98

THE BEARING OF GENETICS ON THEORIES OF EVOLUTION

Address delivered before the Royal Society of Dublin, January 31st, 1932.

BY R. A. FISHER, Sc.D., F.R.S.
Rothamsted Experimental Station, Harpenden

WE are all familiar with the story of the Tower of Babel, one of the strangest and most dramatic of the Old Testament. The peoples of the earth, having, at that time, a single universal language, and constituting apparently a single nation, arrive, under the leadership of the heroic Nimrod, on the fertile plains of Shinar. There they determine to erect a central city, and a colossal tower, worthy of a world-metropolis, and reaching even as far as heaven. Whether the motive of this grandiose project was merely, as the text says, to make a name for themselves, as in the case of the transatlantic sky-scrapers, or whether it was the ambition of the leaders to establish a colony in the Utopian region beyond the clouds, is not made altogether clear, for the Deity, we are told, put a stop to the entire project by confounding the language of the builders, so that they could no longer understand each other.

A common metaphor represents the labours of men of science as the construction of a gigantic edifice, upon the wings and annexes of which workers in different branches of natural knowledge are engaged. The various methods and techniques in which we have been trained correspond to the crafts of the different classes of artisans, the stone-cutters, masons, plasterers, sculptors, and painters, whose co-operation is needed to produce a finished and habitable building. The contemplation of this similitude, of the savants of all nations proving, by their example, that man is capable of something better, and more fruitful, than the pursuit of international rivalries, or mutually destructive contests, whether by economic or by military methods, has certainly in it something both elevating and encouraging. Yet the old story of the Tower of Babel, itself a noble, though doubtless a presumptuous and misguided, enterprise, bears a sufficient resemblance to the edifice of science for it to contain, perhaps, some hints to guide us in our own endeavours.

 Science Progress, 27: 273-287, (1932).

We are not told exactly in what manner the confusion of tongues originated ; whether by a sudden and miraculous transmutation in the word-centre of each individual, he began forthwith and, all unconscious of the change, to express his ideas in a babbling jargon, meaningless to his fellows ; or whether, as the work progressed, groups of workers so concentrated their attention upon special parts of the building, and on the particular technical problems of their crafts, that they gradually came to use words unintelligible outside their own little circle ; or, still worse, to use the old words with meanings quite unknown to the workers on the floor above, until their old common language had been lost irrevocably.

Enterprising men, especially kings, have from time to time endeavoured to ascertain experimentally what was the primitive tongue spoken in the infancy of mankind, before diversity of language had arisen. James IV of Scotland, for example, had two children reared by a dumb foster-mother, in solitude, on the island of Inchkeith. When old enough, it is said that they gave tongue in excellent Hebrew. Against this encouraging result we must, however, set the definitely negative conclusion of a much more thoroughly replicated experiment by the Mogul Emperor, Akbar Khan. In this case thirty "parallels" were employed, who, on growing up, since they spoke no particular language, confirmed the sceptical Emperor in his adhesion to no particular religion.

If we were to ask, on the other hand, what universal language could enable men of science to understand each other sufficiently well for effective co-operation, I submit that there can be only one answer. If we could select a group of men of science, completely purge their minds of all knowledge of language, and allow them time to develop the means of conveying to one another their scientific ideas, I have no doubt whatever that the only successful medium they could devise would be that ancient system of logic and deductive reasoning first perfected by the Greeks, and which we know as Mathematics. Deductive and inductive reasoning, to change the metaphor, are the means by which alone we can ascertain whether or not a new slab of observational fact will fit into its place in our edifice; and the mathematical expression of such reasoning is the only effective cement which we possess, by which such new facts can be held fast as parts of a coherent structure.

I do not at all anticipate that this view will be readily conceded. It is quite contrary to the prevalent opinion, for which mathematicians themselves are largely responsible, that mathematics is the most specialised and isolated of scientific studies. It is contrary, too, to that scheme of classification of the sciences, which, I believe, originated with the philosopher

Comte, in which we ascend a kind of hierarchy from mathematics, the simplest and most fundamental, through physics and chemistry, to the biological sciences ; and thence, with increasing dignity and importance, to psychology, and to the Queen of the Sciences, sociology. Although votaries of the natural sciences generally would doubtless repudiate this particular monarch, this arrangement appears to have been really influential in the organisation of our universities, and of our scientific societies. It is familiarly incorporated in that aphorism which defines chemistry as "the messier part of physics—and the cleaner parts of biology" ; it was doubtless responsible for the fact that when the publications of the Royal Society of London were divided into two concurrent series, A and B, mathematics should have been without question included with the non-biological, and excluded from the biological group of sciences.

