochal success of his former student, Muller, in "Artificial Transmutation of the Gene" (1927) by means of x-rays, was used by him immediately to call attention to the possibilities of radiation-induced damage to human genes. It was not the first time that mutations in human genes had been considered by modern investigators. Weinberg, in 1912 (*b*), noted the tendency of last-born children to be more frequently affected by dwarfism than would be expected by chance. He suggested that, if more exact analysis should indeed show this to be the case, this would speak for mutation from normal to dwarfness increasing in frequency with age of the parents. Danforth, in 1923, actually estimated human mutation rates, assuming an equilibrium between mutational input and selective outgo of unfavorable genes. His pioneering paper remained without consequences and the same method had to be re-invented, in 1935, by Haldane and Penrose (see Gunther and Penrose).

POPULATION GENETICS

Mendel himself was the first who, on the basis of his particulate theory of inheritance, attacked a problem not only of the genetics of individuals and their progeny, but also of a whole population.

After having established the 1:2:1 ratio for homozygotes of one kind: heterozygotes: homozygotes of the alternative kind in the F_2 generation of his crosses, he asked what ratios would be found in the further generations of the F_2 population. Peas are self-fertilizing plants, and Mendel found that in this instance the proportions of the three genotypes change from generation to generation. He obtained an algebraic expression for this change, yielding the proportions $2^n - 1 : 2 : 2^n - 1$ where n is the number of generations beginning with the F_2 (fig. 2).

Most organisms do not reproduce by selfing, a fact which is obvious for species with separate sexes. It was natural, therefore, that the question arose concerning the proportions of genotypes in various generations of crossbreeding forms, but the way in which this came about and the slow steps by which it was answered make a fascinating chapter of genetics (fig. 3, left).

Before 1900, beginning with Galton and deepened by Karl Pearson, a biometric school had developed in England which formulated laws of inheritance of a statistical nature. Basing their work primarily on measurements of human stature, the biometricians determined correlation coefficients between groups of parents and children, and between other groups of related individuals. Galton (1897) derived from his data a "Law of Ancestral Heredity": "The two parents contribute between them, on the average one-half . . . of the total heritage of the offspring; the four grandparents, one-quarter . . .; the eight great-grandparents, one-eighth . . ., and so on." Pearson (1904) modified Galton's specific conclusions but upheld its basic tenets. It was the assumption of genetic contributions of the preparental ancestors which disturbed the Mendelians. Mendel's law of segregation centered on the

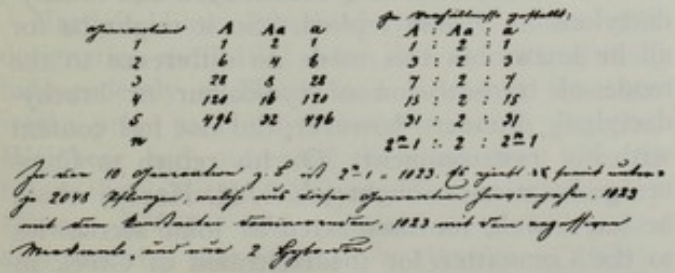

FIG. 2. Mendel's analysis of a problem in population genetics. From pages 37–38 of the facsimile of Mendel's manuscript of his "Versuche über Pflanzen-Hybriden" reprinted in L. Gedda, *Novant'anni delle leggi Mendeliane* (Istituto "Gregorio Mendel," Roma, 1956).

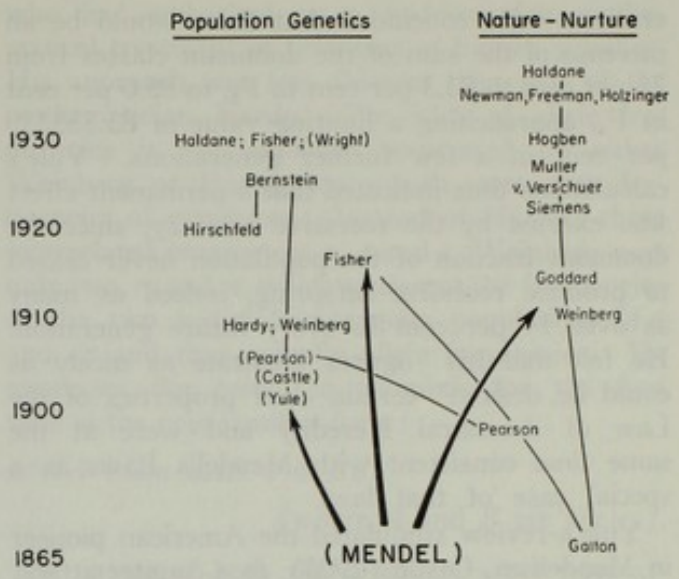

FIG. 3. Trends in the history of human genetics: population genetics, and nature-nurture.

purity of gametes. A homozygous recessive parent, even if derived from two heterozygotes, would only transmit his own recessive genes, uncontaminated with dominant ancestral influences. Likewise, a homozygous dominant parent with earlier recessives-bearing parentage would transmit only his own dominant genes, free from recessive ancestral contamination. Bateson insisted that Mendel's law of segregation and the law of "ancestral heredity" could not both be applicable to the same class of cases. The biometricians, on the other side, either felt that there was no inconsistency between the two, or that Mendelian genetics was not applicable generally. The basic conflict between Galton's and Mendel's laws led to a violent controversy in which the standard bearers were Weldon for the biometricians and Bateson for the Mendelians.

In 1902 the statistician Yule published a discussion on Mendel's Laws in which he took Weldon's side, though he was "inclined to agree with Mr. Bateson as to the *possibly* very high importance . . . of Mendelian phenomena." In his paper he correctly derived the fact that an F_2 generation would preserve its 1:2:1 ratio in all later generations, provided that random mating between all individuals took place. This was an important insight but it was lost in what followed in the same and subsequent paragraphs. Yule examined the outcome if only the dominant three-quarters of the F_2 population would be allowed to reproduce, and if the same process of selection were continued in the following gen-

erations. He concluded that there would be an increase of the sum of the dominant classes from 75 per cent to 83.3 per cent in F_3, to 85.0 per cent in F_4, approaching a limiting value of 85.355339 per cent in a few further generations. Yule's calculations thus indicated that a permanent effect was exerted by the recessive ancestry, since the dominant fraction of the population never ceased to produce recessive offspring, indeed as many as over 14 per cent in every future generation. He felt that his "figures illustrate as nicely as could be desired" certain chief properties of the Law of Ancestral Heredity and were at the same time consistent with Mendel's Laws as a special case of that law.

Yule's review stimulated the American pioneer in Mendelism, Castle (1903), to a counter-attack. Castle established once more the constancy of the 1:2:1 ratio in any panmictic generation following the F_2, but pointed out that Yule's deductions from the model of reproduction, by the dominant genotypes solely, were marred by an elementary error. He showed that the true expectation for the frequency of the first two classes together would never lead to a limiting value, but be a continuous increase from 75 to 88.8 for the first generation following selection of the dominants, to 93.7 for the second generation, to 96 per cent for the third, gradually approaching 100 per cent with continuous selection in each generation. Castle went beyond this. He found that whatever ratio of the genotypes had been reached during the generations of selection this would remain constant in future generations once selection had been discontinued. "In general, as soon as selection is arrested the race remains stable at the degree of purity then retained. . . ." Thus, he had discovered an equilibrium law not only for the 1:2:1 ratio but for the infinitely large class of all ratios resulting from selection against recessives. With this successful defense of Mendelism against Yule's position, Castle returned to his breeding experiments, little aware of the gold which he had found in the still undefined area of population genetics. His paper remained largely unnoticed. When, twelve years later, Norton provided Punnett (1915) with a table on the effect of selection against Mendelian genes and, a further two years later, Punnett (1917), with help from the mathematician Hardy, wrote a note in which he showed the slow progress to be expected from the elimination from reproduction of supposedly simple homozygous recessive feebleminded individuals, they essentially followed Castle's steps (1903) but did not know that they had a predecessor.

Within a year after Castle, and obviously without knowing of his findings, Pearson himself proved the stability of the 1:2:1 ratio in a panmictic population. He also derived the results of panmixis when more than one pair of alleles were involved but always still based on an initial F_2 generation.

In modern terms, Pearson considered only the case of equal frequency of the two contrasting alleles A_1 and A_2 (or A and a), while Yule and Castle included a series of selected frequencies. It is strange indeed that the outstanding biometrician, Pearson, did not see the need for expanding the study to all frequencies.

The matter rested until 1908. On the twenty-eighth of February of that year Punnett, one of the closest associates of Bateson, gave a lecture before the Royal Society of Medicine in London entitled, "Mendelism in Relation to Disease" (Punnett, 1908). In the discussion which followed the lecture, and which is reported in the printed *Proceedings*, Yule referred to some of the figures illustrating the Mendelian cases, which puzzled him very much.

> Assuming that brown . . . eye-colour was dominant over blue, if matings of persons of different eye-colours were random . . . it was to be expected that in the population there would be three persons with brown eyes to one with blue; but that was not so. . . . The same applied to the examples of brachydactyly. The author said brachydactyly was dominant. In the course of time one would then expect . . . to get three brachydactylous persons to one normal, but that was not so.

Now it was occasion for Punnett to be puzzled. He reworded, somewhat inaccurately, Yule's comments as "Mr. Yule wondered why the nation was not slowly becoming brown-eyed and brachydactylous . . ." and replied, "So it might be for all he knew, but this made no difference to the mode of transmission of eye-colour or brachydactyly." Punnett, however, did not feel content with his own comment. On his return to Cambridge he at once sought out G. H. Hardy, whom he knew well, for they acted as joint secretaries to the Committee for the Retention of Greek in the Previous Examination and also used to play cricket together (Punnett, 1950).

> Knowing that Hardy had not the slightest interest in genetics I put my problem to him as a mathematical one. He replied that it was quite simple and soon

handed me the now well-known formula $pr = q^2$.[3] Naturally pleased at getting so neat and prompt an answer I promised him that it should be known as "Hardy's Law"—a promise fulfilled in the next edition of my *Mendelism*.

The essence of Hardy's finding is the constancy of the distribution of the three genotypes after the second generation whatever the values of p, q and r may be, that is, whatever the frequencies of the two alleles may be. Specifically, Hardy showed through two examples that the proportion of brachydactylous persons, if the trait is dominant, will have no tendency whatever to increase, and if it were recessive, would have no tendency to decrease. It may be added that, while Hardy pointed out that he had considered only the very simplest hypothesis possible, he had actually treated, for the first time, the problem of genetic drift which was to become so important in Wright's later work. There is a postscript to Hardy's one-page note according to which Yule would accept its substance "as a satisfactory answer to the difficulty that he raised." It has been said that Nature yields answers only to correctly formulated questions. Hardy's solution to Yule's difficulty shows that wrong questions may sometimes be fruitful also.

I have wondered occasionally whether the statistician Yule's original question was asked seriously or rather with tongue-in-cheek in order to embarrass the Mendelian lecturer. Apparently this suspicion is quite unjustified. The question rather shows how a distinguished statistician could miss the general concept of allele frequencies which appeared so obvious to Hardy who could find nothing more subtle to apply to it than "a little mathematics of the multiplication-table type." Hardy's note was published *Science*. "The reason why it appeared . . . [there] is that *Nature* at that time was extremely hostile and refused to publish anything tainted with Mendelism." [4]

Hardy's Law remained known under this designation until 1943 when it was realized that, independently of Hardy and indeed at least six weeks prior to Hardy's involvement in genetics, Weinberg had presented the equivalent formula before the Society for Natural History in Stuttgart (Stern, 1943). The publication of his paper also preceded that of Hardy's (Weinberg, 1908). Weinberg came to it as a biologist and physician who had embarked on a wide-ranging mathematical treatment of problems of human genetics. His approach was less abstract than that of the mathematician Hardy. The idea of allele frequencies is not explicitly expressed by either Weinberg or Hardy, since both start with frequencies of genotypes. Instead of Hardy's three interrelated parameters p, q and r, Weinberg uses only two, m and n, which represent the frequencies of the two initial homozygous populations AA and aa and thus actually allele frequencies. He expresses the result of panmixis for the first time in the now familiar form:

$$m^2AA + 2m \cdot nAB + n^2 BB$$

(where A and B are alleles).

The names of both the discoverers are now attached to the population formula: The Hardy-Weinberg Law.

In 1909 Weinberg generalized the theorem in terms valid for multiple alleles, and investigated polyhybrid populations in which he recognized their essentially different method of attaining equilibrium. Since that time the concept of allele frequencies and the formula for equilibrium in case of panmixis in Mendelian populations have been the foundation for population genetics in general.

