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GENES, PLANTS AND PEOPLE

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by C. D. Darlington

RECENT ADVANCES IN CYTOLOGY
2nd ed. Churchill (1937)

THE EVOLUTION OF GENETIC SYSTEMS
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with E. K. Janaki Ammal
CHROMOSOME ATLAS OF CULTIVATED PLANTS
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ESSAYS ON GENETICS

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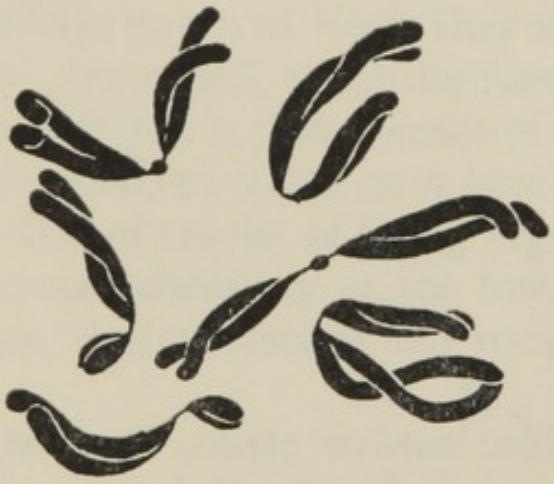
and K. Mather



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PREFACE

THE present essays are here published in a collected edition to meet the demand for the separate articles of which reprints are no longer available. They have been written over a period of nearly twenty years during most of which time the two of us have been working together to solve the same problems from different points of view. They are problems, it is now becoming recognised, which are fundamental for biology as a whole and it is in consequence of this that the different essays have come to cover, or at least to infiltrate, almost the whole field of studies of living organisms from gene, virus and cancer chemistry at the lowest level, to population genetics, mating systems and social science at the highest.

These articles were of course written individually for different immediate ends but one who now reads them together may discern a unity of purpose. That purpose has been to reduce the foundations of biology to a single system of prediction, a system of cause and effect coherent with the physical sciences. It is a purpose which the developments of the last ten years in many countries have splendidly combined to fulfil. We hope we have in our references sufficiently acknowledged the diverse achievements in theory, in experiment, and in technique of our many colleagues, achievements which have made these astonishing advances possible.

Apart from any interest in the individual articles we believe therefore that the series as a whole will be of some value in two other ways. In the first place it should show

the sequence of ideas in genetics during a critical period in its development and especially the interaction of the two methods of experimental breeding and microscopic observation which has led to the establishment of modern genetic theory. And in the second place it should serve to introduce the concepts and methods of genetics to the general student. These concepts and methods we have presented in greater detail in our Elements of Genetics.

It remains to add a postscript on Soviet Russia, the subject of two of the essays. In that country genetics, far from being advanced, has been destroyed—since our essays were written. Those who read this book will be able to judge for themselves something of the causes and the consequences of this significant event.

C. D. DARLINGTON
K. MATHER

John Innes Horticultural Institution
March, 1948

NOTE

We are indebted for permission to reprint our articles to the publishers and editors of the periodicals in which they first appeared, as follows :—

Nature, *Discovery*, the *Scientific Journal* of the Royal College of Science and the *Quarterly Journal* of the British Association for the Advancement of Science.

Introduction *Herbertia*, 1937, 63-69.
Essay 1 *Nature*, **124** : 62-64, 98-100.
,, 2 *Nature*, **127** : 709-712.
,, 3 *Nature*, **140** : 759-776.
,, 4 *Nature*, **149** : 66-69.
,, 5 *Nature*, **152** : 315-319.
,, 6 *Nature*, **154** : 164-169.
,, 7 *Nature*, **145** : 484-486.
,, 8 *Nature*, **149** : 54-56.
Essay 9 *Nature*, **149** : 427-430.
,, 10 *Nature*, **151** : 68-71.
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,, 12 *The Royal College of Science Journal*, **14** : 58-64.
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,, 15 *Discovery*, **6** : 331-333.
,, 16 *Quarterly Journal* of The British Association for the Advancement of Science, **10** : 124-126.
Appendix : The Nineteenth Century and After, September, 1947.

The microphotographs of the first essay have been arranged in a plate and two further contemporary photographs inserted. Magnifications have also been given, and a bibliography added to this article.

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ILLUSTRATIONS

INTRODUCTION

THE EARLY HYBRIDIZERS AND THE ORIGINS OF GENETICS

THE importance of the early hybridizers, Kölreuter and Gärtner, Knight and Herbert, lies in what their work did to lay the foundations of genetics as we know it to-day, and in order to understand what this means we have to enquire what those foundations are.

The Greek philosophers who first speculated about the nature of things paid more attention than is generally realized to problems of heredity. And what they said is worth considering, because they disputed about questions that we still dispute about. Their problems are still alive. They were mainly concerned with animals so far as sexual reproduction was concerned, although they, or at least some of them, realized that a differentiation of sexes occurred in plants. They had already learnt what some primitive people have not yet learnt, that the male as well as the female is necessary for reproduction. Some even considered the male the more important, a view still expressed in our social usage. It was generally held that evolution of some kind had taken place, though its comprehensive nature was not generally grasped. In regard to its mechanism a wide cleavage of opinion arose between two schools. There were, on the one hand, those who like Aristotle supposed that a purpose, divine or natural, worked by the inheritance of acquired characters to produce conformity with an imagined harmony of nature. On the

other hand, there were those who saw no purpose or design in the order of things, and conceived of living organisms as growing and changing according to deterministic laws, laws which equally governed non-living beings. Such a cleavage still persists to-day.

These disputes did not rest on the strict experimental evidence that can now be adduced but merely on observations of a world which clearly provides by its ordinary changes the means of testing many fundamental hypotheses, as it still does in astronomy or cytology. From such observations emerged one theory which we ought to keep in mind because it agrees in so many respects with the views underlying modern genetics. This was the theory developed with closely reasoned argument by the atomic and materialistic philosophers and preserved for us largely in the great poem of Lucretius. It may be summarized under five heads—(1) Material bodies handed down from one generation to the next determine heredity both of body and mind. Matter being atomic, inheritance is atomic or particulate as we now call it; (2) The offspring are derived from materials of both parents, sometimes more of one than of the other, the two being, therefore, merely statistically equal; (3) Separation and recombination of these bodies in the course of sexual reproduction is responsible for the separation, recombination and reversion of characters; (4) Evolution occurs in the sense that some species become extinct while others change. Man, for example, has developed from brutish ancestors without law or language. There was no all-embracing scheme of evolutionary change and there was equally no conception of species being fixed; and (5) New structures arise by chance and survive if they are useful. Nature eliminates unprofitable types. They do not come into being for a purpose or in response to use. Aristotle thought this was leaving too much to chance, an argument that was equally to be used against Darwin.

There is no doubt that with the coming of Christianity the unpalatable views of the atomists were suppressed.

Divine purpose and the inheritance of the effects of sin are part and parcel of revealed religion as well as of popular prejudice. When philosophical support was needed by the mediæval church to satisfy the growth of intellectual enquiry, Aristotle was established as the authority and the materialistic explanations of heredity, if they had not already been forgotten, were left unheeded. Just as the flat earth and geocentric theories already rejected by Greek mathematicians had to be disproved again by modern astronomy, so the fixity of species and the inheritance of acquired characters rejected by the atomists had to be unlearnt again by modern genetics. In both cases the new discovery seems to have disregarded the old. The traditional opposition to it has also been deeper and the proofs, therefore, have had to be more rigorous and more repetitive.

Modern science is not derived from Greek atomism, but it is in harmony with it. Modern science is philosophically inarticulate. Its philosophical method has been expressed by Bacon, but it was intuitive in Bacon's contemporaries and has remained so in most of their successors. The complexity and specialization of science has recently aggravated this fault and has led to special errors that we shall see later. Modern biology has, therefore, developed in complete ignorance of Greek materialism. It has had to start from the beginning again. Indeed, worse than that, it has had to start with the special incubus of the dogma of special creation, a dogma which has taken 100 years to destroy. One effect of this dogma was probably to attach greater interest to the precise determination of species than would otherwise have arisen. Since species were as they always had been, they would likewise remain as they always had been. Their describers borrowed an eponymous immortality from the dogma of fixity they religiously applied. The vastly increased flora and fauna thrown open to our study by the great navigations have occupied systematists ever since. But it would be a mistake to

imagine that the founders of systematics considered species in the formal way that has been adopted by most of their imitators. John Ray, in 1686, gave us a definition of a species which cannot be improved upon to-day. It is not a definition generally used by systematists. No more certain criterion of a species exists, he says, than that it breeds true within its own limits (nulla certior occurrit quam distincta propagatio ex semine). In other words, the species of convenience is also the species of descent.

Ray's definition, like Linnaeus's which followed it, was genetic. It was with them a working hypothesis and no dogma at all. The need of testing it was to a great extent the stimulus of the early hybridizers. During the lifetime of Linnaeus it became gradually realized that species of plants as well as animals would cross and even give fertile hybrids. The foundations of the notion of fixity were being undermined. And Linnaeus realized it although, again, his disciples did not. In his essay on the sexes of plants in 1760, we find him asking himself whether all the members of a genus cannot be supposed to have a common ancestor, and bravely advocating the study of hybrids to his fellow botanists.

Linnaeus's advice had been anticipated by the work of Kölreuter, who published the first extensive treatment of artificial hybrids in the following year. Kölreuter's book marks an important advance in two ways. He not only made controlled crosses between species; he attempted to find out what the physical means of reproduction was at the same time. He examined pollen grains and he tried to see whether individual pollen grains would succeed in fertilization. His observations showed the lines on which future progress would be made, but he was not very successful. The microscope was still inadequate. Consequently Kölreuter spoke of mass effects where we would now speak of individual combinations. Kölreuter, unlike Linnaeus, did not consider that hybridization made possible the production of new species or could be held to account

for the origin of old ones. To him and to his contemporaries the sterility of hybrids proved the fixity of species, and if a hybrid was not sterile its parents were not different species. The important evolutionary bearings of hybridization were, therefore, lost until the question was taken up by Herbert in 1819.

William Herbert was at once a practical gardener, a practical hybridizer and a practical systematist. He knew that he could "create" (as he called it) new forms by hybridization within genera. He knew that in some genera all the species would cross. He believed that organisms had been created by the Almighty at a relatively recent date. He therefore concluded (as Linnaeus had done, but with more evidence and more conviction) that the genera had been created and that the species were derived from them by later change. With his religious convictions no more was possible. It was, however, the thin edge of the wedge that Darwin drove home.

At the same time Herbert reaffirmed the genetic definition of species as groups which "naturally maintain themselves distinct" (almost the words of Ray) while there was "no real or natural line of difference between species and permanent or descendible variety" (almost the words of Darwin).

Herbert bridges the gap, not only between Ray and Darwin, but also between Kölreuter and Mendel. In his early years men spoke of forces of heredity (perhaps they still do); others spoke of essences and fluids; and others still of tinctures and tendencies. The ancient notion popularized by Linnaeus that the outside was derived from the mother, the inside from the father, was still prevalent. But by the time Herbert writes, in 1847, a change has taken place. Pollen tubes have been seen to grow down the style and enter the ovule. It is no longer necessary to cut off the styles to prove, as he had done, that fertilization is not instantaneous. The structure of the plant has been reduced to cells as units. Nuclei have been observed in these cells. Herbert concludes that "the fecundation of the ovules is

not a simple but a complicated process." Nevertheless, he concludes also that "we are utterly in the dark as to the mystery of fertilization."

Herbert was evidently born too soon to appreciate the later cytological discoveries. His industry led him to try innumerable experiments many of which would have been unnecessary in the light of microscopic observation, and often with results which were bound to be confusing, working as he did with species of various kinds whose nature he could not possibly tell. When, for example, he produced true breeding hybrids in *Amaryllis* and *Œnothera* he could not know that he might be dealing with polyploids in the one case and permanent interchange hybrids in the other, from whose behaviour no general rule could be drawn. Others have been less discreet. Again in the absence of cytological observation the distinction between self-sterility and cross-sterility was a baffling one. Only later was Darwin able to distinguish between the failure of the pollen tube and the failure of the embryo. Microscopic observation showed the way to genetic analysis.

A younger man was bound to look at the matter differently. The discovery between 1840 and 1860 of the unitary and cellular character of the processes of fertilization naturally made it possible to look at the whole of heredity from a new point of view. At the same time Darwin had been collecting the diverse evidence of variation and hybridization, palæontology and stratigraphy into one consistent and deterministic account of evolution. These two advances brought men back to the materialistic way of thinking that had been lost in biology for so long. The one who profited by this was Mendel. In a sense he did nothing that had not been done before. He crossed different varieties of peas and discovered a dominance of the characters of one parent in the first generation, as Knight had done. He discovered segregation of their differences in the second generation, as Goss and Seton had done. He explained the properties of the cotyledons as properties of the

seedling generation, as Knight had also done. He proved, according to a letter of 1870, that single pollen grains effected fertilization, as Kölreuter had at least attempted to do.

The difference between Mendel and his predecessors was that he knew the material processes underlying heredity and had the kind of mind that could explain their results in a material way. He understood that the simplest assumptions always had to be used until they were disproved. The cell-theory and the evolution theory displayed to him "the unity in the developmental plan of organic life." The importance of studies of the fusion of cells in the fertilization of fishes and algæ would not, therefore, escape him. We find also that he rejects continuity in variation. This continuity Darwin had brought back into biology just when discontinuity had been established in chemistry, a mistake the Greeks looking at science as a whole would never have made. We also find that Mendel rejected the improvement of plants by cultivation and the general Lamarckian theory into which Darwin lapsed only a few years later. In view of all these things we cannot even be surprised when we learn from the convincing argument of Fisher that Mendel knew what he was going to get before he began his critical experiments in hybridization. He did not draw his bow at a venture.

Mendel directed his enquiries with a rigorous determinism. He assumed that every property of every seedling was determined by something that happened in its two parents. He had, therefore, to consider all the progeny from a cross and all their characters. In order to do so and find out the law governing what happened in the parents he had to take their characters individually and he had to take their progeny individually. He had to count them. None of his predecessors had the audacity and conviction in determinism to make such a task seem worth while. De Vilmorin, who recognized the importance of individuals, worked only on inbred stocks. Goss and Seton began counting, but they were baulked by not realizing that an

exact equality at segregation will not necessarily give an exact equality in the progeny because every germ cell will not act. A conviction of determinism and uniformity led Mendel to the view that the same rules applied to all organisms; nevertheless, the great majority of biologists were then (and still are now) too faint-hearted to use such bold assumptions in their work. They are afraid of being swept off their feet by a revolutionary hypothesis.

Mendel's theory, therefore, meant a release from prejudice that was as important to purely scientific thought as Darwin's theory had been. Together they undid the superstitions of two thousand years and brought us back to the principles enunciated by Lucretius.

The inevitable relationship between the practice of breeding and the observation of the reproductive structures—sperm, eggs and, nowadays, chromosomes and genes—is made doubly clear owing to the freak of history by which Mendel's work was lost for 30 years, overshadowed by Darwinism. Mendel knew of cells and nuclei. He went further to something inside the nuclei. We may say that he predicted the genes. While his paper was still unknown, in 1892 Weismann arrived at just the same conclusion on entirely different evidence, on the evidence in fact that the microscope had only just brought to light. Fertilization had been found in 1875 to consist in the fusion of nuclei. The division of nuclei had been found to perpetuate a constant number of chromosomes. Weismann predicted the occurrence of a reduction to compensate for the addition of chromosomes in the nuclei at fertilization. The chromosomes consisted of units or particles responsible for heredity. Variation must, therefore, be discontinuous and the differences responsible must separate and recombine as the chromosomes are observed to do. The chromosomes being handed down from generation to generation unchanged, except in their combinations, the inheritance of acquired characters was excluded. We now know from a consideration of plants that the distinction between body

cells and germ cells is not, as Weismann thought, the basis of this separation, but rather the distinction between changing cells and the permanent nuclei contained in them.

This great parallelism of independent discovery is matched by smaller parallels at the same time. The atomism implicit in both Weismann's and Mendel's theories was independently proclaimed, again on quite different grounds, by Bateson as discontinuity and by de Vries as mutation. The distinction made between germ and body on cytological grounds was immediately paralleled by Johannsen's distinction, on breeding evidence, between genotype and phenotype. In defining a *genotype* as that internal and hereditary character which reacted with the environment to produce the external and observed character or *phenotype*, Johannsen established the primary and operative axiom of genetics. He thus defined, as Weismann had done, the contrast between the static system of the permanent chromosomes which is responsible for heredity and the dynamic system of reactions they set in motion, which is responsible for development. In the experiments on which he based his definition he established the independence of genotype and environment and abolished all the loose and slippery arguments on which Lamarckian doctrines have always depended.

Never before in the history of science had the same theories been arrived at independently on such entirely different evidence. In such circumstances we might expect that the new discipline would be readily embraced. In fact, however, the process of conversion, in spite of the powerful advocacy of Johannsen and Bateson, has been gradual and is still incomplete. There are many who still find it difficult to separate the character from the individual who bears it. There are many who dare not follow Mendel's analytical way and think of gametes in breeding instead of zygotes, many who consequently cannot face Mendel's definition of a hybrid without misgiving. They will still imagine that they can recognize a hybrid by its appearance, by its mere

phenotype. And there are many who refuse to believe that visible agents are sufficient to effect visible results and that there is not something else behind the chromosomes which will permit mystical definitions of heredity and species. The reformation has been too profound to be accepted by those brought up in the old tenets. They prefer to halt between two opinions.

The most immediately obvious and direct conclusion from Mendel's work was that a new individual or zygote produced by fertilization owes its constitution directly and predictably to the germ cells or gametes which go to make it, and not to the parents which provide those gametes. A hybrid is, therefore, the product of the union of dissimilar gametes and not necessarily of dissimilar zygotes. Yet this definition is scarcely recognized outside experimental genetics to-day.

In learning the properties of hybrids we have not merely discovered the general laws of heredity and variation, we have come to understand the nature of particular species. The troubled history of *Œnothera* has been a struggle for fifty years between those who considered its forms as species and those who objected to them as hybrids. The solution came when it was realized that they were both. The paradox of the permanent hybrid then revealed how sex-chromosomes came about and how sex-determination developed in its multifarious ways.

It must not be supposed, therefore, that the earlier development of genetics was smooth. The separation of breeding work and cytology led to many unfortunate results. Each technique has its own vices. Just as experimental breeding unrelated with cytology led de Vries and Bateson up several false trails, so cytology unrelated with experimental breeding led Roux to the struggle of the parts and Weismann to a theory of germinal selection, as he called it, in which all differentiation depended on a sorting out of determinants within the body during development. We find as late as 1911 Johannsen saying

that "The question of chromosomes as the presumed 'bearers of hereditary qualities' seems to be an idle one." And Bateson, in 1926, maintains much the same view. Genetics, we see, as indeed other sciences, has been like a drawer that we pull out by uneasy jerks, first one side, then the other.

All this shows the prejudices with which present-day genetics is struggling in establishing itself in a proper relationship to other branches of biology. But the weapons with which it is now equipped make its task much easier than it was in the time of Herbert and Darwin. The immediate consequence of the union of breeding and cytology was the development of exact genetics in *Drosophila* on extremely mechanistic lines. It was assumed that since heredity is particulate, variation is also particulate, and by the combination of these particles or genes evolution resulted. Gradually, however, it was realized that variation is not necessarily particulate. Changes of proportion and position in the genes make a direct and mechanical description of variation impossible. Variation and likewise hybridization are of many kinds, depending on the many kinds of change that can take place in genes and in their arrangement. Simplicity has again given place to complexity, but it is a complexity within the reach of our understanding, a complexity we can use in showing the forms and processes of living things as parts of a single system.

The refined technique of breeding, the high power of magnification of chromosomes, the X-ray method of producing mutations and also of analysing molecular structure are bringing nearer the time when we shall be able to say that genetics has demonstrated the unity not merely of biology, but of science itself.

I

POLYPLOIDS AND POLYPLOIDY

1929

WHEN a cell divides to produce two daughter cells having the same genetical properties as itself, the nucleus resolves itself into a definite number of structures, the chromosomes. These, splitting lengthwise, give rise to two identical groups which go to make the daughter nuclei. In this process, known as mitosis, it is evident that, with certain exceptions which need not be gone into here, the chromosomes into which the nucleus resolves itself are always identical in number and form with those which went to constitute it at the preceding division. The chromosome number is said to be constant. It follows that when, in the course of sexual reproduction, two germ-cells unite to form a zygote and their nuclei fuse, the new generation of cells thus established will show at mitosis a new chromosome outfit or "complement," the sum of those of the two germ-cells. When these are identical the number will be simply doubled, and in these circumstances the number of chromosomes in the germ-cell is said to be "haploid" and the double number of the zygote is said to be "diploid" (Plate 1, Fig. A). Further, when the new zygote comes to produce germ-cells, which by their union will reconstitute a diploid individual like itself, the zygote nuclei undergo a process of "reduction," by which a new cell generation is produced having the haploid number of the gametes.

These three processes provide the mechanism that determines the Mendelian laws of inheritance, and so long as mitosis, fertilization, and reduction follow a regular

course, the Mendelian laws, with all the complications that are implicit in them, are obeyed. But all three processes are liable to error. In the first place, we frequently find body cells, both in plants and animals, the chromosome numbers of which are double those characteristic of the individual and its species. This type of "doubling" probably follows the failure of two bodies of chromosomes to separate after mitosis, or the simultaneous division of two nuclei which have not been separated by a cell-wall after the preceding cell-division. In plants, owing to their unlimited growth, such "doubled" cells sometimes produce germinal tissue, and a new tetraploid race, such as *Primula kewensis*, with four times the haploid chromosome number, is established. Doubling is so frequent in the formation of a callus in the tomato that we can be certain of obtaining a proportion of tetraploids amongst the adventitious shoots thrown up from the callused wound when the stem is cut off. In the normal course of development, doubling has been found to occur frequently in the embryo-sac nuclei of several plants belonging to the Liliaceæ. Usually the doubling occurs at the opposite end of the embryo sac from the egg-cell, but sometimes the egg-cell itself is affected, and in these cases fertilization of the diploid female gamete will produce a new triploid individual.

In the second place, abnormalities in fertilization occur which give rise to a different kind of change. Various stimuli may excite the development of the egg-cell without fertilization. For example, when an interspecific cross, such as hexaploid *Solanum nigrum* by tetraploid *S. luteum*, is attempted, the stimulus of pollination sometimes excites the development of the egg-cell with the reduced (triploid) number, although the pollen-nucleus does not fuse with the egg-nucleus. Similarly, by the stimulus of changes of temperature, an egg-cell in *Datura* can be induced to develop. In these ways a haploid, or relatively haploid, individual arises having the hereditary material of a germ-cell and the outward form, on a reduced scale, of a diploid plant. Experimentally

it has been found possible to induce the fusion of two male germ-cells with one female; in the formation of the endosperm we have virtually the reverse case of the fusion of two female germ-cells with one male. From both these unions a triploid cell generation is produced.

It is in the finely regulated processes of reduction, however, that irregularities most frequently occur, and these irregularities are of great importance in the production of polyploids. In considering reduction, two properties of the chromosomes should be particularly borne in mind. First, the material of which the chromosomes are made up has specific physiological properties, so that, to take a simple example, if one type of chromosome is represented in the organism three times instead of twice, constant physiological changes are produced. To take another example, if one of the chromosomes of a haploid gamete is lacking, the gamete is not usually viable. Secondly, where, as is usually the case, the diploid organism is the result of the union of two similar gametes, the chromosomes contributed by these gametes must correspond in pairs. They must be structurally and functionally homologous. When, therefore, we see pairs of chromosomes formed at reduction, it is a legitimate assumption that these are pairs of homologous chromosomes and that they pair because they are like. Further, where pairing fails, it is perhaps natural to conclude that this failure is the result of lack of likeness or affinity. Exceptions to this rule we shall return to later. In the main it is true, and it is as a consequence largely of failure of pairing that irregularities in reduction arise in hybrids.

The simplest form that these irregularities can take is the failure of the two corresponding groups of chromosomes to separate, and the consequent formation of a single nucleus with the diploid number. This nucleus then divides to give two nuclei in which the number is similarly unreduced. Germ-cells have been shown to arise in this way in large numbers of plants, which are either of known hybrid origin (like *Raphanus-Brassica*) or believed on

independent grounds to be hybrids (like species of *Hieracium*). In *Pygæra* hybrids, where the formation of diploid germ-cells, with complete failure of chromosome-pairing, was first observed, the nuclear phenomenon was shown to be correlated with the fact that the character differences completely fail to segregate. This is one of the discoveries on which the chromosome theory is based.

If the conditions of the origin of polyploids *before the fact* are almost universal, the conditions *after the fact* impose important limitations on their maintenance. These limitations are almost all bound up with the processes of sexual reproduction. Where the sexes are differentiated, doubling of the chromosome number may be associated with sterility on one side, as in *Pygæra* hybrids, and consequent failure of the tetraploid to perpetuate itself; or there may be a change in the method of reproduction, as in *Artemia* where a tetraploid is parthenogenetic, or *Empetrum* where a tetraploid is hermaphrodite, the diploid that probably corresponds being in each case unisexual.

In a different way the purely mechanical conditions of reduction greatly limit the success of those polyploids which reproduce sexually. The conditions under which the corresponding chromosomes separate regularly when present in pairs are not always equally satisfactory when more than two of each kind are present. For example, in a triploid, where there are three of a sort, the odd chromosomes, whether associated with the pairs or not, separate at random to the two daughter cells. Consequently the germ-cells produced have chromosome numbers varying between the haploid and the diploid number (Plate 1, Fig. C). In these new intermediate types the balance of the physiologically differentiated chromosomes is new, untried, and in most cases unsuccessful. Most triploids are therefore sterile so far as sexual reproduction is concerned. Triploidy s none the less common both in natural species and in cultivated plants, but a study of its incidence shows that in these established triploid forms sexual reproduction has

lost its value. Triploids occur, for example, in plants with various kinds of natural vegetative propagation in *Hyacinthus*, *Tulipa*, *Iris*, *Rubus* (Fig. 1), *Canna*, and *Tradescantia*; with reproduction by grafting in *Prunus*; with

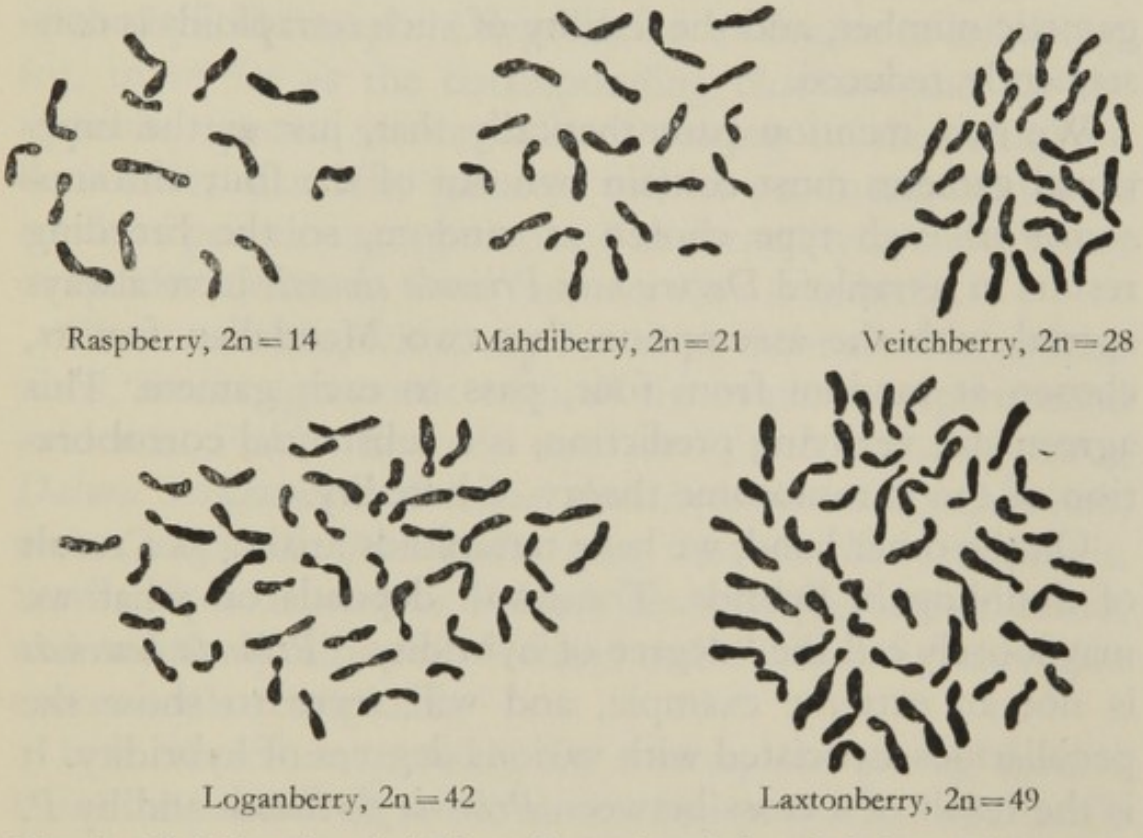


Fig. 1.—Diploid and polyploid species and varieties of *Rubus*. All the even multiples are fertile although the tetraploid and hexaploid are known to be interspecific hybrids. The odd multiples are both sterile in a high degree.

apogamy in *Hieracium*; with partial parthenocarpy in the cultivated apples; and probably with both apogamy and parthenocarpy in cultivated *Citrus*. To such forms as these it is clear that ordinary seed fertility, so far from being an advantage, may actually become a hindrance.