Such a division is logically indefensible. What is more important is that it is becoming inconvenient. Mathematics has been described as the subject in which we never know what we are talking about, nor whether what we say is true, and the description, though something of an over-statement, has the merit of emphasising the important fact that it is the method of reasoning, and not the subject-matter, that is distinctive of mathematical thought. A mathematician, if he is of *any* use, is of use as an expert in the process of reasoning, by which we pass from a theory to its logical consequences, or from an observation to the inferences which must be drawn from it. Speaking thirty years ago, it would have been proper to speak of mathematics as providing the technique only of deductive reasoning. Such a limitation would no longer be appropriate at the present time ; for, owing primarily to the work of "Student," mathematically exact inferences *can* now be drawn from the sample to the population—from the particular to the general—in an important and increasing class of cases. I refer to the Tests of Significance. The importance of this advance, for human thought in general, is, I believe, roughly equivalent to that of the first mathematically exact use of deductive reasoning, by the Greek geometers of the generation of Euclid. It is not my purpose now to enter into the logical revolution effected by "Student's" work ; but it has this immediate bearing on our subject, that, whereas the points in which the physicist requires mathematical aid lie chiefly in the deduction from a theory of its logical consequences, the biologist most frequently needs assistance in the inductive process by which general theoretical conclusions are drawn from bodies of observational data.

How greatly this has become a practical need, in all fields in which biological work is being put upon a quantitative basis, will not easily be realised without personal contact with the scientific workers, agronomists, entomologists, botanists, geneticists, marine zoologists, and many others, from Europe, Asia, Africa, and America, who, in the first five or ten years of their research experience, discover that their really urgent practical problems are essentially statistical; and who, if they are fortunate enough to have the opportunity, apply to attach themselves as voluntary workers to a statistical research laboratory, such as the department for which I am responsible at Rothamsted. Diverse as the qualifications of these workers are, they all have this in common—that while they are of a generally high intellectual capacity, they have received, in their university training, no preparation whatever for the statistical problems which are bound to confront them, as soon as they come into real touch with the questions they are set to investigate.

That is one criticism of the unnatural separation of mathematics from biology, with which I am brought personally into daily contact. What I want to discuss more particularly this evening is an historical example, by which we can judge of the effects of this separation, not on the work of any one individual, but on the course of development of a whole science. I propose to illustrate the general theme of the function of mathematical contacts with the sciences by reference to a little Babel of misunderstandings which has occupied, for a generation or two, the principal court of that part of the edifice of Science in which the biologists are at work.

Faraday and Darwin were alike in possessing transcendent powers in scientific reasoning and experimentation. By some chance of character or upbringing they were both devoid of any command of mathematical symbolism. The one devoted his life to physical and chemical, the other to geological and biological, researches. There is the basis, one might say, of a well-controlled experiment. For Faraday's discoveries were early taken up by mathematicians, especially by Maxwell, and built into a coherent electro-magnetic theory, so firmly and compactly that almost alone of the older physics it has survived the revolution caused by quantum theory and wave-mechanics. Meanwhile, accident contributed to delay the application of mathematical ideas to Darwin's theory of Natural Selection. While the *Origin of Species* was being written, the Austrian monk and mathematician, Gregor Mendel, must have been already conducting his experiments ; and six years later was able to demonstrate, in the garden pea, those statistical laws of inheritance which have since been verified throughout the animal and vegetable kingdoms. His work was fully published in a not very obscure journal, but was ignored and forgotten for thirty-five years. Presumably, it was not the kind of work which the German-speaking biologists of the time were prepared to appreciate.

If the neglect of Mendel's work for a whole generation forms a striking illustration of my theme, the immediate reactions of its rediscovery in 1900 illustrate my point even more remarkably. For two of the most prominent exponents of the importance of the new knowledge, Prof. Bateson in England, and Prof. de Vries in Holland, had already, in the nineties of the last century, made themselves notable advocates of the theory of discontinuous evolution of specific forms—the theory of evolution *per saltum*, as opposed to the gradual process of selective modification proposed by Darwin. They, therefore, seized upon the discontinuous hereditary factors demonstrated by Mendel's work, as though these had been specific differences, instead of differences, generally, between close varieties ; whereas, as we now know, forms which are ranked by systematists as specifically distinct, differ, as a rule, not in one, but in a large assemblage of Mendelian factors.