A very impressive application of an expanded Hardy-Weinberg formula was made by Bernstein (1924, 1925). This mathematician had earlier become interested in human genetics and had interpreted population data on variations in singing voice and direction of hair whorl as found in different populations in terms of allelic differences of single pairs of genes. His evidence consisted in a fit of the proportions of phenotypes to the $p^2 : 2pq : q^2$ expectation (where p and q correspond to Weinberg's m and n, and not to Hardy's terms). Bernstein then turned to a population genetic analysis of the frequencies of the four blood group types O, A, B and AB. Numerous records of racially variant blood-group frequencies were available, beginning with the discovery of this phenomenon by L. and H. Hirschfeld.

As noted earlier in this paper, a genetic interpretation of the blood-group variations had been given. It assumed the existence of two pairs of alleles, A-a and B-b. When Bernstein compared the expectations for the blood-group frequencies according to the dihybrid Hardy-Weinberg formula with the observed proportions, he found significant and consistent differences. He

[3] "Where p, $2q$ and r are the properties of AA, Aa, and aa individuals in the population varying for the A-a difference." See footnote p. 9 in R. C. Punnett, 1950.

[4] R. C. Punnett, Feb. 5, 1950 in letter to the author.

concluded that the blood-groups were not inherited in the hitherto accepted fashion and searched for a different interpretation. He thought of a triple-allelic system of a single locus, applied the appropriate equilibrium formula, and found excellent agreement between expectation and observation in frequencies in diverse populations. This Bernstein regarded as proof of his multiple allele theory, notwithstanding the fact that the limited amount of published pedigree data contained cases not in conformity with expectation from the theory. Later the apparent exceptions could be ascribed to various sources of error, and Bernstein's interpretation has long been fully established.

It may be permitted to record an incident which illuminates the newness and the power of the population genetics approach in the analysis of modes of inheritance. In the spring of 1933, Bernstein gave a seminar at the California Institute of Technology in which he reported on his mathematical approaches to human genetics with emphasis on blood groups. In the discussion, T. H. Morgan commented in his quizzical manner that Bernstein's approach was interesting, but could the solution not just as well have been obtained from pedigree analysis? Bernstein, as I remember it, replied that it could but that it wasn't!

Weinberg had early shown (1909, 1910) that the biometricians' Law of Ancestral Heredity was fully compatible with a Mendelian interpretation if it included significant contributions to variance of non-genetic type as well as considerations of polygenic inheritance. The latter had become famous since Nilsson-Ehle's analysis of continuous variation in the color of wheat grains, but this concept of multifactorial inheritance had been fully conceived by Mendel, who had used it to provide a tentative explanation for continuous variation in flower color as observed in the F_2 crosses between two species of beans. In countries other than England the controversy between the biometricians and the Mendelians had never played an important role. Weinberg's demonstration, therefore, made no impression on non-British geneticists and was apparently missed by the British school. Only in 1918 did an analysis by R. A. Fisher lead to a generally accepted Mendelian interpretation of the pre-Mendelian findings of Galton, Pearson, and their school. The subsequent rise of higher population genetics, beginning with the work of Haldane, Wright, and Fisher in the 1920's, cannot be a topic of this survey, even though it has exerted a fundamental influence on human genetics.

NATURE AND NURTURE

Mendel was aware of variability in gene expression due to environmental conditions, specifically as regards the flowering time of his plants. He also noted that some characters do not permit a sharp and certain separation but exhibit continuous variation. For his main studies he deliberately selected such traits as appeared in the plants "clearly and definitely," a virtue in experiments whose purpose was to clarify the basic ways of hereditary transmission. Unfortunately, it led some of his intellectual descendents to reverse the argument. They would classify in alternative ways what was not clearly and definitely distinct, and then account for the alternatives in terms of single gene pairs. Among the many examples of this procedure, one of the best known was Goddard's attempt to explain all feeblemindedness as due to a single homozygous recessive gene (fig. 3, right). We now know that such types of feeblemindedness do indeed exist, but that they make up a small minority of all afflictions of this type. Of the majority, some are caused by birth injuries, others are due to complex and poorly understood polygenic types of inheritance, still others by perhaps even more complex and poorly understood social influences which help to push an individual below the arbitrary line separating low normality from "feeblemindedness" (or "mental retardation" as contemporary nomenclature prefers to call it). Perhaps most important, there are complex and poorly understood interactions between genetic and non-genetic agents which assign a person to his place in the continuous array of mental performance.

It was the nature-nurture problem which played such an important role in Galton's early creation of human genetics in pre-Mendelian terms. In this pioneering work the influence of the environment on many traits, particularly those involving mental abilities and achievement, was clearly realized in a general way. On the other side, Galton (1908) concluded "when the nurtures of the persons compared were not exceedingly different" that under these circumstances "the evidence was overwhelming that the power of nature was far stronger than that of nurture." [5] Based

[5] A penetrating treatment of the nature-nurture problem with special reference to Galton is given in A. Weinstein, 1933.

on this conviction, Galton founded the eugenics movement, which attracted many well-meaning but often class-prejudiced adherents. When Weinberg began his population genetics work, he became the first investigator who partitioned the total variance of observed phenotypes into genetic and environmental portions and therewith reconciled the two independent doctrines in genetics originated by Mendel and by Galton (Weinberg, 1909, 1910).

Galton made use of the similarities and differences between twins to judge the relative importance of hereditary versus environmental agents in human variation. In the nineteen-twenties twin research by Siemens and von Verschuer became a widely practiced area for the study of normal and particularly of medically significant traits. The interpretation of the findings of the investigators who studied twins depended on the fact that identical twins have identical genotypes, while non-identical twins are genetically different. Since twins of both kinds are usually raised in the same home, it was often assumed that the environmental influences on pairs of identical twins were of the same degree of similarity as those on pairs of non-identicals. Additional parameters were desirable such as those provided by cases where twins had been reared apart in different homes, or where children had been adopted away from their biological parents, or where groups of children from different parents had been raised in the relatively uniform environment of an orphanage. Muller (1925) described in detail the first case of identical twins reared apart, with emphasis on mental attributes, Barbara Burks compared foster-parent—foster-child resemblance in mental scores and achievement with that of true-parent—true-child resemblance, and Evelyn Lawrence studied the children in an orphanage. This type of analysis culminated in *Twins: a Study of Heredity and Environment,* a joint work by Newman, the biologist, Freeman, the psychologist, and Holzinger, the statistician.

While such fundamental studies went on, the unscientific literature on class and race genetics, with its ultimately tragic consequences, exerted an inhibitory influence on wider participation in research in human genetics. Some of these interrelations have recently been traced by Dunn and Haller. But while many biologists stayed away from human genetics, other outstanding investigators with deep interest in the social consequences of science entered the field as scientists. They dissected unproven or false opinions, and made contributions of their own which strengthened human genetics as an objective discipline. As eminent examples of influential critics we may cite Hogben with his book on *Nature and Nurture* (1933) and Haldane with *Heredity and Politics* (1938), and both, in their research reports, as creators of new tools and concepts.

CYTOGENETICS

It was historically impossible for Mendel to have been directly involved in cytogenetic problems. When he wrote his paper in 1865 chromosomes had not yet been discovered. He did refer to the factors which were responsible for the traits he observed as cell-elements. He did establish the basic fact—although he communicated it only in two letters to Nägeli (3 July and 27 September, 1870)—that a single pollen grain is sufficient to fertilize an egg cell. And he carried out crosses involving plants with separate sexes—again reported in a letter only (27 September 1870)—whose results suggested to him that perhaps sex is inherited in a way similar to that of other segregating characters.

If Mendel had nothing to do with cytogenetics, Mendelism, of course, was one of its two pillars. Very briefly, therefore, the earlier history of human cytogenetics will be sketched here (fig. 4, left). It was Flemming, the pioneer student of mitosis, who first estimated the number of chromosomes in human tissue cells and believed it to be close to 24. This was corrected by von

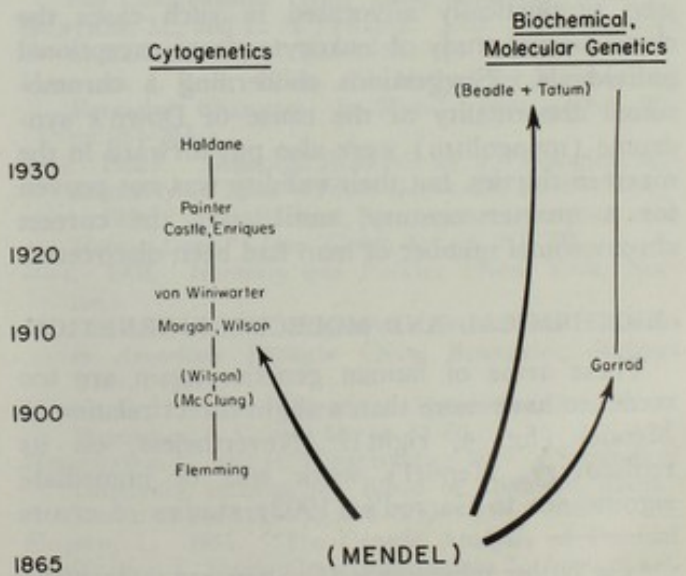

FIG. 4. Trends in the history of human genetics: cytogenetics, and biochemical molecular genetics.

Winiwarter (1912), who counted 47 chromosomes in male and 48 in female cells. Painter, eleven years later, confirmed von Winiwarter's findings except that he saw 48 chromosomes in both sexes. It is well known now that the true somatic chromosome number in man is 46, a fact established by Tjio and Levan only in 1956, well beyond the period which our survey covers.

The relation of specific chromosomes to sex determination had first been discovered in insects. It was assumed that sex chromosomes also exist in man. The uneven number of chromosomes seen in cells of the human male by von Winiwarter indicated an $XX = ♀$, $XO = ♂$ mechanism, but Painter demonstrated clearly that while women have indeed two *X*-chromosomes, men have one *X*- and one *Y*-chromosome. Morgan as well as Wilson recognized in 1911 that the type of transmission of red-green color blindness could be understood on the basis of color vision genes located in the *X*-chromosome. In 1922, Castle, and Enriques suggested that the *Y*-chromosome was the bearer of a gene for webbed toes whose transmission in a certain family seemed to follow the male line exclusively. But while the nature of the *X*-chromosome as carrier of numerous *X*-linked genes has been firmly established, the existence of *Y*-linked inheritance apart from determination of male sex is still under discussion.

Chromosomal abnormalities as causes of unusual transmission of human traits were first suspected in a family with a defect of color vision independently by T. H. Morgan and several other geneticists, among them Haldane (1932*b*)[6] who prophetically advocated in such cases the chromosomal study of leukocytes from exceptional individuals. Suggestions concerning a chromosomal abnormality as the cause of Down's syndrome (mongolism) were also put forward in the nineteen-thirties, but their validity was not proven for a quarter century, until after the correct chromosomal number of man had been discovered.

BIOCHEMICAL AND MOLECULAR GENETICS

These areas of human genetics again are too recent to have more than a slight direct relation to Mendel (fig. 4, right). Nevertheless, on its rediscovery, Mendel's work was of immediate significance to Garrod's (1902) studies of errors of metabolism in man. That these errors have a tendency to occur in more than one member of a family was apparent to Garrod in 1899 in the case of alkaptonuria, but its specific Mendelian nature was only recognized three years later. Biochemical genetics, which began with these studies on man, developed in its modern form in flies, meal moth, silkworm, and particularly the mold *Neurospora* (Beadle and Tatum). Stimulated by its concepts, human genetics reentered the field and, with its analyses of inherited variations of the hemoglobin molecules, made pioneering contributions to general molecular biology. Mendel could hardly have foreseen these developments, but there is an inkling of a premonition in his reference to the cell elements in the basic cells which stand in dynamic interaction to one another ("welche in den Grundzellen . . . in lebendiger Wechselwirkung stehen").

MENDEL'S ACCOMPLISHMENT

It is possible to regard the growth of knowledge as a superpersonal accomplishment of the Human Mind. In such a view there is little place for heroes and hero-worship. Each investigator contributes only what some other one would also have been able to contribute. And if specific personality has given a special touch to the discovery, such a feature is nothing but an ephemeral phenomenon. From the point of view of eternity this may well be true. Yet, the Human Mind exists only in individuals. Those alive who search for knowledge can gain guidance and inspiration from their predecessors. Mendel's accomplishment is unique not only for its pioneering success but also for the way in which it was attained. With hardly any prior experience in original studies, for eight years Mendel systematically bred and crossed his plants. Without prematurely talking or writing about the facts he discovered, he thought about them—we do not know for how long. When his search had led him to see the principles which stand behind his observations, when he had made the synthesis between the many bare facts and the few generalities, when he, the physics teacher at the local high school, had found their formulation by means of simple theorems of chance combinations, he wrote a single paper of forty-eight neatly handwritten pages. It is indeed justified that today, after a century, we look up to his example as an ideal of scientific accomplishment.