The case of tetraploids is more complicated, both in regard to chromosome behaviour and to the fertility that largely depends on it. For the sake of simplicity, let us take two opposite types. From a haploid *Datura*, itself the result of the development of an unfertilized egg, diploid offspring have arisen by failure of reduction, and from these again tetraploids. In such tetraploids there are four identical representatives of each chromosome type, which usually

associate to form quadrivalent bodies at reduction. These quadrivalents are, of course, capable of dividing into two and two, but seem to be subject to irregularity in division, for gametes arise (as in tetraploid *Prunus cerasus* and *Tradescantia virginiana*) both with more and less than the normal gametic number, and the fertility of such tetraploids is consequently reduced.

We may mention parenthetically that, just as the functional gametes must contain two out of the four chromosomes of each type chosen at random, so the breeding results in tetraploid *Datura* and *Primula sinensis* have always agreed with the assumption that two Mendelian factors, chosen at random from four, pass to each gamete. This agreement, verifying prediction, is a substantial corroboration of the chromosome theory of heredity.

On the other hand, we have tetraploids arising as a result of doubling in hybrids. The result depends on what we may loosely call the "degree of hybridity." *Primula kewensis* is not an extreme example, and will serve to show the peculiarities associated with various degrees of hybridity. It is the result of a cross between *Primula floribunda* and by *P. verticillata*, which gave in the first instance a sterile intermediate diploid hybrid, as might have been expected. This diploid produced a giant fertile shoot the offspring of which were fairly constant, giant, and fertile like itself. This shoot was tetraploid and must have arisen as a result of the formation of tetraploid somatic cells, as in *Solanum*. In the diploid hybrid, the corresponding chromosomes of the two parental species paired at reduction; its sterility must therefore be assumed to be the result of failure of the new genetic combinations brought together in the gametes. In the tetraploid, however, pairs are usually formed as in the diploid, but the general absence of segregation means that identical mates must pair and pass to opposite gametes.

This conclusion is justified by the fact that a small proportion of segregates is produced bearing certain characters of the parental species, that is, no longer intermediate in

every respect. In a similar small proportion of cases the chromosomes associate in fours, derived therefore from both species and capable of yielding gametes pure in the characters of one species carried by the chromosomes concerned. It follows that the constancy and relative fertility of the hybrid tetraploid depends on its degree of hybridity, for, in so far as the corresponding chromosomes of the opposite species are capable of pairing in the tetraploid derivative, dissimilar gametes will be produced, both as a result of genetic segregation and abnormality in the division of quadrivalents. In both cases fertility is reduced.

These remarks, which are based on theoretical considerations, are in agreement with all the available experimental evidence. Fertile diploids such as *Œnothera Lamarckiana*, *Datura Stramonium*, *Primula sinensis*, *Solanum Lycopersicum*, and *Campanula persicifolia* give less fertile tetraploids. Sterile diploids such as *Primula kewensis*, *Raphanus-Brassica*, and relatively diploid *Nicotiana* and *Solanum* hybrids give more fertile tetraploids.

It is, therefore, possible for a tetraploid arising from a hybrid diploid to have the mechanical properties of a fertile diploid. But it combines with these certain genetical peculiarities. Not only is it a hybrid, with such physiological advantages as hybridity may confer, but occasionally the corresponding chromosomes of the opposite diploid parents may pair. The tetraploid will then show the segregation of a hybrid, and may give rise to offspring with any workable combination of the characters of its two parents.

Another means of variation, closed to the ordinary diploid, is open to the polyploid. This is variation by loss. Gametes of a diploid which are not equipped with the full chromosome complement are not as a rule functional, but in a tetraploid, where every part of the hereditary material is represented twice in the gametes, loss of a chromosome or part of a chromosome does not necessarily lead to nonviability and is a possible source of a new chromosome balance, a new genetic type. This kind of change is probably

responsible for a great deal of the variation in that highly variable species *Tradescantia virginiana*.

It is not surprising, therefore, that many polyploid species, both in breeding behaviour and in chromosome behaviour, resemble this second type, the type of *Primula kewensis*. The hexaploid *Prunus domestica*, having three times the chromosome number of its diploid relatives, itself usually behaves like a diploid, but when it is crossed with one of these diploid relatives the hybrid behaves like a tetraploid of the *Datura* type. Pairing takes place not merely between corresponding chromosomes of the diploid and hexaploid, but also between corresponding chromosomes, derived each from the hexaploid, but not normally pairing. In spite of the regularity of chromosome behaviour, this analytic method of investigation is unsatisfactory from the genetical point of view, for the sets of chromosomes of the original diploid parents have probably ceased to be competent by themselves. The processes of variation found in diploids have continued in the polyploid without the same physiological restrictions. The result of splitting up the complement of a polyploid species is therefore sterility.

Hexaploid wheat or oats, when self-fertilized, breeds true in the main, but from time to time seedlings appear having the characters of related species, which have evidently remained submerged so long as the hybrid has behaved like an ordinary diploid. This segregation has been shown to follow the exceptional pairing of homologous but non-identical chromosomes, presumably of specifically distinct origin. We must, therefore, distinguish between the *primary segregation* that results from the normal pairing in a polyploid, and the *secondary segregation* of the characters of its ultimate diploid parents, which results from the exceptional pairing of their unlike chromosomes. The behaviour in these cases is an exact parallel of that in the experimentally produced *Primula kewensis*.

When two hybrid tetraploid species such as *Triticum polonicum* and *T. durum* are crossed, complicated results are

naturally to be expected from the combination of these two types of segregation. As in the *Prunus* hybrid, not two species but four are really concerned, and *a priori* we can have no reason for predicting one kind of pairing and segregation rather than another. Breeding results show that, in respect of certain chromosomes at least, there is regular pairing of the chromosomes derived from the ultimate diploid parents of each species, with the consequent segregation of their characters, and the suppression of the characters of the immediate tetraploid parents, which are never recovered in subsequent generations.

A hybrid in *Rubus* shows another complexity in segregation. Three seedlings were raised from a cross between the diploid *R. rusticanus inermis* and the tetraploid *R. thyrsiger*. Two of these were indistinguishable and, as might have been expected, closely resembled the tetraploid parent; they were triploid. The third, although obviously a hybrid, resembled the diploid parent more closely in seven well-marked characters which chiefly distinguished the two parental species. This seedling was tetraploid, and evidently the result of the union of a normal reduced male with a diploid female gamete. Thus where the female parent had made a double contribution of hereditary material, its genetical influence was increased.

This tetraploid seedling was fertile; the triploids were, as usual, sterile. In its breeding it showed two types of segregation: first a random segregation with the recovery of approximately 1 in 36 of the quadruplex recessive; secondly, the complete suppression of the characters of one parent. These results would be expected if the several chromosome types of the two species had varied independently, so that in one type there was indifferent affinity, in another a rigidly determined system of pairing. The behaviour of this cross, in both the first and second generation, affords a neat example of the application of the chromosome theory to the theory of interspecific hybridization.

It may be worth while pointing out that, in so far as

Continued on page 11

PLATE 1

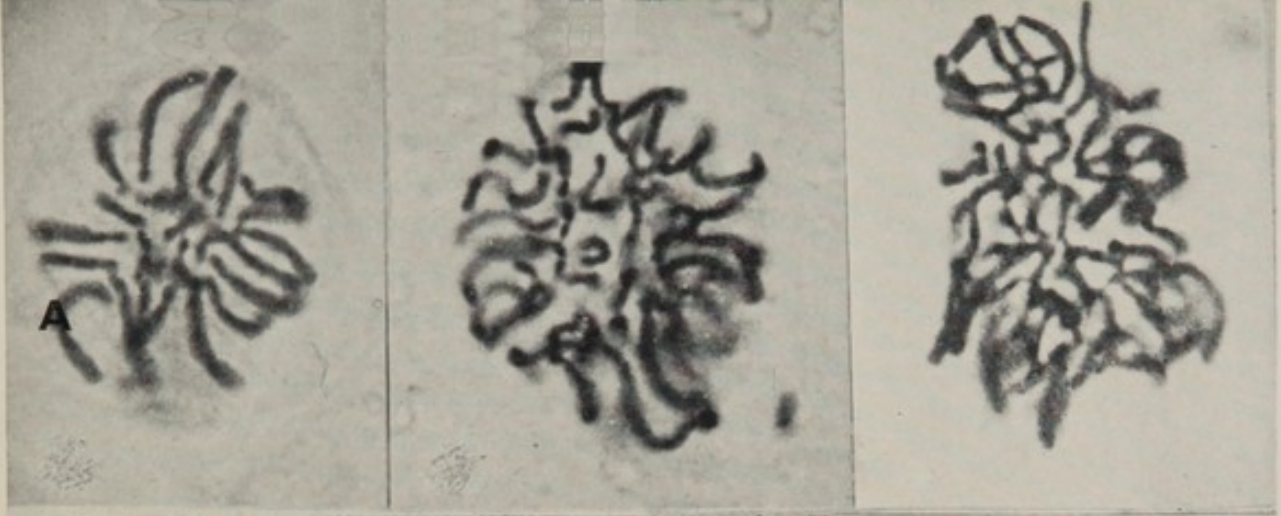
A.—The diploid chromosome number (24) in a root tip of *Tulipa Clusiana*, a form from Tibet, together with the tetraploid from Chitral and the pentaploid from the Mediterranean. ×1400.

B.—Pollen mother-cell division in a pentaploid form of *Tulipa Clusiana* (60 chromosomes) showing associations of various numbers of chromosomes, and some chromosomes unpaired. ×2500.

C.—A pollen grain of a triploid hyacinth (somatic number, 24) showing 12 chromosomes and a micronucleus; numbers between 8 and 16 have been found. Note the three chromosome types. ×600.

D.—Metaphase of the second division in a pollen mother-cell of a tetraploid cherry. As a result of the formation of quadrivalents at the first division, two unequal bodies of chromosomes (13 and 19) have separated. ×2400.

E.—Conjugation of chromosomes in a triploid tulip. Left, chromosomes lying parallel in threes before association. Right, chromosomes associated in pairs with exchange of partners. ×1600.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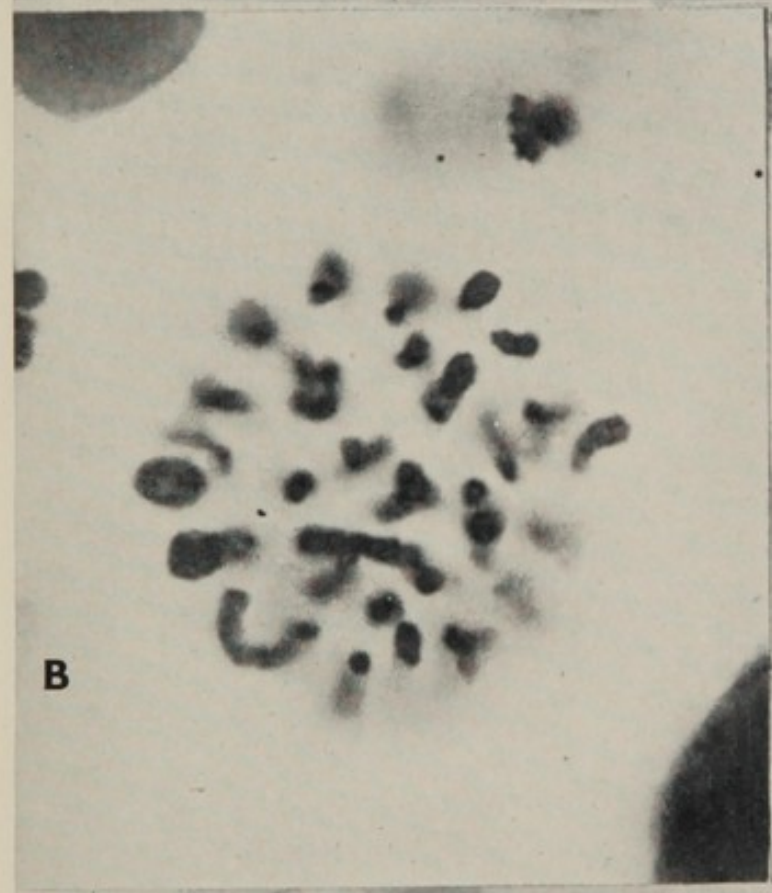
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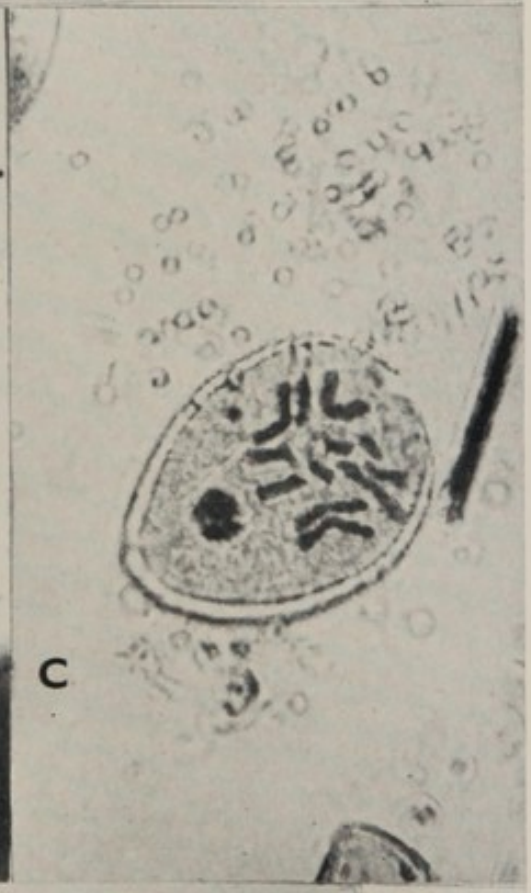
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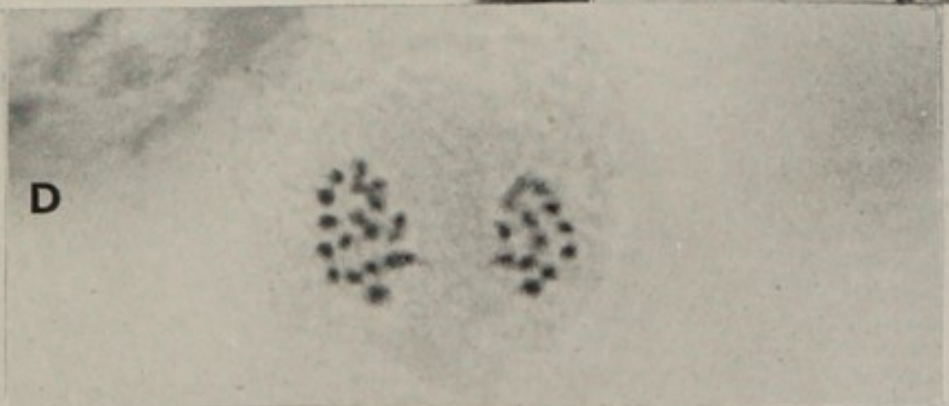
D


E

there are species in *Rubus*, this fertile seedling is a new species. Similarly, in so far as there are species in *Primula P. kewensis* is a new species, and, in so far as there are species or genera in the *Cruciferæ*, the *Raphanus-Brassica* tetraploid is a new species or a new genus. Polyploidy is therefore evidently a means of species-formation. Its importance in evolution is more doubtful. Polyploids in their origin pass through a process that is virtually irreversible, and the advantages of their peculiar properties are, therefore, to a great extent meretricious. But if polyploids are not themselves of evolutionary importance the occurrence of polyploidy is probably a symptom of evolutionary processes, such as hybridization, that are of great importance. Moreover, polyploids afford a field for the study of the hereditary material under conditions which apply critical tests of its properties. These must now be considered.

Since not merely the fertility of a polyploid but also the genetical behaviour in every other way depends on the pairing of its chromosomes, the conditions of this pairing are well worth our study. These conditions are evidently not simple, for chromosomes may regularly pair in certain circumstances (as in the diploid *Primula kewensis*), but rarely pair when identical mates are available. This problem we may shelve by saying that pairing depends on "relative affinity". But we may also get, as in triploid *Hyacinthus* and tetraploid *Datura*, the failure of association of chromosomes known to be identical or nearly so.

This problem, evidently related to the other, is not so easily dismissed. To understand it we must examine the processes leading up to "metaphase" of the reduction division at which pairing is chiefly studied. At an early (prophase) stage in *Hyacinthus*, three or four threads, according to the number of corresponding chromosomes of a particular type, are seen to *pair*; that is to say, each part of each thread takes as partner a corresponding part of one of the other threads, and, furthermore, in doing so it acts independently of sections higher up and lower down the

thread (Plate 1, Fig. D). We find, with three threads, one of the three is always unpaired, but it is a different one of the three that is unpaired at different points. With four threads interchanges of partner occur amongst them. Thus pairing depends not on any general affinity of the chromosomes for one another, but on the capacity of the individual parts of the chromosomes to pair. This seems equally clear from the results of genetical analysis of the forms of *Drosophila*, in which parts of chromosomes have been reversed. The basis of the affinity of chromosomes seems then to be similar arrangement of their parts. A dissimilar arrangement giving a lower affinity need not necessarily be correlated with genetic differentiation, but it nearly always will be, as it will indicate different descent.

Let us now see why these chromosomes, which probably always pair at prophase, fail to associate at metaphase. In the triploid hyacinths the failure to form a trivalent falls almost exclusively on chromosomes of a short type, and similarly with quadrivalents in the tetraploid. If the pairs formed by this type of chromosome are compared with those of the longer types, it is seen that they are relatively simple. Both kinds consist of four "chromatids" or halves of longitudinally split chromosomes associated in pairs, but in the longer chromosomes these chromatids change partners, forming what are called "chiasmata", two, three, four, or five times. In the short chromosomes, on the other hand, there is rarely more than one chiasma.

The chiasmata are formed at random both as regards number and position, and with an average frequency proportional to the length of the chromosome. Only by the failure of a proportion of chromosomes to form any chiasmata at all can this normal frequency be maintained in the short type, for one of the three chromosomes must be associated with the other two and have two chiasmata.

The expected proportion of failure agrees approximately with the proportion (about one-fifth) of unpaired short

chromosomes found. It therefore seems probable that pairing fails merely because no chiasma is established. This implies that the relationships of the chromatids at reduction are the same as at ordinary mitosis; they are attracted in pairs. The association of the chromosomes is then the result of a failure of the pairs of chromosomes that conjugated at prophase to separate, in respect of their constituent chromatids, as they came together.

If this is generally true, then short chromosomes newly arisen by fragmentation should fail to pair regularly, and this is so wherever it has been studied, as in *Secale*, *Zea*, and *Tradescantia*. Such variation in pairing is analogous to that found in hybrids and polyploids, for in all these types the length of the chromosome pairing at prophase is reduced as compared with that in the non-hybrid diploid. It may be reduced so that in a proportion of cases chiasma-formation, and therefore pairing, fails altogether. From the opposite point of view we may say that the mechanism of reduction is fitted to give a regular segregation of chromosomes of the normal types in a non-hybrid diploid.

It would be possible for dissimilar chromosomes to pair along a sufficient length to establish a single chiasma, in the absence of competition, but with competition in a polyploid, clearly a chiasma will be most likely to be formed between the pair which is capable of association through the greater length. Differential affinity can therefore be regarded as a measure of linear identity. In this way the behaviour of the chromosomes, derived from different species, which rarely pair in tetraploid *Primula kewensis* or hexaploid *Prunus domestica*, yet always pair in the diploid *Primula* or the tetraploid *Prunus* hybrid, is intelligible in more or less physical terms.

We have emphasized what may be called the mechanical conditions which determine the origin and variation of polyploids. This is because the physiological conditions are already widely recognized, and are not specific to polyploids, but in the study of polyploids the two types of restriction

on the origin of new forms are equally evident, and it is impossible to show that one is more important than the other. Each has a final effect, and nowhere yet has any clear relation been shown between them.

This sketch of certain features of their behaviour should show that the investigation of polyploids is of importance, not merely in determining their own peculiar properties of inheritance and variation, but also in making out principles of behaviour that are equally important in the diploid organism.

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2

CYTOLOGICAL THEORY IN RELATION TO HEREDITY

1931

THE chromosome theory of heredity, by relating chromosome behaviour with the phenomena of inheritance, has obviously made it possible to apply the cytological method to the study of inheritance. With this profitable field before them, geneticists and cytologists have not hesitated to draw conclusions in the one field from observations made in the other, but in order to do so they have had to apply certain rules of interpretation. Their method has naturally been to assume, so far as possible, a direct relationship between cytological and genetical observations. The geneticist has therefore not only assumed that the material of every part of the chromosome has a specific genetic effect, which is a widely verified assumption; but also that the capacity of the chromosome for variation is equally specific, so that it is possible to refer to hereditary differences, and to particles of chromosome alike as "genes". This second assumption is also widely verified; but it is subject to serious exceptions in that two different kinds of change have been shown to befall the same particle, namely, internal change and external change such as loss or re-arrangement. This constitutes no primary objection to the theory of the gene but rather indicates a necessary enlargement of its scope.

Cytologists, on the other hand, in translating their observations into genetical terms, have sought to apply the chromosome theory to the interpretation of meiosis. With

the help of the simple rule that the pairing of chromosomes is a criterion of their relationship, they have set to work to examine meiosis in hybrids and in ring-forming plants (such as various species of *Œnothera*). The results of these studies have been confusing because investigators have not first examined the principles they were applying to see if they were indeed principles or merely empirical rules of special derivation and therefore of limited application. We now have evidence by which to test them.

Meiosis consists in the occurrence of two successive divisions of a nucleus in the course of which the chromosomes divide once instead of twice as they would in two ordinary mitoses. Where the distribution of the chromosomes is regular, the four daughter nuclei therefore have half the number of chromosomes of the parent nucleus (Fig. 2).

At the first division, the chromosomes come together in pairs, and a whole chromosome of each pair passes to one pole to divide at the second division of the nucleus. To express this comparatively with regard to mitosis, we may say that while two half-chromosomes (or "chromatids") are associated in pairs at a mitosis, four are associated at the first metaphase of meiosis. A numerical reduction in the chromosomes must be attributed directly to the lack of any splitting of the chromosomes in the interval between the two divisions of the nucleus such as ordinarily occurs. But this is readily related to the fact that each chromosome is already split into the two chromatids which have passed together to one pole. This in turn is related to the pairing of the chromosomes.

It has therefore seemed natural (since 1890) to regard the essential difference between meiosis and mitosis as consisting in the pairing of the chromosomes. Since different pairs of chromosomes pass at random to the two poles (so that A_1-A_2 and B_1-B_2 may give daughter nuclei A_1B_1 and A_2B_2 or, equally, A_1B_2 and A_2B_1), and since the chromosomes are qualitatively differentiated, it follows that those which pair and pass to opposite poles must be similar if

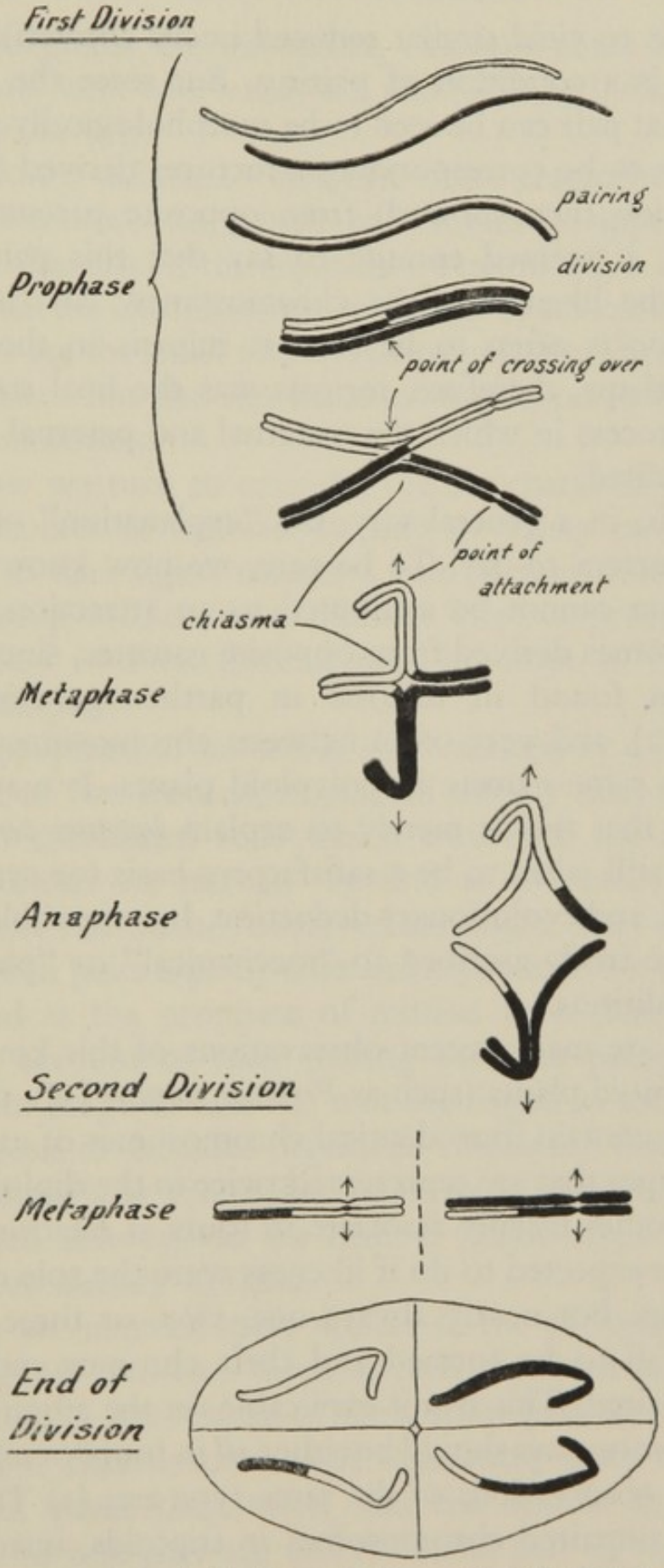

Fig. 2.—Diagram to show the development of one pair of chromosomes at meiosis, and their relationship on the assumption that crossing over is the cause of chiasma formation. The four stages of prophase shown are: (1) leptotene, (2) pachytene before division, (3) pachytene after division, (4) diplotene to diakinesis.

meiosis is to yield similar reduced nuclei (Boveri). Clearly, likeness is a condition of pairing. But since the chromosomes that pair can be seen to be morphologically alike and therefore to be corresponding structures derived (so far as observation then showed) from opposite parents (Montgomery), it seemed enough to say that this pairing was due to the likeness of the chromosomes. An "incipient" association is often to be seen at mitosis in the somatic cells. Perhaps, therefore, meiosis was the final step in the sexual process in which the maternal and paternal elements at last united.

Such is, in a general way, the "explanation" of meiosis that is current to-day. To be sure, we now know that the association cannot be attributed to an attraction between chromosomes derived from opposite gametes, since pairing has been found in meiosis in parthenogenetic organisms [1, 2], and very often between chromosomes derived from the same gamete in polyploid plants. It may also be objected that this is merely to explain *ignotum per ignotius*. But it is still taken to be a satisfactory basis for cytological, genetical, and evolutionary deduction. Incompatible observations are freely ascribed to "mechanical" or "physiological" conditions.

There are many recent observations of this kind. There are tetraploid plants (such as *Primula sinensis* [3]), the nuclei of which contain four identical chromosomes of each of the twelve types that are represented twice in the diploid. These chromosomes usually associate in fours at meiosis, as they would be expected to do if likeness were the sole condition of pairing. But nearly always one, two, or three of these groups fail to be formed and their chromosomes appear merely paired. This is not explicable on the affinity theory. The chromosomes should be either *all* in fours or *all* in pairs.

Other observations of the same type are: (1) The occurrence of unpaired chromosomes in triploids, instead of all three identical chromosomes of each type being associated (*Zea* [4], *Tulipa* [5], *Lilium* [6]). (2) The occurrence of un-

paired fragment chromosomes, although these have identical mates with which they can pair (*Secale* [7], *Matthiola* [8], *Tradescantia* [9]).

The only difference between these fragments and the other chromosomes which pair regularly appears to be their smaller size. If the triploids are examined, it is similarly found that the chromosomes which fail to associate regularly in threes are the small ones (*Hyacinthus* [10]). Therefore, not only *likeness* but also *size* bears some relation to the pairing of chromosomes.

