Papers and Originals

Gregor Mendel

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I. Biographical

Gregor Johann Mendel was an enigma in his life and has remained a puzzle to posterity. Three somewhat conflicting personalities emerge from what little we know of him. That a rather humdrum boy and youth should, in early middle-life, become an epoch-making investigator is not particularly unusual in the annals of genius, but that this second personality should be short-lived, unrecognized, and change into a querulous administrator of no particular merit is distinctly exceptional. These complexities are not made any more intelligible by the fact that the flaring-up and extinction of Mendel's genius went unnoticed by his contemporaries and by a whole subsequent generation—and possibly by Mendel himself.

Born on 22 July 1822 at Heinzendorf, in Moravia, then part of Austria and now of Czechoslovakia, Johann was the second of three children in a struggling peasant family who stretched their resources to give the boy in the family an education beyond what he had received at the village school. At the secondary school he experienced privation and perpetual anxieties about his livelihood, and it would seem that partly as an escape from these difficulties he became at the age of 21 a novice at the Königinkloster at Brünn, the capital of Moravia, assuming the monastic appellation of Gregor before, or instead of, his baptismal name. At the age of 25 he was ordained priest and subsequently adjunct in the incumbency of the local Collegiate Church. As a parish priest he was not outstanding and by 1849 he had been transferred to teaching duties in a near-by high school. For this post to be permanent he had to have adequate qualifications, and these he failed to obtain in an examination at Vienna in 1851. He stayed on at the University there for some two years, and in 1854 was appointed assistant teacher at the newly opened Modern School at Brünn to teach physics and natural history in the lower forms. He appears to have been a natural teacher, but unlucky in his attempts to obtain the necessary qualifications: a second attempt in 1856 was no more successful than the one five years earlier, and till the end of his teaching career in 1868 he remained an assistant teacher. But the fifteen years of such duties—all at the Brünn Modern School—included the eight meteoric years of 1856-64.

At 34, Mendel, a competent but unqualified teacher, and an amateur botanist with an undistinguished paper published two years previously on the damage done by the pea-weevil on pea plantations in Brünn, began his experiments on the hybridization of the pea. This work was communicated to the fairly recently formed Brünn Society for the Study of Natural Sciences on 8 February and 8 March 1865 and published a year later in the *Proceedings* of the society. In undertaking work on hybridization Mendel followed contemporary practice. Hybridization had both practical and theoretical aspects—practical in so far as horticulturists and animal breeders were anxious to establish new strains and were constantly balked by unexpected results, sterility of the hybrids, and apparent lack of any predictable patterns; theoretical, for in spite of the wide acceptance of

Linnaeus's and Cuvier's theories of the fixity of species naturalists were unhappy with this assumption in face of the similarities repeatedly observed in the immense diversities of nature, and it was felt that hybridization might be the cause of variation and new species. In using the pea for his experiments Mendel likewise followed a contemporary trend, for *Pisum* was a not unusual experimental plant. What was not contemporary was the plan of the work and the militant confidence proclaimed in the opening paragraphs of his classical paper.

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

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

"The paper now presented records the result of such a detailed experiment. This experiment was practically confined to a small plant group, and is now, after eight years' pursuit, concluded in all essentials. Whether the plan upon which the separate experiments were conducted and carried out was the best suited to attain the desired end is left to the friendly decision of the reader."

To plan a long-term experiment which was "to determine the number of different forms under which the offspring of hybrids appear, to arrange these offspring according to their separate generations, and to ascertain their statistical relations" was turning away from the past with its verbal quicksands and its repetitive standard answers to standard questions. It was stepping into the future.