The discovery of an essential fact unknown to Darwin ought, naturally and properly, to have formed the basis of a criticism and revaluation of Darwin's theories. The particular use to which it *was* put, however, showed that neither the logical consequences of the Mendelian laws, nor the logical place in Darwin's reasoning of the erroneous "blending" theory of inheritance, were appreciated by the most prominent writers in the early history of Mendelism.

A rather careful examination of Darwin's writings, and especially of the reasoning in his two unpublished essays, in which he first developed his views, is needed to discover exactly to what extent, and in what ways, the theory of blending inheritance, which he accepted, influenced his deductions. The principle of Natural Selection itself is wholly unaffected. If a population exhibiting heritable variability experiences differential rates of mortality, or of reproduction, its average character will on any view be gradually changed. The urgent question which assailed Darwin's early thought was whether natural populations could be assumed to contain an abundant supply of heritable variability, and this, on a blending theory of inheritance, is really an urgent question. For by the continual blending of the characters of different parents all variability must be rapidly annulled. Speaking mathematically, the quantity of variability, or "variance," as we call it, will, approximately, be halved in each generation, and this carries with it two important consequences:

(i) That causes of new variability, or "mutations," as we should now say, must be exceedingly abundant (they must account, for example, for all heritable differences between whole brothers, for their entire ancestry is identical). And,

(ii) That practically all the heritable variance available for selection to work on must be of extremely recent origin, ascribable to mutations occurring within about the last ten generations.

Darwin rested his theory on the demonstrated fact that domesticated animals and plants certainly possess sufficient heritable variability to be modified perceptibly by the human breeder ; but his theory was harassed by the possibility that such heritable variability might be absent or rare in wild species, being due to quite recent mutations, induced, in domesticated species, by the conditions of domestication themselves. Hence his elaborate attempt to ascertain by inductive reasoning what are the circumstances of domestication which induce abundant mutation, and, judging these to be changed conditions and increased food supply, his inference that these circumstances must also act, though much less intensely, upon species in a state of nature. Darwin's difficulty in this respect is entirely removed when we replace the blending theory by the particulate theory of Mendel. On the particulate theory there is no possibility of the variance dying away rapidly. The existing variance is due not principally to recent mutations, but to mutations which have occurred during thousands or tens of thousands of past generations. The greater variability of domesticated species is evidence, not of a higher mutation rate under domestication, but only of man's proclivity for selecting and propagating novelties, and for the survival, under the shelter of a domesticated environment, of types which could not survive in the wild state.

The second inference from the blending theory, by which speculations were embarrassed, lay in what we should now call the enormous mutation-rates which it requires should be postulated. Darwin had no objection to these high mutation-rates, for no experimental data as to the actual rates of mutation then existed ; but he recognised that in a system in which almost every individual born was a mutant and even a multiple mutant, the environmental circumstances by which mutations might be expected to be controlled, or at least influenced, might themselves possibly be powerful agents of evolutionary change. He was therefore extremely ready to believe in "the direct effects of environment," although, by the study of the adaptive mechanisms of animals and plants, he was continually being brought back to the conclusion that such direct effects in fact achieve extremely little.

Now all possible theories of evolution fall, in this matter, into two classes. In the one class is Natural Selection, the efficacy of which is proportional merely to the actual amount of heritable variance maintained in the population, and is totally unaffected by whether that heritable variance is supplied by a mighty flood of mutations, which are always rapidly wasting away, or by a feeble trickle of mutations, the variability due to which is jealously conserved. In the other class fall all theories of evolution in which the direction of evolution is itself supposed to be governed by the direction in which mutations are occurring. Thus the Lamarckian theory postulates not merely that a mechanism exists by which use-modifications are able to induce mutations in the germ-cells, but requires the further postulate, that the mutations so induced are capable actually of controlling the evolutionary changes in progress in the organism. The case for and against has been invariably discussed in reference only to the first postulate. The second postulate has not, until recently, seriously been challenged ; but it is the more important of the two, for it is equally necessary to all such other theories as "Orthogenesis" and "Nomogenesis," by which it has been hoped to account for evolutionary modification. Now it is this second postulate, that evolutionary modification can be governed by the kind of mutations which are occurring, that is challenged by the particulate theory of inheritance. When we reject the blending theory and accept Mendelism we thereby cut down the supply of mutations by at least ten thousand fold. And calculation shows that they are no longer able to avail against even the faintest adverse selection.