If now we turn to consider the structures of the paired chromosomes at meiosis we find a variety of form that shows, at first sight, neither a rule in itself nor any clear relationship with ordinary mitosis. The two processes must be studied in their development in order to be seen in relationship.

The prophase of mitosis is characterized by a linear contraction of two threads, associated side by side, to become the two cylindrical rods which constitute the metaphase chromosome. At meiosis we find at the earliest stage a difference. The threads observed are single. They soon come together in pairs side by side and reproduce the conditions observed at the prophase of mitosis very closely indeed. But on account of their pairing they are present at this pachytene stage in half the number found at the prophase of a mitosis in the same organism. Evidently, therefore, the single threads at the earlier stage were chromosomes still undivided although in the earliest visible stage in mitosis they have already divided.

After an interval, splits appear in the pachytene thread, separating it into two threads, each of which is now seen to be double. But instead of these splits passing right along the paired chromosomes and separating them entirely, it is found, when they meet, that the double threads that separate in one part are not the same pair of threads that separate in another. The separated pairs of threads, therefore, change partners, and the points at which they change

partners (there are often several distributed along the paired chromosomes) are called "chiasmata". This stage is diplotene (Fig. 2).

Between diplotene and metaphase there is further linear contraction, and the structure of the paired chromosomes may remain the same in regard to the relationships of the four threads of which they are composed: that is, the chiasmata may remain stationary. But they may undergo a change which consists in the opening out of the loop that includes the spindle-attachment, at the expense of the adjoining loops, as though the spindle-attachments of the chromosomes were repelling one another. In other words, the chiasmata appear to move along the chromosome towards the ends: finally, the chromatids are associated in pairs with changes of partners only at the ends. Such changes of partners are called "terminal chiasmata", and the frequency of the end-to-end unions at metaphase corresponds with the frequency of the chiasmata seen earlier, when they were still interstitial, in small chromosomes (fragments) which only have one chiasma at most[11]. Further, in organisms with large chromosomes it is still possible to see the change of partner: at the end the association is double; it is between the ends of two pairs of chromatids, not merely between the ends of one pair of chromosomes.

These observations point to the chiasmata being the immediate cause of pairing between chromosomes. How can such a hypothesis be tested? It is found that given pairs of chromosomes have a constant range in the number of chiasmata formed. For example, in the *M* chromosome of *Vicia Faba* [12, 11] from 3 to 13 chiasmata are found at the metaphase, with a mean of 8·1. The *m* chromosome, which is much shorter has a range of 1 to 6, with a mean of 3·0. If we suppose that small chromosomes arising by fragmentation have a chiasma frequency proportionate to their length as compared with their larger neighbours, then we can predict from observations of their size and of the

observed frequency of chiasmata in the large chromosomes what their frequency of pairing will be, on this hypothesis. Thus, in the variety "Yellow" of *Fritillaria imperialis* it was found that the chiasma-frequency was 2·58 in the large chromosomes. The fragments were about one-ninth of the length of the large chromosomes. They should, therefore, have chiasmata in a frequency of 2·58/9 per pair, or 0·29. This means that they should pair in 0·29 cases (neglecting the frequency of one pair forming two chiasmata, which should be slight). They were observed to pair in 0·22 of cases[11]. Here is an example of the type of observation which is susceptible of statistical analysis and supports this hypothesis.

Now, if we admit chiasmata as the condition of chromosome pairing, a considerable simplification is possible in stating the relationship of mitosis and meiosis. Throughout the prophase of mitosis, the threads are held together by an attraction in pairs. The same rule applies to meiosis, for the evidences of failure of pairing of fragments, of odd chromosomes in triploids, and of the four chromosomes of a type in tetraploids all point to the chromosomes having no present attraction at metaphase. They are merely held together by the chiasmata—that is, by the attraction between the pairs of half chromosomes and the exchanges of partners amongst them; and this attraction exists equally at mitosis.

This being so, we must look to the earliest stage of prophase to find the essential difference between the two types of nuclear division. It evidently lies in the time at which the chromosomes split into their two halves. At mitosis, it is probable that this has already happened before the chromosomes appear at prophase. At meiosis, it does not happen until pachytene (possibly at the moment at which the diplotene loops appear). The prophase of meiosis, therefore, starts too soon, relative to the splitting of the chromosomes. If we consider that there is a universal attraction of threads in pairs at the prophase of any nuclear

division, as we see it at mitosis, it follows that this condition is fulfilled by the pairing of chromosome threads when they are still single, and their separation at diplotene when they have at last come to divide. The decisive difference would, therefore, appear to be in the singleness of the early prophase threads in meiosis. This singleness may be attributed to one or both of two causes: (i) a delayed division of the chromosomes, (ii) a precocious onset of prophase. The second of these seems the more likely explanation, on account of the short duration of the premeiotic prophase in some animals. Either assumption would account for the most characteristic of all secondary features of meiosis, namely, the exaggerated linear contraction of the chromosomes, paired or unpaired, if the time relationship of metaphase to the division of the chromosomes remains the same. This hypothesis of precocity [13] may be tested by the observation of a correlation between irregularities in meiosis and (*a*) abnormality in the timing of meiosis, and (*b*) diminished contraction of the chromosomes at metaphase.

The first of these tests is applicable to many organisms with occasional suppression of reduction; the aberrant nuclei enter on the prophase of meiosis either earlier or later than the normal nuclei [14, 15, 16, 17]. When they are too early, it may be supposed that a premature division of the chromosomes has precipitated the prophase; when too late, it may be supposed that the prophase has been delayed. In either case, the chromosomes would no longer be single at early prophase and the condition of their pairing would be lost.

Such a cause of failure of pachytene pairing may be expected to be distinguishable by its effect on the contraction (the second kind of test). For when failure of metaphase pairing is not due to an upset in the timing of prophase but merely to failure of chiasma formation, we might expect normal meiotic contraction; this is the case in maize [18]. Where the prophase has been delayed, we might

expect an approach to mitotic conditions; this is the case in *Matthiola* [19, 20]. Other critical evidence in favour of the hypothesis has already been quoted in these columns [21].

By trying to define in this way the relationship of meiosis to mitosis, we find out what is essential and therefore universal in meiosis, and what is unessential and secondary. Only when the direct interpretation of events in the nucleus is clear (as it now seems to be) can we attempt their genetical interpretation on a satisfactory basis.

Two examples of the genetical interpretation of chromosome behaviour at meiosis are of immediate importance. It has been shown in every organism that has been adequately tested that crossing-over can occur between corresponding parts of the paired chromosomes at meiosis, actually between the chromatids, so that crossing-over in the region between *C* and *D* in a pair of chromosomes *ABCDE* and *abcde* will give four kinds of chromatid; *ABCDE*, *ABCde*, *abcDE*, and *abcde* (Fig. 2). We may suppose that this crossing-over has no relation with anything observable cytologically; that it takes place when the chromosomes are intimately associated at pachytene and has no connexion with later behaviour. This view can only be taken when other possibilities are eliminated. We may also assume that crossing-over has some relationship with chiasmata, either as a cause ("chiasmatypy") [22, 23] or as a consequence, through breakage and reunion of new threads [10, 9]. The last possibility has been eliminated by the statistical demonstration that terminal unions correspond in frequency with interstitial chiasmata [11], and that the number of terminal chiasmata increases *pari passu* with the reduction of interstitial chiasmata [3, 4, 20]. The first possibility, that the chromosomes fall apart as they come together, and that the exchanges of partners at chiasmata are therefore due to exchanges in linear continuity or crossing-over between the chromatids, has been demonstrated in two ways.

In tetraploid *Hyacinthus* and *Primula* associations occur with such a spatial relationship that they can only be

interpreted as the result of crossing-over [3, 25]. In ring-forming *Œnothera* [28], chiasmata occur interstitially between a pair of chromosomes associated terminally with two others to give a "figure-of-eight". Such an arrangement also can arise only on the assumption of crossing-over. These demonstrations confirm Belling's interpretation of the *Hyacinthus* trivalents, which was not in itself indisputable [5]. Whether the observations are of universal application (the simplest assumption) or not, can only be shown by cytological tests of organisms which have been studied genetically.

A second problem is that of ring formation. Since, on the present hypothesis, the pairing of chromosomes at metaphase is conditioned by the formation of chiasmata at prophase between *parts* of chromosomes of identical structure, it follows that ring formation (where one chromosome pairs in different parts with parts of two others) must always be due to different arrangement of parts, that is, different structure, in the chromosomes contributed by opposite parents [26, 27, 9]. Thus the relationship of the chromosomes of two organisms can always be specified from the observation of the pairing behaviour of the chromosomes at meiosis in the hybrid. It is, therefore, possible to study differences of such a magnitude as will sterilize a hybrid and are, therefore, not susceptible of genetical analysis. This method is now being widely applied.

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3

THE BIOLOGY OF CROSSING-OVER

1937

SEXUAL reproduction consists of two alternating processes: *fertilization*, by which two germ cells containing each a single set of chromosomes fuse and produce a zygote with the double number of chromosomes, and *meiosis*, by which the double number is reduced and germ cells are again formed with the single number. As Weismann first pointed out, the biological importance of these processes is that they enable the hereditary differences between the chromosomes to be recombined in the greatest number of ways to give the greatest number of different individuals and therefore the greatest scope for natural selection to act in directing evolutionary change.

In recent years we have come to know precisely how this recombination takes place, not merely in one organism, but probably in all sexually reproducing organisms. The method is both more complicated and more efficient than Weismann imagined. In the mother-cells which are to undergo meiosis, the chromosomes are present as single, instead of the usual double, threads of particles. By a combined study of ultra-violet photographs of the particles in *Drosophila*, and of the genetic effects of breaking the threads with X-rays at a series of points along their length, the particles have been identified as genes, the atomic units of heredity[1]. The chromosome threads correspond, as we should expect, in pairs, and come to lie side by side in pairs, gene by gene. Their attraction is therefore specific. They then coil around one another, and this coiling proves that they have

two properties that might well be expected of them. It proves that they are each in a state of torsion such as that which determines the ordinary contraction of a chromosome into a rod-shaped body at mitosis. It proves also that the threads do not slip around one another. They stick together like two threads of wool placed side by side. The attraction of their genes for one another must therefore be specific in position, that is, not merely between the genes, but between the parts of the gene [2].

If we imitate the physical condition of the chromosomes while they are paired and coiled by placing two woollen threads under torsion side by side, we find that they coil round one another but at the same time necessarily uncoil themselves internally. The relational and internal coiling (as we may call them) are opposite and in equilibrium. The stability of this system is attested by its use in all spinning operations.

The coiling equilibrium of the paired chromosomes is upset by their division, and we then find that the half-chromosomes, or chromatids, arising in this way are as we should expect coiled round one another. But other changes take place at almost the same time as the division and are presumably determined by it. First, the divided chromosomes separate: they no longer attract one another. Secondly, chromatids of partner chromosomes break at opposite points and the broken ends uncoil and rejoin so that exchanges of chromatids occur between the separating chromosomes. The chromosomes, although no longer attracting one another, are held together by these exchanges, or chiasmata, which appear in varying numbers and positions in different chromosomes and in different cells.

The special mechanical situation of chromosomes dividing while they are paired thus determines the breakage and reunion which we call crossing-over. In the absence of crossing-over the partner chromosomes fall apart and are unpaired at all later stages. On this process, therefore, the later reduction in number and segregation to opposite

daughter-cells equally depend (Fig. 3). Thus crossing-over, which is the only regular genetic change that the chromosomes undergo in their history, is the immediate condition

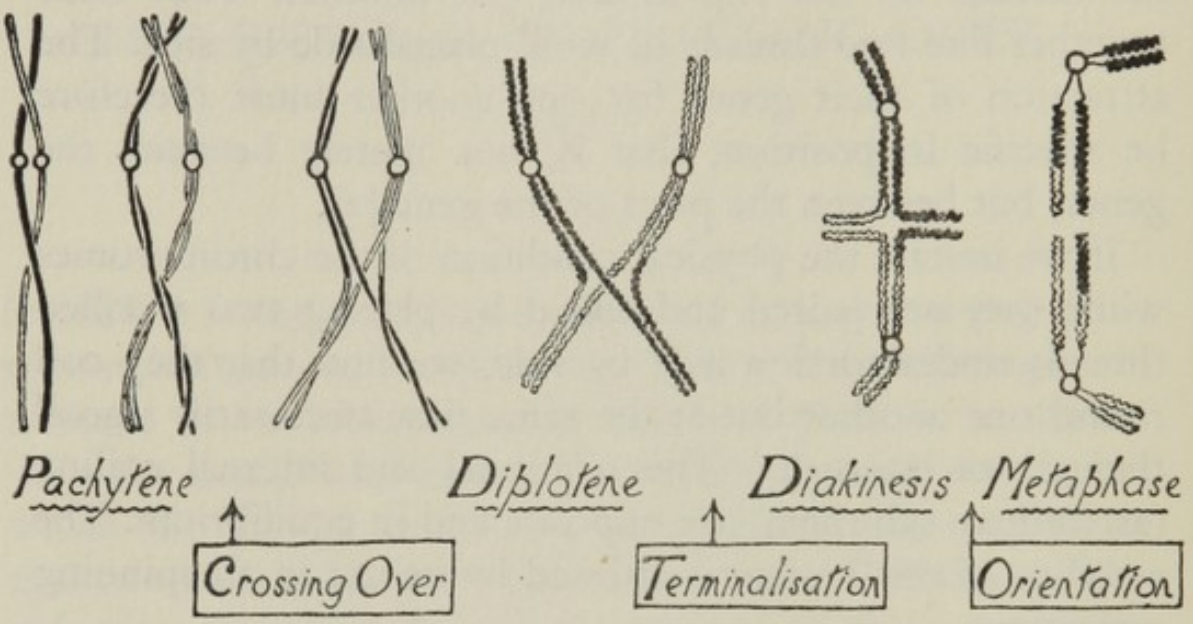

Fig. 3.—Diagram showing the series of changes by which crossing-over determines chiasma formation and the later association, orientation, and separation of a pair of chromosomes. The circles represent centromeres or spindle fibre attachment chromomeres.

of reduction and segregation, which are the external changes essential for sexual reproduction. Special exceptions to this rule we will consider later.

Crossing-over within every pair of chromosomes is thus essential to sexual reproduction, but, leaving out this primary consequence, we can sort out its secondary biological consequences into several convenient groups.

First, we must take the simple effect of crossing-over in recombining parts of chromosomes, the effect which has been made the basis of genetic analysis in *Drosophila*. Without crossing-over, each chromosome would be a permanent individual, varying and being selected as an individual like a plant clone or any other asexually reproducing organism. With crossing-over, the individual unit of variation and selection will be the unit of crossing-over, which in practice is the gene. Cytological observation has, therefore, shown

that the gene structure established by crossing-over experiments in *Drosophila* is applicable to all sexually reproducing organisms. The sizes of the genes and their physiological activity or inertness will be different in different organisms, but their methods of inheritance, variation and selection will be essentially similar. We may expect, for example, that, as in *Drosophila*, chromosomes or parts of chromosomes in which crossing-over is reduced or suppressed will mutate to an inert state in which they will continue until by chance breakage they are lost [3].

One respect in which species differ most significantly is in the amount of crossing-over taking place in their whole chromosome complements. This is one factor affecting the amount of total recombination that will take place among the genes at meiosis. The other factor is the number of pairs of chromosomes themselves. By adding this number to the average total frequency of chiasmata in the mother-cell, we can obtain a *recombination index* which will be a measure of the average total number of independently segregating gene-blocks in the species. This index is 6 in male *Drosophila melanogaster*, 12 in the female, 36 in *Zea Mays* and about 75 in man [4]. It is clear that these enormous differences will affect the character of variation in a species, though in what way it remains for us to find out.

One general property of the recombination index may be noted. A low index has a positive selective value. This may be shown in the following way. The chiasma frequency is under genotypic control; it is therefore capable of selection and is usually as low as is consistent with regular pairing of the chromosomes. On the other hand, it is much easier to increase chromosome numbers, both by doubling individual chromosomes and whole sets, than it is to reduce them. Nevertheless, we have to-day a very large proportion of organisms with low chromosome numbers. More than half the angiosperms have twelve pairs of chromosomes or fewer. It follows that while some recombination is a great advantage, too much is a disadvantage. Presumably a

certain stability in combination gives the maximum efficiency in the selection of different combinations. In this regard Fisher has remarked [5] that there is more crossing-over in Nature than would seem desirable. The reason is now clear: each pair of chromosomes has to have at least one chiasma in order to undergo meiosis.

There is another genetic effect of crossing-over that is entirely different from that of recombination; namely, its effect in certain kinds of structural hybrids. Most organisms that have not been closely inbred are structural hybrids of one kind or another. The commonest kind is the inversion hybrid, which has a segment of a chromosome inverted relative to its partner. When crossing-over takes place within such a segment two new chromatids are produced, one joining the two centromeres of the chromosomes and the other joining their two ends and lacking any centromere (Fig. 4). When the bivalent formed in this way attempts to divide, the "dicentric" chromatid forms a bridge between the daughter nuclei, and the "acentric" one,

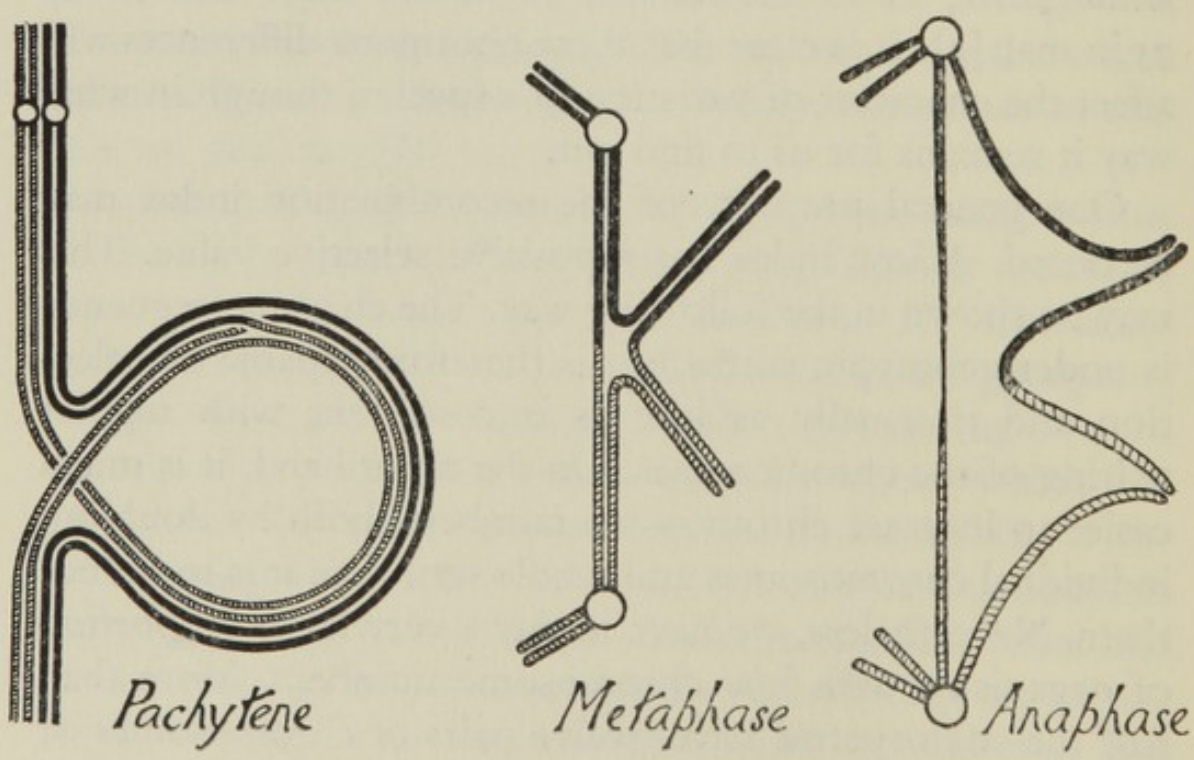

Fig. 4.—Diagram showing the series of changes by which a pair of chromosomes, differing in regard to the inversion of a segment, have crossing-over in that segment with the consequent formation of one dicentric and one acentric chromatid.

incapable of movement, is lost. The bridge may break anywhere along its length, so that new chromatids are produced having some genes in excess and others lacking. Thus the primary structural change of inversion gives rise to secondary changes such as reduplication and deficiency. These are changes of "balance," and rank with intra-genic changes and position changes as one of the three effective means of variation. The original variation becomes the basis of future variability. This does not mean that variation within an endogamous group will be cumulative. Equilibrium is presumably reached by the effect of structural change in decreasing fertility, or a new system is established by the breaking up of the group into two smaller genetically isolated groups, that is, by the fission of the species. This property of genetic isolation brings us to the last important relationship of crossing-over.

So long as we have a structurally homozygous stock with crossing-over taking place at intervals between all the varying genes, no stable combination of variants can be maintained without elimination of cross-overs and loss of fertility. Optimum adaptation always demands such a combination, for adaptation depends on the integration of the whole gene system. The most generally recognized way of securing stable combinations is by geographical or ecological isolation. In the same way inter-sterility may secure a genetic isolation of two types of combination. All these methods depend on an isolation of zygotes. But an equally important method is the isolation of chromosomes or parts of chromosomes by structural change. When a small inversion or translocation occurs in one chromosome of a species, crossing-over is restricted or abolished between this changed segment and its normally arranged partner. Any gene differences occurring within this segment are held together in a more or less permanent combination. A new unit, a new order of integration, is established in this way.

It is through this special type of unit that three important types of discontinuity arise in Nature. The simplest type is

that by which two groups which remain interfertile diverge within a species. It is probably the basis of the discontinuity between *Avena fatua* and *Triticum Spelta* and their allied forms, which differ essentially in a group of genes lying in a part of one chromosome. A second type is that by which the sex-determining chromosomes (*X* and *Y*) come to be distinguished. Originally one pair of genes in these chromosomes determines the sex difference by their segregation. Later other genes become associated with them in two groups which show no crossing-over. Their crossing-over may be suppressed structurally by an inversion or some other similar change. It may also be suppressed genotypically, and here we come to the exceptions in which crossing-over does not take place at meiosis at all. This situation arises in the heterozygous sex in certain insects where a new pairing mechanism is introduced instead of chiasmata. It is only one sex, however, that is affected, and this shows us that in the last resort it is not chiasmata which are indispensable for meiosis but crossing-over which is indispensable for the species. The exclusion of one sex from crossing-over has a special effect on one chromosome, the *Y*-chromosome. Where sex is determined by the segregation of *X* and *Y*, the *Y*, being confined to the heterozygous sex, is permanently excluded from crossing-over. The result of this is shown in evolutionary series when we compare different animals. First the *Y* becomes inert as in *Drosophila*, later it becomes smaller as in the Mammalia, finally it is lost as in many Orthoptera [3]. The intermediate stages show different transitions according to the positions in which crossing-over is localized before its eventual suppression. In whatever way crossing-over may lapse, a group discontinuity arises between the two sex-determining chromosomes. This discontinuity differs in its effect from that arising between species merely in that the two types it distinguishes are mutually adapted for sexual reproduction [6].

The third type of discontinuity occurs in plants. It is that

which arises between chromosomes in establishing a permanent hybrid of the *Œnothera* type. Here an interchange of segments between two different chromosomes is the origin of the system. It operates by suppressing crossing-over between the middle segments of the chromosomes, and when all the members of the complement are affected by the interchanges and are held together in a single ring at meiosis, only two types of gamete are produced, and all the chromosomes of one type are prevented from crossing-over with those of the other in their middle segments. Thus complex differences arise owing to the isolation not of zygotes nor of parts of one pair of chromosomes but of parts of all the chromosomes of the gamete, a gametic isolation. The differences between the two gametes are of the same order as the differences between two species.

Other mechanisms occur in the dog roses and with certain kinds of parthenogenesis whereby, as in *Œnothera*, a large part of the genes are prevented from recombining. With such systems stability has been achieved at the expense of variability, and we have arrived at what we may call a sub-sexual method of reproduction.

In these various ways and in many others the study of crossing-over shows us that this simple and universal mechanical property underlies most of the important relationships with which we are concerned in genetics. Variation and adaptation, hybridity and discontinuity, sex-determination and species-formation operate and develop according to the varying occurrence or suppression of crossing-over. Crossing-over is the primary variable in the evolution of genetic systems.

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4

CHROMOSOME CHEMISTRY AND GENE ACTION

1942

THROUGHOUT plants and animals the cell nucleus has a uniformity of structure corresponding to the uniformity of its work. This structure has to reconcile the mechanical requirements of cell division and reproduction with the physiological requirements of heredity and development. Its primary importance has led to its study by a great variety of physical and chemical techniques; indeed, a greater variety than has been brought to bear on any other type of structure. Differential staining, X-ray diffraction and X-ray destruction, double refraction, micro-dissection, micro-incineration, ultra-violet spectroscopy and differential digestion as well as bulk analysis and the vast magnifications of genetic experiment have been used. They have all played their different parts in the solution of the problem.

The important agents are few and well defined. The nucleus consists of chromosomes which are enormously extensible protein fibres shown by digestion [1] to resemble the protamines and histones making up the bulk of sperm heads [2]. To these fibres, or rather to specific points on them, the chromomeres, are attached desoxyribose-, or thymo-, nucleic acid which is responsible for the specific aldehyde reaction given by the chromosomes in Feulgen's test [3]. Underlying the cycle of mitosis and cell-division is a cycle of attachment and detachment of this nucleic acid to

and from the chromosomes. This goes with the cycle of coiling and uncoiling of their protein framework. The maximum attachment corresponds with the maximum spiralization of the chromosomes at metaphase of mitosis. At the other extreme, within the resting nucleus, they are uncoiled and relatively free from nucleic acid [4].

At the end of every mitosis the chromosomes give up their nucleic acid charge and at the same time secrete *nucleoli* which dissolve at the beginning of the next mitosis when the chromosomes are taking up nucleic acid again. These nucleoli contain no thymo-nucleic acid, but instead the ribose form which is characteristic of cytoplasm and of viruses.

The two nucleic acids differ only in the central sugar radical of the nucleotide. The desoxyribose radical apparently, however, gives its nucleotides a flatness to which they owe their capacity for polymerization. They form columns of plates which, as shown by polarized light, lie crosswise to the protein thread [5]. These plates agree in spacing at 3·34 A. with the extended polypeptide chain of the chromosome. It is this capacity which seems to make thymonucleic acid indispensable in the reproduction of the chromosome. For reproduction takes place by division of each fibre into two at the end of the resting stage, when the attachment of the nucleic acid charge is beginning [6].

The chromomeres, photographed by ultra-violet light, have been shown in a simple case to correspond with the units of X-ray breakage, which provide the physical definition of a gene [7]. Among chromomeres three special kinds of structure and function are found (Fig 5). First there is the *centromere*, the movements of which control the movements of the chromosome on the spindle. The centromeres reproduce, or at least divide, not within the nucleus, but on the mitotic spindle. This delay in their reproductive cycle goes with a deficiency of nucleic acid at all stages of mitosis. If undivided lengthwise they will split crosswise on the spindle. They are, therefore, compound genes [8].

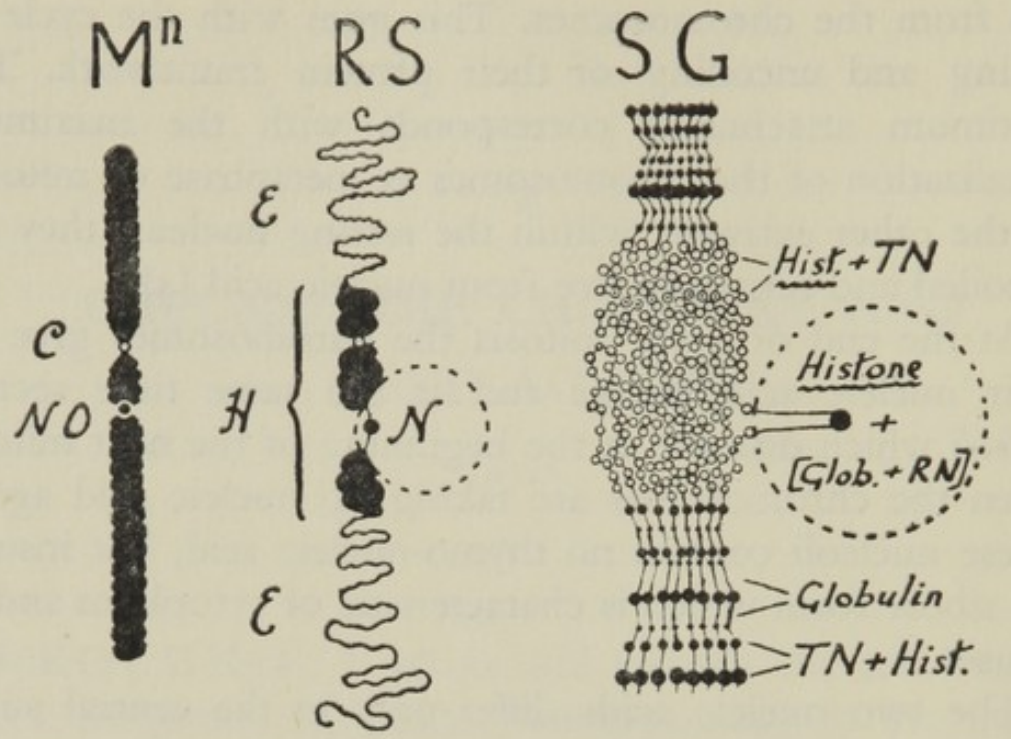

Fig. 5.—Diagram of a chromosome of Drosophila at metaphase, normal temperature (M^n), resting stage (RS) and as a " polytene " structure in the salivary gland (SG) showing the different organs referred to in the text and their chemical content as determined by Caspersson. C, centromere ; NO, nucleolar organiser ; H, heterochromatin ; E, euchromatin.