The answers he gave to the questions he formulated were derived from observations he had to make on a severely limited patch of soil at the Monastery. In this, fate was kind to him, compelling him to limit his attention to the pea—a particularly favourable experimental plant. Most of the races of pea are constant and have distinct characters; they breed true from seed, and hybrids, far from being "botanical mules," are fertile, allowing succeeding generations to be studied. Furthermore, the flowers of the pea are naturally self-fertilized before the bud opens, so that the process of fertilization is not interfered with by insects which visit them. In addition, the structure of the flower makes it easy to fertilize it artificially because the pistil is ripe before the stamens, so that the pollen can be easily applied. Large numbers of individuals can be grown in a limited space, and, as the pea is an annual, a generation can be sown each year. Individual characters, such as colour and shape, could therefore be readily followed up in succeeding generations. Observations on other plants, particularly on *Hieracia* (the hawkweed), carried out from 1867 to 1871 led to difficulties mainly because no one recognized at that time that this plant had an asexual phase of reproduction. To-day the apparent contradictions shown by *Hieracia* are readily intelligible, but to Mendel they appear to have signified the end

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of any hope he may have had that his findings on *Pisum*, and his interpretation of these findings, represented fundamental principles applicable to all life and not merely a special case.

Still more unfortunate was Mendel's elevation on 30 March 1868 to the vacancy of Prelate of his Monastery—one of the wealthiest in Austria. This election for life by his 12 fellow priests at the monastery to a post ranking next only to the Bishop carried heavy responsibilities. Mendel was now 46 years old and the promotion was not unexpected by him. He succeeded an outstandingly good administrator who had played an important part in the cultural life of the country. Mendel obviously stood well with his colleagues and it is clear that the task of Prelate was not uncongenial to him. He appears to have responded enthusiastically to the calls on his time and to have valued the tinsel glory of the automatic social honours that now came his way. Though still struggling to continue his investigations on *Hieracia*, all botanical work appears to have come to an end not much after 1871. Some meteorological observations and some observations on bees were carried on in a desultory manner for a few years longer, but from 1874 until his death ten years later he spent an immense amount of energy in disputing with the central government the legality of their taxing his monastery. In this he showed a stubbornness worthy of a better cause. He fought relentlessly till his death in 1884, but his successor had no difficulty in settling an unnecessary conflict.

His Obituary Notice

Hugo Iltis, his biographer, gives the announcement of Mendel's death as drafted by himself. With its lack of any reference to his scientific work, and its emphasis on social distinctions, it is a strange document.

"The Augustinian monastery of St. Thomas at Altbrunn in Moravia respectfully and with profound regret informs the public of the death of the Right Reverend Abbot GREGOR JOH. MENDEL, mitred prelate, companion of the Royal and Imperial Order of Francis Joseph, emeritus chairman of the Moravian Mortgage Bank, member and one of the founders of the Austrian Meteorological Society, member of the Royal and Imperial Moravian and Silesian Agricultural Society, and various other learned and useful organizations, etc., etc. Born at Heinzendorf in Eastern Silesia on July 22, 1822. After a long, severe, and painful illness, having received the holy sacrament and having submitted himself to the will of the Most High, he departed this life at half-past one in the morning of January 6th.

"The funeral ceremony will take place at the monastery church on January 9th at nine in the morning, and thereafter the body of the deceased will be conveyed to the Brunn central cemetery for the last rest.

R.I.P.

Brunn, Monastery of St. Thomas
January 6th, 1884."

Sad as this document is, there is tragedy of historical magnitude in the fact that no one else among his contemporaries would have said anything different. "A kindly and beloved priest rather than a Titan of thought was praised and laid away."

Physical Factors in his Decline

What little is known of Mendel suggests the possibility of contributory physical factors in the decline of his genius. The available portraits show him bespectacled, but it is not known why or how early in life he took to glasses. Writing on 3 July 1870 to Naegeli, he says:

"Only during the last few days have I been in a position to resume my favourite occupations, which have been interfered with by eye trouble since about the beginning of June [1869]. There was a very great danger that I should have to give up hybridization experiments altogether, and I have to thank my own carelessness for this. Since ordinary dispersed daylight was in-

sufficient for my work on the tiny *Hieracium* flowers, I made use of an illuminating apparatus [a mirror and a lens], without thinking what damage I might thus do to my eyesight. Well, during May and June, when I had been busied upon *H. auricula* and *praealtum*, I began to suffer from a peculiar sense of fatigue and tension in the eyes, and, though I now spared my sight as much as possible, this trouble became intensified, making me quite unfit to bear any sort of eye-strain until well on in the winter. Since then, I am glad to say, the trouble has almost completely passed away, so that I can now read for long stretches once more, and have been able to resume my fertilization experiments with *Hieracia*, in so far as these are possible without artificial illumination."