That is the quantitative aspect ; and it is fully in accordance with our deductions so far, that even the largest mutation-rates, determined experimentally, seldom exceed 1 in a million in each generation. But it is the qualitative aspect which will appeal most to biologists, because it allows the greatest scope for observational verification. If, as so many theories have assumed, evolutionary change is governed by the occurrence of mutations, whatever may be the mechanism (Lamarckism, Orthogenesis, etc.), by which it is supposed that such mutations are induced, it follows that the mutations must, generally speaking, cause changes of the same kind as those which have occurred in the course of evolution ; changes, that is, towards greater complexity of organisation, and more perfect adaptation to the conditions of life, and to the ecological relations with other organisms. The breeze of mutations by which evolution is supposed to be wafted forward must not only be sufficiently powerful, but must be very prevalently in a favourable direction. Again, the experimental evidence is decisively against such a view. Some two or three hundred mutations have been studied in the fruit fly *Drosophila*, and of these not one can be said to be advantageous, while the great majority are patent defects and deformities. In addition to these, however, the most numerous class of all are actually lethal, the mutant form being totally incapable of development, and perishing, either in the egg, or at an early larval stage. That the vast majority of mutations should be deleterious is a perfectly natural consequence from the view that the organism is maintained in a highly adapted condition by natural selection, for a highly adapted condition can mean nothing else than one which is more easily injured than improved by a change in its organisation. But the observation is incompatible with the view that evolutionary change is governed by mutations, unless we are willing to believe that those organisms so far studied have almost run their evolutionary course, and are rapidly plunging towards degeneration and extinction.

From considering the two views which have been held upon the nature of inheritance, we have been led to divide theories of evolutionary modification into two classes, contrasted, and sharply contrasted, in one single characteristic. On the one hand the great majority of evolutionary speculations have rested on the unformulated assumption that it would be sufficient, to explain any particular evolutionary change, if we could explain why mutations in that organism had occurred in a particular direction. The fallacy is the common one of assuming that the truth of a proposition implies the truth of its converse. The extinct reptile *Diplodocus*, for example, evolved a neck some 20 or 30 feet long. It can, I think, reasonably be inferred from this, that in the course of its evolution a succession of mutations must have occurred, the effect of which was, amongst other things, to lengthen the neck. These mutations are *necessary*, but they are not *sufficient* to explain the particular evolutionary modification which has taken place. What cannot be inferred is that, given the occurrence of such mutations, the lengthening of the neck must follow. Had this converse proposition ever been explicitly stated, and challenged, it would have been evident that no solid grounds could have been put forward in its support, and that numerous facts well established in other organisms rendered it totally untenable. If we knew, for example, that mutations lengthening the neck were occurring now in the crocodile, we should have no reason to think that the average length of neck was increasing in that species.

But it is as well here to emphasise the limitations of our knowledge. Mutations occur so scantily that it is only possible to study them in organisms in which enormous numbers can be bred and examined. The conclusions I have mentioned from the genetical work on the fruit flies are based on the examination of between 20 and 30 million specimens, and it is obvious that, though our direct knowledge of mutations will doubtless become more detailed, and more exact, we cannot hope that it will ever become, biologically speaking, extensive. Biologists, too, have every reason to be cautious of extending conclusions from one group of organisms to another ; and, if we are to accept the view that evolution, in the hundreds of thousands of plants and animals which have evolved, has made its way in the face of a blizzard of predominantly unfavourable mutations, containing only a small minority of those that are favourable ; if, I say, this is the *prevalent* condition of evolutionary change, we may well ask whether it has not left unmistakable traces throughout the length and breadth of the animal and vegetable kingdoms. I believe this reasonable challenge can be met ; at least, if we accept certain recent interpretations of genetical phenomena, which appear at present to have substantial observational support, but which will probably be more exactly scrutinised in the near future.