They may be regarded as spindle organizers playing a similar part to the centrosomes although living within the nucleus instead of outside it.

Secondly, there is *heterochromatin*. Parts of certain chromosomes have long been known to show an abnormal retention or even extra charge of nucleic acid between metaphases. This property was first recognized in the sex chromosomes of animals, where it often goes with a modified timing of the reproductive cycle. Genetic evidence likewise reveals a differentiation. Certain parts of chromosomes, such as the *Y* in *Drosophila*, have long been held to be inert. They made little or no observable difference whether present in excess or absent altogether, and as might be expected, underwent no observable mutations. Recently it has been shown in plants and animals that the two properties of inertness and abnormality of nucleic acid cycle are combined in the same genes or chromomeres, whether making whole chromosomes or parts of them.

These are then said to be heterochromatic as opposed to the active or euchromatic genes [9].

Thirdly, the nucleoli usually arise next to one or more particular chromomeres, the nucleolar organizers, which are again compound genes breakable by X-rays, and may be either at the ends or in the middle, either in a heterochromatic or a euchromatic part of the chromosome [10, 11] (Figs. 5 and 6).

All these different elements of nuclear structure, except the centromeres, are clearly visible in the giant nuclei of the salivary glands of *Drosophila*, and to these ultra-violet spectroscopy has been applied by Caspersson in combination with other methods. By these means he can distinguish quantitatively and qualitatively between the two nucleic acids or their nucleotides on one hand, with a very high maximum absorption at 2600 A., and the proteins with a vastly lower absorption and a maximum at 2750-2900 A. Of these he is able to distinguish between two types which he labels provisionally a histone type with a maximum above 2800 A. and a globulin type with a maximum which changes with the *p*H of the medium but is below 2800 A. in acid medium [4, 12].

The use of this technique has confirmed the picture so far outlined. But is has also gone much further. It has shown that the heterochromatin and nucleolus agree in having a high histone content. On the other hand, in the euchromatin the regions between the chromomeres contain globulin-type proteins. These higher proteins are lost in metaphase chromosomes or ripe sperm, in which only histones and thymonucleotides are recognizable. This leads Caspersson to argue that the active chromomeres or genes in the resting or gland nucleus are producing large globulin molecules while the inactive ones are producing small molecules of histone type which, although still individual, will be less specific in their interactions. The difference between activity and inertness would then be the difference between specificity and non-specificity; or better, perhaps

we might say, between high specificity and low specificity. Further, Caspersson considers that the similarity of content between heterochromatin and nucleolus means that one secretes the material of the other, or we might suppose some precursor of it.

This view is confirmed by experiment. The addition of extra heterochromatin to the nucleus increases the size of the nucleolus in the pollen grain of *Solanum* [13]. A similar addition, in the shape of a *Y*-chromosome, to a *Drosophila* egg increases the concentration of ribose-nucleotides, or other pyrimidine-containing molecules, in the cytoplasm and likewise in the nucleolus [14].

Another connexion is revealed by the fact that the nucleoli are proportionately largest in cells which (with the exception of nerve-cells) are concerned with the most rapid protein production, for example, animal egg cells, meristematic and tumour cells. They are smallest in cells where no protein is being made, for example, in young animal embryos and in leucocytes. It is, therefore, significant that ribose nucleotide concentration increases as cells turn to protein formation. This is especially clear in yeast: nucleotides appear as soon as a source of nitrogen is added, having been entirely lacking even in the most actively fermenting yeast in the absence of such a source. Furthermore, the increase of ribose-nucleotides and of proteins goes with a specially high concentration of them next to the nuclear membrane where the proteins are shown by polarized light to be laid down in lamellar formation. They must be constructed on the very surface where nucleus and cytoplasm meet [15].

This is the argument. And Caspersson concludes that the nucleus is, as we should expect on even more general grounds, the centre of protein synthesis in the cell, that the nucleic acids are the essential agents of this synthesis, whether as polymerized thymo-nucleotides attached to the genes or unpolymerized ribose nucleic acid elsewhere. Further, Caspersson looks upon the changes in nucleic acid

cycle of the heterochromatic genes as depending on differences in rate of protein production of the nucleus in different tissues, the genes being discharged of nucleic acid, their spiral threads uncoiled and their chromomeres separated in so far as the products of their own activities accumulate around them [4].

This account represents the first attempt to describe chromosome structure and activity in relation to cell processes as a whole. It is concerned with the types of molecules whose interactions govern these processes, but it does not tell us the sequence of their interactions. In order to discover this sequence, different methods are needed. Two kinds of experiment have so far proved successful. The first depends on the control of the general metabolism of the cell, or of the organism, by its inert chromosomes. The second depends on the control of the nucleic acid attachment of the inert chromosomes themselves by conditions which are developmental and genotypic as well as external.

The activity of the inert chromosomes or genes might plausibly be deduced from their widespread occurrence. But the precise study of their life-cycle in the individual organism and their distribution in the species makes it certain. Inert chromosomes frequently happen to have a defect of the centromere, which leads to their loss at mitosis. Even when this is not so, their irregular pairing leads to their loss at meiosis. Nevertheless, in species as remote as *Cimex lectularius*, the bed bug, and *Zea Mays*, Indian corn, there seems to be a stable equilibrium of inert chromosomes in races or populations. The same is true of wild millet and cultivated rye (*Sorghum* and *Secale*). Such inert chromosomes must be preserved by positive selection. In some way they must be useful to the cells and the organisms containing them.

The case of *Sorghum* bridges the gap between plants and animals in another way. The inert chromosomes having weak centromeres are lost sooner or later in the development of all somatic cells. They are retained in the germ track.

This distinction between soma and germ track recalls *Ascaris*, where parts of chromosomes, and *Sciara*, where whole chromosomes, are lost in all somatic cells. But in *Sorghum* we know that the chromosomes which undergo "diminution" are in fact dispensable not only in parts of the plant but also in parts of the species. More than half the population have none. Diminution in the individual and equilibrium in the population are therefore two properties of inert chromosomes related by their common dependence upon being useful without being indispensable [16].

This condition of usefulness brings us back again to the notion that they are not indeed inert but rather non-specific in their activity; that their different products do not take part in a series of specific reactions co-ordinated in time and space with those of different active genes, but rather take part indiscriminately in all gene and cell reactions. This character might be due either to their production of smaller types of protein, as suggested by Caspersson, or merely to the control they have been shown to exercise over the production of nucleic acid.

Whatever the means, the end result, an effect of heterochromatin on cell division, is shown by the behaviour of pollen grains containing inert chromosomes in Sorghum. The first pollen grain mitosis, which produces the vegetative and generative nuclei, is normally followed after a week by the division of the generative nucleus to give two sperms. Instead, the vegetative nucleus in pollen grains with extra chromosomes at once divides again and goes on dividing until it has produced four or five generative nuclei, and in so doing has killed the cell. The thick wall confines this growth within the grain and makes it an encapsulated tumour.

These morbid mitoses suggest that the activity of the inert chromosomes in healthy tissues will serve to stimulate nuclear and hence cell division. Further, that healthy growth will depend on a correct euchromatin-heterochromatin balance, morbid growth on an incorrect balance, perhaps

in cancer on a difference in balance between different cells of the same tissue.

The control of the nucleic acid attachment of the heterochromatin itself becomes from this point of view of more than trivial interest. Certain plants and animals with the largest mitotic chromosomes have well-defined blocks of heterochromatin amounting to a quarter or even half of the whole bulk. When the nucleus is brought into mitosis at a low temperature, below 6° C., equally in plants such as *Trillium* [17], *Fritillaria* or *Adoxa* [18], or in the newt *Triton* [19], the heterochromatin is starved of its nucleic acid. The segments in question appear scarcely stained by the Feulgen reaction. It seems as though the supply of nucleic acid has been reduced and the heterochromatin has been unable to compete equally with the euchromatin for the reduced supply (Fig. 6, below).

This controlled starvation leads to derangement of two vital chromosome functions. First, the reproduction of the starved segments is hindered. Sister chromatids stick together, either at the ends or in the middle, and form bridges when they should separate at anaphase. This, when conditions other than temperature have happened to be abnormal, is a common source of chromosome breakage which in turn, by the way, must always lead to a change in heterochromatin balance [17]. Secondly, spiralization may be stopped and the heterochromatin appear as an entirely uncoiled thread at metaphase. This happens at meiosis in the male newt. Here the chromosomes have just emerged from a diffuse stage intercalated in the middle of the prophase and remarkable for having the heterochromatin uncharged, that is, for having no store of thymonucleotides. Similarly, it happens at mitosis in polyploid species of *Paris* and *Trillium*, which differ from diploids in having so small a stock of heterochromatin that again no thymonucleotides will be available within the nucleus (Fig 6, below). Thus the nucleic acid attachment is necessary, not only as predicted for reproduction, but also for spiralization.

Conditions found in nature advance the argument another step. In many animals of the heterozygous sex there is a large heterochromatic segment of the *X*-chromosome which is unpaired. In resting stages of the sperm mother cells and their antecedents this segment is strongly supercharged and there is no nucleolus. Apparently the transference of histones and exchange of nucleic acids surmised

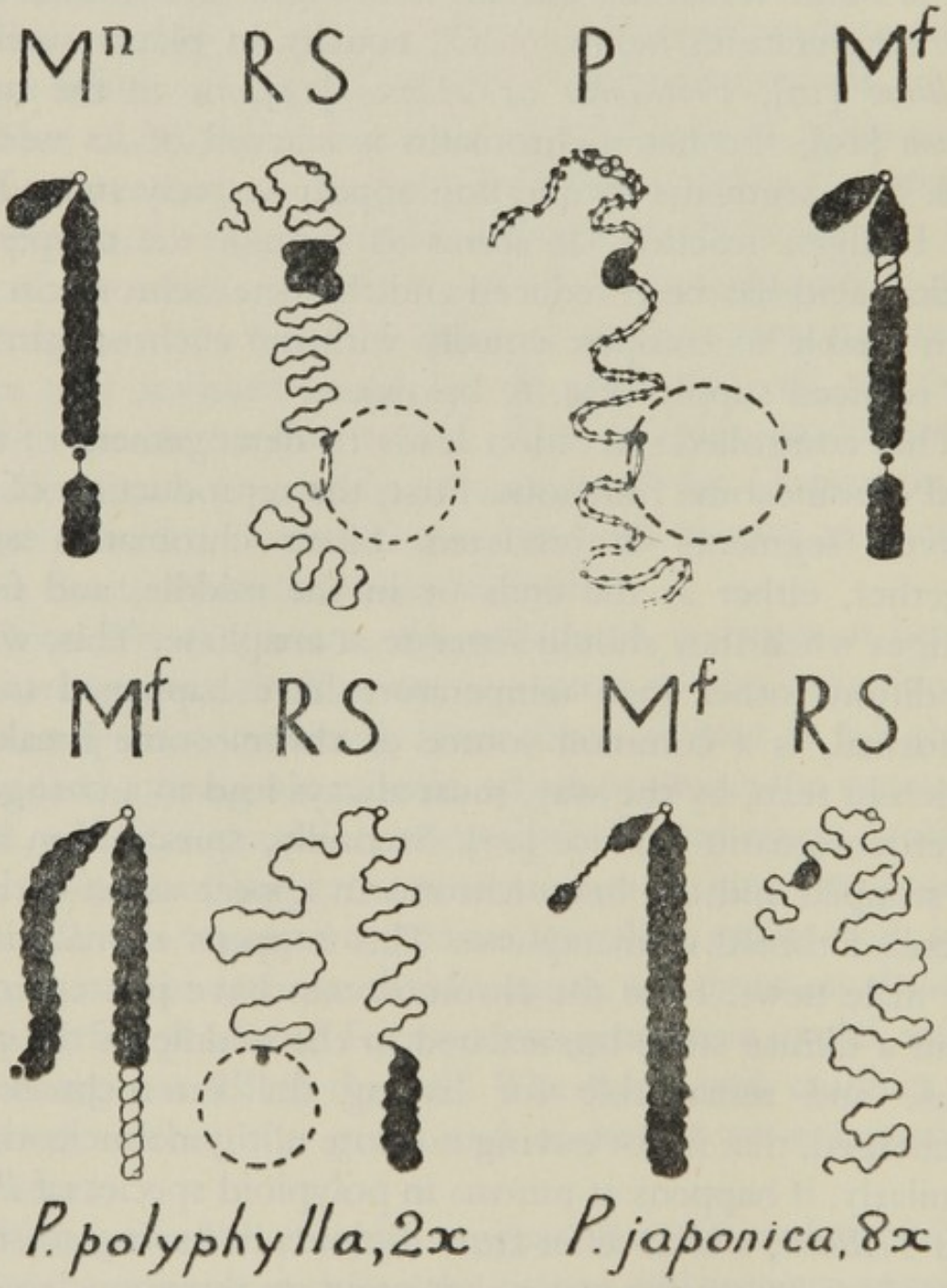

Fig. 6.—Above: Diagram showing the nucleotide cycle of a chromosome of *Fritillaria pudica*. *P*, paired at pachytene and M^f, at metaphase after freezing. Below: Inversion of nucleotide attachment as between resting stage and a chilled metaphase in diploid and octoploid species of Paris. Spiralization of heterochromatin is successful in *P. polyphylla*, unsuccessful in *P. japonica*.

by Caspersson between heterochromatin and nucleolus has been blocked. During the prophase of meiosis this super-charging is strongest, and at the following metaphase a second remarkable property of the *X*-chromosome shows itself. Subject to variations in supply due both to genetic and to external conditions they are liable to fluctuate in their nucleic acid charge. They may be super-charged or sub-charged, or in the extreme case of the hamster *Cricetus* they may be so little charged that they are unspiralized as in the experimental *Triton* [21]. Thus, like a lowering of the temperature, a suppression of the nucleolus can upset the regulation of the nucleic acid supply.

An adaptive effect of super-charging on reproduction is found in the Heteroptera. The normal pairing of the sex chromosomes is suppressed, and they divide at the first division instead of the second. Similarly, in many species of *Drosophila* there is a gene-complex "sex-ratio" which exists in equilibrium in the population. Its effect is to increase the nucleic acid supply and, therefore, the charge on the heterochromatin at meiosis in the male. In consequence the division cycle of the *X* is advanced so far that it divides twice instead of once, and the *Y*-chromosome, immobilized by its heavy coat of nucleic acid, is lost in the cytoplasm. Hence the sperm all have *X* and the progeny are all female. This effect is reduced at higher temperature so that up to six per cent of male offspring are produced. Evidently a causal sequence, temperature—nucleic acid charge—gene reproduction, is operative and can be used as part of the adaptive machinery of the species when it is combined with the usual high heterochromatic content of the sex chromosomes [22].

The imitation of natural abnormalities by experiment can take us further. Unfavourable conditions often produce a super-charging of the chromosomes. In maize a gene has this effect on the metaphase chromosomes, and an X-ray dose of 100r. has the same effect. It is then found that the chromosomes are "sticky". What does this mean? When

cold-treated chromosomes are X-rayed they show both stickiness and starvation. The charge on the heterochromatic segments remains less than that on the rest. They are thinner, but they are nevertheless coated with nucleic acid which stains deeply. It seems, then, that the stickiness is due to an excess of nucleic acid over the normal attachment and an excess with different physical properties [23].

The meaning of this effect becomes clearer when we realize that the X-rays act on the cell primarily by their effect on fibre formation. 50 r. will upset spindle development [23], but the germination of ripe pollen grains, a simple process not requiring fibre formation or even immediate nuclear control, is not disturbed by 80,000 r [24].

In this regard the distinction between fluid and fibrous elements, or at least surfaces, in the nucleus is important. The centromere, the nucleolus, the super-charged heterochromatin and the sticky chromosomes have a fluid surface. They run together. The normally charged chromosomes have a fibrous surface based on their fibrous framework. They stand apart. This difference between fluid and fibre would seem to depend on the polymerization of thymonucleic acid in contact with the chromosome. Here, again, there is a minor interlocking system of control, for while we saw that the nucleic acid charge controls the division of the centromere as well as of the whole thread of the sex chromosomes, the centromere itself often appears to act as the organizing centre for the charging of the chromosomes. At meiosis it then controls their pairing, which runs on a zip principle from the centromere to the two ends. In a word, the centromeres organize fibre formation both in the nucleus and on the mitotic spindle.

Thus we see a chain of reactions: the chromosome thread controls the polymerization of its thymonucleotide charge. This in turn controls the spiralization and, as would be expected, the reproduction of the thread with its genes. Hence the whole course of events can be controlled by

temperature and other cell conditions as well as by the balance of heterochromatin and the organization of the nucleolus.

In this way the pattern of nuclear structure and organization is beginning to appear. But in answering some old questions we have, of course, raised far more new ones. Is the protein fibre of the chromosomes a single or a multiple chain? Is a difference in multiplication or in charge responsible for differences in chromosome size? Why have the prosthetic groups, which represent the genes and express themselves so clearly as chromomeres, active or inert, remained unidentified? How does the nucleic acid attach itself to these groups and so control mating and reproduction (both limited to pairs)? Is nucleic acid the agent of reproduction, or only of separation, of the main chain or of the prosthetic groups or of both? If it controls spiralization, is it itself polymerized in a spiral with a limited number of stable positions? How can the nucleic acid charge at prophase of meoisis be limited in quantity or arrangement so as to avoid reproduction and spiralization long enough to permit pairing?

These and many other questions we can now attempt to deal with in a co-ordinated way. This we can do because at the same time that a new means of knowing the chemical structure and activity of the chromosomes and genes has been placed in our hands we also find ourselves provided with a variety of means of controlling this activity and modifying this structure; with the instruments, in fact, for showing cell physiology and chromosome mechanics, no longer as opposite sides, but as interlocking parts of one system.

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5

RACE, CLASS AND MATING IN THE EVOLUTION OF MAN

1943

THE BACKGROUND

QUESTIONS of race in man have been the subject of increasing dispute for the last hundred years. Most of the positive opinions that have been advanced owe little to our recent knowledge of heredity, but they show the background on which we have to work in applying this knowledge. Our starting point has to be the primitive or Old Testament view. It was expressed by Archbishop Trench when he gave the opinion that the savage "is a dead withered leaf, torn violently away from the great trunk of humanity, and with no more power to produce anything nobler than himself out of himself, than that dead withered leaf to unfold itself into the oak of the forest" [1]. On the other side Darwin opposes to this pessimism the more hopeful view that "all the races of man . . . are descended from a single primitive stock" and have come to differ in heredity during a continuing process of improvement [2].

These opinions differ in the direction of change, backwards or forwards, but they agree that there has been change. Powerful hereditary differences both in mind and body distinguish the races of man. A third view, which springs from the New Testament and also owes something

to Rousseau and Marx, emphasizes, both for race and class, the importance of differences in the environment rather than in heredity. Such a cleavage of ideas as to the genetic evaluation of human races is assisted by the facts recognized by Darwin. "If we reflect on the weighty arguments," he writes, "for raising the races of man to the dignity of species and the insuperable difficulties on the other side, in defining them, the term 'sub-species' might here be used with much propriety. But from long habit the term 'race' will perhaps always be employed" [2].

To-day the "weighty arguments" and the "insuperable difficulties" are still at war. On one side stand those who, following Gobineau, assert that modern peoples spring from hypothetical pure races, from one of which, happily superior to the rest, they themselves are descended without contamination. Further, they hold that races described as Nordic and Mediterranean, and even their mixtures, can be recognized by the forms and features of individuals [3]. Even, by a further stretch of theory, they take language as an independent and sufficient criterion of race, and it is from this simple view that the "ethnographical" maps which appear in our atlases take their title. At the same time, on the other side are those who say that every population "includes many types and their various combinations" and therefore "the word *race* should be banished, and the descriptive and non-committal term *ethnic group* should be substituted" [4]; and further, "the so-called racial explanation of differences in human performance and achievement is either an ineptitude or a fraud" [5]. Again, by a stretch of this theory, it is held that primitive peoples can, by prolonged subjection to the benefits of European rule, be brought to develop a culture comparable with our own, when they will be, as it is said, ripe for self-government.

Both these lines of argument are now being politically applied. It is therefore worth our while to try to form an opinion of their scientific value. Such an opinion

can, I believe, be reached on the basis of the postulates, and on the analogy of the conclusions, of experimental genetics.

MATING SYSTEMS

We must begin, following the example of Darwin, with something we understand better than man, namely, the breeds and races of domesticated plants and animals. If a plant is regularly self-fertilized—a rare condition—we can agree that all the descendants of one plant, or of a group of indistinguishable plants, will, as a rule, conveniently constitute a race or variety. Even so, if they are divided into groups that undergo mutations and are differently selected, the groups will become separable, and sometimes are separated, as distinct races.

When we turn to cross-fertilized plants and animals we find quite another state of things. It is now a question, not of one parent, but of the group from which any individual may take its two parents, and from which all individuals will later take their ancestors. The mating group and the group of common ancestors are the same type of unit. In no such group will all the individuals be alike, and they may be highly diverse. To what then does the group owe any unitary character it may possess? It owes its character to what we may call its chromosome pool. It is a property of germ-cell formation that half the chromosomes of the parent are rejected in the formation of each germ-cell. In a stable population therefore, where two parents have two off-spring, one quarter of their chromosomes are lost to the chromosome pool in the next generation and one quarter are doubled in frequency; only a half reappear once. By mere chance the pool suffers regrouping and by mere chance two separate pools will be differently changed, and, if they are small, rapidly changed [6].

There is something more than chance, however, at work. Different groups are inevitably differentiated by selection whether natural or artificial. The original and subsisting

function of sexual reproduction is to expose to selection all the gene-combinations it can produce at every level of their activity and in the greatest possible range of environments. The conditions of survival and reproduction of the individuals produced by the recombinations of genes and chromosomes are different in different countries, climates and ways of life. Selection is continually changing the character of the chromosome pool by differences of survival and of fertility. Every couple will not have two offspring; and most of the genes concerned are individually invisible in their effects. Furthermore, selection is throwing away, not only unsuitable genes, but also unsuitable combinations of genes, and so balancing the genes contained in the chromosomes against all the others with which recombination from the pool brings them into relationship. This internal selection is producing what Mather calls a "relational balance" which is characteristic of the particular mating group [7]. Thus at three levels, the environmental, the genetic, and the jointly genetic and environmental, or cultural, level any mating group has a unified selective response which differentiates it from all others.

With two inbred groups, the cross-breeding of which is prevented, the point at which we shall begin to refer to them as races is then a question of pure convenience. We can merely say that that point will be reached more quickly if the groups are smaller; if the original differences between them, and the heterogeneity within them, are greater; if their mutation-rates are higher; if their selection is more rigorous or more divergent.

In our domesticated races we are accustomed to use as our index of pure-breeding certain clear genetic differences, the "points" of the breed. These are determined by major or "marker" genes. We cannot attend so strictly to the minor or "polygenes". Artificial cross-fertilized breeds are therefore always more heterogeneous than they seem. Marker genes are also used by the classifiers of wild plants and animals. They are not, however, the most important

agents in separating natural groups in animals or man. This is recognized by the use of geographical and historical criteria in addition to morphological ones. We now know that natural groups have often become inter-sterile without any difference having been noticed by the morphologist; and if invisible polygenic differences separate races their internal homogeneity due to their inbreeding must also be invisible. Natural races are, therefore, more homogeneous internally than they seem, by comparison with artificial breeds. Thus convergence as well as divergence is partly cryptic, and so far as it is cryptic its only measure, apart from experiment, is the breeding history of the group.

GROUP LIMITATION IN MAN

It is our business to find out how this group effect has worked in the history of mankind. Man is derived from a group, at the beginning of his independent history, of ten, or perhaps a hundred, thousand ancestors. These common ancestors were genetically diverse, perhaps as diverse as any living men. Their progeny have continually expanded in numbers, and these numbers alone have set the *genetical* limit to the inter-breeding group in man. Within this expanding population, however, there have been *physical* limits to the effective breeding groups and these have not always expanded. Mobility has depended on a geography and on a civilization, either of which may help or hinder it. Navigation helps, agriculture hinders. Finally, there have been *social* limits to the mating groups which restrict the choice of mate to a fraction of those who are physically accessible. They depend on man's intellectual discrimination, which itself has developed with his cultural evolution. They have, therefore, been applied with increasing rigour as the density of human population has increased; and, though cultural in origin, in effect they are always genetic as well, since culturally separated communities must always become genetically distinct.

When the cultural barrier arises from the physical limitation we have the characteristic origin of race. When it arises from a social differentiation we have the origin of class. When the two are combined and stabilized we get the formal climax of caste in India.

How large in effect are the mating groups into which man is divided? Keith [8] has surveyed the action of "tribal instincts" in restricting their size in primitive peoples. The invisible divisions of civilization can be measured in other ways. One is from the frequencies of the blood group genes [9, 10]. The distinctness of Jewish and Gipsy minorities from the neighbouring majorities shows the strictness of their previous inbreeding. Prof. Fisher tells me that, in rural Ulster, groups with English and Scottish surnames still remain distinct; with a minor religious distinction scarcely any intermixture has occurred during ten generations. Church records of Ulster communities in North Carolina show that the same endogamous habits have been carried across the Atlantic [11]. In the same way the frequency of conditions due to recessive genes can be used to establish the separation of groups. If deaf mutes are $4\frac{1}{2}$ times as frequent among Jews as among Gentiles in Berlin, the two groups must be effectively separate breeding units [12].

Again, Dahlberg has inferred the average size of the group among which mates are chosen from the frequency of cousin marriage [13]. This frequency has changed in Bavaria, for example, as though the size of the group had increased during the last fifty years from 2,000 to 5,000. Increased mobility has been breaking up the agricultural breeding system.

Other methods of measuring the mating system and its effects, using the frequency of *X*-chromosome genes and of heterozygotes, will doubtless be used in the future [12, 13, 14]. But we can already infer in these different ways that the mating group among civilized peoples, although less stable, is not always larger than

among primitive peoples and is smaller than is usually believed by the individuals concerned.

ADAPTATION OF CLASSES

A part of the subdivision of a race into smaller mating groups is inherently adaptive. The closer social intercourse within groups following the same trade favours the mating of similarly adapted individuals. This effect is reinforced by assortative mating. As Pearson found, there is correlation between the heights of husbands and wives. Like mates with like. All over the world, not only in India, fishermen, cotton-workers, coal-miners and peasants are inbred groups. Moreover, groups lose those individuals who are least suited to them. Thus selection will exaggerate itself. First a man selects his mode of life and then his mode of life selects him. The saying that it takes three generations to make a cotton spinner may well reflect this process. Nor can we doubt the advantage that has come to the world from the assortative mating of musicians. These are processes which will continue to be refined by each new development of human culture so long as individuals are free to choose their mates and their means of livelihood.

In monogamous societies based on hereditary wealth, economic differences cut across adaptive differences and establish a still finer subdivision of mating groups. This effect will always be strongest in the layers constituting the governing class. This class is of paramount importance in determining the real and apparent "national character" and hence in controlling racial evolution. In its origin, like other groups, a governing class must in a sense be adaptive, that is to say, selected for its capacity to govern under the conditions prevailing at the time. Is it capable of maintaining its adaptability? The answer is that there are two main conditions operating to prevent it doing so.

The first is that groups within it are not highly inbred and specialized for their function. Among eminent churchmen (the most inbred profession in England) for the last

fifty years only 25 per cent have been sons of churchmen, and the proportion who have married the daughters of churchmen is now even lower than that ("Who's Who", 1890-1940). From the mixture that is going on, segregation of unsuitable types is, therefore, likely to be more frequent than in the working classes. But the inheritance of wealth (or power) gives a governing class the means, which it is bound to use, of releasing itself from selection pressure, of preventing its members taking their adaptive level. This effect is partly a cultural effect of family life, but it can be assisted by the development of such special educational barriers between classes as we find in England.

The second condition lies in the mechanism of social diffusion by which governing classes may be reinforced and their deterioration avoided. On one hand, diffusion between classes may be prevented. Then, not only are human individuals wasted but also genetic materials, useful to the race, are apt to be thrown away, since they are tested in the wrong environment. For a while, of course, such materials may accumulate until changes such as the English, French, or Russian Revolutions occur to make use of them. If, however, they are to be stored, as in India, for thirty or forty generations, these elements will be lost before they can be used. The social tension will be released and the system internally stabilized. The economic and professional castes of India temporarily broken by Buddhism and loosened by the Mohammedan invasion have been given by British rule an organic rigidity to which every process of ordered government, even the Census, contributes a stabilizing effect [15].