What the eye trouble in June 1869 was is not clear, but at 47 presbyopia—at that time not readily corrected except in the simplest cases—would have been an additional trouble (unless Mendel was a low myope, and for this there is no evidence). How far the eye symptoms interfered with further work on cross-fertilization is not known, but this remains a possibility.

A more far-reaching disturbance is suggested in an earlier letter to Naegeli (6 November 1867) in which Mendel speaks of declining physical capacity:

"I am no longer well-fitted for botanical expeditions, seeing that Heaven has blessed me with an excess of avoirdupois, and this makes long walks and especially hill-climbing very difficult for me in a world where universal gravitation prevails."

Mendel may have been right in ascribing his declining fitness at 45 to obesity, but his death 17 years later followed on increasing dropsy from cardiac and renal failure. The end came with uraemic coma. The post-mortem examination showed chronic inflammation of the kidneys (*morbis Brightii*) as the primary disease, with hypertrophy of the heart as a complication. It is just possible that when he was appointed Prelate in 1868 he was beginning to experience some of the disabilities associated with cardio-vascular-renal disease. Such an assumption is perhaps justifiable on the basis of the post-mortem findings.

II. The "Experiments in Plant Hybridization" (1865) and the Letters to Naegeli (1866-73)

A hundred years after they were reported, Mendel's results and conclusions appear as simple as they must have seemed difficult to his contemporaries. Though both these readings are unwarranted, the fundamental aspects are simple enough and are readily summarized:

1. When a cross is made of true-breeding peas with contrasting characters—such as tallness or shortness of the stem, the yellow or green colour of the seeds, the smooth or wrinkled form of the ripe pods, and a number of suchlike features (Mendel used seven such characters)—hybrids show only one of the two contrasting characters. Thus tallness prevails over shortness—the prevailing character is dominant over the other which is recessive.

2. These hybrids do not breed true: the progeny of self-fertilized hybrids ("selfed") show a ratio of 3:1 of dominant to recessive characters—for example, three tall to one short. At further self-fertilization the short breed true, and of the tall one-third breed true and two-thirds give 75% tall and 25% short. These results are shown diagrammatically in Fig. 1. Here the capital letter indicates dominance and the letter in parentheses a hybrid constitution. Thus T and s are pure for tallness and shortness and breed true, and (T) differs from T in that it does not breed true, though outwardly T and (T) cannot be distinguished.

3. As the hybrids of the first generation did not breed true, but returned to the ancestral forms, the dominant and recessive characters—contributed by the parents—had not become blended in the hybrid. These characters are assumed to have been determined by factors of inheritance, and these must have remained discrete; they segregated at gamete (germ cell) formation, and reappeared in subsequent generations. Mendel did not speculate on the nature of these factors, but used alphabetical symbols for

representation. Interpreted in terms of these units or factors of inheritance, and using the symbol A for tallness and a for shortness, the results shown in Fig. 1 are analysed in Fig. 2.

FIG. 1.—Actual observations. The types of pea plants seen over three filial generations in hybridizing experiments. T=Tall. s=Short. (T)=Tall in appearance, not breeding true.

FIG. 2.—Interpretation. Mendel's explanation of the data recorded in Fig. 1. AA=Tall pea plant breeding true when self-fertilized. aa=Short pea plant breeding true when self-fertilized. Aa=Hybrid plants not breeding true; they produce the ancestral forms as well as hybrids when self-fertilized.

Mendel's units or factors of inheritance are the genes of to-day; his hybrids and true-breeding plants are the heterozygotes and homozygotes of present-day literature. Our modern terms of genotype and phenotype summarize his clear recognition that the outward form is no reliable guide to hereditary constitution. ("It can be seen how rash it is to draw from their external resemblance conclusions as to their internal nature.") The essential aspect of Mendel's teaching is thus the recognition that hereditary characters are determined by a pair of units, of which only one is carried by a germ cell, and that of a given pair one is dominant to the other; the mathematical ratios show that these units segregate and combine in a random—that is, chance—manner.