[6] For further references see C. Stern, and G. L. Walls, "The Cunier Pedigree of 'Color Blindness,'" *Amer. Jour. Hum. Genet.* **9** (1957) : pp. 249–273.

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A CENTURY OF BIOCHEMICAL GENETICS

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IT MAY be said flatly that at the time when Mendel presented to the world his astonishing—and unappreciated—conclusions about the elements of heredity, nothing whatsoever was known about the biochemical nature of material responsible for the transmission of hereditary traits from parents to their offspring. The mitotic division of cells was unknown, and it was even uncertain whether the nuclei of cells had a permanent existence or not. It was suspected that in sexual reproduction one or more sperms penetrated the egg cell, but the equal contribution of male and female to the nuclear constitution of the offspring through fusion of the sperm nucleus and the egg nucleus was not demonstrated until 1873–1874. The existence of chromosomes within every nucleus was not suspected, since staining had not been employed to render them visible within the otherwise transparent and seemingly homogeneous structure of the nuclear vesicle. The chemical identity of the nuclear materials, and in particular of the chromosomes, was even less suspected.

Mendel's refined analysis of the inheritance of alternative traits was therefore performed in a cytological and biochemical vacuity. It was a purely abstract, mathematical analysis of the segregation, combination, and independent assortment of hereditary characteristics. Mendel was therefore justly cautious in attributing any specific reality to the material entities which he supposed to lie at the basis of the phenomena he observed. The word "gene" was of course not invented until more than forty years later. The word "factor," so often attributed to Mendel, was apparently introduced by William Bateson, in the first decade of the twentieth century, following the rediscovery of Mendelian inheritance. Mendel himself speaks only of the segregation and combination of characters ("Merkmalen") and the "forms" of the pollen and egg cells. His sole use of the term "factor" was in a very general sense; and his one use of the term "elements" to refer to abstract units of particulate heredity scarcely makes the concept material. Whether Mendel ever thought of these elements as chemical entities of any sort, we shall probably never know. His entire bent of thought was more mathematical than chemical, and perhaps, like Thomas Hunt Morgan forty years later, the idea that the entities responsible for the characters must be embodied in some material, biochemical molecules or structures within the germ cells, was one to be eschewed.

Every historian of genetics, indeed every biologist of this century, has expressed wonder at the long neglect of Mendel's discoveries, and many reasons have been suggested. Perhaps it has not been realized as it should be that this prolonged neglect of a scientific discovery is not at all unusual; even the science of genetics abounds in such. Two of these relate, respectively, to the biochemical nature of the genetic materials and to the biochemical nature of gene action. It will be worth while to consider each of these in some detail.

THE CHEMICAL BASIS OF HEREDITY

The first biochemical investigation of the nuclear materials that might be supposed to serve as the physical basis of heredity was made by Friedrich Miescher.[1] With remarkable perspicacity, Miescher reasoned that the material basis of heredity must lie within the nuclei of living cells, and that the most important of all biochemical tasks was to isolate and characterize these substances. In 1869, his first year of postdoctoral work, Miescher extracted from pus cells a nonprotein, acid material rich in phosphorus. Nothing like it was known at the time, the only known biochemical compound that contained phosphorus being lecithin. Miescher called this new material "nuclein."

[1] See Jesse P. Greenstein, "Friedrich Miescher, 1844–1895," *Scientific Monthly* 57 (1943): pp. 523–532.

The time was even before the chromosomes, in 1873, were discovered to be a regular type of nuclear organelle, the orderly division of which was the primary function of mitotic cell division. Later, Miescher concentrated his efforts upon the biochemical analysis of the material in the head of salmon spermatozoa, since it had become recognized not only that the sperm is a cell, but that virtually its entire head is nucleus. From the sperm cells of the Rhine salmon, Miescher in 1871–1872 obtained not only nuclein but also a basic substance, of lower molecular weight than characteristic proteins. He called the latter substance protamine. His view of the association of these substances in the living cell was one of profound insight, as Greenstein (1943: p. 530) says.

> Toward the end of this classic paper he [Miescher] pointed out that sodium chloride, protamine, and nucleic acid formed a three-component, dynamic system, the equilibrium point of which was governed by the relative concentrations of each of the components as well as by the *Alkalescenz* (*p*H in modern terms). The basic reason for these dynamic interchanges Miescher recognized in the polyvalent character of both nucleic acid and protamine and in the ionic dissociation of the salt.

How little this was understood is evident from the fact that Richard Altmann, who in 1889 also separated the associated protein (protamine or histone in the case of sperm) from the nuclein, which he renamed nucleic acid, is commonly given credit for this feat by later writers (e.g., E. B. Wilson, 1925: p. 642). To compound confusion, Miescher's nuclein was thenceforth supposed to be the associated protein and acid, although he had clearly used the term to refer strictly to the acid alone.

In 1881 E. Zacharias added an observation of great interest. He showed that in plant tissues one could locate the nuclein more specifically among the intranuclear structures. In nondividing cells it was well dispersed in the nucleus, but in dividing cells it was localized in the chromosomes grouped on the equator of the spindle. It was thus made clear that nuclein is identical with the substance called by Flemming and others chromatin, and already identified as the physical basis of heredity. Several biologists were prompt to point this out. Among them were Julius von Sachs, noted master of plant physiology, and Albrecht von Kölliker, dean of German-speaking zoologists. Sachs (1882) postulated the existence of many kinds of nuclein, since any substance responsible for the enormous differences of heredity and variation must itself be of vast molecular complexity, although conceivably chemical means might be too crude to reveal it. Kölliker (1885) asserted boldly that nuclein must be the primary active substance in living beings and the material basis of heredity.

These were promising beginnings, and during the last decade of the nineteenth century the opinion among biologists seems to have been quite general that nuclein (by then interpreted to mean *nucleoprotein*) was the principal material of the chromosomes and the very stuff of heredity. A few quotations from the works of the great American cytologist Edmund B. Wilson and the distinguished French embryologist and cytologist Yves Delage will make this clear. In 1895 (p. 4), Wilson wrote:

> Now, chromatin is known to be closely similar to, if not identical with, a substance known as *nuclein* ($C_{29}H_{49}N_9P_3O_{22}$, according to Miescher), which analysis shows to be a tolerably definite chemical compound composed of nucleic acid (a complex organic acid rich in phosphorus) and albumin. And thus we reach the remarkable conclusion that inheritance may, perhaps, be effected by the physical transmission of a particular chemical compound from parent to offspring.

A year later, in the first edition of his classic textbook, *The Cell in Development and Inheritance* (p. 247), he speaks with even greater insight:

> . . . chromatin may pass through a certain cycle in the life of the cell, the percentage of albumin increasing during the vegetative activity of the nucleus, decreasing in its reproductive phase. In other words, a combination of albumin with nuclein or nucleic acid is an accompaniment of constructive metabolism. As the cell prepares for division, the combination is dissolved and the nuclein-radicle or nucleic acid is handed on by division to the daughter cells. It is a tempting hypothesis, suggested to me by Mr. A. P. Mathews on the basis of Kossel's work, that the nuclein is in a chemical sense the formative centre of the cell, attracting to it the food-matters, entering into loose combination with them, and giving them off to the cytoplasm in an elaborated form.

In the second edition of *The Cell* (1900) Wilson repeated these ideas in almost the same words. Shortly thereafter, Delage (1903) expressed the view that nucleic acid unites with protein, as an acid unites with a base to form a salt, and thus forms the nucleines, of which there are numerous varieties. The richer the nucleines in nucleic acid, the richer they are in phosphorus, and the more important seems their role. ("Plus ces nucléines sont riches en acide nucléique, plus

elles sont acide et riches en phosphore, et plus aussi leur rôle semble important.")

By 1925, when Wilson wrote the weighty third edition of *The Cell,* the detailed 1,200 pages of which so profoundly shaped the thinking of my own generation of biologists, the general opinion about nucleic acid had greatly changed. Wilson summed up contemporary opinion by saying:

> It is an interesting fact, which has been emphasized by biochemists, that apart from the characteristic differences between animals and plants . . . the nucleic acids of the nucleus are on the whole remarkably uniform, showing with present methods of analysis no differences in any degree commensurate with those from the various species of cells from which they are derived. In this respect they show a remarkable contrast to the proteins, which, whether simple or compound, seem to be of inexhaustible variety. It has been suggested, accordingly, that the differences between different "chromatins" depend upon their basic or protein components and not upon their nucleic acids.

How can we account for the *volte-face,* and the consequent loss of interest in the study of the nucleic acids?

In part the story is one of neglect, in part of a limited choice of materials, and in part of shallow generalizations based on poor methods. In the first place, there were scarcely ever more than two or three biochemists simultaneously working on the nucleic acids. After Miescher there were Albert Kossel in Basel (from 1879), and P. A. Levene in New York and Walter Jones in Baltimore, who from about the turn of the century, with their students and associates, formed the small band who pursued these arduous studies. In contrast to the enormous amount of work done on proteins and peptides, the nucleic acids were in fact so neglected that until quite recently all textbooks of biology and biochemistry divided the organic compounds of living organisms into only three classes of substances: proteins, fats, and carbohydrates. The detriment done to the advancement of biological thinking can scarcely be exaggerated.

The relative neglect of what had started out so promisingly was compounded by the use of harsh methods which depolymerized the nucleic acid molecules, that is, broke them into small fragments. The accidental choice of material played a catastrophic role, for the most convenient and almost always utilized animal tissue for extraction of nucleic acid was calf thymus glands from the slaughter house, while for plant material it was the readily available yeast culture. It thus happened that from the former the workers extracted chiefly deoxyribose nucleic acid, (DNA), from the latter ribose nucleic acid (RNA), and they then concluded that all animals possess one sort of nucleic acid, all plants the other. The startling error is reflected in a diagram in the third edition of Wilson's *The Cell* (p. 643), in which animals are depicted as possessing one kind of sugar in their nucleic acid, plants another; animals thymine, and plants uracil.

One final scientific catastrophe buried Miescher's work for decades more. This was the tetranucleotide hypothesis of Levene and his associates, a conceptual model which seemed well based on the equimolecular proportions of the four bases obtained by complete hydrolysis of deoxyribose nucleic acid. The hypothesis, in brief, proposed that the nucleic acid molecule was formed from a chain of nucleotides linked through a sugar-phosphate-sugar-phosphate backbone, in groups of four nucleotides arranged probably in an alternating sequence of purine-pyrimidine-purine-pyrimidine. This widely adopted model had the unfortunate effect of greatly restricting the possible variations of the nucleic acids. It led directly and inevitably to the conclusion expressed by Wilson and quoted above, namely, that the differences between different chromatins depend upon their protein rather than their nucleic acid components.

One would not do justice to Kossel, Levene, Jones, and their contemporaries if one merely blamed them for the unfortunate consequences of their errors. They did much basic work in elucidating the nature of the nucleic acids. They determined the nature of the purine and pyrimidine bases, the existence of thymine in one sort of nucleic acid and of uracil in another, the difference between the deoxypentose sugar of DNA and the pentose sugar of RNA, the nature of the sugar-phosphate bonding between the succession of nucleotides, and many other important matters. Yet it is undeniable that the misconceptions they generated about the nature of the nucleic acids delayed recognition of the true genetic material until the mid-forties and fifties. Cytologists who were well aware of the universal presence in chromosomes of DNA, and who used the Feulgen stain for DNA to identify chromosomal material, nevertheless continued to regard the nucleic acid as subsidiary to protein in the composition of chromosomes and as essentially too simple and undifferentiated a material to be capable of serving as

the basis of the genetic information passed from each generation to the next.

The neglect of the work of Mendel and of Miescher differs only in degree. In the case of the former, a thirty-five-year period of total obscurity was followed by brilliant verification and a burst of investigation almost unparalleled, as the formulation of the Chromosome Theory of Heredity heralded the new twentieth-century science of genetics. In the case of Miescher's work, it might almost have been better had it been similarly neglected for a time. Known, but of interest strictly to a small group of biochemists, Miescher's discoveries generated little further investigation. The dismal blindness of scientists to the significance of a chemical substance so uniquely limited to the nucleus, and indeed to the very chromosomes themselves, endured until 1944, when the work of Avery, MacLeod, and McCarty on the transformation phenomenon in Pneumococcus at last reawakened geneticists to the importance of DNA, and revealed that in the native state it is a highly polymerized molecule. Thus three-quarters of a century passed from the time of Miescher's first isolation of nucleic acid to the beginning of the modern era of DNA biochemical genetics. The twenty-one years since 1944 represent an incredible burst of molecular biology into the full flower of a new science. Miescher's time was indeed late in arriving.