On the other hand, where social promotion occurs, at first sight it might appear that social merit must always be its chief agent. But just as a governing class in its origin is always mixed, so it will be in its reinforcement. To this process Fisher [15] ascribes the decay of governing classes and in turn the decay of the empires they govern. He suggests that social promotion of men is favoured by the reduced

fertility of their parents, which has been shown to be heritable. This effect will be all the more important for exaggerating itself. But it is only a part of the story. The social promotion of women will always be based on qualities of a different kind from those favoured in the promotion of men and often conflicting with them. Its effect will be predominant where the governing class is legitimately polygamous. We may, therefore, see in the excessive fertility of sultans and emirs a process contributing to the rapid decay of Islamic cultures.

Thus class division combined with diffusion are necessary for the efficient utilization of the race where the differentiation of the culture is stable; but the conditions of diffusion, unless suitably controlled, may make it little better than no diffusion at all.

CONFLICT OF SYSTEMS

If mankind had long been broken up into genetically isolated fragments it would at once be obvious to us that race made culture and language. Any group, however heterogeneous, would have to be held genetically responsible for its aggregate cultural activities. Now both races and cultures are continually being mixed, but culture is a more important obstacle to this mixing than race. Hence the relationship becomes reciprocal. Culture and language often make race just as much as race makes culture and language. It is this argument, combining genetic premises with a dialectical change, which has hitherto defeated historians and philosophers.

When languages are mixed or transferred the process is always selective. In Burma social advancement is often the incentive and tribes "change their language almost as often as they change their clothes" [15]. The same principle applies in the West. Owing to the dominant cultural influences of certain Western languages (English, French, German, Spanish, Swedish, Russian, Turkish or Persian) minor language and dialect groups have at various times

become socially and culturally depressed. Where the depressed group has held on to its language in spite of this, it has by social diffusion lost genetically useful elements to the dominant group. In recent times we have seen the resurrection of such depressed and genetically extracted classes as nations, and the artificial result has sometimes been disappointing. A similar genetical extraction and depression has commonly benefited the town at the expense of the country and the capital at the expense of the provinces. Again, where a caste system is fixed, as in India, this extraction is prevented to the common disadvantage.

When conquest breaks down a mating barrier, and races fuse, outbreeding momentarily succeeds inbreeding with results which historians again have found hard to explain. The most instructive of these changes is that accompanying the expansion of Islam, for here the same experiment was repeated, extending in time over a thousand years, and in place from Marakesh to Delhi. The choice Islam offered to the vanquished with varying emphasis was a simple one: exogamy or death. The result was nearly always the same. New genetic combinations were able to take advantage of new cultural combinations and a striking cultural development took place, although limited for the reasons we saw to seven or eight generations. This effect was due to the breakdown of class as well as race barriers assisted by polygamy. The conversion to Christianity, on the other hand, had no such striking cultural consequences, because it did not destroy the existing mating barriers established by class or by race.

Polygamy thus affects both class structure and sexual selection; and sexual selection is biased by changing social conditions. The two sexes must always be complementary in reproductive function but otherwise their adaptations are, genetically at least, as different as those of two closely related species. Karl Pearson [17] showed how the average cranial capacity of different races differed and how the proportions of male to female also differed. His summary led

him to the conclusion that in the older civilizations which were closer to a matriarchal stage of development, women's cranial capacity was relatively larger than in modern civilizations. Whether or not this inference is sound we cannot help assuming that human history has been a process of intellectual specialization of the two sexes which for the reasons we have seen will have led to different results in different races and classes.

The historic change from matrilinear to patrilinear inheritance has also led to important conflicts. In all groups of mankind exogamy rules have probably existed at one time. Marriage has been forbidden within certain degrees of relationship, real or imaginary. The system has reached its highest development in the sparsest and, therefore, most inbred communities, as in Australia [18, 19].

The exogamy rules often break down. They do so especially when the inheritance of property develops during an unresolved conflict between matrilinear and patrilinear inheritance. The result is an instructive experiment. In the Ptolemies, successful incest began after a half-cousin marriage. In the whole line of thirteen, eight had full brother-sister marriages, but only three were fruitful. No two of these were in successive generations. The legitimate inbred line died out and Cleopatra's mother is unknown [20]. Similarly in Peru only one of the royal Incas is known to have been the issue of a brother-sister marriage. In neither case was there any continuous incest [21].

Successful and regular incest, on the other hand, has frequently been maintained by half-sister marriage, for example, in the Eighteenth Dynasty in Egypt [20]. Such marriage was common also in ancient Athens and among the Mongols and it occurred in Ur and in the royal house of Siam. The practice is no doubt helped by half-sisters being very numerous and also by the action of the matrilinear incest taboo. The evidence of experimental breeding in turn makes sense of this taboo. Only in five generations of self-fertilization and in ten of brother-sister mating will

sterility usually wipe out the inbred stock. The effect will will be most drastic when inbreeding is suddenly introduced in an outbred stock, and the inbreeding must be continuous to be cumulative. The exogamy rules of man like most moral laws seem, therefore, to have been derived by an extreme extrapolation. Incest is directly dangerous to the progeny only under special conditions which have nothing to do with those governing the indirect effects of inbreeding on a whole group.

The group effect of inbreeding is that it gives homogeneity, predictability of offspring from parent, rapid adaptation, easy transmission of culture, sometimes too easy, and hence potential stability of culture. It is a conservative agent and it conserves itself best in the most conservative peasant communities. It opposes initiative. It reduces conflict, sometimes disastrously. If applied to specialized classes it conserves their differences and increases their fitness. In India the endogamous caste system has preserved a store of variation which, if released by free crossing or recombination, might well enable us to reconstruct the whole genetic range of mankind.

On the other hand, inbreeding, while increasing temporary fitness, reduces flexibility. It reduces the means of acquiring fitness to new conditions. The Andaman Islanders steadily decreased in number from 4,800 in 1858 to 460 in 1931 [15]. This is said to be due to the deleterious effect, either of inbreeding, or of the contact of civilization with a primitive people. It would be more accurate to say that it was due to a homogeneous race being confronted with conditions to which it was not adapted. Homogeneity provides the optimum condition for an epidemic. Heterogeneity permits selective survival and recovery.

This advantage of heterogeneity merely shows in a special way how inbreeding frustrates the long-term function of sexual reproduction, the recombination of genetic differences, recombination which cannot take effect without the combination of these differences by outbreeding.

The long-term function of outbreeding has moreover come to imply a short-term advantage. Species become adapted to outbreeding and the adaptation, as we saw in regard to incest, cannot be overridden without risk. This adaptation has been explained in general polygenic terms by Mather [7]. His explanation is all the easier to apply owing to the probable importance of super-genic differences arising through inversions of groups of genes. These are more likely to favour the heterozygote than are single gene systems since they cannot be broken up by recombination in the heterozygote. The equilibria of blood group and taste genes which seem to have persisted in man since before his separation from the apes [22] suggest such a favouring of heterozygotes.

Hybrid vigour might be expected to be shown in these circumstances. Dahlberg [23] attributes the increase of average height of recruits in Sweden by 9 cm. to the increased outbreeding following increased mobility. The change is steady over a hundred years and cannot, therefore, be due entirely to improved nutrition. We are accustomed to regard such a change, which is noticeable also in England, as advantageous, and that may be so. But if the previous range of heights was an optimum, secured by adaptation to conditions which have not changed, we must now be too tall. Thus there is a conflict between the advantages and the disadvantages of outbreeding at both genotypic and phenotypic levels and as between the short view and the long one.

How then is this conflict to be resolved? In general the combination of inbreeding and outbreeding in parallel rather than in sequence gives the greatest efficiency in the utilization and selection of the available variation of mankind and, consequently, the most rapid evolution. A subdivision of mankind into races and classes is, therefore, highly advantageous provided that we can assure its instability. This seems to be no insuperable difficulty at present. The rapidity of differential population changes, the

increase of mobility, the changes of methods of production, and the technical requirements of government, have upset the stability of races and classes as well as the adaptation which partly justified that stability. In these circumstances the "young" peoples newly derived from a mixing of races or of classes have obvious advantages over the most permeable of stable societies yet known. Outbreeding for the moment is in the ascendant because cultural evolution is increasing its pace; and this again is a reciprocal and therefore self-exaggerating effect.

CONCLUSION

Man's intellectual and cultural evolution has led not to an absence of the races found in other species but merely to a special character in these races, due we may say to a special combination of artificial and natural selection. He uses a cultural and intellectual discrimination in the subdivision of his mating groups which must artificially accelerate his evolution. His habits of migration and conquest, on the other hand, continually constitute new groups of hybrid origin. These must therefore be, for most of their lives, groups, not of decreasing, but of increasing homogeneity. The common posterity, rather than the common ancestry, is what matters in human races and classes. Moreover, these groups are not classified by marker genes. For all these reasons human races and classes are more homogeneous than they seem; animal breeds, by contrast, less so.

We must, therefore, regard those who would have us shut our eyes to the genetic differences between races and classes, lest the recognition of unlikeness should generate antagonism, as offering us the counsel of timidity and escape. Let us rather consider that all the races and classes of men, however distinct, and usefully distinct, are likely in the end to have their posterity in common and to the common advantage; and that this posterity will still be classified and subdivided. Meanwhile, let us use the methods

at our disposal for evaluating the different genetical and cultural prospects of different races and classes and systems of mating. In doing so we shall recognize the reciprocal connexions that exist between changes in the mating system, the economic system and the political system. For in changing one we are likely to change all three, and the systems which are functionally the most advantageous have a prospect of being eugenically the most desirable.

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6

HEREDITY, DEVELOPMENT AND INFECTION

1944

1. THREE LEVELS OF HEREDITY

THE development of genetics has depended on the separation between determinants and what they determine, between factor and character, between gene and gene-product, between genotype and phenotype. Once the separation had been admitted in theory the connexion could be examined in practice.

This examination has proved that there are three systems or levels of determinants [1]. The first system and highest level is that which is most accurately and equally distributed at the division of the cell and most equally transmitted by the two parents in sexual reproduction. It is responsible for the Mendelian heredity of genes; it determines the widest range of hereditary variation; and its equilibrium is mechanical. Its transmission (with odd exceptions) is not influenced in any regular way by external or developmental conditions. It therefore predominates in the government of heredity as well as in the government of the cell. This is the *nuclear system*.

The second system, recognizable only in green plants, is liable to be unequal in its distribution at cell division and is always unequal in inheritance, being largely maternal in transmission. Its equilibrium is best described as physio-

logical. This is the plastid or *corpuscular system*. The third system constitutes the undefined residue of heredity, not associated with any visible bodies in the cell and hitherto supposed to be purely maternal in transmission. This cytoplasmic or *molecular system* must depend on chemical rather than on mechanical, or even physiological, equilibrium for its continuance.

The study of the plastid and cytoplasmic systems has been long delayed. For, as we now see, their properties can be resolved only in terms of a previously acquired knowledge of the nuclear system with its differentiation into chromosomes and genes. We can get to know extranuclear heredity only in terms of relationships. The first steps were made by the study of differences between reciprocal crosses of species or races in flowering plants. These were frequently male-sterile in the F_1 one way, although normal the other way. In other crosses, for example in the tomato, the difference was one of size and expressed itself both in F_1 and in the segregating F_2 [2]. Or again, if the F_1's were similar and normal, as in an upright-procumbent flax cross, abortion of the anthers, varying in degree, according to the races used, appeared only in a quarter of the F_2's from crossing one way [3]. Thus the defect arose out of the reaction between a single, ambilinear, recessive gene from the nucleus of one parent and a matrilinear cytoplasm from the other.

The commonest markers in these cases are defects, and this suggests that the cytoplasm in heredity is to be regarded as a negative factor; but recent evidence points to a positive activity. Mather [4] finds that the cytoplasm of a self-compatible species of *Petunia* frequently gives male-sterility with the nuclear system of a self-incompatible species. The opposite combination is always normal. The same is true in *Nicotiana* [5]. Mather, therefore, suggests (unpub.) that the nuclear and cytoplasmic systems of self-incompatible plants are mutually and constructively related. Thus we may have to admit that the cytoplasmic

system is not an obstacle to adaptation but an instrument of it.

2. PLASTOGENES

If the cytoplasm is adaptive, it obviously cannot be considered as a unit in adaptation. It must be composed of different determinants. The simplest evidence of this kind of organization, however, comes from the plastids. The plastids differ from other organs in the cytoplasm in that their separate inheritance and separate actions can be seen in individual cells. The critical step in their understanding was made by Renner [6, 7].

By reciprocal crossing of two species of *Œnothera*, *muricata* and *hookeri*, Renner combined the ambilinear nuclei with the largely maternal plastids in four combinations, with the following significant result :—

		Nuclei	
		hookeri	Hybrid
Plastids	*hookeri*	Green	White
	muricata	Green	Green

The *hookeri* plastids thus turn white with the hybrid nucleus; but they turn green again in the next generation when restored by back-crossing to the *hookeri* nucleus. Evidently two kinds of nuclei with their genes are at work, and two equally permanent kinds of plastids. Such plastid differences imply the action of determinants or *plastogenes*, as Imai has called them [8]. How then do the plastogenes act? We might say that the nuclei control their activity. But it would be safer to say that the joint reaction of nuclei and plastogenes determines whether the plastids are white or green. The nuclei and the plastogenes are then, as Renner says, mutually adapted in each species to the production of chlorophyll, and this adaptation is upset in hybrids.

There is one way in which the nucleus might, however, be said to control the plastogenes. It might control, not their activity, but their mutation, which (as soon as we separate determinant from product) is an entirely different thing. The distinction between joint action and controlled

mutation is well recognized in the relations of nuclear genes. Not only the genotype as a whole but even a specific, mutation-producing, gene can be shown to control the time and place of mutation of another gene the action of which is directly observable [9]. Control of plastogene mutation by the nucleus is unlikely in the *Œnothera* case, for it would require capacities in nuclei for instantaneously producing and reversing mutations in particular kinds of plastogene. If, however, we were to find delayed, and preferably irreversible, changes arising in otherwise autonomous plastids when they were in association with specific nuclei we should have evidence of controlled mutation. Such situations have been described by Imai [8, 10] in barley, rice and elsewhere.

In barley the recessive "variegated" homozygote is characterized by casual mutation in early life of some of its green plastids to white; and the plastids, being corpuscular, are sorted out to give green cells and tissues and white cells and tissues. The plastids are then autonomous. They are inherited only from the mother and they do not mutate back to green under a "green" nucleus, which is indeed merely effective in stopping further mutation. Thus, equally in "variegated" selfed and in its cross with "green" pollen, a small proportion of the seedlings contain only white plastids and die; a still smaller proportion are mosaics from mixed egg cells; the rest are variegated in the selfed family, green in the cross (Fig. 7).

The same principles apply to a variegated rice [11], but a third instance in maize extends the technical possibilities[12]. Plastid equilibrium is physiological. The times and stages of mutation, and of sorting out or distribution, are both under genotypic control. They begin earlier in the maize than in the barley. Hence it gives wholly white ears which, with any pollen, bear wholly white seedlings. Late mutation, as in barley, gives egg cells having mixed plastids, green and white; these eggs, with any pollen, yield mosaic seedlings, again with some wholly white ears; and these, in the

next generation, give purely white seedlings, some of which have homozygous green nuclei. Thus no kind of nucleus can make the mutated plastids change back from white to green.

In all these cases the variegated gene has a capacity (a limited capacity) for changing the plastogenes, irreversibly, from green to white. Thus the control of the nucleus is not

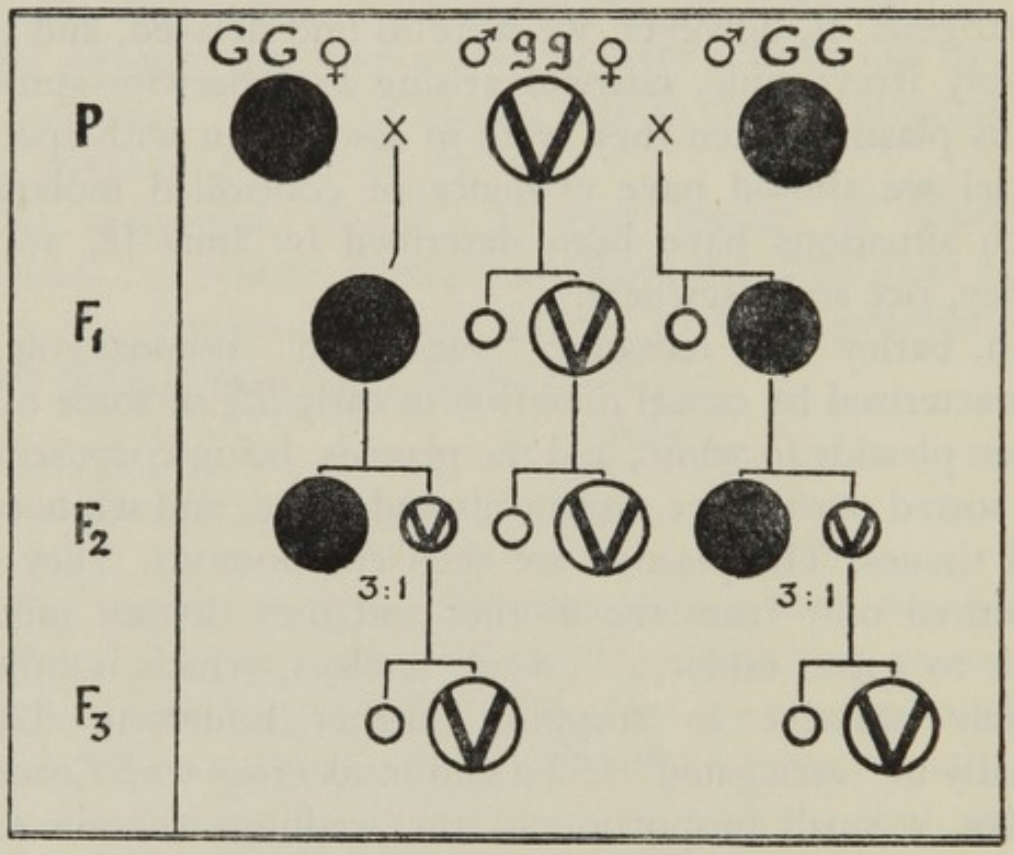


Fig. 7.—*Hordeum vulgare* after Imai. Black circles are green plants; white circles white plants; and V circles variegated. Size of circle indicates frequency of seedlings.

continuous and direct but *mutafacient* and indirect. Imai, Pal, and Rhoades are able to prove this because the mutafacient capacities of the two alleles are sharply contrasted. Reactions might be otherwise if the genes and plastids concerned were recombined with the corresponding elements in the nearest relative (for example, teosinte for maize); but this could only reveal a more complex situation, not a less complex. In another variegated rice Imai has indeed shown such a complexity. Here the plastids behave like those in maize and barley, but the nuclear control is different. Individuals with

non-mutable plastids arise from those with mutable plastids and the change is not controlled by a single nuclear gene. The plastids, therefore, simulate an autonomous mutability. Such a continuous variation in mutability, however, merely suggests polygenic control by the nucleus which in this field, as elsewhere, has hitherto been left to the account of indeterminacy.

3. PLASMAGENES

How far are we justified in assuming the same kind of determinant in the cytoplasm where determinants are not fastened to the immediate products of their activity? If we can show that there is not only an activity relation of nucleus and cytoplasm but also a mutafacient relation, the analogy with the plastids will be broadened and the assumption of unattached determinants vindicated. This relation has now been established by Sonneborn [13] in *Paramecium aurelia*, although his interpretation, failing to distinguish between "factor" and "substance" in the cytoplasm, does not relate it to the present discussion.

Alternative types exist in two races of this protozoan, one of which, the "killer" (race 51), poisons the water for the other, the "sensitive", type (race 32). The reciprocal F_1's between them are each of the maternal type. The F_2 in the "sensitive" line continues entirely sensitive. The F_2 in the "killer" line, however, yields one quarter of "sensitive" individuals which behave like the original "sensitive" type. Thus between the two races there is a gene difference as well as a cytoplasmic difference: and while the "killer" gene *K* cannot change the "sensitive" cytoplasm to "killer", the "sensitive" gene *k* can change the "killer" cytoplasm to "sensitive" (Fig. 8).

As in the plastid cases, this effect is not instantaneous, although it might appear so in a larger organism: it takes place in 2-5 fissions; it waits on reproduction. Thus the *K* gene is ineffective and its *k* allele does nothing beyond causing a specific and irreversible hereditary change in the

cytoplasm, that is, a mutation in a *plasmagene*, or the creation of a new plasmagene. The incidence of the mutation or creation in the *Paramecium* cross is thus the same as the incidence of the defect in the flax cross, namely, one quarter of the F_2 in one direction.

Two practical points will be noticed. From the crossing of the two races it is possible to get "killer" and "sensitive" stocks which are both *KK* and differ only in cytoplasm.

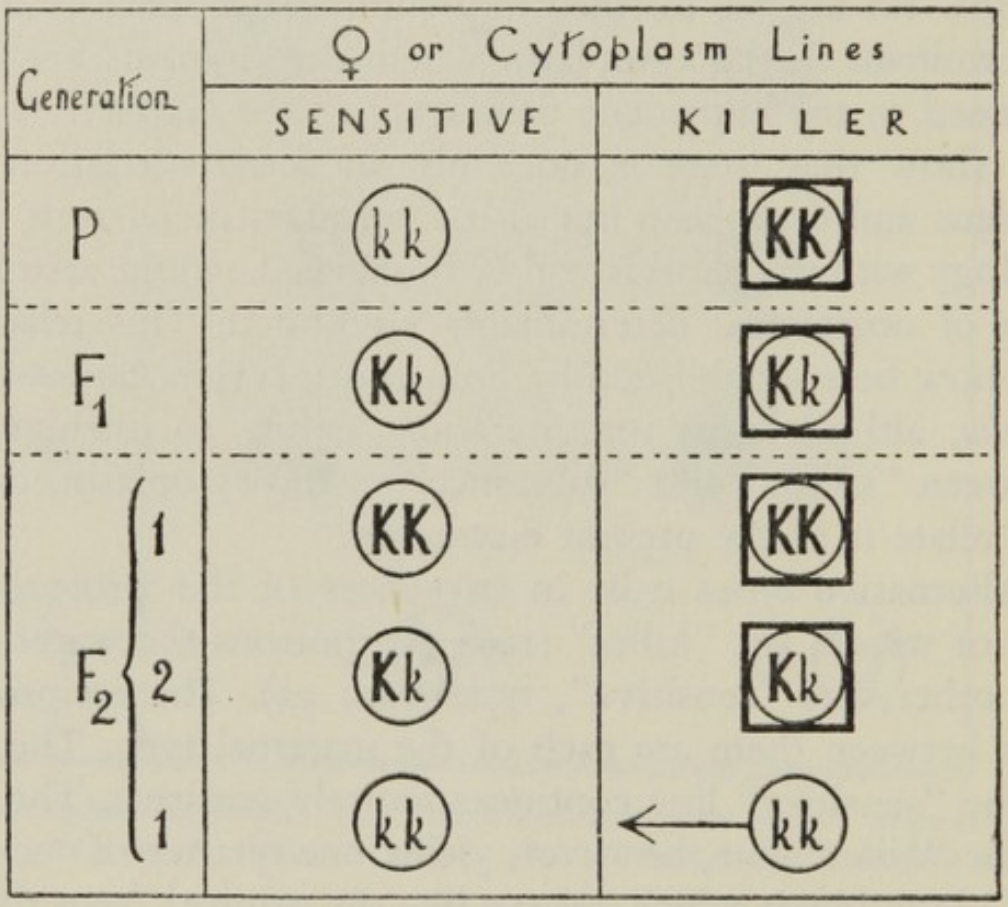


Fig. 8.—*Paramecium aurelia.*

Indeed, Sonneborn has a natural "sensitive" stock (race 47) of the *KK* type although he does not ascribe such an origin to it. Further, it is also possible to get purely "sensitive" stocks with uniform cytoplasm and differing only in having *K* and *k*, which difference will be seen only in the F_2's that they will give with "killer" stocks. As in all such cases the effective variable may be either nucleus, or cytoplasm, or both, as we choose to arrange the experiment.

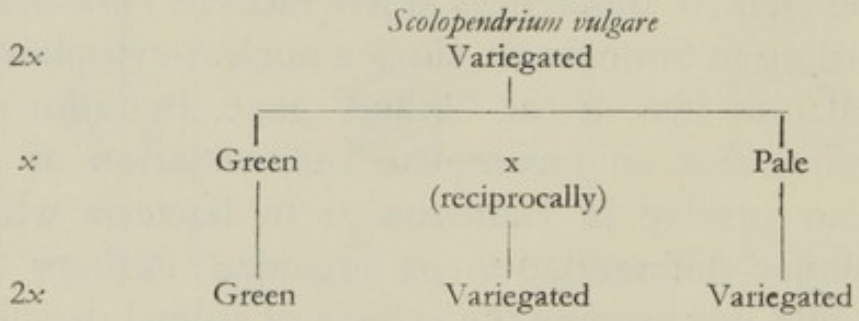
The question now arises as to how such plasmagenes maintain themselves. There are not only the two types responsible for the "killer" and "sensitive" reaction. Different strengths of reaction are also found in different " killer" races. Are the plasmagenes of each of the different types uniform or can they be mixed in one individual? Here again an experiment of Sonneborn's is decisive. Permanent fusion of individuals sometimes occurs and gives rise to offspring of mixed cytoplasm. When two *KK* individuals fuse, one with "sensitive", the other with "killer" plasmagenes, all the progeny have "killer" plasmagenes. Mixture is unstable and "killer" is, we must not say dominant, but rather *suppressive*.

Thus the "sensitive" plasmagene which is determined by the action of a nuclear gene is suppressed by the action, or by the competitive reproduction, of another plasmagene. This does not exclude the possibility that the "sensitive" plasmagene is itself created by nuclear action.

Nine other genetic differences in five races of *Paramecium aurelia*, according to Sonneborn, show a nuclear-cytoplasmic relation similar to that of the "killer" gene. It might not seem surprising that an incomplete subordination of the cytoplasm can survive in Protozoa or in Bacteria which have no cellular differentiation to organize. Perhaps the cytoplasm could not become the vehicle of animal development until it had largely ceased to organize heredity. A merely technical explanation is, however, sufficient. Unicellular organisms by their size, and plants by their plastids, and by the absence of such confusing elements as sex chromosomes, provide the experimental and theoretical conditions that are required for these delicate tests.

If we admit the hereditary and physiological validity of plastogenes and plasmagenes we must next look for evidence of their interaction; we must expect them to show evidence of that control of one another, mutafacient or direct, which

the nucleus shows over all three levels of determinant. The fern *Scolopendrium vulgare* [14] shows such a relationship. Variegated sporophytes are pale with dark green mutant sectors. They produce two kinds of gametophyte from different whole sporangia: greens which breed true and pales which again produce variegated sporophytes, ever-sporting like the parent. Evidently there is a determinant which limits the formation of chlorophyll in the plastids. This determinant is stable in the gametophyte, but unstable in the young sporophyte. Crosses both ways between green and pale gametophytes are wholly variegated. The determinant therefore is not in the plastids. Nor is it in the nucleus, for it does not segregate at meiosis to give differences within sporangia. The determinant must be a plasmagene. Further, it must be a suppressive plasmagene since the reciprocal crosses are both of the pale type. Owing to this suppressivity even the spermatozoid is able to impress the offspring with its cytoplasmic type, and we have to admit the existence of ambilinear plasmagenes.



What does suppressivity imply? It implies that plasmagenes have rates of reproduction which can be varied widely, subject to the control of the nucleus and of one another. It implies also that their chemical equilibria must be subject in some degree to developmental as well as environmental conditions. These consequences we may now consider.

4. DIFFERENTIATION AND MUTATION

The knowledge that plasmagenes can be suppressive, and hence are ambilinear, as well as mutafacient, not only

raises the question of their stability or instability in development; it at once enables us to reinterpret the relevant experiments. Rogues in peas provide a starting point. They are empirically well understood [15, 16]. They appear in nearly all garden varieties as more or less frequent mutations with pointed leaves and curved pods. They breed true in selfs and usually in crosses. The rogue character is, therefore, like the paleness of *Scolopendrium*, ambilinear and suppressive in its determination. But its inheritance shows more than that. Crosses between rogues and types of the same variety give some seedlings which begin as intermediates, especially when the pollen is transmitting the rogue determinants rather than the eggs. In one variety the mutated seedlings themselves begin as intermediates which turn into full rogues before maturity. We might suppose that in these intermediate mutants and crosses the suppressiveness of rogue over type was, as in *Paramecium*, gradual instead of instantaneous, the unstable equilibrium being expressed in the unstable form. Breeding bears this out. The numbers of normal types in the progeny of any pod are correlated with the degree of normality of form at the level of this pod. As Bateson says, the genetic properties follow the changes of the somatic character.