In his work on the pea, Mendel also studied the effect of crossing plants which showed contrast in two or three characters, such as tallness of stem, colour of seeds, and the form of the ripe pods. These crosses gave respectively dihybrids and trihybrids in the first generation, and in the subsequent generation complex ratios appeared; thus with dihybrids dealing with the second and third of these characters there would be nine round yellow, three round green, three wrinkled yellow, and one wrinkled green. These ratios, as also the still more complex ratios for trihybrids, were predictable on the assumption derived from his work on simple hybrids (monohybrid inheritance). Thus Mendel showed that if with monohybrids the first filial generation hereditarily consists of AA + 2 Aa + aa, then for a dihybrid which combines these proportions with the proportions BB + 2 Bb + bb, the result would be 1 AABB, 2 AaBB, 2 AABb, 4 AaBb, 1 AAbb, 2 Aabb, 1 aabb, 2 aaBb, 1 aaBB—or, if appearance is judged, 9 AB, 3 Ab, 3 aB, and 1 ab—exactly the types and proportions to be found in actual experiment. (Mendel used the symbols Aa for round and for wrinkled forms of the pea respectively and the symbols Bb for the yellow and green colour of the seed albumen [cotyledons]; but he also used these symbols abstractly.) It will also be seen that these ratios are a modified version of the 3:1 ratio seen with monohybrids: with dihybrids there are 12 A to 4 a and likewise 12 B to 4 b, derived from the 16 types.

Mendel had followed the behaviour of each of the seven characters he studied for six or seven generations; he had the exhilarating experience of seeing in the successive years what he had foreseen. The sober language of the report barely hides the excitement of watching how "Around the ancient track, marched rank on rank, The Army of unalterable law." How extensive his observations were on species other than peas is not known. Though his paper on *Hieracium* hybrids is available (1869) none of his notebooks have survived, and except for the fortunate accident that Naegeli kept Mendel's letters to him we would have known little of Mendel's disappointing trials with the hawkweed. These letters, which began with the request to a leading botanist for confirmatory work on the pea, led to little else than a recital of failures which Mendel had experienced with hybrids of the hawkweed—a subject very near to Naegeli's heart and recommended by him to Mendel, whose work with the pea he regarded as "merely a beginning." There is no indication that Naegeli, for all his repute, understood anything or did anything.

The sum of Mendel's work is therefore the epoch-making use of isolated features (or characters) instead of the individual as a whole in the study of inheritance, and the demonstration that at this level each character depends on two unequally expressed units of inheritance which combine in an individual but never blend. His assumption of segregation of units of inheritance at gamete formation and recombination at the zygote stage thus opened the possibility of an immense number of combination of such units, and this was the first valid experimental approach to the problem of variation.

Fundamental Implications

In fact, Mendel's work had fundamental implications for two closely related fields—the mechanism of inheritance and the nature of variation. His contemporaries were more concerned with the second than with the first, for this was the age of Darwin. The concept of evolution was of course not new; for, long before Darwin, Lamarck had held that the inheritance of environmentally induced changes led to new species. In Darwin's scheme it was natural selection of variations which was the force behind evolution, but Darwin and his contemporaries had no clear conception of variation. They failed to distinguish clearly between changes induced by environment and those that occur inherently in species, and had no clear understanding of the frequency of such changes. In addition, they barely suspected the existence of mutations and had no notion at all of changing patterns produced by the recombination of genes. They therefore knew little of basic variations on which natural selection operated. Critics of Darwin had no difficulty in showing that the relatively rare variations actually known and stressed by him would be swamped by the normal pattern. Darwin was steadily driven to admit other agencies than natural selection as necessary factors, and never knew that Mendel had provided an endless and ever-present source of variation in the recombination of the units of heredity.