From 1944 on, the development of our knowledge of the biochemical nature of the genetic material accelerated ever more rapidly. One need mention only a few highlights, for the story has been amply covered by George W. Beadle in his Jayne Lectures before the American Philosophical Society in 1962. Especially important was the work of E. Chargaff (1950) and his colleagues, for it disposed of the misleading tetranucleotide theory. It was established that DNA is characteristic of each species of organism. It may differ between species, but not within tissues of the same animal or plant. Chargaff discerned an AT type in which the adenine and thymine bases predominate and a GC type in which the guanine and cytosine bases predominate. The already recognized equality in amount of purines and pyrimidines in the nucleic acids was thus seen to rest upon an essential equality between adenine and thymine, and between guanine and cytosine. It was the recognition of this relationship, together with the advancing knowledge supplied by M. H. F. Wilkins' x-ray diffraction studies of the structure of DNA, that led J. D. Watson and F. H. C. Crick in 1953 to their now-famous hypothesis of the structure of the DNA molecule: a double helix of two polynucleotide chains with complementary pairing between adenine and thymine, guanine and cytosine.

The crucial proof recognized by most geneticists of the identification of DNA as the chemical stuff of heredity was provided by an experiment of A. D. Hershey and Martha Chase (1952). Since protein contains sulfur but no phosphorus, and nucleic acid contains phosphorus but no sulfur, they tagged bacterial viruses with radioactive phosphorus-32 or sulfur-35. The bacterial virus consists essentially of a coat of protein and a tail which is used for attachment to the surface of the bacterial host, while inside the protein coat there is a very long single filament of DNA. The virus was permitted to attach itself to the bacteria for a limited period of time and then, in a kitchen blender, the empty virus coats and the bacteria were sheared apart and separated in a centrifuge. It could then be seen that virtually all of the radioactive phosphorus enters the bacteria; but very little of the sulfur does so. In other words, the injected, infective material which is sufficient to produce more virus particles is the DNA. The protein part of the virus is discarded and must be made anew in each generation.

With this demonstration of the full responsibility of DNA for heredity the prescience of Miescher was vindicated. Further studies in the biochemistry of genetics must deal not so much with the identity of the genetic material as with its organization, its mutation, and the way in which it produces its effects.

THE BIOCHEMICAL NATURE OF GENE ACTION

The second example of profound neglect of a great biochemical discovery in genetics has recently become quite widely known. In 1908, in his Croonian Lectures, the distinguished British physician Sir Archibald Garrod summarized a decade of studies of four human disorders he very aptly termed "inborn errors of metabolism." The lectures were published in book form in 1909, and a second edition was issued in 1923. As the work of Miescher was known among biochemists, so too the work of Garrod was certainly known among men of medicine. Nevertheless, its preg-

nant insight into the nature of gene action was disregarded among geneticists, even though Garrod had relied upon the help of William Bateson in his genetic analysis of the four hereditary errors, albinism, alkaptonuria, cystinuria, and pentosuria. The analysis of alkaptonuria was especially fine. Garrod's own words are worth quoting:

> . . . in alkaptonuria the failure to break up the benzene ring extends to acids with hydroxyl groups in the 2:5 position other than homogentisic acid, and . . . the essential error resolves itself into an inability to destroy the ring of acids so constituted. Homogentisic acid is apparently the only compound formed in normal metabolism which offers itself for such disruption, and accordingly the alkaptonuric excretes it.
>
> This conception of the anomaly locates the error in the penultimate stage of the catabolism of the aromatic protein fraction. . . .
>
> We may further conceive that the splitting of the benzene ring in normal metabolism is the work of a special enzyme, that in congenital alkaptonuria this enzyme is wanting, whilst in disease its working may be partially or even completely inhibited.[2]

Thus Garrod clearly and explicitly interpreted this and the other "inborn errors of metabolism" as blocks at specific points in the normal pattern of intermediary metabolism, where some specific enzyme, normally present, was absent because of alteration of the controlling gene. Garrod himself believed that the clinching evidence was provided in favor of this view by Gross, who in 1914 reported the presence in normal blood plasma of an enzyme capable of oxidizing homogentisic acid, and its absence in the plasma of the alkaptonuric person; and Garrod so stated in the second edition of his book. However, this claim by Gross has never been substantiated. It was actually not until 1958 that La Du and his colleagues demonstrated the actual absence of the enzyme in liver biopsy specimens from an alkaptonuric patient.

Garrod's interpretation of gene action was far more explicit and more directly based on evidence than any of the somewhat similar suggestions made by geneticists in the ensuing years. Among these Cuénot (1903), Bateson (1909), Moore (1910), Troland (1914, 1917), Goldschmidt (1916, 1920), Haldane (1920), Muller (1922), Bridges (1923), and Wright (1916, 1917; review, 1941) offered a theoretical suggestion that enzymes are involved in gene action. Cuénot, for example, postulated that in mice the color of the hair is determined by a chromogen and two enzymes. A gray mouse has chromogen and both enzymes; a black mouse chromogen but only one enzyme; an albino both enzymes but no chromogen. This was a hypothesis of considerable predictive value. But Garrod went far beyond them all. As H. Harris (1963) summarized it:

> Garrod's fundamental idea about the biochemistry of the "inborn errors of metabolism" was that each condition could be interpreted as a block at some particular point in the normal course of intermediary metabolism due to the congenital deficiency of a specific enzyme.[3]

Years later, George Beadle after his work with Boris Ephrussi on *Drosophila* implants from donors of one eye-color genotype to hosts of another and after his work with E. L. Tatum on the nature of mutants in *Neurospora* that require a particular nutrient substance in order to live and grow, arrived independently at the concept: "one gene: one metabolic block: one specific enzyme deficiency." With Tatum and other associates the concept was refined into the "one gene—one enzyme" hypothesis. No words describe the relation of this work to Garrod's so well as those used by Beadle himself, in his Nobel laureate address in Stockholm in 1958.

> In this long and roundabout way, first in Drosophila and then in Neurospora, we had rediscovered what Garrod had seen so clearly so many years before. By now we knew of his work and were aware that we had added little if anything new in principle. We were working with a more favorable organism and were able to produce, almost at will, inborn errors of metabolism for almost any chemical reaction whose product we could supply through the medium. Thus we were able to demonstrate that what Garrod had shown for a few genes and a few chemical reactions in man, was true for many genes and many reactions in Neurospora.[4]

Since that day in 1958 many such relationships of gene to enzyme, or later of gene to protein, and still later of gene to specific polypeptide chain have been established in man, too; and biochemical human genetics has become a primary proving-ground for the study of the nature of gene action. Why was this development, so surely foreshadowed in Garrod's work, postponed for nearly forty years? Muller, in his paper of 1922, refers to the analysis of alkaptonuria, although he does not state its source. Others, too, must have known of Garrod's lectures on human heredity. But there

[2] Quoted from H. Harris, *Garrod's Inborn Errors of Metabolism* (London, Oxford University Press, 1963), p. 50.

[3] H. Harris, *ibid.*, p. 121.

[4] Quoted from H. Harris, *ibid.*, pp. 123–124.

was a common attitude among geneticists who worked with *Drosophila* or maize or other experimental organisms that human heredity was refractory to analysis and that little basic insight could be gained from studies of hereditary abnormalities in an organism that could not be bred at will.

Also, perhaps strangely, one finds little direct concern with enzymes. Haldane's book of 1942, *New Paths in Genetics,* illustrates the matter particularly well, because Haldane, of all geneticists of his time, was best trained in biochemistry and most open to see its genetic significance. Yet the book is singularly lacking in analyses of possible gene-enzyme relationships. Garrod's work of 1923 is cited for its example of human metabolic abnormalities inherited as simple recessives; the relationship of phenylketonuria and alkaptonuria to blockage of specific steps in amino acid metabolism is implicitly, but not explicitly, recognized, but the enzymatic relationship is scarcely hinted at. Haldane seems to have been struck by the relationship of genes to antigens and to anthocyanin pigments in flowers so strongly that I find only such sentences as the following.

> We may, then, take it as a working hypothesis that some genes produce antigens directly. . . . Now enzymes have a similar structure to these antigens. That is to say, they are proteins, often, if not always, with prosthetic groups such as metallo-porphyrins and flavine-sugar compounds. Some of them are antigens. It is not unreasonable to expect that enzymes will be found among the immediate products of gene action.[5]

That is the only mention of enzymes in the entire book, so far as the index and a scanning of the text indicate. The rest of the discussion focuses on the level of the gene-controlled metabolic and developmental processes; while the chapters on human genetics become more formal analyses of pedigrees, linkage, and gene frequencies in populations.

Ten years later, in *The Biochemistry of Genetics* (Haldane, 1952), the case is quite different, but that is after the work of Beadle and Tatum, and of others, had refocused attention upon the enzymes as primary gene products.

Thus we see that three of the greatest conceptual advances of genetics in its first half-century, 1865–1915, were profoundly neglected by geneticists for periods extending up to seventy-five years. Mendel's own bitter words, "Meine Zeit wird schon kommen," are echoed in those of Miescher in a letter to his life-long friend His, "I know better than anyone else that my work is only the preliminary study to a future Histo-chemistry."[6] The isolation of workers in different fields long kept geneticists from understanding and appreciating the significance of Miescher's work, and their ignorance was abetted by the misguided effects of two erroneous concepts, the concept of DNA and RNA as representative of the two great kingdoms, animal and plant, respectively, and the tetranucleotide theory which apparently excluded any great variability in the make-up of the polynucleotide chain. Miescher had the esteem of his fellow chemists, as Mendel failed to receive that of his fellow plant breeders; but the growing army of cytologists and geneticists, who had most to learn from Miescher's work, passed him by. Garrod, too, possessed the full esteem of the world of medicine, but geneticists and biochemists paid him little heed, to their own great loss. If these examples are of any value to scientists today, perhaps it is to serve as a warning that the greatest discoveries await those who see the significance of work in one field for advancement in another, who introduce the concepts of one field in that of another. The price they may pay is that of neglect, at least for one's own lifetime. The prize is inestimable, as Mendel, Miescher, and Garrod bear witness. We may hope that today it is more feasible to do what they dared to attempt with a greater chance of meeting with understanding.

GENESIS AND DEVELOPMENT OF THE CONCEPT OF GENETIC CONTROL

Genetics began, as I have said, with only the concept of hereditary characters, the potentialities for which segregate in pure form into the egg cells and pollen grains. It is worth emphasizing that Mendel's analysis of the combinations of egg cells and pollen grains was strictly based on the idea that *one* egg cell unites with *one* pollen grain to form a particular kind of zygote. That conclusion was forced upon him by the ratios obtained among the offspring of particular crosses, and their interpretation as the results of segregation of the elements producing a given character and the random combination of the kinds of pollen present with the kinds of egg cells present according to the laws of probability. This realization that fertilization is one male to one female gamete was far

[5] J. B. S. Haldane, *New Paths in Genetics* (New York and London, Harper & Bros., 1942), p. 60.

[6] Quoted from Jesse P. Greenstein, *ibid.*, p. 532.

ahead of any cytological knowledge about sexual reproduction that had been established at the time. That only a *single* spermatozoon is required to fertilize an egg was first demonstrated by Hermann Fol in 1879, in his study of starfish eggs. [It had not been demonstrated by Barry or by Newport or by Pringsheim in their more general observations of the fertilization of frog or rabbit eggs, or eggs of the freshwater alga *Vaucheria* (1843–1855)]. The studies of Edouard Strasburger on fertilization in flowering plants were not made until 1884, and these were the observations which showed that the pollen tube delivers to the embryo sac a male gametic nucleus that fuses with the nucleus of the egg cell. Strasburger thus confirmed for flowering plants, among them Mendel's peas, what Oscar Hertwig and Hermann Fol had observed in sea urchin and starfish eggs, namely, that fertilization is essentially the fusion of two nuclei, one derived from the egg, the other introduced by the sperm. In the many discussions of the reasons for the long neglect of Mendel's work, it appears not to have been stressed that at the time of his report no cytological basis was known to exist for the regular union in fertilization of a *single* egg cell with a *single* pollen cell, to say nothing of a single female nucleus with a single male nucleus. To some extent it may have been this notable lack that baffled Nägeli, who was ideologically inclined to look always for mechanisms.

Following the rediscovery of Mendel's work and its confirmation in 1900 by Carl Correns, Hugo de Vries, and Erich von Tschermak, Mendel's abstract "elements" or "units" became quickly materialized, first as "factors," and soon as "genes." During this part of the development of the science of genetics, the conceptual scheme most widely accepted was that of "one gene—one character." Why this concept ever gained currency is mystifying, since even among the seven pairs of alternative characters in the common pea studied by Mendel we find one which, according to his description, is pleiotropic, that is, which affects more than one character. The case is that of seed color and flower color. Dominant gray seed-coat color is associated with purple flower color; recessive white seed-coat color is accompanied by white flower color. Nor are the dominance relations always the same for associated characters dependent upon the same Mendelian factor. Round peas contain ellipsoidal, "potato-shaped" starch grains; wrinkled peas contain round starch grains subdivided into portions by radiating partitions. In the hybrid between the two pure varieties, as Mendel reported, round is dominant over wrinkled; but, as Darbishire (1908) discovered, the pollen grains are intermediate, being divided only into halves by the partitions.