Similar conditions obtain elsewhere. In rogue tomatoes suppressiveness is the other way round; type is moderately suppressive of rogue, and rogue mutation is subject to powerful environmental effects which are not yet understood [17]. But again the proportion of rogues varies with the roguishness of the plant and with the stage or state of development of any one plant. In *Dahlia*, *Tagetes*, and other Compositæ [18] breakdown of the pigmentary effector system is ambilinear in its determination, and its inheritance is correlated with its expression. But here intermediates are so stable that we cannot say that either normal or abnormal is suppressive, but only that both are slightly suppressive of the intermediate conditions. Many other analogous but more difficult cases are known [1].

If these observations have any general importance they mean that, where plasmagenes are concerned, transmission in heredity and expression in development can control one another. In doing so they are likely to defy the analytical methods appropriate to the study of either and, indeed, to threaten this primary boundary in biology. Already we must allow that this boundary is likely to hinder the solution of many problems now put on one side of the fence and now on the other.

It will be well, therefore, to examine other border-line cases. Among garden roses the change from the bush to the climber (not rambler) type is known in about a hundred varieties. It has the appearance of a genetic mutation. It is sudden and complete, and its occurrence is unpredictable. But its reversal is partly predictable since the chance of reversal is greatly increased by bud-grafting on to a dwarf stock. Six out of thirty-two reverted in one budding experiment [19].

Cancer is also a border-line case on account of its heterogeneity. It ranges between two extremes. At one end it is congenital, hereditary, and highly determinate, being sometimes determined by an excess of heterochromatin [20]. At the other end it is mutational, or even invasional, and therefore inherently non-hereditary. The mutational changes may be induced in the cytoplasm of normal cells by chemical agents, the carcinogens [21], which also induce in plants dauermodifications of limited or unlimited persistence [22].

In all such cases, where the vegetative individual ceases to be the genetic unit, we have an analogy with changes that are proved to be hereditary in peas and elsewhere. How, then, are we to make the distinction between what is hereditary and what is not? Outside the nucleus it must be a physiologically trivial one. It must depend on the fact that certain self-propagating bodies, presumably nucleoproteins in the cytoplasm, are, in one class, transmitted by the fertilized egg and, in the other class, are excluded, or

liable to be excluded, from it. The distinction is physiologically trivial because, within their sphere, there are evidently different kinds of plasmagenes which vary widely in their developmental stability and selective distribution, and in their suppressiveness, or, in other words, in the type of chemical equilibrium on which they depend for their continuance.

5. INFECTION AND HEREDITY

At this point it is worth asking how much the virus and the plasmagene have in common. In disease as well as in heredity there are three orders: nuclear, corpuscular and molecular. Viruses like plasmagenes belong to the molecular order. The chemically recognizable viruses, apart from vaccinia, chemically resemble what we know or assume of plasmagenes. They are proteins reproducing with the help of ribose nucleic acid [23], thereby being distinguished from the nuclear genes which use desoxyribose nucleic acid [24]. Viruses are subject to the developmental control of the host, being excluded from certain tissues and reduced in others. They are also subject to its nuclear control, being suppressed by some host genotypes and permitted by others, either within limits or, pathologically, without limits. There are, therefore, "susceptible" and "carrier" genotypes, as Baur showed in *Abutilon* [25]. The difference between the two types of host is genetic and may be controlled by a single nuclear gene [26]. Infection of one susceptible species can take place from another through an immune carrier species [25]. A virus, injurious to one host, can exist in equilibrium for hundreds of years with another, like the broken Zomerschoon tulip [27], damaging nothing but its chromosomes [28]. It thus becomes part of the developmental system of its host. It may be specific in its action on plastids or on pigment production, or highly generalized in its effects. It is apt to undergo mutation and consequently shows adaptation. This mutation is under the nuclear control of the host. Indeed, in the attenuation

process, the nucleus is mutafacient with respect to the virus. Related viruses show suppressiveness; for example, the wild type of tobacco common-mosaic suppresses its mutants in combined infections [29]. In all these respects viruses resemble certain kinds of plasmagenes. Further, unrelated viruses may interact, and even reinforce one another, as nuclear genes do.

We are thus left with nothing to distinguish between virus and plasmagene except the two criteria used by Baur in 1906. The first is curability or environmental control as opposed to stability. But curability is rare in the absence of the antibodies produced by animals. Hot water may kill a virus without killing such a host plant as the periwinkle, for example. Similarly, Baur found that infected *Abutilon*, from which variegated leaves are regularly removed in a dim light, eventually produces green leaves which remain green in full light. The disease is curable.

The cure has two physiological analogies. On one hand there is chlorosis determined by nuclear genes, where the destruction of the chlorophyll likewise seems to depend on its own production: it can be stopped by low lighting, but, of course, the cure is not permanent [30]. On the other hand. there is the known environmental control of mutation or reproduction in plasmagenes. Putting the two together, we see that cure of the virus is merely the removal of the conditions of its reproduction in the cell.

The second criterion is infection or invasion as opposed to inheritance. Regular transmission of viruses by the egg of the host plant (the insect vector does not concern us unless it suffers) probably does not occur, and only in a *Phaseolus* mosaic disease is the virus said to be transmitted by the pollen [31]. Clearly, regular inheritance of a regularly unfavourable virus, combined with infection, is an unstable condition which can end only in the whole species, either becoming adapted to carrying or resisting [31] the virus, or being extinguished by it. In the first case, the virus will have become part of the host's heredity. Both situations are

found in the viruses of bacteria the rapid reproduction and adaptation of which make them observable [32].

6. MOLECULAR ORIGINS

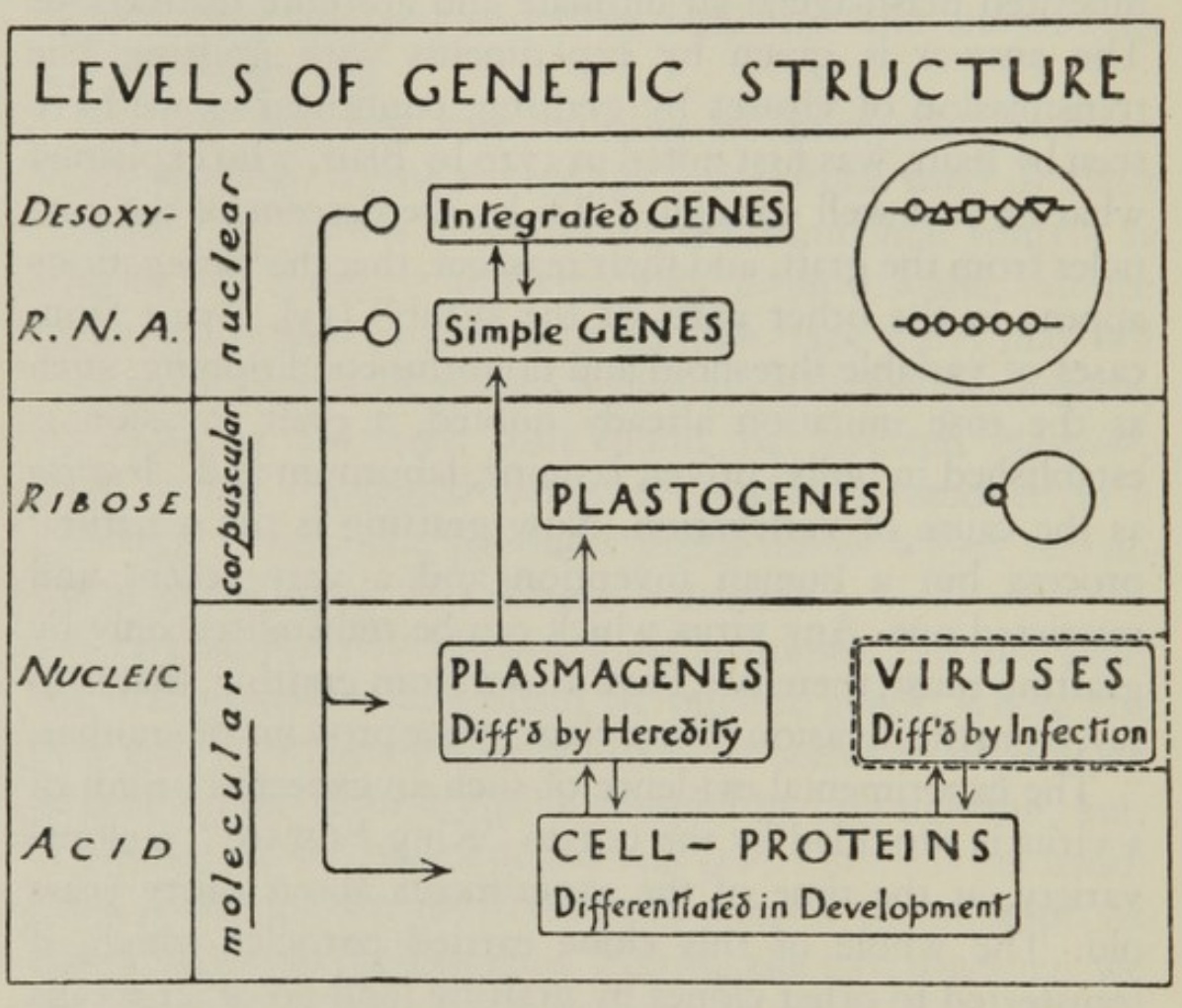
Is there, then, between the infective virus and the inherited plasmagene an ultimate and absolute distinction? The answer is given by experiments with grafting. The transmission of viruses by grafting, confirmed as we have seen by Baur, was first noted in 1720 by Blair, who explained what he saw well enough: "'Tis by the descent of the particles from the graft, and their reascent, that the variegations appear in the other parts of the shrub" [33]. Apart from cases of variable threshold and doubtful conditioning, such as the rose mutation already quoted, a graft invasion is established in holly, privet, jasmine, laburnum and *Abutilon* as the cause of variegation. Now grafting is not a natural process but a human invention and a very recent and restricted one. Any virus which can be transmitted only by grafting must, therefore, have arisen from grafting, that is to say, from the invasion of one plant by the proteins of another.

The experimental evidence of such an expected origin of a virus is provided by the potato "King Edward", a clonal variety, at the time of the experiments about thirty years old. The whole of this clone carried particles which, if transferred to other clones by grafting (and no other means is possible) produces disease [34]. What is a stable and presumably useful cell protein with one plant genotype acts as a destructive agent with another. Just, in fact, as plasmagenes do.

The same principle applies to the origin of the viruses causing the Rous sarcoma [21] and presumably mammary cancer in mice. Since they are transmitted, the one only by injection, and the other only by injection or through the milk, they can scarcely have arisen otherwise than from the cell proteins of the fowl, or the mouse, in which we find them

These viruses are distinguished from plasmagenes not by their origin or action but only by their transmission.

There is, therefore, nothing surprising in the fact that reproductive particles can suddenly appear in the cytoplasm by the action either of the mutafacient nucleus or of external carcinogens, nor again that such particles may either be transmissible or only transplantable.



The grafting of related species of plants throws light on the position of more beneficent particles. Stocks of *Phaseolus lunatus* confer their own symbiotic specificity on scions of *P. vulgaris* and on the seedlings of these scions, and vice versa[35]. Here we have to suppose that a normal and necessary cell particle has become both infectious and hereditary, both a virus and a plasmagene, at one stroke.

The ultimate distinction between plasmagene and virus, therefore, seems to be the accidental one of transmission by heredity or by infection, in respect of which both are variable and both differ from their ancestral cell proteins which were used merely in development (see Table). The

plasmagene is a protein which can be made outside the nucleus and comes to be inherited through the egg. The virus is a similar protein which is capable of being acquired later. It is a protein which prospers through being in the wrong organism and gets there by infection [1, 29]. Both classes are, of course, immensely heterogeneous. In addition, both are continually arising *de novo*, rapidly evolving, as their conditions change and partly by direct action of those conditions. They are, therefore, bound to diverge adaptively as they get older. But rapid divergence of the two classes merely helps to justify the supposition of their common origin.

7. CONCLUSION

Proteins in the cytoplasm can now be put in a rough genetic classification. On one hand there are some proteins, perhaps the bulk, put together by the nucleus with the help of desoxyribos nucleic acid. Perhaps, as Caspersson has suggested [24, 36], the larger types of protein arise from the euchromatic genes, the smaller from the heterochromatic. And perhaps, as Pontecorvo has suggested [37], the heterochromatic genes, or polygenes of Mather, are characterized by the repetition of similar and, no doubt, simple elements. They would then be more like plasmagenes. The euchromatic genes would act by the integrated effects of dissimilar elements producing complex proteins. These proteins from the nucleus need not be self-reproducing. On the other hand, there are other proteins, plasmagenes and viruses, formed in the cytoplasm only from pre-existing proteins of similar types. These molecular types depend for their reproduction on ribose nucleic acid and are conditionally self-perpetuating. But their relative quantities are under cell control; they depend on the interaction of nucleus and cytoplasm, varying with this interaction both in heredity and development.

Between these two extremes of protein formation there are intermediate conditions where proteins, although

formed by the nucleus, are potentially self-perpetuating. Their capacity for completing the life-cycle in the germ-track, and so becoming part of heredity, or for being carried by an insect, and so becoming an effective disease, will depend on suitable nuclear and cytoplasmic conditions. With limited self-perpetuation they are responsible for "maternal inheritance" and dauermodifications.

The high frequency of plasmagene and virus mutations, aggravated by the rapidity of their selection, both under nuclear control, gives an almost Lamarckian colour to their adaptation; and in particular it accounts for their frequent and common origin from proteins in the unstable developmental zone beneath them.

To put this situation in the most general terms we must say that, at the molecular level, heredity, development and infection are under nuclear and environmental control, and that this control operates in production and reproduction, in action, in distribution, and in mutation. Further, there is interaction at the molecular level itself as shown by competition, reinforcement or suppressiveness. There is also adaptation at this molecular level and between it and the higher levels, an adaptation which obeys special rules, since mutation at the molecular level is to some extent directly determined at the nuclear level. Finally, owing to this capacity of adaptation, there is a common reservoir from which the new material of heredity and infection is continually being drawn.

The frontiers that exist between the studies of heredity, development and infection are thus technical and arbitrary, and new possibilities of analysis and experiment will arise when we have learnt the passwords to take us across them.

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7

OUTBREEDING AND SEPARATION OF THE SEXES

1940

GAMETIC DIFFERENTIATION AND SEPARATION OF THE SEXES

THE process of sexual reproduction shows two remarkable features, namely, that in all but some of the lowest organisms there is gametic differentiation, the male and female gametes being morphologically and functionally distinct, and that there is, in some plants and most animals, separation of the sexes, the two kinds of gametes being produced by different unisexual zygotes.

The former phenomenon may very reasonably be interpreted as showing a division of labour. The female gamete is larger and contains, or is associated with, food stores, which may be utilized by the developing embryo, while the small male gamete is more motile and seeks out the less active egg prior to fertilization. Such a division of labour would appear to have a selective advantage and so would be favoured.

The reason for the separation of sexes is, on the other hand, not so easy to understand, more especially as it is far from being a universal property of sexual reproduction. A number of arguments have been put forward seeking to account for the known facts, and nearly all of them in some way or other, relate unisexuality to differentiation of the gametes. Two fairly recent examples may be mentioned.

Waddington [1] discusses the phenomenon in the following words: "Probably, then, the original mechanism [of sex determination] was an alternative mode of reaction in the gamete itself. . . . Usually, however, the time at which the alternative is decided is pushed further back in the life cycle, probably on a safety first principle. Eventually, in the higher animals and plants, the sex determination of a gamete has been pushed back to the fertilization of the zygophase before". The sexes are separated supposedly in order to ensure that the gametes are differentiated.

In the higher plants, however, separation of the sexes is sporadic rather than regular, although the gametes and their associated tissues are as successfully differentiated, morphologically and functionally, as in animals. Furthermore, in certain plants and animals the sex of a unisexual individual may be controlled environmentally though its gametic differentiation is perfect and regular. Nor should gametic differentiation itself be regarded as a necessary part of sexual reproduction. Many Thallophyta have successful sexual reproduction with no differentiation, or, at least, no morphological differentiation of the gametes. Thus sexual separation can scarcely be considered to be merely a predetermination of gametic differentiation, though this aspect may, of course, play some part in the evolution of the diœcious state. Any hypothesis seeking to account for unisexuality in most animals must also provide a reason for the widespread hermaphroditism in plants.

Altenburg [2] has advanced a different view. He notes that hermaphroditism is related to sluggishness and sessility. Then by means of a highly ingenious argument he concludes that the monœcious and diœcious states are adapted to the minimization of the work involved in reproduction. Thus insect-pollinated plants are, he claims, all hermaphrodite, as they need expend little work in the production of male gametes, the insect ensuring that the pollen is transferred to a stigma; so they can distribute the reproductive

load evenly between individuals only in this way. Wind-pollinated plants, on the other hand, expend relatively more energy in the production of pollen, much of which is lost in the air, and, the male and female loads being more nearly equal, they may as economically be diœcious as monœcious.

A similar argument is advanced for sessile and motile animals. Sessile forms have, like wind-pollinated plants, a large male load and so are indifferently hermaphrodite or unisexual. Motile animals may minimize the expenditure on sperm production by transference following coition, and so should be analogous to insect-pollinated plants. They are, however, unlike the plants in that they are not in general hermaphrodite. The reason given for this is that they overcome the difference in male and female reproductive loads by polygamy, sexual dimorphism and sexual differences in life-span.

There are a number of objections to this argument. In the first place, it is not clear why freely motile animals should be hermaphroditic less often than sluggish ones, when insect-pollinated plants are supposedly less often unisexual than anemophilous forms. In the second place, Altenburg goes too far in supposing that all insect-pollinated plants are hermaphrodite. *Silene Otites*, *Melandrium dioicum* and *Rubus Chamæmorus* are examples of diœcious entomophilous forms. Whether separation of the sexes is actually less common among insect-pollinated species is difficult to say as the available records are not always trustworthy, though some such correlation is suggested (cf. Lewis [3]). Finally, it is far from certain that wind-pollinated plants do in general produce more pollen per seed set than do insect-pollinated ones. Extreme examples of excessive pollen production by both kinds of plant could be cited, but it is doubtful whether statistics adequate to settle the question have been obtained. The same may be said of sperm production by animals. Until these objections have been successfully met, Altenburg's hypothesis cannot be accepted without

crippling reservations, though it may be applicable to special cases.

SEXUAL REPRODUCTION AND SEPARATION OF THE SEXES

There is, however, another approach to the question which helps to make clear the reasons for sexual separation occurring in some cases and not in others.

First of all, it is necessary to dismiss the developmental-genetic idea that separation of the sexes is of necessity related to gametic differentiation. Such differentiation has its own function in relation to nutrition of the ensuing zygote and is present, often in an elaborate form, in both hermaphroditic and unisexual organisms. The morphological analogy between gametic and zygotic differentiation is only misleading.

There is, however, one inevitable consequence of the diœcious state which enables us to understand its occurrence. If the sexes are separate, fertilization must always involve gametes from different zygotes and, in the vast majority of cases, these zygotes must be genetically distinct. It is essentially a mechanism for the promotion of outbreeding.

Now the importance of sexual reproduction to living organisms is that by its aid a higher degree of hybridity and effective recombination may be achieved than would be possible with purely asexual propagation. An increase in the effective recombination allows of a more rapid response to the action of natural selection (Fisher [4], Muller [5], Darlington [6]). Thus outbreeding is an essential feature of sexual reproduction in that it necessarily leads to greater hybridity and so, ultimately, to a greater response to selection, than does inbreeding. It is not clear that the maximum advantage will always follow from maximum outbreeding. On the contrary, there is some evidence that species have an optimum degree of hybridity, which optimum may depend on the environment. This question is, however, too complex and uncertain to be given detailed consideration here. It is

sufficient to note that outbreeding is an essential part of sexual reproduction.

It is, then, easy to see that unisexuality is of advantage by virtue of its ensuring some degree of outbreeding, and hence its occurrence is a simple adaptation for the more successful result of sexual reproduction.

There are, however, other mechanisms which will achieve the same purpose. Incompatibility is found in Angiosperms and the Fungi, and also most probably in the sea squirt *Ciona*. In the Fungi it apparently depends on the aversion of the haploid hyphæ, and in the Angiosperms on a rather complex relation of the pollen tube and stylar tissue. The genetical basis of incompatibility varies, though in Angiosperms it is usually of the type first described in *Nicotiana* by East. A related mechanism is that of illegitimacy found, for example, in *Primula* and *Lythrum*. It differs from incompatibility in that it is dependent on the genetical relations of the zygotes bearing ovule and pollen, and not on the genetical relations of male gamete and female zygote. These species, together with others, also show heterostyly, which presumably encourages crossing, though the efficacy of this mechanical method is open to doubt, as it is so frequently accompanied by an incompatibility or an illegitimacy mechanism. Protandry, protogyny, special floral arrangements and other devices could also be listed.

Now these various methods, though widespread, are rarely, if ever, found where the sexes are separated. They are alternatives to unisexuality. So our conclusion that the separation of sexes is simply a method of encouraging cross-breeding is strengthened, as such encouragement is the only effect common to all these mechanisms.

DISTRIBUTION OF OUTBREEDING MECHANISMS

If we are to regard unisexuality simply as one of a number of outbreeding mechanisms, it is necessary to account for the fact that it is frequently found in some groups, for example, the higher animals, but rare in others, for example,

the higher plants, being often replaced in the latter case by one or other of its alternatives.

To understand this, let us compare the action of unisexuality and incompatibility. In a diœcious species an individual can cross with only a portion of the remaining population, namely, those of the other sex. Unless some way is available whereby each individual of at least one sex can seek out a member of the other sex with which to mate, so ensuring that its gametes are not wasted, there must be a large loss of reproductive energy due to maldistribution of the gametes. In most animals such wastage is, however, much reduced by the presence of such a discriminatory mechanism whereby the motile male seeks out the female and transfers sperm directly to the egg by coition. This cannot be done in higher plants.

The incompatibility mechanism is superior to unisexuality in that it leads to less gametic loss where indiscriminate mating prevails. In the *Nicotiana* type of behaviour, pollen only fails to function when it falls on to the stigma of a plant carrying the same allelomorph of the incompatibility gene as does the pollen itself. There may be a very large number of such allelomorphs: more than a hundred have been found in wild *Trifolium*. The actual gametic loss is inversely proportional to the number of allelomorphs and so may be very small. Hence the incompatibility mechanism has an advantage over unisexuality where no discriminatory mating is possible. On the other hand, no easy mechanism, such as mobility, can be developed to assist discrimination where so many genetic classes are involved. So unisexuality with discrimination may exceed incompatibility in efficiency in the case of motile organisms, where the loss due to unisexuality can be reduced effectively to zero. Furthermore, there must be some mechanism for sorting out incompatible male gametes before they meet the egg, or otherwise loss of female gametes may result. This is done in the higher plants by the stylar tissues, but it would not be possible in most

animals where fertilization takes place in a duct or in open water.

Hence it can be seen that there is a reasonable explanation for motile animals depending mainly on unisexuality while higher plants usually adopt incompatibility or an analogous system of gametic discrimination. In the former case, wastage from separation of the sexes is reduced by means of mate discrimination, whereas an incompatibility mechanism would be difficult to operate. In plants, mating discrimination is difficult but incompatibility easy to operate.

The above remarks about incompatibility apply equally well to the closely allied illegitimacy mechanism. The other outbreeding devices found in plants may also be considered in a similar way. Protandry, for example, discourages self-pollination in the same flower, where its risk of occurrence would be greatest, while ensuring that the rest of the population are capable of receiving the pollen after its release. It is not, however, a fool-proof device for securing outbreeding.

Thus unisexuality may be regarded as one of a number of devices which arise by reason of their encouragement of outbreeding. The one to be adopted in a particular species depends on its special features, though the most suitable mechanism may not always develop. Thus if the disadvantage of wastage following on separation of the sexes in a plant is less than the advantage gained by the encouragement of outbreeding, unisexuality might occur but would be liable to be weeded out as soon as environmental conditions reversed the magnitudes of these opposite effects. So the diœcious state is a transient feature of some Angiosperms. It is also clear that some species which are in a stable environment, to which they are highly adapted, may find recombination a disadvantage and so suppress outbreeding mechanisms or even substitute inbreeding adaptations as in *Pisum* and *Triticum*, where premature anthesis vitiates a highly developed crossing mechanism. This is easier to do where the sexes are not separated. "Fertility"

allelomorphs are, for example, known at the incompatibility loci of many plants which normally show this particular outbreeding mechanism. But to reconstitute hermaphrodites from highly developed unisexual species would seem to be more difficult. Hence inbreeding mechanisms are commoner, or at least more obvious, in plants than in animals. The marked sexual dimorphism of animals, developed as an ancillary arrangement for the more effective operation of the outbreeding mechanism, has prevented a return to hermaphroditism in any special cases where inbreeding would be desirable, except by the adoption of extreme devices, as in *Pediculopsis*.

Gynodiœcy should not be confused with unisexuality in this connexion. It resembles unisexuality in that a proportion of the individuals are female, but differs in that the remainder are hermaphrodite, not male. Clearly the females are at a disadvantage as compared with the hermaphrodites, since they produce but one kind of gamete. Hence gynodiœcy will only survive where the females enjoy some compensating advantage, which is most likely to depend on the outbred nature of their offspring. My colleague Dr. Lewis has shown [3] that the equilibrium proportion of females is directly dependent on the magnitude of this advantage; so such gynodiœcious species have a ready means of adaptation to change in the hybridity optimum. The proportion of females and so of outbreeding increases with increasing advantage of hybridity and decreases as the advantage of hybridity decreases. Thus gynodiœcy, unlike unisexuality, is a highly adaptable outbreeding mechanism.

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8

HETEROTHALLY AS AN OUTBREEDING MECHANISM IN FUNGI

1942

ALL organisms are dependent on a supply of heritable variation for future adaptive changes; but the presence of free variation means that some members of the population show a poor adaptation to existing circumstances. The balance between present and future adaptation is thus conditioned by the amount of heritable variation which the population can maintain. This, in its turn, depends on the system of breeding or mating in force in the species. Where close inbreeding is in force the individuals tend towards a high degree of homozygosity. Heritable variation is then reduced to a low level, with the result that present adaptation is good but the prospect of future adaptation to changed circumstances poor. When, on the other hand, outbreeding is the rule, great genetical heterogeneity is maintained and in consequence the chances of good future adaptation are improved at the expense of present fitness [1]. In this way genes which control or affect the breeding system of a species have a profound effect on its genetical structure and evolutionary history. They have an adaptive value and will be subject to evolutionary changes.

Many genetically controlled breeding systems have been recognized, and some partly analysed, in the higher plants. Sex separation, incompatibility and heterostyly are now well-known as outbreeding systems which depend for their action on genetical diversity in the population. In each case

the action of the mechanism is by the reduction of effective mating between genetically like zygotes, while genetically unlike individuals intercross with relative freedom. In the extreme, and most common, case this reduction is complete, though in other cases it may only be partial. The extent of the reduction is itself subject to further genetical control [2]. Since male and female gametes are always distinct haploid individuals, the achievement of wide outbreeding is ensured by the complete prevention of fusion between gametes from the same zygote. All three of the mechanisms mentioned render this possible.

Though showing the same genetic organization as Angiosperms, the fungi, and, indeed, nearly all lower plants, may be expected to present somewhat different types of breeding system for two chief reasons. In the first place the mating behaviour is a property of the haploid phase in the life-cycle, unlike the situation in the higher forms where the diploid zygote plays such a predominant part. The genes determining the breeding system in fungi must act solely in the haploid, after it has become freed from the influence of the parent zygote. Secondly, a given haploid individual may produce both male and female gametes, or, amounting to the same thing, gametic differentiation may be lacking, in contradistinction to the higher plants where the haploid phase is almost non-existent except in the form of the individual gamete. In view of these differences it is very instructive to consider the type of genetically controlled outbreeding system which might be operative in lower plants, and Buller's recent review of heterothally in fungi [3] provides a very suitable opportunity.

What kind of breeding system, involving genetical diversity, might be expected *a priori* in fungi?

The first essential of any outbreeding system in a species with an independent haploid phase is the prevention of fusion between two gametes produced by a single haploid individual. (It may be noted in passing that this occurrence would lead to a more rigorous inbreeding than is ever

possible in a species having a predominant diploid phase, as haploid self-mating gives immediate homozygosis.) Assuming that the same broad possibilities of cell behaviour exist here as in the Angiosperms, self-mating of a haploid may be prevented in either of two ways. The male and female gametes, if distinct, may be isolated on different haploids, or an incompatibility gene may operate in such a way that only haploids carrying unlike allelomorphs can mate. Where gametic differentiation is not present the former possibility is ruled out; but in any event the two systems have a similar genetical basis, for each depends on the production of two (or, in the second case, possibly more) genetically distinct haploids, the allelomorphs determining the two groups acting so as to prevent mating of like types.