The significance of heredity was likewise vaguely assumed rather than understood. Obviously no variation has any significance for evolution unless it is inherited, and the mechanism of inheritance was a closed book. The disputes were on the question whether environmentally induced changes could be inherited.

Mendel's work, quite apart from the beautiful simplicity of his technique and the relentless logic of his conclusions, was therefore highly relevant to the problems of his contemporaries. That Naegeli at Munich, and all the other learned men of his age, should have failed to appreciate this immense contribution must remain a puzzle. Mendel's observational approach could hardly have jarred on his contemporaries, even if there might have been resentment to the introduction of mathematical procedures in biology. The most effective barrier between Mendel

and the rest of his generation was probably Mendel's choice of criteria—his insistence on studying marked and contrasting differences. The Darwinians were concentrating on natural selection as being operative over aeons on minute differences—the continuous variations of subsequent biologists. Mendel's characters were in contrast what came to be known as discontinuous variations—that is, marked differences. In Mendel's scheme, tallness and shortness were markedly and sharply contrasted, but stature in man and animals showed no such marked differences: they were in fact a range of continuous variations, and to Mendel's contemporaries his work on marked differences might well have appeared rather far-fetched. It is clear that Mendel's simple experiments ran counter to many ingrained attitudes.

Perhaps in consequence of all this there was no immediate impact from Mendel's work. Retrospective searches show that his work appears to have been noted on only four occasions before 1900—three times in reference lists and once, in 1881, in a book by Focke on hybridization, in which Mendel is given credit for work very much like that of his predecessors; in addition there is the obtuse remark that "Mendel believed he

had found constant ratios amongst the types produced by hybridization."

III. The Rediscovery

In the last two decades of the nineteenth century the work of Weissmann had made the study of heredity a central issue in biology. By postulating the continuity of germ-plasm (the body or soma being a transient husk which does not influence it but acts as a mere custodian of germ-plasm) he concentrated attention on a possible material basis of heredity. The parallel work on chromosomes by Boveri and others provided this material basis, while the recognition of the changes in chromosomes in germ cells during conjugation was the beginning of an understanding of the mechanism involved. Heredity was also coming into its own by the studies of Galton, who sought statistical relationships, and by the work of De Vries, who was seeking evidence of heritable changes of a marked and sudden character—the mutations of a later day as opposed to the accumulation of barely perceptible changes postulated by Darwin.

2. Zuerster Versuch: ABC Kreuzung
A. gelbbl. Körnchen
B. Erbäcker gelb
C. Pflanz. grüner
abc Kreuzung
a. gelbbl. Körnchen
b. Erbäcker grün
c. Pflanz. weiß

Der 2. Versuch wurde in zwei Reihen durchgeführt, die sich in der Anzahl der Pflanzen unterscheiden. In der ersten Reihe wurden 24 Pflanzen in der zweiten 28 Pflanzen in der dritten 29 Pflanzen in der vierten 30 Pflanzen in der fünften 31 Pflanzen in der sechsten 32 Pflanzen in der siebten 33 Pflanzen in der achten 34 Pflanzen in der neunten 35 Pflanzen in der zehnten 36 Pflanzen in der elften 37 Pflanzen in der zwölften 38 Pflanzen in der dreizehnten 39 Pflanzen in der vierzehnten 40 Pflanzen in der fünfzehnten 41 Pflanzen in der sechzehnten 42 Pflanzen in der siebenzehnten 43 Pflanzen in der achtzehnten 44 Pflanzen in der neunzehnten 45 Pflanzen in der zwanzigsten 46 Pflanzen in der einundzwanzigsten 47 Pflanzen in der zweiundzwanzigsten 48 Pflanzen in der dreiundzwanzigsten 49 Pflanzen in der vierundzwanzigsten 50 Pflanzen in der fünfundzwanzigsten 51 Pflanzen in der sechsundzwanzigsten 52 Pflanzen in der siebenundzwanzigsten 53 Pflanzen in der achtundzwanzigsten 54 Pflanzen in der neunundzwanzigsten 55 Pflanzen in der hundertsten.