The first big steps forward in understanding the nature of gene action were those made by Garrod, so ignored by the fraternity of geneticists who perhaps were too engrossed in their experiments to read anything not published by another recognized geneticist. Garrod, in fact, took two big steps at once: from recognition of the relation of the specific altered gene to the particular blocked step in the metabolic pattern, and thence to the lack of the specific enzyme governing that metabolic step. Yet neither Onslow (1915), who worked with the effects in the mouse of coat-color genes known to involve an enzyme-mediated path leading from tyrosine to melanin, nor Muriel Wheldale Onslow, who analyzed the gene-controlled anthocyanin pigments of flowers, nor Goldschmidt, who related genes to enzymatically controlled rates of developmental processes, nor others quite grasped the beautiful simplicity of Garrod's concept. Some of them saw the unit process controlled by the gene, some glimpsed the mediation of the enzyme. Yet not until 1941 and after, in the remarkable analyses of *Neurospora* mutants carried out by Beadle and Tatum, was the "one gene—one enzyme" hypothesis clearly put forward.

That hypothesis was of course too simple. Not all proteins are enzymes, and it gradually became apparent that some structural proteins, such as hemoglobin, might be direct gene products just as readily as any enzyme. In fact, Haldane's tendency was always to reason from the work of Muriel Onslow and others on the flower anthocyanin pigments to a conclusion that genes control the formation of large molecules such as the anthocyanins, maybe directly; thence to accept the control of genes over antigens; and finally to argue by analogy that enzymes too might be directly gene-controlled in structure. Resolution of the difficulty required more work on the structure of proteins, and in particular of the exact nature of the change introduced when a mutant gene was substituted for its normal allele.

In 1949 Linus Pauling, Harvey A. Itano, S. J. Singer, and I. C. Wells found that sickle hemoglobin is electrophoretically different, and therefore chemically different, from normal hemoglobin.

Also in that same year Neel and Beet independently demonstrated that sickle-cell disease is inherited in simple Mendelian fashion, the heterozygote possessing both sickle hemoglobin and normal hemoglobin. Thus evolved the concept of "molecular disease," involving a genetically altered molecule, as an elaboration of Garrod's conception of the "absent enzyme" in the hereditary disease, or inborn error of metabolism.

The work of F. Sanger and L. F. Smith (1957), fingerprinting the insulin molecule until its full sequence of amino acid residues had been deciphered, together with that of C. H. W. Hirs, W. H. Stein, and S. Moore (1954) on ribonuclease, paved the way for the work of Vernon M. Ingram (1957) on the nature of the genetic change introduced in the hemoglobin molecule by the mutant sickle hemoglobin gene. After it had been shown that the hemoglobin molecule actually consists of four loosely combined polypeptide chains (Schroeder, Rhinesmith, and Pauling, 1957; Kendrew and Perutz, 1957), the "one gene—one enzyme" hypothesis, already modified into a "one gene—one protein" hypothesis, became a "one gene—one polypeptide" hypothesis. For Ingram showed that only one of the two kinds of polypeptide chains (α and β) in the hemoglobin molecule is modified by the sickle hemoglobin mutant, and that both identical (β) chains are correspondingly modified. The climax was his discovery that only a single amino-acid residue in the entire polypeptide was replaced as a consequence of the mutation. Thus geneticists were led to the conclusion that, as predicted from the Watson-Crick model of the DNA molecule, the sequence of nucleotides in the DNA molecule specifies the sequence of amino acids in the polypeptide.

In 1955 and 1956 Severo Ochoa and Arthur Kornberg commenced, respectively, the synthesis of RNA and DNA in the test tube. This work led ultimately to the technique of producing artificial polynucleotides composed of one or more different nucleotides, and of using these in the protein-synthesizing system of the ribosomes to determine what amino acids would be incorporated into polypeptides in the presence of a specific polynucleotide. Marshall W. Nirenberg and J. H. Matthaei, in one laboratory, and Ochoa and his associates, in another, were successful at almost the same time (1961) in "cracking the genetic code." That is, they began the intricate series of determinations which led to the establishment of a code in which a sequence of three particular nucleotides determines the incorporation into a polypeptide of a particular one of the twenty commonly occurring amino acids. It would require far too much detail to describe, even briefly, the work of the past five years, during which scientists have confirmed the existence of messenger RNA that communicates the code from the DNA of the cell's nucleus to the ribosomes (Brenner, Jacob, and Meselson, 1961); and also the existence of transfer RNA molecules of twenty different kinds (see Nirenberg, 1963) that respectively transfer the twenty kinds of activated amino acid molecules to appropriate places specified by the code of the messenger RNA (Jacob and Monod, 1961). Not only has the code been well-nigh completely worked out, but it has been shown to be, in high probability, the same for all living organisms. That is, it is a universal genetic language, read and interpreted by the protein-synthesizing systems of human and bacterial cells alike. Probably not since the days of the discovery of mitotic cell division and the cellular basis of sexual reproduction, in the 1870's, have so many contributors added to so full an understanding of so great a biological mystery in so short a time. And this time, nearly a century later, the achievement is far greater from the technical point of view, as it merges the work of electron microscopists, geneticists, and biochemists. A new science, molecular biology, has indeed been born.

As we look back on this century of advance since the work of Mendel, we see that in the first seventy-five years, while genetics and biochemistry were advancing independently, almost no insight was gained into the real nature of the genetic material or the way in which genes produce their effects. The work of Miescher and of Garrod lay dormant, scarcely heeded until after 1940. The 1940's were ushered in with the catalytic work of Beadle and Tatum, followed by the introduction of the genetics of bacteria and bacterial viruses and the exciting revelation of the role of DNA in bacterial transformation. The 1950's were the decade of the analysis of the structure of the hereditary material—the Watson-Crick hypothesis, the artificial synthesis of nucleic acids, and the correlation between the alteration of a single gene by mutation and the substitution of a single amino-acid residue in a polypeptide chain. The first half-decade of the 1960's brings the cracking of the genetic code and a compre-

hensive understanding of the nature of gene activity in the control of protein synthesis. The enlargement of our understanding is in truth growing exponentially. Were Mendel and Miescher and Garrod here today, they could better understand all the advances of genetics in the first ninety years than in the past ten of this century, the close of which we celebrate today. It may not be long, if this pace of discovery is maintained, before some scientist will have made an artificial gene and then will have introduced it successfully into a living organism to see the effects of the substitution. What else may be done surpasses the imagination. All one may be sure of is that it will require only years, or only months, to equal the entire biological advance of this first post-Mendelian century!

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GENETICS AND MAN'S VISION

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MAN'S vision of controlling his own destiny invokes all of his resources in the humanities and sciences. The part that might be played by genetics raises not only scientific problems, but also particularly difficult ethical and moral questions and perplexing value judgments. This paper will attempt to do little more than acquaint non-biologists with current genetical ideas about the possibility of molding the genetic endowment of future generations. Some of the current ideas are based on classical genetics and represent fairly direct extensions of Mendelism and Neo-Mendelism to man. Others are based on recent startling genetic investigations of microorganisms, chiefly at the deepest molecular level. To propose applications of genetics, especially molecular genetics of microbes, to man is hazardous; but, as you will see, it is being widely done. In the past, the main findings of genetics have proved to be universal in applicability; this underlies the confidence of many contemporary biologists in the applicability to man of the main new findings about microbes. Whether this confidence is justified remains to be seen. To mention only this much about the status of the current ideas should suffice to alert the reader that, unlike the preceding papers which dealt mostly with the past and present and were on firm ground, the present paper deals mainly with future possibilities and will be speculative and controversial.

Choice of mates and relative fertility of various couples obviously determine the genetic endowment of descendants and the genetic character of future populations. How they do so was expressed in elegant mathematics by Fisher, Haldane and Wright. Their lesson was on the whole disappointing. It made clear that selective mating and differential reproduction would as a rule operate exceedingly slowly unless selective pressure is extreme. Such pressure means large-scale deliberate direction of mate choice and fertility. Rarely has this been attempted with man. The recent odious example of Hitler's program was hardly necessary to impress upon man that eugenic programs should be based upon free choice by the individual.

Muller [1] and others have argued eloquently that genetic and social education could and should inform and inspire considerable numbers of people to accept responsibility for helping to shape the genetic character of their descendants. He argues that, even if relatively few do so and their effects on the population as a whole are slight, the numbers so inspired would increase in the course of generations; and this would have an increasingly appreciable effect in improving the genetic endowment of man. Specifically, Muller proposes to exploit the discovery that sperm can be frozen and, after long periods, thawed and used successfully in artificial fertilization. Since artificial fertilization is carried on to some extent anyway, presumably using in the main the sperm of medical students, Muller holds that a beginning could be made now by building up stores of frozen sperm from men of outstanding achievements or outstanding qualities of various kinds and by permitting those who wish to be fertilized artificially to select the type of person whose sperm they wish to use. There are of course difficult problems in such a program. For the pros and cons, the reader should consult the proponent [1] and opponents [2,3]; in this brief paper, I can call attention only to

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[1] H. J. Muller, "Means and Aims in Human Genetic Betterment," ch. 5 in *The Control of Human Heredity and Evolution*, ed. T. M. Sonneborn (New York, Macmillan, 1965), pp. 100–122.

[2] Thedosius Dobzhansky, *Mankind Evolving* (New Haven, Conn., Yale University Press, 1962), ch. 12, pp. 319–348.

[3] John Maynard Smith, "Eugenics and Utopia," *Daedalus*, Spring 1965 (*Proc. Amer. Acad. Arts and Sci.* **94** 2) : pp. 487–505.

the kinds of proposals that have been seriously made by competent geneticists.

Another proposal suggests exploiting the method of nuclear transplantation developed by Briggs and King.[4] They remove the nucleus from an amphibian egg and replace it by a nucleus taken from a body cell of a developing embryo. The reconstructed egg develops normally if the donor cell comes from a very young embryo. Although nuclei of cells from older embryos did not work so well, it is conceivable that this limitation might be overcome by technical tricks. If so, and if the method can be further extended to cells of adults, then it might be possible to take nuclei from people who had proved their worth and implant them in an enucleated egg. This would be a much more effective procedure than merely using sperm from such a person, for his sperm cells contain *new* combinations of the genes while his body cells contain exactly the combination that made him what he was. Moreover, this procedure could use nuclei from women as well as men. If it were combined with artificial cultivation of the body cells of people in test tubes or petri dishes, as is now routinely done, a person's nuclei could be available for transplantation into eggs in unlimited numbers long after he died. A technical snag here is that such artificial cultures, when long maintained, undergo drastic chromosomal changes; but this technical difficulty may also be overcome before long. More serious perhaps is Maynard Smith's [3] comment: "Sons of famous fathers not infrequently suffer because too much is expected of them; much more might be expected of children known to be genetically identical to a famous ancestor."

Entirely different and even more fantastic proposals have been made in recent years. The principal ideas were clearly formulated by Tatum [5] in his Nobel Prize speech of 1958. Subsequently they have been elaborated further by him and many others. They have of course been much discussed, most recently in Maynard Smith's article [3] already mentioned and in two books.[6,7] The new ideas are based upon studies of microbes and molecules. There is little or no evidence that some of them can be applied to man; but, as already mentioned, the universality of the main findings of genetics inspires hope that they can, in spite of the fact that there are several possibly critical differences between microbes and all higher cells and organisms. Unlike the previously mentioned ideas, which are based mainly on known facts, some of the newer ones require for their working out much presently unavailable information. However, molecular biologists have been so amazingly successful that some of them are confident that no secret of living nature is beyond their power to overcome. When critics point out the obstacles and the difficulties, they answer, "Would you have believed fifteen years ago that we could have accomplished what we have? Then you can't reasonably say we won't succeed in doing what we now foresee in the next fifteeen years. After all, half the battle is formulating the problem." So, we must at least listen seriously to their bold imaginative new ideas on the control of human heredity and evolution. In brief, the new ideas are about how to achieve two main objectives: directed mutation, that is, changing existing genes to a desired new type; and direct replacement of existing undesired genes by existing or even constructed desired genes.

It is not now possible to direct the mutation of any gene in any organism. Agents that induce mutations act indiscriminately on all genes. The main reason for this is that all genes are composed of exactly the same small number (four) of kinds of parts and have a very large number of repetitions of each kind of part. Genes differ only in the ordering or arrangement of these parts and less importantly, in the total number of parts. We can hardly visualize the problem of directed mutation and proposals for solving it without having before us a more concrete image of the structure of the gene. The following symbolic model will serve our purpose.