Whether the action is one by which allelomorph A_1 gives a haploid with male gametes and A_2 one with female gametes, or whether the action of A_1 and A_2 is of the physiologically unanalysed type known in the higher plants by the name of incompatibility, is genetically immaterial. In either event the matings $A_1 \times A_1$ and $A_2 \times A_2$ are impossible and self-mating of a single haploid is ruled out. Prevention of self-mating in its simplest form requires only two allelomorphs A_1 and A_2. The existence, possible with an incompatibility system, though not with sex separation, of more than two types of haploid does, however, have an advantage over the two-group system when we turn to the next aspect of inbreeding prevention, namely, the control of mating between haploids having a recent common ancestry.

Even if self-mating is prevented, a considerable measure of inbreeding is possible provided that haploids deriving from the same diploid zygote, where, it should be remembered, the all-important recombination occurs, can mate as freely, or more freely, *inter se* than they can with haploids descended from other zygotes. Inbreeding at this level cannot be prevented or even reduced by any system of incompatibility or sex-separating genes consisting solely of

allelomorphic pairs. Where a single allelomorphic pair exists all the zygotes must be A_1A_2 and will give A_1 and A_2 haploids. Furthermore, all the zygotes will give equal proportion of A_1 and A_2 haploids; so in any population the ratio which the number of A_1 haploids deriving from a given zygote bears to the number of A_2's from other zygotes will on the average be the same as the ratio of the A_2 haploids contributed by these various zygotes. Hence an A_2 gamete will find possible mates from different zygotes in the proportions of the contributions of any kind of spore by those zygotes to the population. The same will be true of the mating choice open to A_1 haploids and so the relative rate of mating between sister haploids from the same zygote is independent of the existence of the two allelomorphs, A_1 and A_2.

Thus all that this pair of allelomorphs does, other than to prevent self-mating, is to halve the number of possible mates for a given haploid individual in the population. It can mate with half its sisters, that is, with the A_2's if it be A_1, or A_1's if it be A_2, just as it can mate with half the haploids from any other zygote.

Two elaborations of this simple system are possible *a priori*, one of which will decrease the frequency of mating between sister haploids and the other of which increases the frequency of mating between non-sisters. The first one is the introduction of a second independent locus B, such that $B_1 \times B_1$ and $B_2 \times B_2$ are impossible matings while $B_1 \times B_2$ is possible. This new gene has, in fact, just the same action as the gene A. All zygotes must be $A_1A_2B_1B_2$ and will produce four types of daughter haploid, A_1B_1, A_1B_2, A_2B_1, A_2B_2. Only two matings are possible between the four, namely, $A_1B_1 \times A_2B_2$ and $A_1B_2 \times A_2B_1$, all the others being prevented either by gene A or by gene B, or, of course, by both. Self-mating is, obviously, also impossible. Any given haploid can mate with only one of the four types, so that only one quarter of the possible combinations in pairs are fertile in the sense that they can give progeny.

This compares with the half given by a single gene. When a third member, *C*, is introduced the freedom of mating is reduced to one eighth.

This type of elaboration certainly reduces the chance of a successful mating between haploids from the same zygote, but, as all zygotes must be $A_1A_2B_1B_2$, it equally reduces the chance of successful mating between haploids from different zygotes. The latter may, however, be increased by the second elaboration. So far in the argument each gene has comprised two allelomorphs, but if a multiple allelomorphic series exists at each locus the freedom of non-sister mating is increased. Suppose that locus *A* has three allelomorphs, A_1,A_2 and A_3. Three types of zygote will occur, namely A_1A_2, A_1A_3 and A_2A_3. A haploid can mate with only half its sisters from the same zygote, but it can mate with more than half its non-sisters; for one type of zygote, and, it must be noticed, the most unlike and hence the most distantly related, type of zygote, gives daughter haploids with all of which the first haploid is fertile as it differs genetically from them all. When the three types of zygote are equally frequent the non-sister pairs can mate in 2/3 of cases as compared with the sister mating figure of 1/2. When there are four allelomorphs still more types of zygote are possible and non-sister mating is again increased to 3/4. Non-sister mating increases as the number of allelomorphs increases, but sister mating remains at 1/2.

This increase in the freedom of non-sister mating may be combined with decreased sister mating if several genes each of several allelomorphs are in operation. With two genes each of three allelomorphs, that is, A_1 A_2 A_3 and B_1 B_2 B_3, all allelomorphs being equally frequent in the population, sister mating occurs in 1/4 of cases and non-sister mating in 4/9, giving a non-sister: sister ratio of 16:9. This compares with 4:3 when only one gene of three allelomorphs is in control. With two genes of four allelomorphs the ratio is 9:4, that is, the rate of outbreeding as measured by relative frequency of non-sister and sister

mating is once again increased. Thus by a combination of several unlinked incompatibility loci each with several allelomorphs, a high rate of outbreeding can be achieved. It may be noted, however, that mating between haploids from the same zygote can never be completely prevented in the way that any of the three breeding systems mentioned earlier for higher plants completely prevents it. To do this would require that the diploid phase could implant in all its daughter haploids some single incompatability character which overrode their own constitution and determined their behaviour in mating. This is in fact done by higher plants [2, 4], but, perhaps as a result of the lower degree of organization of their diploid life, has not, so far as I know, been encountered in any lower plant.

When Buller's review is examined in the light of this system, built up from principles developed to explain the behaviour of Angiosperms, it will be seen that all levels of elaboration, and hence of controlled outbreeding, are found.

In forms like *Coprinus lagopus* and *Schizophyllum commune* the complete system involving multiple allelomorphic series at more than one locus is found. It may be remarked that, when viewed in this new light, the true nature of the so-called sexual races of these fungi is very clear. They are no more races than are any pair of fully cross-compatible plants in species like the sweet cherry and the red clover. The different diploid fruit bodies, which, by being fully inter-fertile, gave rise to the idea of sexual races, are seen merely to have different allelomorphs at each of the incompatibility loci which, taken together, control the breeding system. The next generation from a cross between such diploids would contain sister zygotes which, on this criterion, could equally well be classed as belonging to different sexual races. It can be predicted that a suitable search should bring to light wild fruit bodies which have one allelomorph in common at either or both of the loci. These would exhibit an inter-fertility which, though incomplete, would be greater than that observed when

haploids from the same fruit body are interbred. Such a find would complete the evidence for the artificiality of the sexual race concept.

There are also examples of intermediate elaboration where only one incompatibility locus is found. Though apparently less fully investigated from the point of view of multiple allelomorph detection, at least one of these species, *Coprinus rostrupianus* [5] has such a series. No doubt other cases could be found without much difficulty.

The last stage of control is shown by fungi such as the heterothallic Mucor species where a single gene of two allelomorphs prevents self-mating but where the degree of outbreeding beyond this point is a matter of chance. Sometimes this mechanism appears to survive as a relic after another form of control has been superimposed. Such a case is provided by certain Ustilago species, for example *U. hordei* [6] where the four products of meiosis unite in pairs in the single-celled stage, at which self-mating would appear to be ruled out in any case. An inbreeding system has been developed by the retention of the four spores in such a way that the most likely pairings are those between unlike products of the same meiosis, that is, of the same diploid zygote. It would appear that this is an example of adaptation to secure an intermediate degree of inbreeding similar to those obtaining in higher plants like Triticum and Pisum. In these higher plants, too, the present inbreeding mechanism has been superimposed on an outbreeding system, the relics of which may still be observed.

Lastly, there are the cases where heterothally is not found and self-mating may occur. Such homothallic species are capable of rigorous inbreeding, but this may be controlled at an intermediate level by a display of incomplete or partial heterothally. When this happens a haploid is capable of self-mating, that is, of homothallic behaviour, but will in particular circumstances show a preference for mating with other individuals, that is, show heterothallic behaviour. It is as though the individual possessed partially

effective heterothally genes. In this way a balanced inbreeding-outbreeding system can be maintained.

It is also possible that such behaviour exists as a stage in the transit between full homothally and full heterothally. In *Primula sinensis* [2] and Petunia sp. [7] the efficiency of the key outbreeding genes is probably controlled by modifying polygenes. The main genes for heterostyly in the one case and for incompatibility in the other may then give either increased or decreased outbreeding by selection of the polygenic complex. Though not yet proved, it seems likely that selection could even reduce the efficiency of the outbreeding genes to zero, that is, completely to remove their power of affecting the breeding system. If this is so, it is easy to see that polygenic selection could lead to the gradual development of an adaptive breeding mechanism. The intermediates between homo- and heterothallic behaviour are susceptible to a similar interpretation and this could be tested by suitable selection experiments. The question of how a + and a — nucleus can occur in different parts of the same homothallic haploid then resolves itself, as, on this view of polygenic modification, the nuclei, though capable of developing heterothallic behaviour, will not inevitably possess a "sex".

Such a brief survey forbids the detailed mention of special cases, but it can be seen that the complications of heterothally fit into an ordered scheme when viewed as adaptations to the control of outbreeding. Basically, the function and genetical structure of heterothally are the same as those of systems found elsewhere. The superficial differences are imposed by peculiar circumstances arising from the existence of an independent haploid phase.

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9

GENETICS AND THE RUSSIAN CONTROVERSY

1942

A CALL to reject in its entirety forty years work in a science which has engaged widespread attention and earned distinction for many, including a Nobel laureate, is both very unusual and very disturbing. Yet this is what Lysenko and his followers at the Russian Genetical Conference of 1939 would have us do [1]; and, what is still more disturbing, no one other than those directly engaged in genetical research has found it desirable actively to oppose Lysenko's views. Indeed his allegations have been repeated, and, it would appear, supported, in Great Britain [2].

The situation so created cannot lightly be dismissed by geneticists as the failure of others to appreciate the fundamentals of their subject. It is true that many of the charges are based on a misunderstanding of genetics and its theory, but we must inquire into the reasons why such a misunderstanding can exist. The study of inheritance must have attracted the sympathetic interest of many biologists, especially those engaged in evolutionary studies and the improvement of crops and stock. Yet genetics has apparently proved so disappointing that they do not feel sufficiently concerned to protest at Lysenko's attack. This implies a sense of frustration, and in order to see how such a feeling could arise, side by side with the rapid development of a sound genetical theory, it is necessary for us to

examine the progress of genetical science during its forty years of active propagation.

Gregor Mendel formulated two laws of heredity from which our theory of particulate inheritance has developed [3]. But to do so he devised an experimental technique for investigating genetical differences, and this is, perhaps, his major achievement. Without the technique he could not have made his own discoveries. With the technique he could solve his problems and, what is more, later geneticists could test, modify and extend his laws into the modern theory. Mendel's technique ensured the development of genetical science.

Now this technique of Mendel's depended on the use of single differences. He treated the differences between tall and dwarf, between round and wrinkled seeds. Only when he understood their individual behaviour did he proceed to investigate joint segregations. Once the 3:1 single-factor ratio was understood, the 9:3:3:1 and 27:9:9:9:3:3:3:1 could easily be interpreted. Thus his success depended on treating the simplest cases first. It is even clearer that the successful analysis of factor interactions, characteristically modifying the 9:3:3:1 into 9:7, 15:1, 12:3:1, 9:3:4 and so on, was impossible until both single-factor and two-factor segregation was fully understood.

Carried to its conclusion this process of investigating segregations of steadily increasing complexity would have led to an attack on the problems raised by those characters, like stature in man, which can only be interpreted as under the control of many genes, and which are hence termed polygenic. The task would have been more formidable than most early Mendelian researches, for these polygenes have individual effects which are small when compared with non-heritable fluctuations. That the approach was, however, then contemplated we may infer from Nilsson-Ehle's discussion of duplicate and triplicate factors in cereals [4]. Furthermore, Emerson and East soon afterwards published a paper on polygenic inheritance in maize [5], and their

example was copied by a few other geneticists. But it happened that circumstances, which we shall discuss in a moment, directed interest into other channels. This was the beginning of loss of touch between genetics and the other branches of biology mentioned above; for evolutionary change, as well as the improvement of crops and stock, depends on these complex characters. Species differences and the commercial qualities of plants and animals are polygenic, and it is polygenic, not simple, inheritance which evolutionists and breeders wish to see analysed.

Why then was the attention of geneticists directed elsewhere? There were several contributory reasons. Mendel was not the first man to investigate inheritance, and when his work was re-discovered at the beginning of this century investigations of a different kind were being actively pursued. Galton and Pearson had attempted the analysis of polygenic inheritance, especially in man, by methods quite unlike those of Mendel, and their conclusions were also quite divergent from Mendel's [6]. Thus with Pearson defending biometry and Bateson advocating Mendelism a feud arose, and to geneticists polygenic inheritance assumed a heretical appearance. In the second decade of the century a few geneticists, notably Emerson and East [5] and Fisher [7], showed that the biometrical results could be interpreted as due to the action of many factors behaving in the Mendelian way, but their findings aroused little enthusiasm either in the biometricians or in the Mendelians, who had been, in Great Britain at least, antagonistic for many years. Thus we see that the first reason for the failure to press polygenic analysis was that it had become somewhat improper in the eyes of geneticists.

The second reason was that polygenetics had technical difficulties. Sharp segregations are never shown by polygenic characters and so their analysis requires a combination of genetical and statistical techniques, such as was not then available. If of course interest and enthusiasm had

been sufficiently great we may be sure that the necessary technical advances would have been made; but, in point of fact, we can find no contribution to the combination of genetical and biometrical techniques before that of Fisher, Immer and Tedin in 1932 [8]. Genetical theory had by this time developed to a stage at which polygenic analysis of a kind impossible fifteen years earlier could be attempted, but slight use has since been made of the methods of these authors. Indeed, there is little reason to believe that even to-day the full technical equipment for polygenic analysis is available. Perhaps no single method will be adequate, though selection experiments have proved of considerable value from the time of Johannsen [9] up to the present [10].

In the meantime Mendel's methods had, in Drosophila, led to an astonishing series of advances. Bateson and Punnett discovered in 1906 [11], that unit factors do not always segregate independently. Sex linkage was found shortly afterwards, and the field was clear for the proof of the chromosome theory of heredity, with all its corollaries, when Morgan and his associates began to apply the back-cross technique to *Drosophila melanogaster*. In a very few years sex linkage, the linear order of the genes, non-disjunction of chromosomes, crossing-over and sex balance had all been investigated by this method, and shown to be attributable to the special properties of chromosomes [12]. Here we have the greatest reason of all why polygenetics was neglected. Its technical difficulties stood in such sharp contrast with the basically simple and highly fruitful methods of the "Drosophilists". The trickle of papers on polygenic inheritance which had appeared after 1910 almost ceased when the full value of the Drosophila research was apparent to all. Instead similar work was undertaken in maize and other plants, in some cases by the few who had a short time earlier been pursuing polygenic studies.

The first phase of Drosophila genetics was as good as over by 1925 when triploids and attached X females had been investigated. It appeared about this time that interest

in polygenic behaviour might be revived by the use of marker genes for the sorting out of complex genetical variation in terms of the chromosomes. In fact one paper of this type, on egg size in Drosophila, appeared in 1924 [13], but a new departure in genetical research put paid to this promise. In 1927 Muller [14] announced his discovery that gene mutation could be induced by X-ray treatment and so started a line of investigation which is still being actively pursued. This was followed by Darlington's re-casting of cytology in an inductive-deductive form in the early 1930's [15], by the use of the giant salivary gland chromosomes by Painter in 1934 [16], and by Beadle and Ephrussi's investigations on gene action in 1935 [17]. Polygenic characters seemed to have sunk completely out of sight under this competition.

Interest was, however, to be revived once more by the turn which genetics has taken towards the experimental study, as opposed to theoretical discussion, of evolution during the last ten years. Though at first attempted by the use of the familiar major mutations this departure forced geneticists to the conclusion that species differences are polygenic (see Timoféeff-Ressovsky and Muller [18]). The stage is again set for an attack on this complex type of inheritance, and, as result of the extra power given to genetical analysis by the chromosome theory and by Fisher's statistical techniques, the opportunity is greater than ever before. Let us hope that it will be seized.

During these forty years of consistent failure to get to grips with the type of inheritance which is, above all others, of importance to evolutionists and breeders, geneticists have not been slow to point out that their science is basic to the practice of research in these other fields. Much of the discussion has been valuable. The theory developed by Fisher, Haldane and Wright has cleared the ground for the new genetical research on problems of evolution, and Timoféeff-Ressovsky, Sturtevant and Dobzhansky have already shown what can be accomplished. But much of the

genetical discussion has been unfortunate and harmful, especially in the absence of any experimental results. Though the later geneticists interested in the question have been, to a man, Darwinists, the earlier writers, notably Bateson [19] and de Vries [20], have left a deep mark on the attitude of the average biologist towards genetics, because they continually emphasized the sharply discontinuous nature of variation, when the practical examples of discontinuity to which they could point were generally mutations which appeared, to all but the geneticist, to be almost pathological in their effects on the organism's viability. Here we can see the origin of Lysenko's attack.

Mendel's discoveries appeared shortly after the "Origin of Species", and we may take it that they would have profoundly affected Darwin's later work if he had been familiar with them. Fisher [21] has shown that the particulate theory of inheritance provides the solution to Darwin's most troublesome difficulty, that of seeing how the store of variability, which Darwin took to be blending, was saved from rapid decay. Darwin accepted this rapid decay and sought to overcome the trouble by assuming an equally rapid replacement by new, or, as we should say, mutational, variation, under the stimulus of novel environmental conditions. This view he developed in "Animals and Plants under Domestication", which Mendel's findings rendered unnecessary as a central part of the theory of evolution. It is thus necessary when discussing genetics and Darwinism, to state which Darwin is concerned, the author of the "Origin of Species" or the author of "Animals and Plants". Genetics is wholly consistent with the "Origin of Species" but has little concern with "Animals and Plants", which in its turn is unnecessary for evolutionary theory.

This effect of particulate inheritance on Darwinian theory was, however, overlooked in the early years of the century. Mendel's paper was re-discovered at a time when small apparently continuous variations were being decried and the younger biologists, of whom Bateson was one, were

turning to the view that the variation from which evolutionary change flowed was sharply discontinuous. Mendelian segregation and de Vries "mutations" in Œnothera apparently fitted so well to this view that they were immediately seized on as good evidence in its favour. It was only much later, when the true nature of de Vries mutations was known [15], and the effects of natural selection on major genes had been considered, that the superficial nature of this evidence was realized. The return to Darwinism and polygenetics then became inevitable. The speculation of Bateson, de Vries and their followers was vitiated by their failure to assess accurately the evolutionary significance of the major variants which they observed, and there was insufficient experimental information to provide an adequate check on this speculation. It is now clear that discontinuous genotypical variation is not incompatible with continuous phenotypical variation; when each of the many genes has a small effect and non-heritable fluctuations occur. Polygenetics integrates genetical discontinuity and Darwin's smooth variation. Bateson and de Vries failed in not seeing that such an integration was possible.

We are now in a position to see Lysenko's charges in their true perspective. We are not immediately concerned with the method of plant breeding that he advocates. If it should prove sound, its basic theory must be incorporated in genetics; but this is a matter for the future, and in the meantime cannot affect our judgment on his specific charges against genetical theory.

When Lysenko states that genetics has not contributed very much to the improvements of crops and stock, we must agree with him. In special cases, like the development of autosexing poultry, genetics has been of great value, but these cases are exceptional. The reason for this failure is not, however, that genetics is unsound, but that its development has, owing to a series of historical accidents, been away from the breeders' problems. This may be

deplorable, but it provides no ground for pessimism about the contribution that suitable genetical research can make to breeding technique. To deny the potential value of genetics would be as great a misjudgment as that of any geneticist who tried to maintain that his subject had, in the past, given results on which all breeding work must be based. The reality of the present lack of touch is well shown by the way that, at the Russian conference, the bearing of genetics on breeding technique became a matter of personal testament rather than one of analytical discussion.

Secondly, when Lysenko holds that genetics is anti-Darwin, he is wrong, at least as regards the "Origin of Species", though when he maintains that geneticists have been anti-Darwin he is obviously right. In the absence of appropriate experimental work, the relation of genetics and evolutionary theory has been a subject for unchecked speculation of which much was superficial and unsound. Perhaps the best evidence of the soundness of the genetical approach, as distinct from genetical speculation, is that, in spite of the lack of polygenic research and in face of the utterances of the early Mendelians, geneticists are to-day realizing more and more that small variations are the material of evolution; though they realize equally that Darwin's argument in "Animals and Plants" is not essential to the theory and may be removed without weakening the general structure in any way.

Finally, we come to Lysenko's condemnation and rejection of what he calls "Morganism-Mendelism". We can see that it arises from a failure to realize the relations of genetical development and the breeder's requirements. He says, in effect, that genetics is useless to the breeder and, therefore, should be abolished. But astronomy is of no great use to the breeder and yet we do not consider abolishing that science. The real situation is that the particulate and the chromosome theories of heredity are founded on a vast body of fact. They have been tested and re-tested,

but never found wanting. Nor has Lysenko himself any evidence of their alleged unsoundness, though he may have plenty of their faulty interpretation by geneticists themselves and by others. As a case to point, we may take his rejection of pure-line theory on the basis of his observation that intravarietal variation exists in self-fertilizing cereals. The existence of such variation cannot in fact vitiate pure-line theory. Indeed, Johannsen himself envisaged this very type of variability [22]. It does, however, show that the application of the theory was faulty because, as Lysenko discusses it, both mutation and the small amount of outcrossing, known to occur in wheat, oats, etc., are overlooked. It is to the investigation of these agents that attention should be turned, rather than to the alleged unsoundness of misapplied genetical theory.

To call for the rejection of genetical theory is useless; for this theory is sound, no matter how disappointed we may feel that, while developing its internal structure, genetics has neglected those aspects which appeal to the breeder. What is required is experimental research on polygenic behaviour, so that genetical theory may be enlarged until the full potential value of genetics to evolutionist and breeder is realized. The task will doubtless be laborious, but the need is obvious and the opportunity great.

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10

POLYGENIC BALANCE IN THE CANALIZATION OF DEVELOPMENT

1943

ONE of the greatest differences between genetics to-day and genetics of thirty years ago is to be found in the changed attitude of geneticists towards the relation of a gene to the character, or characters, which it affects. The early geneticists equated a given gene difference to the character difference from which its existence was inferred. The gene for tallness in peas gave tall peas and its allelomorph gave short peas. The significance of the fact that a tall pea, as Mendel himself observed, could be 6 ft. tall or 7 ft. tall or of intermediate height was overlooked; the variation in height of tall peas was not discontinuous and so was not obviously attributable to a gene or genes detectable by the Mendelian technique. Such an attitude is very understandable because the success of Mendelian analysis lay in its concentration on simple character differences, in its exclusion of all extraneous variation from account. But this outlook carried with it disadvantages too, for concentration on discontinuous variation in experiment led easily to the assumption that the variation by which evolutionary changes were effected was just as sharply and obviously discontinuous. The outcome was the mutation theory of evolution on one hand and the presence and absence theory on the other.

It is true, of course, that after, say, 1906 all geneticists were familiar with the fact that the expression of one gene

could be contingent on the presence of a given allelomorph of another gene. Bateson [1] gives an extensive account of the inheritance of complementary and epistatic genes, but the observations could be interpreted so easily in terms of the presence and absence theory that they did little or nothing to shake the idea of what we may perhaps call the characteristic expression of the gene.

Soon, however, several lines of approach led geneticists to doubt the validity of this simple interpretation and finally to abandon it altogether. Four deserve special mention. Bridges [2] found that the inheritance of sex in *Drosophila melanogaster* could not be explained in terms of the presence or absence of any given gene or genes. The numerical relations, or, as he called it, the balance, of the chromosomes, present in all flies, determined whether they would be supermale, male, intersex, female or super-female. A little later Fisher [3] pointed out that the genes controlling mimetic patterns in insects must be presumed to have been given their special properties by the selection of other genes. He later concluded that even the dominance relations of one gene must be dependent on other genes of the nucleus, and the existence of such dominance modifiers has since been amply verified by experiment. Muller [4] showed that the expression of sex-linked genes must be supposed to be subject to genetical adjustment, for otherwise no reasonable explanation could be given of the equality or near equality of expression of these genes in the two sexes. There exists a means of dosage compensation. Finally, Timoféeff-Ressovsky [5] was able to demonstrate, by direct experiment, that the expression of certain genes in Drosophila was modified by the action of other genes. The dependence in expression of any given gene on the other genes of the nucleus, on the genetical background as it is often called, is thus beyond doubt.

This change of ideas concerning the relation between gene and expression has had a profound effect on the attitude of geneticists towards evolutionary change, as

recent writings have shown. Ford [6], Muller [7] and Huxley [8] have especially developed the application of this new outlook to the better understanding of adaptation and evolution. It is not without significance that the rise of the idea of the dependent action of genes has progressed side by side with a return to Darwinism and the abandonment of the mutation theory.

Some further consequences of this view have now been discussed by Waddington [9]. In particular, he points out that the dependence in expression of one gene on the action of others permits a more co-ordinated response of the organism to its environment. Using both embryological and genetical data he shows that development may be regarded as canalized, that is, that although an organism may follow any one of a number of developmental paths, it is difficult to make it develop along lines intermediate between these possibilities. In genetical language, the integrated genotype acts as a buffering system, in such a way as to limit the variation of the organism's response to environmental fluctuations. Major or switch genes may determine which of the paths will be followed, but systems of other genes, the buffering action of which can be adapted by natural selection, will delimit the possible paths with greater or less precision. The switching action may have originally depended on environmental differences but, as Waddington points out, this function can, and generally will, be transferred ultimately to a genetic difference, and in this way will come to operate with greater efficiency and regularity.

Now, although the distinction between switch genes and buffer genes must not, for reasons which we shall presently discuss, be pressed too far, it is clear that the parts they play in controlling development are quite different. We may then expect them to be detected in different ways, to have effects of different magnitudes and to respond differently to selection. Genetical evidence is now available on these points and with its help we can

form a clearer picture of how such co-ordinated systems arise and of how they change under the action of natural selection.

The familiar genes of genetical experiment fall into the category of what we have called switch genes. They are not usually known by this name, being more often called major mutants or qualitative genes, to distinguish them from the minor genes controlling quantitative characters. These two classes have also been called [10] oligogenes and polygenes respectively from the oligogenic and polygenic nature of the variation which they determine. With some important exceptions, which we shall discuss in a moment, the variant types to which switch, major or oligogenes, call them what we will, give rise, are not to be found in wild populations except as rare, and presumably recent, mutations; for unless some important end can be achieved only by diversity of allelomorphs of such genes, one allelomorph will have an unconditional selective advantage over the rest and will, apart from the slight effect of mutation pressure already noted, oust its competitors. Thus although we can only rarely detect the operation of such genes by the genetical method of observing the different expressions of at least two allelomorphs, we must assume their action in wild organisms.

As but one allelomorph of any such gene is common in the wild, only those buffer genes which control the expression of this allelomorph will be subject to the action of natural selection. The systems buffering the action of the rare, or mutant, allelomorphs will not be so well adapted through selective action to the better fulfilment of their task. Hence when a mutation occurs in the laboratory, or a rare mutant type is found in and introduced from wild material, we should expect its phenotype to be more variable than the wild type, the buffering system of which is constantly adjusted by natural selection. This expectation is in full accord with the observed properties of mutant types, many of which have highly variable phenotypes. It

should be noted that this argument presupposes that the various allelomorphs of a gene guide development into channels the directions of which are determined by unlike buffer genes. This has, in fact, now been verified by Haskell [11] in the case of the gene scute in *Drosophila melanogaster*.

The organization of the system of genes buffering the development of wild type individuals is of paramount importance to the organism. It must primarily determine the production of a relatively uniform type under conditions which may be subject to considerable fluctuations, as indeed is implied by its description as a buffering system. Certain complications may be observed, as, for example, adaptation to show ecological plasticity, but these only serve to emphasize our main point, since they imply buffering in such a way as to produce two or more relatively uniform types according to the action of an environmental switch. But to be successful the system must have some elasticity, even though it is only potential, for the inability to respond to trend changes in the environment would mean that sooner or later the species would die out, no matter how well its buffering system were adapted to coping with non-persistent environmental fluctuations.

The way in which uniformity is combined with potential elasticity has been revealed by Mather's [10, 12] analysis of polygenic variability. The buffering system is built up of polygenes having effects which are similar to one another and individually small as compared with environmentally determined fluctuations. Natural selection builds up linked combinations of these genes, in which the constituent members of the combinations balance each other in action. Inter-combinational uniformity of immediate action is combined with the ability to produce new combinations of different action by means of recombination between the various existing combinations. Thus the buffering action depends on polygenic balance, which can and does change as a result of recombination, so permitting the emergence

of new combinations which are capable of re-aligning the developmental path to give fresh adaptation to changed circumstances. The polygenic variability is hidden, or potential, in the genotype and is not free in the phenotype In other words, we can see how, as Waddington puts it, the system has absorbed its own variability. Inasmuch as the maintenance of adequate polygenic balance depends on the regular action of natural selection [10], it is easy to see that the polygenic system buffering the expression of mutant switch genes will be inefficient, for it will not have been selected for inter- and intra-combinational balance.