8 Pflanzen ABC	22 Pflanzen ABCc	45 Pflanzen ABbCc
14 " ABc	17 " AbCc	36 " aBbCc
9 " AbC	25 " aBCc	38 " AaBCc
11 " Abc	20 " abCc	40 " AabCc
8 " aBC	15 " ABbC	49 " AaBbC
10 " aBc	18 " ABbc	48 " AaBbc
10 " abC	19 " aBbC	
7 " abc	24 " aBbc	
	14 " AaBC	78 Pflanzen AaBbCc
	18 " AaBc	
	20 " AabC	
	16 " Aabc	

FIG. 3.—The manuscript of Mendel's classical paper was discovered by Iltis in the archives of the Natural Sciences Society at Brünn with an endorsement by the editor of the proceedings for 40 reprints to be run off. The extract reproduced here deals with the observed types of plants obtained from self-fertilized trihybrid peas. (Reproduced from the facsimile in L. Gedda, *Novant' Anni delle Leggi Mendeliane*. Rome, 1955.)

It was therefore no accident that a number of biologists, or rather botanists, were studying not so much hybridization as problems of transmission, and were using simple mathematical procedures as well as visual observations. De Vries, a Dutch botanist, was outstanding among these, and when he published in March 1900 the results of his breeding experiments on a whole series of plants he acknowledged the findings of Mendel. His report was followed within four weeks by that of Correns, and a few weeks later by that of Tschermak, both of whom had published similar findings independently of each other and of De Vries, and both of whom had also traced a reference to Mendel. De Vries's acknowledgment of Mendel was given in only the larger of his two almost simultaneously published papers, one in German and the other in French, and both Correns and Tschermak were more emphatic in their acknowledgment. De Vries held that Mendel had established his findings as a special case, unlike himself who had shown it to be valid for a large number of plants. Correns at first believed that Mendel's findings were indeed applicable to only special cases and with some limitations, but subsequently contributed greatly to the recognition of Mendel by discovering and publishing Mendel's letters to Naegeli. Tschermak himself helped enthusiastically in the erection of a monument to Mendel at Brünn in 1910. The discovery of Mendel's work meant, of course, the discovery of Mendel's interpretation as well as his results. It is an open question whether the study of genetics would have advanced so rapidly without Mendel's analysis ready at hand.

Even in 1900 the recognition of Mendel was not uneventful. The discovery of Mendel unleashed a storm of opposition, especially from the biometrical school of Galton and his successors. Galton himself, in 1902, at the age of 80, admitted an affinity to Mendel in that they were both born in the same year, but his followers were less accommodating in their opposition and jeered more rudely. The objections to Mendel's theory of units of inheritance were in the first place that the explanation was much too simple to fit any but special cases in plants, and, secondly, that it could not account for most features in animals and man since physical traits were continuous rather than discontinuous. While on the one hand more and more experimental work confirmed Mendel's findings, exceptions also accumulated. In the event, the exceptions proved valuable confirmatory evidence of Mendel's views, for the breakdown in the expected mathematical ratios, occasionally seen when two or more characters were studied in combination in a particular plant or animal, was ultimately seen to be the result of linkage of units along the same chromosome. Sex-linkage in inheritance—an important apparent exception—proved brilliantly confirmatory when it was recognized that sex itself was determined by units of inheritance carried on the sex chromosomes. As early as 1902 Sutton recognized that the division and recombination of chromosomes in reproduction paralleled the behaviour of Mendel's postulated units.

It soon became clear that instead of being in conflict with each other the mathematical, cytological, and experimental results fitted into a comprehensive theory of inheritance, the one exception being that the biometrical approach was more suitable for continuous variations than for the simpler situations where monofactorial inheritance in monohybrids or polyhybrids could be analysed. Even so, the biometrical approach steadily gave way to factorial analysis when it became clear that some characters were determined, not by one hereditary factor, but by the combination of two or more factors. The continuous variations seen in most physiological features in the higher animals—such as colour and size—were in fact aspects of multifactorial inheritance. In contrast, hereditary disease in man was a discontinuous variation and thus specially suitable for Mendelian analysis.