The four kinds of parts of which genes are composed may be symbolized as A, C, G, and T. Each letter stands for a chemical entity known as a nucleotide. The four kinds of nucleotides are exactly alike except for one chemical grouping. The distinctive grouping is the basis of the four symbols: adenine (A), cytosine (C), guanine (G), and thymine (T). Each gene is composed of many repetitions of these four parts linked together into two long, parallel, connected strands. We may then symbolize a short segment in the midst

[4] Robert Briggs and Thomas J. King, "Transplantation of Living Nuclei from Blastula Cells into Enucleated Frogs' Eggs," *Proc. National Acad. Sci. U. S.* **38** (1952): pp. 455–463.

[5] Edward L. Tatum, "A Case History in Biological Research," *Science* **129** (1959): pp. 1711–1715.

[6] Gordon Wolstenholme, ed., *Man and His Future* (London, Churchill, 1963).

[7] T. M. Sonneborn, ed., *The Control of Human Heredity and Evolution* (New York, Macmillan, 1965).

of some hypothetical gene in this way:

```
------C-C-G-T-A-A-Ḡ-G-T------
      | | | | | | | | |
------G-G-C-A-T-T-C-C-A------
```

The most important feature of this diagram is the relation between the parts lying across from each other in the two strands. Note that wherever there is a *C* in one strand, a *G* lies across from it in the other strand; and wherever there is a *T* in one strand, an *A* lies across from it in the other strand. This "pairing rule" is fundamental to the composition of all genes. Different genes differ mainly in the sequence or order of these nucleotide pairs. Each gene consists of hundreds to thousands of such pairs in a linear sequence. As there are four possibilities at the position of each pair, the theoretical number of different genes is almost inconceivably large.

As might be expected from the account of how genes differ, a mutation consists of a change in the order of the nucleotides, usually just a change in one nucleotide. For example, suppose that the *C* (and *G*) on the left in the diagram represent the 131st pair from the start of the gene; then a change of the *G* at position 137, the *G* with a line over it, to *A* would be a mutation. Of course this would also lead, by the pairing rule, to replacement of the *C* at position 137 (in the other strand) by *T*. This example may also serve to illustrate a *directed* mutation, if one could bring about this change at this spot in this gene (or any other desired change at any spot in any gene) without at the same time or by the same means making any other change at any other spot in this or any other gene. It would probably not be too difficult to find an agent that would change *G* to *A*, for they differ very slightly. Likewise *C* and *T* are much alike. The great difficulty is to change only the desired *G* (or *A* or *C* or *T*) without changing any other, for there are many *G*'s (and also many *C*'s, *A*'s, and *T*'s) in each gene. How then could one hope to change, say, precisely the *G* in position 137 of this gene without changing other *G*'s in the same and other genes? In other words, how hit this narrow bull's eye and nowhere else?

Clearly, if directed mutation is to be achieved by a chemical agent, it must not only be capable of bringing about the *kind* of change desired, but must also find exactly the spot at which one wishes to bring about this change and ignore all others. The key idea of proposals for directed mutations is to employ an agent that "fits" the desired spot and no other. One approach is to take advantage of the fact that the two strands fit each other according to the pairing rule mentioned above. Outside the body, the two strands come apart on heating and go back together on cooling. Inside the body, the strands also come apart regularly at a certain stage of the cell cycle. So, it might be possible to make a mutagenic agent composed of a sequence of nucleotides exactly like a segment of the lower strand in the diagram above, except that it contains at position 137 a chemical, *X*, which can change *G* to *A*: i.e., *GGCATTXCA*. This would then be expected (under appropriate conditions, including separation of the two strands) to pair with the upper segment at position 131–139, bringing the mutagen *X* directly in contact with the one and only the one *G* it is desired to mutate:

```
          131                 137   139
------C-C-G-T-A-A-G-G-T------
      | | | | | | | | |
      G-G-C-A-T-T-X-C-A
```

In this way the desired bull's eye might be achieved. Success depends of course (among other things) on having the mutagen inserted into a chain of "complementary" nucleotides long enough so that it would be a unique sequence that would not fit any other part of this or any other gene. With four different nucleotides possible at each position, a given sequence of ten units would occur by chance less than once in a million stretches of ten units (i.e., $(\frac{1}{4})^{10}$). So, it might not be necessary to build a very long sequence of nucleotides to achieve a unique hit; and desired short sequences have already been synthesized.

Nevertheless, nothing approaching this sort of plan for directed mutation has yet been accomplished or even tried. Enormous technical difficulties and obstacles must first be overcome. For example, we do not yet know the sequence of units in the genes * or what sequence needs to be built to match it. The point, however, is that until recently it was not even possible to think concretely about directed mutations, to frame an approach, and perhaps to work towards accomplishing the task. Tomorrow or next year or

* Since writing this paper, the sequence of units in one gene has become known. (T. M. Sonneborn, "Nucleotide Sequence of a Gene: First Complete Specification," *Science* **148** (1965): p. 1410.)

a decade hence, new and presently unforeseen discoveries may make it possible to bypass present obstacles by opening up a different approach entirely. The *possibility* of eventual success in controlling human heredity by directing mutation as desired can at least be entertained.

The current ideas about achieving such control through direct replacement of undesired by desired genes stem from certain peculiar discoveries about the genetics of bacteria. One is that viruses can carry bacterial genes from one bacterium to another. Fortunately a virus that carries some genes of its host loses some of its own genes. So, while able to infect another bacterium, it cannot grow in or destroy the bacterium it infects. It merely deposits the genes of the first host in the new host. Sometimes these introduced foreign genes pair up alongside of the corresponding genes of the second host and replace them. Pairing of chromosomes and exchange of corresponding genes is a process which occurs normally in all organisms at a certain stage of life. Apparently, similar processes occur between the piece of bacterial chromosome carried by the virus and the chromosome of the recipient bacterium. Once this happens, the incorporated foreign genes are thereafter transmitted to the progeny.

The process is actually to some extent selective. Certain viruses transport only certain host genes; others transport only other host genes. It is thus possible to imagine a whole battery of viruses, one of which would be capable of transporting just exactly the one gene it is desired to introduce, whichever one it may be. The fact that relatively few of the exposed cells acquire the desired gene in this way presents no serious difficulty in work with bacteria. The successes are selected and the failures are thrown away.

Obviously that won't do with man. Moreover, such transfer of genes from one individual to another by viruses has not yet been found to occur in any higher organism, much less in man. However, it may well be discovered some day. If so, the difficulty presented by low frequency of success might well be overcome by using human cells grown outside the body. These can be handled as wastefully and ruthlessly as bacteria. One could then try to introduce the desired gene into them, keep the successes (if they can be identified) and reject the failures. Then put the successes back in the body of the person from whom the cells were taken. Of course, to be of genetic value they would have to be cells that would form sperm or eggs. Unfortunately, no one has yet succeeded in culturing human cells that form sperm or eggs. Even if all of this succeeded, the method would be limited to men only, because the human female at birth already has formed all the egg cells she will ever produce.

Another method of controlled replacement of genes seems to be more promising. No virus carrier is needed. The whole set of genes is chemically extracted from one kind of bacterium and another kind is exposed to the extract. The genes pass from the extract into the bacteria, pair with the corresponding genes of the recipient bacteria, and, as in the case of the virus-transported genes, some from the extract become incorporated in the recipient bacterium's chromosome and are thereafter transmitted to the progeny. Incorporation of genes from chemical extracts has already been reported for mammalian cells grown outside the body. If this is confirmed, it should also work with human cells. At present, however, the method lacks specificity and directiveness. All the genes are extracted together and any gene can be taken up and incorporated into any recipient cell. This difficulty will surely be overcome. Methods are now being devised and used which will probably lead before long to the isolation of single genes and to the separation and purification of the various genes in a total extract. Then it should be possible to use pure preparations of the desired gene to replace the corresponding gene in cultured human cells, screen for the successes, and reimplant them in the body of the person whose cells have been treated.

A still more exciting vista is opened by the possibility of synthesizing genes chemically, making them to order, and then introducing them into cells as replacements or additions. Short pieces of gene-like material have already been made with preassigned sequences of the component parts. This will surely go on to bigger game. An exciting aspect of this sort of work is that it might make possible the construction and incorporation of genes which do not exist and which could hardly be evolved in man by successive mutations if the intermediate steps were deleterious, as they probably would be. Tatum,[7] for example, has suggested that if we knew enough about enzyme action, we might make better enzymes than those we possess and, if so, we might make genes that would produce them. Atwood[7(p.37)] has facetiously suggested that we might increase man's food possibilities by adding to his set of genes

some that would produce enzymes for digesting wood, pulp, or paper. On which Hotchkiss has commented: "I like that. Then I could honestly tell some of my correspondents how much I enjoyed their last letter."

If I have seemed unduly enthusiastic about the possibility for improvement of human heredity, let me say that I have elsewhere [8] in print been very much more critical. I believe I do not underestimate the tremendous technical and genetical problems, difficulties, and obstacles. Among them is the fact, emphasized by Muller,[1] that most of the traits we should like to improve, like intelligence, vigor, and longevity, depend not on one but on very many genes, mostly with small individual effects. The molecular proposals I have discussed would fail utterly to cope with them. Moreover, the human set of genes is an immensely complicated interacting system; tampering with it is likely to throw a monkey wrench in the works. Yet there are some known genes with large and deleterious effects, like the one for phenylketonuria, which results early in permanent brain damage. That is surely the kind of gene—and there are many like it—to start to work on. We may begin to hope for successes at that level long before success can be hoped for with genetically more complicated traits.

[8] T. M. Sonneborn, "Implication of the New Genetics for Biology and Man," *Amer. Inst. Biol. Sci. Bull.* **13** (1963): pp. 22–26.

What then is the major present impact of genetics on man's vision, in so far as this vision includes genetical improvement of future generations? Implicit in classical genetics is the possibility of replacing natural selection by conscious human selection, had we the wisdom to select well. This would be a very slow and unspectacular method, although it could become somewhat less slow by exploiting recent discoveries such as preserving semen and transplanting nuclei. The impact of the new microbial and molecular genetics is quite different. It is bold, perhaps overoptimistic now about what it could do for man and how soon, but its devotees are already being forced by their own discoveries to acquire a healthy respect for biological complexity. Eventually it may lead, in ways presently unforeseeable, to some—even much—of the power over direct manipulative control of human genes that it now prematurely anticipates. Certainly the impact of the new genetics is not what it can now do, but what it can now imagine and work towards. Both the new and the old genetics are facing, and the genetics of the future will continue to face, the challenge of helping to implement, along with the humanities and the social sciences, G. G. Simpson's [9] challenge: "Man has risen, not fallen. He can choose to develop his capacities as the highest animal and try to rise still farther."

[9] George Gaylord Simpson, *The Meaning of Evolution* (New York, Mentor, D66, eighth printing, 1958), p. 155.

GENETICS, AGRICULTURE, AND THE WORLD FOOD PROBLEM

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It is always somewhat difficult to discuss the world food problem with Americans, for in this country we suffer not from food shortages but from embarrassing surpluses. The affluent society has become the overweight society. One authority estimated several years ago that the population of the United States was even then overweight in the aggregate by 500,000,000 pounds.[1] But the United States is only a small part of the world and with respect to food almost a unique part. For the world as a whole, the food problem has become one of the most acute and pressing problems. Today a majority of the world's people are inadequately fed by modern nutritional standards and suffer from chronic malnutrition resulting from insufficient food or from inadequate diets lacking in proteins or in vitamins and minerals.[2] That hunger, in whatever form, is often associated with social unrest and political instability is widely recognized today. Its effects were clearly understood more than two thousand years ago by the Roman philosopher, Seneca, when he said, "A hungry people listens not to reason, nor cares for justice, nor is bent by any prayers."

How is it that we in the United States enjoy such abundance when so much of the world hungers? There are many factors involved in this situation of which four stand out with special prominence. (1) In appropriating the North American continent from the American Indians, people of European origin, of more than ordinary progressiveness, came into possession of large areas of some of the most fertile, productive, and favorably situated land in the world.[3] (2) A little more than a century ago in the midst of a civil war the American Congress with remarkable foresight and wisdom passed, and President Lincoln signed, two acts which were to have far-reaching effects upon American agriculture.[4] One of these was concerned with the creation of a department of agriculture; the other, the Morrill Act, with the establishment in each of the states, supported by grants of land from the public domain, of colleges "where the leading object shall be, without excluding other scientific and classical studies . . . to teach such branches of learning as are related to agriculture and the mechanic arts. . . ." (3) When the science of genetics was born with the rediscovery of Mendel's law in 1900 the consequences of the events of 1862 and 1865 converged. Both the land-grant colleges and the Department of Agriculture were ready to apply the newly discovered principles of heredity to plant and animal improvement and many farmers were sufficiently well educated to recognize the value of the profitable new applications and to adopt them. (4) The improvements produced by genetic techniques were themselves substantial but, more important still, they acted as catalysts affecting the entire agricultural economy and creating a veritable revolution in American agriculture which has produced the abundance that we now enjoy.[5]

The greatest impact of genetic principles on the agricultural sciences has been on plant and animal breeding. These ancient arts have now been transformed into applied sciences. Before 1900, animal and plant breeding was strictly empirical but it was also sometimes remarkably successful. Many of the breeds of livestock which we still maintain were developed by breeders with no knowledge of the laws of heredity. The Here-

[1] Paul C. Mangelsdorf, "Biology, Food, and People," *Economic Botany* 15 (1961): pp. 279–288.