There is, widely observable both in plants and animals, a remarkable tendency to exogamy, which Darwin summarised in the phrase that Nature abhors perpetual self-fertilisation. Among animals, especially those which move freely about, the separation of the sexes is the general rule, and, even where they are hermaphrodite, we generally find either that pairing is obligatory, or that cross-fertilisation is favoured by special devices. In the vegetable kingdom, the importance of cross-fertilisation seems to be the dominating factor in the evolution of the whole group of flowering plants, and to have reacted in a most important way on the evolution of the higher orders of insects. Not content, however, with obtaining facultative cross-fertilisation in this way, numerous additional adaptations are found, which, in certain groups, render it almost or quite compulsory, such are the separation of the male and female inflorescences on the same plant, as in *maize*, the separation of the sexes in different plants in the *hop*, the development of self-sterility in the *tobacco* plants, and that curious form of self-sterility known as hetero-stylism, which in the *primroses* and other genera divides the species into two or three castes, or genders, all hermaphrodite, crosses between which are required for normal fertility. In animals, the separation of the sexes seems to have been sufficient in most species ; yet we cannot fail to associate with the same series of phenomena that dread, which seems to be widely felt in mankind, of the marriage of near kin ; and, some years ago, Dr. Metz of Baltimore found in the genus of fungus gnats, *Sciara,* an intricate genetical mechanism, which distinguishes the females into two classes, male-producers and female-producers, respectively. More recently, Dr. Barnes has shown that the production of unisexual families is widespread in the large family Cecidomyidae (gall midges), and, as these species are exceedingly short-lived, and mate immediately upon emergence, we may see in this complex mechanism an adaptation to prevent the constant mating of brothers and sisters, which, pupating in close proximity, would otherwise very frequently interbreed.

Darwin was led by phenomena of this kind, and by the strong suspicion of the danger of inbreeding entertained by live-stock breeders, to demonstrate experimentally, with a number of species of plants, that the offspring obtained by self-fertilisation were, on the average, less vigorous in their growth than the offspring obtained by cross-fertilising the same parent plants. Naturally much speculation was provoked as to the reasons for which cross-fertilisation stimulated, or self-fertilisation impaired, vigour ; and it was for long widely believed that a mere difference in the genetic elements combined exerted some generally beneficial and stimulating influence. More recent work has carried the matter a good deal farther, and has given a much clearer conception both of the facts and of their causes. The facts cannot be better exemplified than by the extensive researches which have been carried out by American geneticists on maize.

When a maize plant is self-fertilised, and its progeny continued in a number of self-fertilised lines for several generations, the deterioration in yield and in the vigour of vegetative growth is striking ; and perhaps even more surprising is the complete recovery to the full ancestral vigour, obtained, in a single generation, by crossing two of these stunted lines. That alone shows that the racial stock has not been injured. Moreover, a study of the different lines shows that while all are usually inferior in some respect or other to the average commercial maize plant, the defects of different lines are strikingly distinct and individual. Moreover, the experiment of self-fertilisation can scarcely be carried out without revealing, in one or more of the lines, a distinct segregation of sharply marked defects, such as failure to develop the green pigment, chlorophyll, of the leaves. These defects are readily demonstrated to be simple Mendelian recessives. The conclusion is forced upon the investigator's mind that innumerable other recessives of the same kind, but indistinguishable by reason of the similarity of their effects, are responsible for the general lack of vigour by which all the inbred lines, though in very different degree, are characterised. This explanation immediately makes sense of the fact that, in other plants, such as wheat, self-fertilisation may be continued generation after generation without ill-effects ; or that close inbreeding of brother and sister may be continued, apparently indefinitely, as has been done in certain lines of rats ; or that even in species intolerant of inbreeding, such as guinea-pigs, lines may, with sufficient trouble, be found in which inbreeding may be carried on generation after generation without loss of health or vigour. It is the habitual cross-pollination of the maize plant, when grown commercially for seed, that has permitted the accumulation of the great swarm of defects which are revealed by self-fertilisation. In species commonly self-fertilised such recessives would be quickly eliminated, and the habitual procedure in scientific maize improvement now lies in the selection of those self-fertilised lines which are most free from serious defects, and which, on crossing, do, in the first or second generation, outyield every commercial variety of maize obtainable.

The injury observed on close inbreeding is thus exposed in an entirely new light. It is not perpetual self-fertilisation, but the first few generations, and especially the first generation, that is dangerous. The inbred lines show no perceptible further deterioration after eight or ten generations. Moreover, it is not the racial potentialities that are injured, but only the individual expression of them. It is not the species, but the individual, which suffers. The various devices which exist in nature to ensure exogamy are not for the benefit of the species, for which, so to speak, Natural Selection cares nothing, but to ensure the well-being of the immediate progeny ; to guard them against the recessive defects, which may lie latent in their parents.