The rediscovery of Mendel led to the designation of Mendelism to what would now be regarded as merely confirmatory studies, elaborated for analysis initially of monofactorial

and subsequently also of multifactorial inheritance. By 1904 the term "genetics" was introduced by Bateson for the now rapidly growing study, still regarded by him as centred on variation and its nature. Genetics, in this limited sense, grew into something approaching the modern study when a decade later the work of Morgan on the chromosomes of *Drosophila* gave Mendel's factors a local habitation and a name. Henceforth genes and chromosomes constituted the material basis of heredity.

Present-day genetics permeates all branches of biology. In studies of Man, heredity is the basis not only of normal and pathological physical traits but also of many of the complex problems of sociology, and some of these problems are at last becoming amenable to scientific analysis.

IV. Medical Genetics

Inherited deformity and disease excited considerable attention during the nineteenth century. There was in fact some tendency to ascribe to heredity a significance which it did not possess. Thus infectious diseases like tuberculosis and nutritional disorders like rickets were regarded as hereditary diseases because of their frequent familial incidence.

In contrast, there was no appreciation of the fact that what were called familial diseases—the recessive disorders of to-day—were genetically determined affections. Transmission from generation to generation—the present-day dominant diseases—was recognized as hereditary, but transmitted maternal infections were also regarded as hereditary, as the term hereditary syphilis testifies. Nasse's law (1820), elaborated for haemophilia, is evidence of the recognition of sex-linkage as a clinical phenomenon. Sedgwick in 1863 in this country, and Lucas 13 years earlier in France, wrote extensively on the subject of hereditary disorders, but many of their observations were anecdotal or merely curious, and there was no clear distinction between the genuine and spurious, and certainly no appreciation of any fundamental principles. What particularly puzzled the older observers was that an affected parent could have normal children and that in "familial diseases" the parents themselves were normal.

Together with all these uncertainties there were the social revulsion against incest, the theological disapproval of marriages between some ranks of family relationships, and the legal prohibition in many countries of some such marriages. It is likely that these restrictions were based on a traditional recognition of the dangers inherent in in-breeding in man; certainly the significance of parental consanguinity in such affections as retinitis pigmentosa and deaf-mutism was known even if not understood.

At the rediscovery of Mendel's work medicine was still predominantly veered towards the problems of infection, but the considerable literature on inherited diseases posed unanswered questions. To some of these questions the Mendelian hypotheses gave ready answers, for disease was technically a discontinuous variation. The occurrence of healthy people in a family with dominant disease was now easily explained, for 50% of offspring would carry only normal factors; and when Garrod in 1902 published a now classical paper on alkaptonuria in which both familial incidence and the frequency of parental consanguinity were brought out Bateson and Edith Saunders realized that familial cases were instances of recessive inheritance ("the mating of first cousins gives exactly the conditions most likely to enable a rare and usually recessive character to show itself"). The appreciation of recessive disorders and the subsequent recognition that sex-linkage could be explained by factors carried by the sex chromosomes brought considerable clarification. These advances were made by a relatively small group of physicians, for the profession as a whole, with its tradition of taking the patient as the subject of investigation, found it difficult to adjust itself to thinking of the family rather than the individual as the initial unit. In consequence, medical

genetics, which could have advanced rapidly with the rediscovery of Mendel's work, failed to achieve this advance until many years later, and there is some irony in the fact that during these wasted years it was the work of the anti-Mendelians that was outstanding.

The clarification of the status of familial disease made available a mass of clinical observations that in turn could elucidate Mendelian principles. Over the years came recognition of the specific problems of Mendelian ratios in the relatively small numbers presented by human families. There also came the concepts of expression and of penetrance, particularly in dominant disorders, and the concepts of incomplete recessiveness and the carrier state. The multiplicity of blood groups brought much elucidation on multiple allelomorphs. The interaction between heredity and environment seen in an extreme form in the fractures induced by minimal trauma in fragilitas ossium could also be seen in more subtle aspects in other disorders, including possibly tuberculosis and other infectious diseases which were operative only in a susceptible genetic constitution. Haemolytic jaundice of infants was seen not to be strictly genetic in character but a form of induced autolysis because of genetic incompatibility.