[2] Robert C. Cook, "Population and Food Supply," in *The Population Crisis and the Use of World Resources,* edited by Stuart Mudd (Bloomington, Indiana, 1964), pp. 451–477.

[3] For world distribution of most favorable lands see C. Langdon White, "Geography and the World's Population," in *The Population Crisis and the Use of World Resources, loc. primo cit.,* pp. 15–35.

[4] A. Hunter Dupree, *Science in the Federal Government* (Cambridge, Mass., 1957), chap. 8.

[5] Paul C. Mangelsdorf, "Hybrid Corn: Its Genetic Basis and Its Significance in Human Affairs," in *Genetics in the 20th Century,* edited by L. C. Dunn (New York, 1951), chap. 24.

ford and Shorthorn breeds of beef cattle in England as well as the dairy breeds of Brown Swiss of Switzerland, the Holstein-Friesian of Holland, and the Jersey and Guernsey of the Channel Islands were all established before the laws of inheritance were rediscovered.[6] Part of the success in establishing new breeds was due to practicing close matings as a means of fixing a uniform type. Robert Bakewell (1725–1795) horrified his neighbors by the practice of mating brother with sister and parent with offspring but by such means he founded the Leicester breed of sheep and brought it to a high degree of perfection.[7]

Likewise with plants. In England, Thomas Knight, in the late eighteenth and early nineteenth centuries, originated several varieties of potatoes, cabbage, pears, apples, cherries, and strawberries. Several of his varieties are still grown. Because he was the first to employ hybridization extensively in the improvement of plants, Knight has been called "the father of modern plant breeding." [8]

It was also during the nineteenth century that the only new crop of world-wide importance, the sugar beet, was developed. Following the discovery in the eighteenth century by the German chemist, Marggraf, that the sugar of the beets grown for livestock fodder, "mangel wurzels," is the same sugar as that of sugar cane, another German, Achard, began to extract sugar from beets. His factory failed in 1810 but a third German, Koppy, kept a factory going until 1820. Both Achard and Koppy practiced selection to improve the sugar content of the White Silesian stock beet, which they were growing, and raised it from 7.5 per cent to 10–11 per cent. Under the impetus of Napoleon's decree of 1811 curtailing trade with the British Colonies and subsidizing sugar production in France, two French plant breeders, the Vilmorins, father and son, eventually increased the sugar content of beets to 16–17 per cent. It was Louis de Vilmorin, the son, who invented the technique, still widely used by both plant and animal breeders, of progeny testing—evaluating an individual not by its own characteristics but by those of its progeny.[9]

What, then, did the new science of genetics contribute to the ancient arts of breeding? Initially, in many cases, little or nothing. The older generation of breeders continued to practice their traditional methods, some oblivious of the new discoveries, others aware of them but skeptical of their usefulness. But there were exceptions and it was these which soon showed what a powerful tool the principles of inheritance could be when applied to the improvement of animals and plants. To illustrate this fact there is no better example than hybrid corn, a development in applied genetics that has been aptly called "the prize exhibit in the plant breeder's show window." [10]

Hybrid corn, like many other scientific developments, is the product of many men and many minds. The complete history of hybrid corn would include the names of Gregor Mendel; Charles Darwin and his cousin the biometrician, Francis Galton; the Danish botanist, Wilhelm Ludwig Johannsen, author of the pure-line theory; Darwin's principal American correspondent, the botanist, Asa Gray; Gray's student, William Beal; Beal's students, Perry Holden and Eugene Davenport; George H. Shull; Edward M. East, a chemist turned geneticist; his students, Herbert K. Hayes and Donald F. Jones; Henry Wallace; Frederick Richey; and a host of practical corn breeders. Of these, two, Shull and Jones, because of the particular significance of their contributions, stand out.[11]

Shull, then working at the Station for Experimental Evolution of the Carnegie Institution at Cold Spring Harbor, began experiments to determine whether complex quantitative characters follow the laws of Mendelian inheritance as do the more simple ones which Mendel studied—plant height, seed shape, and seed and flower color. He chose kernel-row number in corn as a promising subject for his experiments since there are wide extremes in this characteristic, the number of kernel rows varying from eight to twenty-six. As a first step he undertook to create pure lines similar to those which Johannsen had isolated in beans and since corn is normally a cross-pollinated plant, he did this by artificial self-pollination. This is a form of inbreeding which we now know from the studies of Sewall Wright and others to be about three times as intense as brother and sister matings in animals.[12] This

[6] S. C. Salmon and A. A. Hanson, *The Principles and Practice of Agricultural Research* (London, 1964), chap. 1.

[7] D. F. Jones, *Genetics in Plant and Animal Improvement* (New York, 1925), pp. 292–293.

[8] *Supra*, n. 6.

[9] G. H. Coons, "Improvement of the Sugar Beet," in *Yearbook of Agriculture* (Washington, 1936), pp. 626–627.

[10] *Supra*, n. 6.

[11] Paul C. Mangelsdorf, "Hybrid Corn," *Scientific American* (1951): pp. 39–47. Also Herbert K. Hayes, *A Professor's Story of Hybrid Corn* (Minneapolis, Minn., 1963), chaps. 1–4.

[12] *Supra*, n. 7, p. 338.

intensive inbreeding caused the corn to lose vigor and productiveness at a rapid rate but it also increased uniformity within individual lines. The final result was a number of inbred lines, each one quite uniform but each quite weak and unproductive and completely useless from the standpoint of agricultural production. When Shull intercrossed several of these uniform lines to begin his studies of quantitative inheritance the results were astonishing. The first-generation hybrids, like their inbred parents, were quite uniform, but unlike their parents, they were vigorous and productive, some of the crosses being even more productive than the original open-pollinated varieties from which they had been derived.[13]

Someone has defined genius as the ability to draw valid conclusions from inadequate data. By this definition Shull must be counted a genius since from a limited set of experiments and unreplicated yield tests, both woefully inadequate by the standards of modern statisticians, Shull not only drew valid conclusions about the effects of inbreeding and crossbreeding but also recognized the fact that he had discovered a new method of improving the corn plant by exploiting hybrid vigor, a phenomenon for which he coined the very useful term, "heterosis."[14] Shull's work is a splendid example of what Henry Wallace has called "small gardens and big ideas."[15]

Shull's method of isolating and maintaining otherwise useless inbred strains for the hybrid vigor which was created when they were crossed was revolutionary in concept and effective in practice. However, the seed produced by this method was quite expensive because it came from weak, unproductive inbred strains. Shull was not able to persuade practical corn breeders to adopt his method. Like Mendel, he was ahead of his time.

In 1917 and 1918, Jones, working at the Connecticut Agricultural Experiment Station in New Haven, made two contributions[16a,b] which changed the situation almost overnight. In addition to crossing inbred strains to produce single crosses, as Shull had done, he crossed two single crosses to produce a double cross, a term which to corn breeders is quite wholesome since it was the double cross which solved the problem of hybrid seed production.

Jones' second contribution was his theory explaining hybrid vigor. The phenomenon of hybrid vigor has been recognized since the time of the ancient Greeks when breeders crossed the horse and the ass to produce the mule, a sterile hybrid which is superior in certain characteristics to either of its parents but which having as one parent the ass and being itself sterile has been described as an animal without pride of ancestry or hope of posterity.[17] Hybrid vigor had also been observed in crosses of plants.[18] Today heterosis is recognized as a phenomenon ranking with photosynthesis and the replication of the hereditary material, DNA, in its importance to agriculture and to world food production. Jones was the first to explain the phenomenon in terms of Mendelian principles and the recently formulated chromosome theory of heredity of Morgan and his students, Muller, Sturtevant, and Bridges. Historically, then, hybrid corn was transformed from Shull's magnificent design to practical reality when Jones' method of seed production made it feasible and his theory explaining hybrid vigor made it plausible. Even the most conservative agronomist could not resist this convincing combination. There was a sudden expansion of corn-breeding programs in the United States Department of Agriculture and the State Experiment Stations. By 1933, hybrid corn was in commerical production on a substantial scale. By 1950, most of the Corn Belt was planted to hybrid corn.[19] By 1964, 96 per cent of the total corn acreage in the United States was in hybrid corn.

The impact of hybrid corn upon American agriculture has been dramatic and revolutionary. To get the maximum benefit from their hybrid seed which must be purchased anew each year and which, compared to ordinary seed, is still expensive, farmers began to use more fertilizer. The combination of better seed and more fertilizer, accompanied in recent years by the use of remarkably selective herbicides, which kill weeds

[13] *Supra*, n. 11.

[14] George H. Shull, "Beginnings of the Heterosis Concept," in *Heterosis* (Ames, Iowa, 1952), pp. 14–48.

[15] Henry A. Wallace and William L. Brown, *Corn and Its Early Fathers* (East Lansing, Michigan, 1956), chap. 8.

[16a] D. F. Jones, "The Effects of Inbreeding and Crossbreeding upon Development," *Conn. Agric. Exper. Sta. Bull.* 207 (1918).

[16b] D. F. Jones, "Dominance of Linked Factors as a Means of Accounting for Heterosis," *Genetics* 2 (1917): pp. 466–479.

[17] Conway Zirkle, *The Beginnings of Plant Hybridization* (Philadelphia, 1935), chap. 1.

[18] Conway Zirkle, "Early Ideas on Inbreeding and Crossbreeding," in *Heterosis* (Ames, Iowa, 1952), pp. 1–13.

[19] *Supra*, n. 5.

but do not injure corn plants, has resulted in doubling the yield of corn in the period between 1930 and 1960. One economist has calculated that the costs of research and development in the production of hybrid corn have yielded a return of 689 per cent per year.[20]

What has happened in the United States is now happening in other parts of the world where corn is an important crop. In Italy, Spain, Southern France and parts of Austria and Hungary, hybrid corn has to a large extent replaced open-pollinated varieties.[21] In Mexico, Colombia, the Central American countries, Brazil, Argentina, Chile, Peru, and India, hybrid corn is replacing less productive open-pollinated varieties.

The successful exploitation of hybrid vigor in corn has led to its use in many other plants as well as in animals. In plants which are normally self-pollinated and in which the emasculation preceding hybridization would otherwise be too time-consuming and costly, forms of hereditary male sterility transmitted through the cytoplasm have made it possible to exploit hybrid vigor. Today hybrid seed is being produced in sorghums, sugar beets, onions, tomatoes, carrots, squashes, melons, and a number of ornamental plants including petunias. Hybrid petunias are especially interesting in the fact that their flowers set no seeds so that the plants, apparently in a kind of desperation to reproduce, bloom profusely and continuously.

Although hybrid corn is undoubtedly the most spectacular example of the successful application of genetic principles to crop improvement, it is by no means the only one. There is scarcely any domestic animal or cultivated plant which the breeders have not changed. When he was Secretary of Agriculture, Henry Wallace, himself a highly successful plant breeder and an imaginative innovator, transformed the *Yearbook of Agriculture* from a somewhat dull compendium of statistics and other facts to a comprehensive treatment of broad subjects concerned with agriculture. The *Yearbooks* for 1936 and 1937 were devoted to "better plants and animals" and are veritable cyclopedias on the subject.[22] After almost thirty years they still make good reading. They show that there is scarcely any agricultural or horticultural crop, scarcely any domestic animal which, already in the third decade of this century, had not been reshaped by the breeders. The reshaping has taken many forms.

One of the principal objectives of plant breeders has been to develop varieties which are resistant to diseases. Indeed, one of the recognized agricultural sciences, plant pathology, has become virtually a branch of applied genetics. Crops grown in pure stands over millions of acres provide vast culture media for invading fungi. The use of fungicides is expensive and often ineffective. It is, however, relatively easy, with many of the major crops, to develop varieties resistant to the more prevalent diseases such as the cereal rusts. These, however, are themselves constantly hybridizing to produce new forms and a cereal variety resistant to the once prevalent races of the fungus eventually becomes susceptible to a new race on the ascendancy. The result is a perpetual cold war between the plant breeders and the fungus pests which neither ever completely wins.[23] Within the past twenty-five years, to combat new races of fungi, many once-resistant varieties have been replaced by new productions.[24]

Breeding for resistance to insect pests has also had some degree of success but because insects are in general less specific than fungi in their choice of hosts, the success has been somewhat less spectacular. However, close cooperation between entomologists and geneticists has produced at least one outstanding achievement, the development of wheat varieties resistant to the Hessian fly, *Phytophaga destructor*. In the bread wheats, *Triticum aestivum*, at least five genetic loci are involved in resistance and at least four genetic races of the insect have been identified. By combining the loci for resistance from various sources it has been possible to develop a wheat variety which is resistant to all of the known races of the fly. Larvae in artificial cultures fed on tissue of resistant plants die within a few days of feeding; the resistance is apparently due to substances toxic to the insects.[25]

Other types of resistance to animal pests include resistance to nematodes which has been discovered and utilized in beans, lima beans, peppers, tobacco,

[20] Zvi Griliches, "Research Costs and Social Returns: Hybrid Corn and Related Innovations," *Jour. Political Economy* **66** (1958): pp. 419–431.