Just as we can understand the meaning of the devices which ensure cross-fertilisation, if we already know that self-fertilisation is liable to have immediately injurious effects, so, in turn, we can explain the injurious effects of self-fertilisation when we know that Mendelian recessives are invariably, or preponderantly, harmful. But why should this be so ? Why should there not be as many harmful dominants with correspondingly beneficial recessive allelomorphs ? Or, simpler still, why should either form be dominant or recessive, instead of producing a cross intermediate between its parents ? It is to this question that I believe some quite recent developments are able to afford the answer. But in speaking of them I ought to say that I am expressing my own personal opinions, rather than a body of well-established and authenticated conclusions. Some years ago, in speculating on the Mendelian phenomenon of dominance I was led to make a classification of the non-lethal mutations which had appeared in the most fully studied of the fruit flies, *Drosophila melanogaster.* Out of 221 different mutations available for classification I found that 208 were described as recessive; that is to say, that in these cases the cross-bred or heterozygous fly appeared to be completely normal, and the mutation was entirely concealed. In not one case did the cross-bred fly resemble the pure-bred mutant. But in the 13 remaining cases it was intermediate, showing a defect of the same kind as the mutant, but of less intensity. The distribution of these mutations in respect of dominance or recessiveness was therefore extremely one-sided. That was a fact which influenced me greatly. A second fact which seemed to throw a direct light on its explanation is observable in what are known as series of multiple allelomorphs. In many cases the same gene has experienced, in different individuals of the same species, mutations of different kinds, and we have, as in the Albino series in rodents, an original gene, which determines full pigmentation, and a series of mutant genes which determine different degrees of dilution of the coat colour, extending, in some cases, as far as complete albinism. Using the five genes of this series available in the guinea-pig, Sewall Wright combined them in the fifteen possible ways in which pairs may be chosen from five different sorts of things ; five being homozygous, or containing a pair of genes of the same sort, and ten heterozygous, compounded of unlike genes ; and he bred a sufficient number of animals of each combination to study the average depth of pigmentation, and its variability within each type, both in the black and in the red portions of the coat. He found that the five homozygous combinations were all perfectly distinct with very little variability compared with the differences between the average intensities. Of the ten heterozygous or cross-bred classes, four, which were compounded of the non-mutant or wild-type gene, and one or other of its mutant derivatives, were all completely indistinguishable from each other, and from the pure wild-type coloration. The remaining six heterozygotes, however, were in every case clearly intermediate between the two homozygous types from which they had been derived. The whole body of observations may be summarised in the two rules : that the wild-type gene is completely dominant to all other genes of the series, whilst between these other genes dominance is entirely absent. Now these two rules are found to hold very generally in the many series of multiple allelomorphs which have been studied in other organisms ; and since such an arrangement would be overturned whenever, in the course of evolutionary change, any gene happened to be replaced in the wild population by one of its mutants, unless at the same time the relationship of dominance became reversed, it appeared to me to follow necessarily that dominance, which is after all only the developmental reaction of the organism to a particular gene-combination, was itself a by-product of the evolutionary process.

The mutations which we can observe in the comparatively few individuals which can be kept under experimental observation must represent, on the whole, those which are occurring with the highest mutation-rates, and which must occur regularly in enormously greater numbers in the wild populations. Moreover, many of them must have been occurring in the past for perhaps millions of generations. We know this because we find different related species giving rise to the same mutations. Such a history is, of course, only possible for disadvantageous mutations, always kept rare, in spite of their continual occurrence, by counter-selection ; and in such a situation it may be shown that selection will continually favour the modification of the heterozygote towards the normal condition, and only when the heterozygote has become completely normal, and the mutation has become completely recessive, will any appreciable modification of the homozygote commence to take place. If this second stage also were completed there would be nothing left for the geneticist to observe, and this stage can only be demonstrated in such a favourable case as is afforded by the little tropical fish, *Lebistes reticulatus,* where certain mutants affecting the coloration appear to be beneficial in the male, but unfavourable in the female fish, and where the visible effects have been almost completely suppressed in the female.