To-day both the significance and the scope of medical genetics are increasing rapidly. As the infectious diseases are being brought under control, the constitutional factors of disease are once again assuming a dominant place in pathology, and it is becoming increasingly obvious that these are largely determined genetically. Moreover, an extensive range of clinical appearances previously considered environmental in origin have come to be recognized as merely different stages of hereditary diseases which run an evolutionary course in post-natal life and thus present different aspects in different members of a family.

But present-day medical genetics is no longer a matter of collecting and interpreting pedigrees. Statistical methods have made possible the assessment of the frequency of pathogenic genes and of mutation rates in the population, so that genetically determined disease is no longer an altogether unknown quantity. Recognition of the inborn errors of metabolism of Garrod have led to intensive studies of enzyme systems at the cellular level, and there is hope that the uncovering of biochemical faults as the mechanism of genetic disorders may open therapeutic possibilities. Some such possibilities are already being effected, as, for instance, the relative control of galactosaemia by excluding galactose in the infant's food.

Faulty protein synthesis is yet another possible basis of genetic disorders. This is seen most strikingly in the current studies on sickle-cell anaemia and the other haemoglobinopathies, and it is likely that many other hereditary anomalies, including such classical affections as retinitis pigmentosa, may come to be explained in this manner.

Ever since the gene came to be located in the chromosome, the possibility of chromosomal anomalies as a cause of hereditary disease has been under consideration. Until recently such anomalies—observed microscopically—were held to be incompatible with life if they were present in any but a minimal form. It is now clear that chromosomal anomalies are in fact a substantial cause of pathological states. Down's syndrome (mongolism) is an outstanding example.

The gene itself has followed the atom in ceasing to be the irreducible particle of matter. There is evidence that the gene—which may have a thickness of a millionth of a millimetre—is itself a complex of thinner segments each with its specific effect. The intensive chemical studies on deoxyribose-nucleic acid (D.N.A.) have bearings on both chromosomes and genes.

A Fundamental Problem

The nature of the gene is a problem that goes to the root of all biological thought. Since each cell in the body carries a full complement of chromosomes—so that incidentally each cell in the body is either male or female, and demonstrably so histologically—there must occur in the course of repeated divisions of the fertilized ovum not only development of particular cells giving particular tissues and organs but suppression within such cells of all other potentialities. The puzzle of life therefore begins at a subcellular level, and an understanding of the pathways of gene action has become a fundamental problem in biology, which itself is reaching out towards the control of the energy locked in the gene. To a hypothetical philosophical biologist hereditary diseases represent Nature's experiments in gene action, and as such diseases in man are so intensively studied daily at thousands of centres they would give endless material for genetic investigations, for the study of anomalously acting genes is an excellent exercise in attempts to understand the normal. It is possible that ultimately Mendel's contribution to medicine will be seen to lie not so much in the opening of a new chapter in pathology as in the steering of medicine well into the main stream of biological thought.

Somatic Mutation and Chronic Disease*

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It is common to divide disease into that for which environmental factors are responsible and that which is genetic in origin, or, more correctly, to consider the relative environmental and genetic components that are involved in any given clinical situation. Mechanical trauma, poisoning, and most infections are almost wholly environmental; haemophilia and phenylketonuria are almost wholly genetic; and there is a range of conditions in which the joint effect of heredity and environment is clearly recognizable—for example, tuberculosis and poliomyelitis among infections, primaquine sensitivity among poisonings.

There is, however, another category of disease processes which seem to depend on something additional to the environmental

and genetic factors—namely, somatic mutation. For many years it has been recognized that the age-specific incidence of several types of cancer showed a strikingly simple pattern when plotted against age. If both age-specific incidence and age were plotted logarithmically the points fell on a straight line. This can be interpreted only on the assumption that the condition is determined by the random occurrence of events occurring with equal likelihood over the time-span being considered. The only random event which it is reasonable to consider in a

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