[21] R. W. Jugenheimer, "Hybrid Corn Development in Europe and Mediterranean Countries," *Agronomy Jour.* **47** (1955): pp. 5–7.

[22] *Yearbook of Agriculture* (Washington, 1936, 1937).

[23] E. C. Stakman, "Will the Fight against Wheat Rust Ever End?" *Zeitschrift für Pflanzenkrankheiten und Pflanzenschutz* **71** (1964): pp. 67–73.

[24] *Farm Programs and Dynamic Forces in Agriculture*, Report to Committee on Agriculture and Forestry United States Senate (Washington, 1965), p. 2.

[25] James L. Brewbaker, *Agricultural Genetics* (Englewood Cliffs, New Jersey, 1964), chap. 8.

alfalfa, and some of the clovers. Genes responsible for elongating the minute hairs on the leaves of soybeans and alfalfa have conferred some degree of resistance to injury by leaf hoppers, the pubescence holding the hoppers away from the cells which they seek to puncture.[26] This type of morphological resistance to insect pests may also protect plants to some extent from the many virus diseases which are spread by sucking insects. Sweet and field corn varieties resistant to extensive damage by corn-ear worms have been developed by breeding for long tight shucks which serve to confine the worms to the tips of the ears.

A common objective of plant breeders in recent years has been to adapt various crops to machine harvesting. Varieties of wheat, oats, and barley have been bred with shorter straw and the ability to hold their grains until dead ripe without shattering. Corn hybrids have been developed with several small ears instead of one large one to facilitate harvesting by mechanical corn pickers. Varieties of sorghum with short slender stems and small heads have been bred especially for harvesting by the combine harvesters commonly used on the smaller grains: wheat, oats, and barley. Even the tomato plant, a most unpromising subject for mechanical handling, has been modified to adapt it to machine harvesting. The vining habit has been curbed and plants have been developed which bring about 90 per cent of their fruit to maturity at one time. Fruit size has been reduced and its shape has been changed from round to oblong to produce greater resistance to impact. Now twelve cullers riding a giant picking machine do the work of sixty field pickers.

Too often in plant-breeding programs commercial considerations seem to take precedent over factors of quality. Some years ago Sir Daniel Hall, then Director of the John Innes Horticultural Institute in England, canvassed market gardeners to get their ideas on the ideal strawberry. He was shocked to discover that the demand was for a berry as large as possible, as deep red in color as possible, and tough enough to bounce. Flavor and aroma were not mentioned. The impression that some may have that the strawberries of today are not as flavorful or fragrant as those we once knew is undoubtedly correct.

What has been done with plants has also been done with somewhat different objectives with animals. Cows and goats give more milk; beef cattle develop more of tender hindquarter and less of the tougher forequarter cuts; pigs produce leaner bacon; sheep grow more wool; chickens lay more eggs; broilers grow faster with less feed; turkeys are smaller and have more white meat; bees work harder and make more honey; ducklings grow with almost frightening rapidity, multiplying their initial weight by fifty times in twelve weeks.[27]

In animal breeding one of the most spectacular developments has been the use of artificial insemination. This permits a valuable sire to father many times the number of progeny that would be possible with natural matings. Seminal fluid can also be shipped long distances. I once saw a herd of Holstein cattle in Argentina all said to have been sired by a bull some five thousand miles away in New York State. Seminal fluid can also be frozen and stored indefinitely so that a valuable sire can continue to father offspring long after his death. One wonders what kind of a brave new world this may become when man begins to practice on his own kind the methods which he employs so effectively on his domestic animals.[28]

Breeding has now become a highly sophisticated applied science—a biological counterpart of engineering. Chromosome numbers are doubled or quadrupled through the application of the alkaloid colchicine and by other means. New mutant forms are created through the use of ionizing radiations like x-rays or chemical mutagens such as mustard gas.

Some of the applications of genetics to the improvement of plants and animals have been quite ingenious and have involved combinations of several techniques. One example, not of great economic importance but illustrating the ingenuity of the breeders, is the seedless watermelon developed by Japanese geneticists. The chromosome number of a watermelon variety is doubled by treatment with colchicine. The tetraploid melon is then hybridized with diploid melons to produce hybrids which have the intermediate triploid chromosome number. In many species of plants triploids are completely sterile but in

[26] *Ibid.*

[27] For actual data on some of these developments see Jay L. Lush, "Genetics and Animal Breeding," in *Genetics in the 20th Century* (New York, 1951), pp. 507–519.

[28] For some of the possibilities see Hermann J. Muller, "Better Genes for Tomorrow," in *The Population Crisis and the Use of World Resources, loc. primo cit.*, pp. 314–338.

watermelons they produce perfectly good fruits which, however, are seedless.[29] The adoption of these techniques in the United States has led to the establishment of a seed company with the anomalous name, "The American Seedless Watermelon Seed Company."

X-rays, whose mutagenic effects were first demonstrated by Muller, have been employed by plant breeders to produce a great variety of new mutations. The production of penicillin from the mold *Penicillium* has been substantially increased by the use of an x-ray-induced mutant race. X-rays have also been employed to separate desirable genes from undesirable ones borne on the same chromosome. A classic example of chromosome engineering and gene juggling is that of E. R. Sears, who transferred a gene for rust resistance from a wild grass, *Aegilops umbellulata,* with fourteen chromosomes, to the cultivated bread wheat, *Triticum aestivum,* with forty-two chromosomes. These two species cannot be crossed with each other but both can be crossed to wheats with twenty-eight chromosomes. Sears crossed *Aegilops* with an emmer wheat, *T. diccocoides,* to produce a sterile triploid hybrid. He doubled the chromosome number of this hybrid with colchicine to produce a forty-two chromosome form which could be crossed and backcrossed with the forty-two chromosome bread wheat. Some of the progeny of this cross carried an extra chromosome derived from *Aegilops* which imparted rust resistance but these plants also had too many undesirable characters derived from their wild *Aegilops* ancestor. The final step was to irradiate such plants, thereby producing chromosome interchanges. Among 6,091 plants, Sears found one which was rust resistant and did not have the undesirable grassy characteristics of the wild *Aegilops.* It proved to have a minute translocation involving little more than the locus for rust resistance.[30]

A use of x-rays which is not strictly genetic but which grew out of genetic research is the biological control of screw worms. These are the larvae of the bot fly, *Callitroga hominivorax,* which lays its eggs in the open wounds of warm-blooded animals, causing enormous losses to live-stock growers in the southern states. The method consists of raising large numbers of flies artificially and rendering them sterile by x-raying. The sterile males, which are by no means impotent but have normal mating instincts, are released by plane in infested areas where they mate with females. Since the female of this species mates only once in her lifetime she now also becomes functionally sterile, laying hundreds of eggs which never hatch. Since the sterile males are released in numbers greatly exceeding the males in natural populations, the majority of females are soon rendered sterile. The flies of this species have been virtually exterminated in several areas by this biological method of control.[31]

One of the most sophisticated combinations of genetic techniques is that developed by D. F. Jones to eliminate the operation of detasselling in the production of hybrid corn seed. This represents a third major contribution to hybrid corn by this ingenious geneticist.

For many years hybrid corn was produced by planting the two kinds to be crossed in the same field and removing the tassels—the pollen-bearing male inflorescences—from one kind before pollen was shed. The female flowers of these emasculated plants then received all of their pollen from the tassels of the others. The seed borne on the detasselled plants, being crossed seed, produced only hybrid plants the following season. The operation of detasselling has been called the "peskiest and most expensive" part of producing hybrid seed corn and it has been estimated that on the peak day of the season some 125,000 people were engaged in removing tassels from corn plants.

Jones found that a form of sterility transmitted by the cytoplasm, and similar to one first described by Marcus Rhoades,[32] could be employed to eliminate part of the operation of detasselling. Used in combination with a genetic fertility-restoring factor, detasselling could be completely avoided.[33] The production of hybrid seed corn now has a built-in biological counterpart of automation. It employs hereditary factors transmitted through the cytoplasm to make corn sterile in the generations when sterility is needed as a substitute for emasculation in producing hybrid seed and it

[29] K. Yamashita *et al.,* "Polyploidy Breeding in Japan," in *Proc. Internat. Genetics Symposia* (Tokyo, 1956), pp. 341–346.

[30] *Supra,* n. 25, chap. 6.

[31] E. F. Knipling, "The Use and Limitations of Isotopes and Radiation Sterility in Meeting Insect Problems," *Internat. Jour. Appl. Radiation and Isotopes* 13 (1962) : pp. 417–426.

[32] Marcus M. Rhoades, "The Cytoplasmic Inheritance of Male Sterility in *Zea Mays,*" *Jour. Genetics* 27 (1933) : pp. 71–93.

[33] D. F. Jones and P. C. Mangelsdorf, "The Production of Hybrid Corn Seed without Detasselling," *Conn. Agric. Exper. Sta. Bull.* **550** (1951).

uses hereditary factors transmitted through the chromosomes to restore fertility in the farmer's field where fertility is essential. The combination is saving millions of hours annually of hard arm-tiring labor.

Paraphrasing the title of a paper on viruses presented to the Society some years ago,[34] we may ask the question "Can the hereditary material be managed?" The answer obviously is yes.

The application of genetic principles to the improvement of animals and plants has contributed to revolutionizing American agriculture and has been directly or indirectly responsible for the abundance which we enjoy. Russia's failure to make full use of genetic principles in plant and animal improvement, indeed her failure, under the influence of Lysenko, to recognize the principles of orthodox genetics has undoubtedly been responsible in part for her inability to solve her agricultural problem. In any case, Russia now faces an agricultural problem of tremendous proportions and is planning to spend billions in attempting to solve it.[35] The fact that she must buy wheat from us and that we have wheat to sell is eloquent testimony to the short-comings of Russian agriculture and the success of ours. The integration of theory and practice, an important tenet of Marxism, has been more nearly attained in capitalist United States than in Communist Russia.

That the principles of genetics can be successfully applied to the improvement of agriculture in at least some underdeveloped countries has been clearly demonstrated by the success of the Rockefeller Foundation's agricultural program in Mexico. Initiated in 1943 in cooperation with the Mexican government it has succeeded in increasing wheat production threefold and in doubling corn production. It has developed new varieties of potatoes resistant to the most prevalent disease, late blight, and varieties of sorghum and soybeans adapted to Mexico, thus virtually providing Mexico with three new food crops. Although the population of Mexico has been increasing at a phenomenal rate in the past two decades, the improvement of Mexico's food supply has, so far, more than kept pace—the per capita food supply is higher today than it was in 1943. Similar progress is being made in Colombia and other countries of Latin America and to a lesser extent in India. There is no doubt that the agriculture of underdeveloped countries can be improved, but the rate at which it can be improved is dependent in no small part on the general level of literacy and education in the population and the willingness of governments to provide generous support to agricultural education and research.[36] Unfortunately those countries which need agricultural improvement most are also those least capable of producing it. Thus it is that Mexico and Pakistan have achieved substantial agricultural improvement while the food situation in India is still precarious.

The only possible solution of the world's food problem within the foreseeable future is an increase in the food supply—derived largely through improvements in agriculture—accompanied by a decrease in human fertility. Fortunately the need for fertility control is becoming apparent in both secular and religious circles.[37] Fortunately, too, new contraceptive procedures have been developed which are not only harmless and effective but also cheap enough to be within the reach of virtually all. Extensive research on still others is in progress.[38] Possible solutions to the world's food and population problems are now in sight but the road ahead is long and hard and is beset with many troublesome complexities. To reshape our domestic animals and plants by genetic techniques is much easier than to change the ways of man.

[34] Frank L. Horsfall, Jr., "Can Viruses Be Managed?" *Proc. Amer. Philos. Soc.* **102** (1958) : pp. 442–447.

[35] *New York Times,* March 29, 1965.

[36] Theodore W. Schultz, *Transforming Traditional Agriculture* (New Haven, 1964), chap. 12.

[37] The Vatican now has a commission giving serious study to all aspects of the problem of birth control. See *New York Times,* March 30, 1965.

[38] See "The Growth of World Population," *Nat. Acad. Sci. - Nat. Research Council Pub.* **1091** (1963), pp. 28–36.