I should very unduly prolong this lecture if I were to attempt to give any full account of the experimental evidence on which this theory of the evolutionary modification of dominance can be supported. I have recently put forward the case in some detail in a paper in *Biological Reviews,* and I can do no better now than to mention one very decisive instance for which, when I wrote, the evidence was still incomplete.

The New World cottons form a group of species particularly favourable for genetical research, for the reason that while distinct in many good taxonomic characters, they are mutually fertile, and give fully fertile hybrids. In the Sea Island cotton a mutant known as Crinkled Dwarf has been frequently observed to appear, although it apparently does not occur in other species of New World cotton. In the course of his experiments in Trinidad, Dr. Harland happened to cross a Crinkled Dwarf Sea Island plant with two other American species.

In the first generation the crinkled character appeared not to be completely recessive, for the hybrids showed slight signs of crinkling ; and, on self-fertilising these, instead of obtaining three-quarter normal and one-quarter crinkled plants, little more than a quarter were normal, while the remainder showed a totally unclassifiable series of all grades of crinkling. The importance of this case, for the theory of the origin of dominance, was at once recognised by Dr. Hutchinson, Dr. Harland's assistant ; and the more crucial experiment was set on foot of introducing the Crinkled Dwarf mutant, by successive back-crossings, into a pure race of Upland cotton. The later generations show that, in the Upland species, Crinkled Dwarf is neither a dominant nor a recessive. The heterozygote is about as much dwarfed as is the homozygote in Sea Island ; while in Upland the homozygote is so extremely dwarfed as to be scarcely viable. Moreover, the stages by which this condition was reached during the experiment indicate, Dr. Harland tells me, by the diminishing variability of the crinkled character, that Sea Island cotton differs from the other American species in a group of modifying factors, which together act to make the Crinkled Dwarf mutant completely recessive in that species. It may well be long before we have stronger or more direct evidence that the recessiveness of mutations is itself a consequence of a prolonged evolutionary process, by which each species reacts to the unfavourable mutations with which it is persistently peppered.

If we are asked, then, what evident traces have been left on the organisation of plants and animals in general, by their having made their evolutionary progress in the teeth of a shower of predominantly unfavourable mutations, we can point in succession to three very widespread phenomena. First, the absence of true dominants, and the abundance of recessives, among mutant genes as compared with the genes prevalent in wild populations ; the recessives have become so, *because* they are unfavourable ; next, to the injury experienced on self-fertilisation, or inbreeding, in populations in which harmful recessives have been allowed to accumulate ; and thirdly, to the separation of the sexes, and all other similar devices to favour exogamy, which are evident adaptations for avoiding this injury. Wherever any of these three phenomena can be demonstrated, there we have evidence that the evolutionary process has not been favoured, but predominantly opposed by the mutations which have occurred. Every theory of evolution which assumes, as do all the theories alternative to Natural Selection, that evolutionary change can be explained by some hypothetical agency capable of controlling the nature of the mutations which occur, is invoking a cause which demonstrably would not work even if it were known to exist.

In short, the net results of substituting the idea of particulate inheritance, in accordance with Mendel's discovery for the previous notion of blending inheritance, has been to remove the chief logical difficulty to the theory of Natural Selection, by which Darwin was harassed in the development of the theory, and at one blow to dispose of every alternative proposal which has been made to give a rational account of the evolutionary process. When we cast our minds back over the history of biological theories, both in the last quarter of the nineteenth century and in the first quarter of this, it is, I submit, a question worth considering whether a sympathetic contact with mathematical ideas would not have induced such continuity in the grasp of the logical purport of the arguments used at different periods as would have obviated the chaotic misunderstandings which are so marked a feature of this history. Incidentally I believe that the popular reputation of biology will be raised, and some of the *point* of mathematics will be more widely recognised, the more thorough and extensive such intellectual contact can be made. In the present movement towards a fuller development of the mathematical ideas underlying biological theories, a movement which is active not only in these Islands, but also in Germany and the United States, it is principally the biologists, such as Haldane, Bernstein, and Sewall Wright, who have taken the initiative. It is therefore more particularly for mathematicians to consider whether the academic organisation of their studies is competent to foster, or destined to retard, this further extension of their application.

REFERENCES

R. A. Fisher (1930) : *The Genetical Theory of Natural Selection.* Oxford: The Clarendon Press, 286 pp.

R. A. Fisher (1931): " The Evolution of Dominance," *Biological Reviews,* vol. VI, pp. 345-68.