This concept of polygenic balance, and the storage of variability in its potential form, enables us to approach a number of evolutionary questions. There is, for example, the problem of polymorphism, whether of the kind known in grouse locusts or mimetic butterflies, or the more familiar type, sex, heterostyly, etc., on which the breeding structure of a population depends. These are the exceptional cases mentioned earlier, in which the success of the species depends on diversity of a switch gene. It is of no use having females, for example, if no males are available.

The direct determination of sex depends on the action of the sex chromosome inequality, which is the switch gene in this case. But how is the organism adapted to produce functional females and functional males with but rare exceptional individuals, and how was this sharp difference in type of individual first produced? Though we have stated the question in terms of sexual dimorphism, this is only a particular example of polymorphism, and the answer to this question will apply to polymorphic species in general.

Clearly this answer must be sought in the ability of the polygenic system to distinguish and delimit adequately the paths into which development can be turned by the operation of the switch gene. The latter may itself be composite and so capable of some modification [13], but, in the main, close adaptation must be polygenically determined. Only

a polygenic system is capable of giving all grades of expression between wide limits. The balance achieved by the polygenic combinations will determine the end products, and if this balance is adequate the end products of the developmental paths will be functional male or functional female according to the line into which development was guided by the switch gene. Each type can, and will, be adjusted by the action of selection on the buffering system of polygenes; and in so far as the types are capable of such adjustment, dimorphism will arise and develop continuously, under the action of selection, from the store of potential variability which lay hidden in the polygenic combinations of the undifferentiated ancestral form. The action of the switch gene, giving so obvious and sharp a discontinuity, is made possible by the continuous adjustment of polygenic balance.

Two predictions follow from this argument. In the first place, it should be possible to change the polygenic balance of a polymorphic system by operating on it with unbalanced combinations from a related system which is not adapted to show polymorphism. The polymorphism need not be lost in such a case: the switch gene will merely determine a less efficient polymorphism after the operation. This has been shown to happen to the incompatibility system in Petunia [14]. In *Petunia violacea* gametic incompatibility, which is a type of polymorphism affecting the breeding system, is determined by a series of *S* allelomorphs of the kind well-known in Nicotiana species. The related *P. axillaris* shows no incompatibility. It was possible to isolate, from the F^2 of a cross between these species, plants identical in constitution with the *P. violacea* parent in regard to switch gene (that is, the *S* gene), but which were less strongly self-incompatible than was that parent. Furthermore, the two plants, *P. violacea* and the second generation species hybrid, were reasonably freely inter-compatible, though two plants of like *S* constitution within *P. violacea* would have been quite inter-incompatible. The polygenes from

P. axillaris, not balanced to give incompatibility, have recombined with the balanced combinations of *P. violacea* to give new combinations determining a new incompatibility system, which, however, depends on the same switch gene. As we should expect, this new system is not so precise in action as the old one, for these new combinations have not been fully balanced by the operation of natural selection.

Turning to the second prediction, we can see on the polygenic view that two related species, or populations, may show the same end result, yet reach it by balancing different polygenes of similar effect. Indeed, if the groups are isolated, this will be inevitable, because a polygenic system is in a constant state of flux. Its balance is stable but the constituent polygenes producing this balance are changing by mutation, fixation and so on. Now in such a case the joint balance of any pair of combinations can only be maintained by the continual operation of natural selection, and if two combinations are never present in the same nucleus, that is, are isolated, they will have a poor joint or relational balance, though they may have the same internal balance, and though each may be capable of working harmoniously with other combinations from which it is not isolated. Isolation means divergence of polygenic organization (but not of necessity of intra-group polygenic balance as expressed in the phenotype), because it prevents inter-group balance being maintained by natural selection.

It is to such inevitable cryptic divergence that we must attribute hybrid sterility in species crosses, though, of course, bars to crossing must have a selective origin. In particular, however, we should expect that two related species showing the same polymorphism, operated by the same switch gene, would depend on different sets of balanced polygenes to give this common result. On intercrossing, therefore, the character in question should lose its sharp definition in later generations after the two sets of polygenes had recombined and so lost balance. This is

found to be the case with incompatibility in Nicotiana. *N. Forgetiana* and *N. alata* show pseudo-compatibility only in exceptional circumstances, that is, the actions of the various allelomorphs of the switch gene are always distinctive; but in *N. Sanderæ*, a horticultural type derived by hybridization of the two foregoing species, pseudo-compatibility is rife, though the operative switch locus, *S*, is the same as that of both parental species [15]. Pseudo-compatibility marks the breakdown of the distinction between the types produced by the *S* allelomorphs. We can see that it is not the switch mechanism, but the buffering system of polygenes, to which the breakdown must be attributed, exactly as expected.

Thus the character or reaction, the expression of which is apparently dependent on the switch gene, is in fact conditioned by the buffering polygenes. If the latter are not adequately balanced the operation of the switch gene is partially or even wholly vitiated. The buffering system can also change in such a way that it endows the switch gene with an apparently new set of properties. The path or paths into which the latter directs developments are so remoulded and redirected that the outcome is quite a new type.

Such changes can be recognized as having taken place in the evolution of flower colour differences in the genus Petunia [14]. *P. violacea* has magenta coloured, and *P. axillaris* white, flowers. The latter is homozygous for the allelomorph *w*, giving lack of anthocyanin in this species, of a gene the other allelomorph of which, *W*, homozygous in *P. violacea*, results in the presence of anthocyanin. When, however, the species are inter-crossed the F_2 contains coloured plants of the constitution *ww*, and what is more, these plants may have a flower colour indistinguishable, at least by inspection, from that of other plants which prove to be *Ww* when tested. The effect of the gene *W*,*w* is conditioned by the genetical background of the species. The background of *P. axillaris* is so adjusted that *w* switches

flower development into a track leading regularly to white pigmentation. The buffering system of *P. violacea*, which does not carry *w*, is naturally not so adjusted and, in an F_2, affects the path of development so that *ww* expresses itself in a new way, namely, by giving coloured flowers. Thus the discontinuity in effect of *W* and *w* is a reflection of the buffering system. The switch gene has been given its characteristic properties by the adjustment of the genetical background or buffering genes. Clearly the evolution of such a specific difference can proceed gradually by continuous steps, even though the eventual discontinuity between the species is controlled by a few major genes.

This leads us to the problem of the relation of switch genes, major genes, oligogenes or whatever we choose to call them, which have large effects, to polygenes, the effects of which are so small as to be individually unrecognizable. It does not seem reasonable to suppose that the nucleus contains two kinds of genes, having sharply distinct properties (though it must be pointed out that there exist two kinds of chromatin, eu- and hetero-chromatin, the latter of which appears in general to be devoid of major genes but to contain polygenes). We have, however, seen that the apparently large phenotypic effect of a major gene is, at least in part, a property of the polygenes which determine the ultimate result of the major gene's action. In fact we may surmise that the difference in phenotypic expressions between the allelomorphs of some major genes could be reduced to nothing by the reverse of that process of polygenic adjustment which has endowed them with the property of conditioning sharp phenotypic discontinuity.

But it would be straining both evidence and reason to suppose that a major gene was originally, in all cases, merely one of a number of like polygenes, any one of which might by chance have had the switching role thrust upon it by adjustment in balance of the rest. Rather it would seem that the switch gene operates at an earlier ontogenetic stage, the later acting genes then having the

power of reducing or magnifying the difference in outcome of the paths into which this major gene directs development; and inasmuch as the latter genes do operate later, their own effects are small and, at least in part, interchangeable. We may note, too, that in such a case the organism could, without undue loss in fitness, afford to carry a greater store of variability for the later acting polygenes than for major genes; for their individual disruptive action will not only be smaller, but will also be conditioned by the other polygenes present.

This leads us to the speculation that major, switch or oligogenes were at one time polygenes. The distinction between the two classes is one of time of action, and hence of magnitude of average effect, the apparent discontinuity of type being due to the buffering or enhancing action which the polygenes exert on the effects of the earlier acting major genes. In other respects the two kinds of gene are alike, for both mutate, segregate and show linkage. It then follows that a gene which is now a polygene acting at a late stage in the development of an organ may, either alone or as part of a complex of linked polygenes, assume the role of a switch gene if and when the developmental history of that organ is extended by its morphological and functional elaboration. A gene which has a minor effect on the corolla structure of a relatively unspecialized flower could have a drastic effect on the corolla of a flower elaborated and specialized in the way observed, for example, in an orchid.

This is, perhaps, an unduly simplified discussion of the problem, and the questions raised, for example, in neoteny require consideration at a length not now possible. But the principle that genes have evolved in function can scarcely be denied. Indeed, the evolution of an organism is an expression of the functional evolution of its genes.

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11

GENETICAL CONTROL OF INCOMPATIBILITY IN ANGIOSPERMS AND FUNGI

1944

ALTHOUGH the majority of organisms agree in showing some special control over their breeding systems, whether to encourage inbreeding or outbreeding, they display a great variety of devices by which control is achieved. In most animals the sexes are separate and so self-fertilization is impossible. In spite of this, however, a high degree of inbreeding can be achieved by controlled brother-sister mating, as in the grass-mite; or, on the other hand, inbreeding may be discouraged by various ancillary devices such as the production of unisexual broods or cyclical changes in sex. Discriminative behaviour in mating may also favour either outbreeding or inbreeding, or some combination of the two. In fact, it appears that the controlling devices are likely to depend for their working on any of the special characteristics and faculties of the organisms in question. This is strikingly illustrated in man, whose unique power of combining the transmission of rules of conduct, by means of what has been called tradition, with their enforcement by communal action, is used to govern mating in many different ways to give various degrees of outbreeding. Human matings may vary in advantage for non-genetic reasons in civilized and semi-civilized communities; but the occurrence of mating control

even among the most primitive tribes shows that control must have arisen originally for genetical reasons [1].

In plants, as in animals, breeding control abounds, but it depends on a different set of devices. Plants are not mobile, and hence sex separation, or diœcy as it is here called, is not an efficient method of control, for it would involve an undue waste of gametes. Consequently, diœcy is relatively uncommon in plants, which rely on other means of governing the breeding system. Controlled inbreeding evidently may be achieved relatively simply, but outbreeding demands more complex devices [2].

First of all there must be some means of placing gametes from different individuals in appropriate juxtaposition. This may be done by growth of the parent individuals, as in fungi, but it often depends on the use of some intermediary, like water, wind or insects in higher plants. Thus we find adaptations to the use of such intermediaries, especially in the Angiosperms, where, for example, the means of attracting insects to the flowers are both complex and striking. But such adaptations, though clearly essential to outbreeding, will not of themselves suffice to secure its regular occurrence. The mere transport of gametes to another generative structure is not enough, because this structure may not be borne by an appropriate individual. Pollen may, for example, be carried by an insect merely from stamen to stigma of the same flower, or of a second flower borne by the same zygote in the Angiosperms. The plant must, in the last analysis, control the functioning of pollen for itself, if it is to exercise reasonable control of its own breeding. In the same way, though adjacent cells may not achieve fertilization in fungi, separate hyphæ of the same individual may grow together and mate unless some further restriction is imposed.

These further restrictions on inbreeding seem to be imposed in Angiosperms in two chief ways. There may be a time difference in the release of pollen and the receptivity of the stigma, such that certain types of mating are

impossible. In protandry and protogyny this time difference will serve mainly to prevent effective pollination within a single flower, where, of course, it is most likely to be brought about; but it is unlikely seriously to hamper pollination between flowers of the same plant—a procedure which in the vast majority of cases has genetical consequences equivalent to those of self-pollination within a flower, as Darwin showed experimentally [3].

The second means of controlling effective pollination in Angiosperms is through the sorting out of the pollen, as delivered to the stigma, by the plant itself, with the prevention of functioning of inappropriate gametes. In fungi the same broad process is seen at work in the aversion, or at least ineffectiveness of contiguity, of inappropriate hyphæ. This general type of behaviour is described as incompatibility and appears to be widespread in the plant kingdom, though it is known by special names in some cases, for example, as heterothally in fungi. The underlying genetical and physiological mechanisms may vary too, but the main principle is always the same, namely, that there exist means whereby an individual, whether haploid or diploid, or even a single gamete, can discriminate for mating purposes among the functional gametes with which it might come into contact.

Incompatibility has been chiefly investigated in the fungi and in the Angiosperms. Discussion must, therefore, turn largely on the behaviour of these groups. In the former the haploid phase, generally speaking, dominates the life-cycle; though in the Basidiomycetes there is a compromise, a diplophase, with haploid nuclei and diploid cells. In the flowering plants, on the other hand, the haploid phase is so reduced as to be parasitic on the diploid. It is not, therefore, surprising, in view of the way in which special features of an organism appear to be used, where suitable, in the control of the breeding system, to find that while incompatibility is manifest between haploids in the fungi, the diploid phase plays its part in the Angiosperms.

In the fungi two levels of genetical elaboration may be recognized in the control of breeding [4]. The first involves control by a single gene of two allelomorphs, as in Mucor spp. and Ustilago spp. This prevents self-mating of the haploid, such as would lead to immediate homozygosis, but has no effect on the relative frequencies of homo- and hetero-zygosis following crossings of distinct haploids. In many of the higher fungi, however, greater elaboration is found, the genetical structure comprising one or more series of multiple allelomorphs, similarity for any one of which is sufficient to prevent effective mating. This is interpretable as an adaptation which, in addition to eliminating self-mating, decreases the relative frequency of mating between haploids originating from the same diploid or diplophasic zygote.

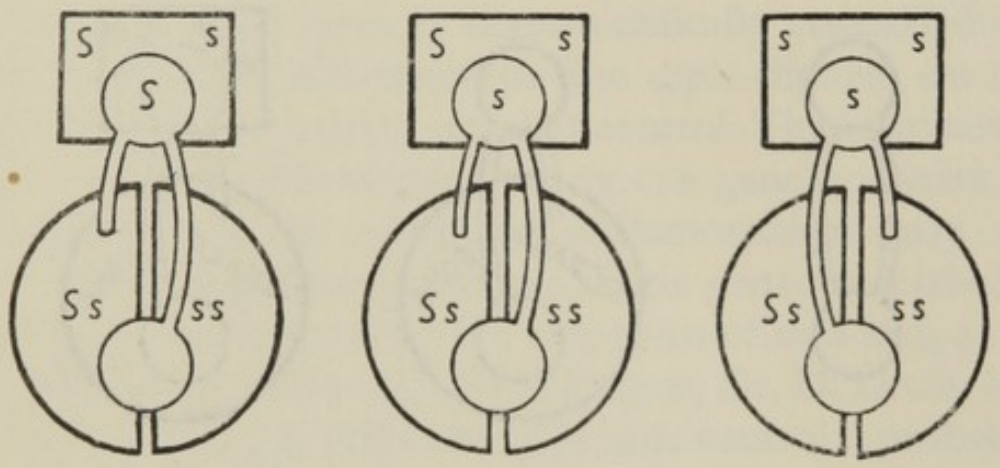
In Angiosperms self-mating of the haploid is ruled out by the separation of sexes between pollen and embryo-sac consequent on the extreme reduction of the gametophyte. The incompatibility mechanism is then concerned with the control of mating between haploids from the same zygote, which it can eliminate altogether and not merely reduce as in fungi. This elimination is achieved by the interposition of diploid somatic tissue, mainly in the form of the style, between pollen and egg. The stylar tissue, and perhaps also other somatic tissues of the ovary and ovule, acts as a sieve which stops the tubes of certain genetical types of pollen, while permitting others to grow to successful fertilization. It may be noted that although within species the incompatible pollen is that which bears too close a genetical relation to the stylar tissue, the same system may also serve to exclude pollen which is genetically too unlike the female soma, that is, act as an isolation mechanism between species, as in Petunia [5]. Thus we may regard the stylar tissue as primarily a means of regulating the mating system of the plant, able to exclude both the too like and the too unlike (though, of course, other functions in adapting the flower to pollination by particular intermediaries have also

developed). The female gametes themselves are protected and conserved in the sense that pollen with which these eggs would, as a general rule, give zygotes of inferior genetical constitution is prevented from achieving fertilization and so wasting the eggs. It is said that in some plants, like Gasteria [6] and the cacao [7], incompatibility manifests itself as a breakdown of development after fertilization. Such a situation can, however, scarcely be described as due to incompatibility in the present sense, for it omits the essential selective advantage of conservation of female gametes, and hence must have arisen in some other way. In fact, it is difficult to see how such a system could arise at all by direct selection. It must be a by-product of some other development [5].

The female haploid of the Angiosperms plays a purely passive part in mating discrimination, except perhaps in situations of the kind supposed to occur in Gasteria and the cacao. If the pollen tube can penetrate the female somatic tissue, it appears not to be repelled by the haploid organs of the embryo sac, and so encounters no further barriers to success. The diploid phase has taken full control on the female side. This is, however, frequently not the case on the male side. In incompatibility of the type first described in Nicotiana and Veronica, and now known to be widespread [8], the reaction is one between haploid pollen and diploid female soma. In all clear cases the genetical control is by a series of multiple allelomorphs, which act in such a way that pollen carrying an allelomorph also present in the stylar and related tissues is discriminated against. Pollen carrying an allelomorph not present in the female soma is not handicapped. It is characteristic of these systems, as of the genetically more elaborate fungi, that there should be a long series of allelomorphs, concerned with normal operation.

There are, however, also cases of Angiosperms in which the pollen grain is not autonomous in incompatibility. These are mainly afforded by heterostyled plants, though

Capsella grandiflora [9] shows the same property without any morphological variation. In Capsella and distylic plants, such as the many dimorphic Primulas, the reaction of the pollen is most simply regarded as determined by the genotype of the soma which bore it. In Primula species, for example, the thrum type is heterozygous, *Ss*, and the pin



Thrum *Ss*. Pin *ss*.

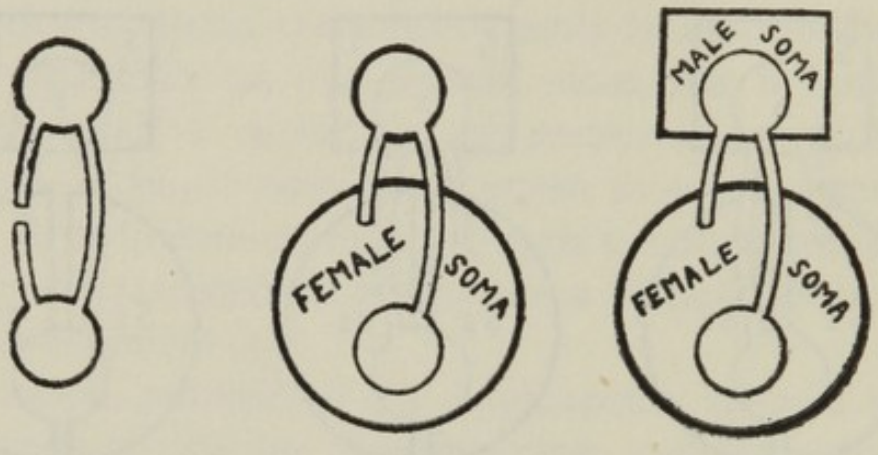
Fig. 9.—Diplo-diploid control of incompatibility in Primula. Success or failure of the pollen (upper circle) in fertilising the egg (lower circle) depends on the relations existing between the genotypes of the male soma (rectangle) and female soma (half circles). The genotype of the pollen itself plays no part in determining the reaction.

type homozygous, *ss*, for the controlling gene. The *s* pollen of a thrum fails on an *Ss* style, where the *s* pollen of a pin is successful, but is successful on an *ss* style, where the pin *s* pollen fails. In other words, the male and female somata must be genetically unlike for success, the genetical constitution of the pollen being immaterial (Fig. 9).

This simple interpretation breaks down with tristylic species, such as *Lythrum salicaria*, for here the position of anthers and stigmata in the flowers comes into play in a more striking way. A given flower produces pollen at two levels and each level has its own characteristic and distinct properties in incompatibility [10]. Thus the effect on pollen behaviour of the male somatic genotype is not so important as the immediate effect of the male soma where the pollen is borne. The behaviour of certain homostyled types of *Primula sinensis* suggests that the same mechanism may be

operative in distylic species [11], but here, however, differentiation between the two possibilities is not final.

Whatever the mechanism of action of the male soma may be in such cases, it is at any rate clear that the behaviour of the pollen in incompatibility is determined by physiological differentiation of the zygote which bore it. Thus we



Haplo-Haploid. Haplo-Diploid. Diplo-Diploid.

Fig. 10.—The stages in control of incompatibility by the diploid phase. In the haplo-haploid, incompatibility depends on the genetical relations of two haploid cells; in the haplo-diploid, on the genetical relations of haploid pollen and diploid female soma (the egg being passive); and in diplo-diploid on the relations between male soma (the reaction type of which is impressed on the pollen it bears) and female soma.

can recognize three main incompatibility systems. The first, as found in fungi, is haplo-haploid in that it depends on a reaction between two haploids. The second is haplo-diploid, as in Nicotiana, where haploid pollen and diploid stylar tissue are involved. Lastly, we have the diplo-diploid type of Capsella and the heterostyled plants, in which the action of the haploid pollen is that impressed on it by the diploid soma from which it came (Fig. 10). There may, perhaps, exist intermediate or compound types of control, since the genetical basis of incompatibility as found in many Angiosperms has not yet been adequately analysed on account of its apparent complexity. In some cases the complications must be due to partial breakdown of the system through hybridization or other cause of disturbance of the polygenic balance on which the maintenance, as

opposed to the operation, of incompatibility appears to depend [12]. It is, however, not yet clear that this accounts for all the complications. But whatever the situation may be, the three types under discussion must represent the basic categories, and all the cases which are fully understood fall into one or other, with or without some breakdown.

As we have seen, normal operation of the haplo-haploid and haplo-diploid types is characteristically controlled by series of multiple allelomorphs. The diplo-diploid, on the other hand, has a simpler genetical control. There are never more than two allelomorphs of any one gene operative in the normal system (multiple allelomorphism may be involved in breakdown), though a little genetical elaboration may be introduced by the operation of two loci, as in Capsella and Lythrum [13]. My colleague, Dr. D. Lewis, has pointed out that this difference in genetic control is probably a reflexion of the two types of gene action involved. In the haplo-haploid and haplo-diploid each allelomorph may be regarded as essentially individualistic in action, for only a single allelomorph can be operative in any one reaction. Hence no question of combining and co-ordinating the action of two allelomorphs arises, in the way that it must with the diplo-diploid system which may thus be physiologically restricted.

The three types of incompatibility systems form a series of increasing control by the diploid phase. Is there any corresponding increase of efficiency and advantage to the plant? It is not difficult to see that the intervention of the diploid phase on the female side is advantageous. Haplo-haploid control can prevent inbreeding at the first and most extreme level, namely, self-mating of a haploid leading to immediate homozygosis; but it can never wholly eliminate the occurrence of inbreeding, at the second or zygotic level, by mating of haploids from the same parent zygote. This may be of lesser importance in fungi, where the spores of a zygote are broadcast widely; but in an Angiosperm it is a matter of considerable moment because self-pollination,

leading to mating of male and female haploids from the same zygote, may be unduly common unless restricted. The interposition of the style in the incompatibility system allows of complete elimination of this contingency, if advantageous, with the result that inbreeding is controlled at the zygotic level.

The second difference in the degree of diploid control, that on the male side, seems to lead to no increase in efficiency. The suppression of inbreeding at the zygotic level is achieved by the action of the diploid style, and given free dispersion of pollen and seed the prevention of self-pollination ensures maximum outbreeding. Breeding systems must be regarded as essentially adjusted to controlling the degree of heterozygosis of the population [14], and the maximum heterozygosis obtainable for all the genes of an organism by this means alone is that given by random mating. Higher values of heterozygosis can be obtained if mating of homozygotes is restricted in highly specific ways, but these are extremely unlikely to be found in Nature for any but special genes such as those which control the breeding systems themselves. Permanent heterozygosis also occurs in Œnothera, for example, but balanced lethals and ring-formation are involved in the mechanism, which thereby does not depend solely on the breeding system in the way we are discussing. Thus, so far as mating control is concerned, inbreeding in flowering plants is largely a matter of self-pollination. Indeed, as measured by Wright's inbreeding coefficient [15], the rate of inbreeding may be calculated to a first approximation, the adequacy of which depends on the adequacy of seed and pollen dispersal, from measurements of the natural rate of self-pollination.

From this point of view the haplo-diploid system is no less efficient than the diplo-diploid, for both can give maximum outbreeding, namely, effectively random mating in all but the smallest populations. Indeed, where pollen and seed dispersal are not free, haplo-diploid systems may

have an advantage over the diplo-diploid as we know it, since the multiple allelomorphs of the former permit somewhat freer mating between non-sister zygotes than between sisters. This opportunity of control at the third, or sibling, level of inbreeding seems, however, likely to be an advantage too trivial to warrant consideration at the present stage of analysis; but a second potential disadvantage of dependence on two allelomorphs is more serious. In distylic plants, with one gene of two allelomorphs, any individual can mate successfully on the average with only half of its fellows. In tristylics this fraction is raised to something like two-thirds, but in the haplo-diploid system, with many allelomorphs, the effective fraction must approximate closely to unity. Thus mating efficiency is higher and gametic loss lower with a haplo-diploid control, though the gametic loss is, perhaps, somewhat reduced in the diplo-diploid type by the heterostyly with which it is so regularly associated.

The diplo-diploid system has, however, one compensating advantage, in that the haplo-diploid requires a minimum of three allelomorphs for its operation whereas the diplo-diploid requires but two. For this reason it may well be that the genetical situation necessary for the origin of a diplo-diploid control is simpler and more likely to occur than that for the haplo-diploid. In view of this it seems that diploid and haploid controls of the incompatibility reaction on the male side cannot on balance differ markedly in the relative advantages which they carry. This is in sharp contrast to the corresponding situation on the female side, where the advantage of diploid control by the interposition of the style is always clear in affording the possibility of eliminating mating between both the too like and too unlike. It is thus not surprising that the structure through which diploid control on the female side is exercised should be a universal feature of the higher plants, whereas there is apparently no corresponding uniformity of control on the male side. Perhaps if a form

of male control should arise, combining the ease of origin of the diplo-diploid type with the efficiency of operation of the haplo-diploid, it would supplant both the existing types. Such a system would presumably use both the multiple allelomorphs of the haplo-diploid and the co-ordination of gene action necessary to impress a somatically determined behaviour on the male gametes in the way shown by the diplo-diploid. It is, however, not yet clear how, or even whether, such a system is a developmental possibility.

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12

THE GENETICAL APPROACH TO IMPROVEMENT IN MAN

1944

CHANGES in an organism may be brought about by the action of a changed environment, or by changes in genetic constitution, or, of course, by the simultaneous action of both causes. Therefore, once we have agreed on what we should regard as improvement in man, we may seek to achieve the desired change by adjustment of his environment, i.e., the conditions under which he exists, or through alteration of his genetical make-up. Great interest is to-day centred on improvement through adjustment of the environment. Not only is it realized that healthy, capable men and women can be produced only if they are adequately fed, housed and so on, but plans are being made and even some action taken in the hope of ensuring an adequate environment for human development at all ages. The Beveridge Report, the Hot Springs Conference and the differential allocations of certain foodstuffs in war-time all bespeak the growing interest in this aspect of human welfare and the growing appreciation of the value of science in promoting it.

The possibilities of human improvement by genetical means attract less attention. A Royal Commission is now investigating the low birth rate, but inspection of the list of members leaves one wondering whether the genetical consequences of the present distribution of births, which may

be serious ones for this country, will receive the consideration they deserve. For only by genetical means can permanent advance be achieved and permanent retrogression prevented. Improved environmental amenities produce no lasting change: as soon as they are relaxed, deterioration will follow. But improvement in hereditary constitution is permanent: its result is as clear, or clearer, in time of adversity as it is in time of relative ease.

What are the potentialities of genetical improvement and what steps are necessary for their realization? In order to answer these questions we must examine the existing variation in man to see how far it is heritable, rather than traceable to environmental causes, and to form some idea of its potential response to manipulation by selective breeding. The study of human genetics, supported and amplified by similar investigations on other species, has already provided us with data adequate for an instructive, even if preliminary, analysis.

It must first be recognized that heritable and non-heritable changes may lead to closely similar results in an individual. A man may be small and stunted because his ancestors were genetically of this kind, or because he has been inadequately fed. We cannot, therefore, distinguish by inspection of a single individual those of his peculiar characteristics to be ascribed to his make-up of genetical determiners, or genes as they are called, from those which are to be attributed to his environment, i.e., to non-heritable causes. Such a decision can only be reached from a study of his ancestors, collaterals, and descendants.

When this is done we find that a great diversity of characters show heritable variation: in fact, it is safe to say that no character is unaffected by heritable variation. But the type of inheritance is not the same in all cases. We can, for example, recognize inheritance of the kind described as being due to dominant genes, where every individual who has the gene, even in the heterozygous condition, clearly and unambiguously shows the trait in question. In

such cases every affected individual is descended from parents one of whom, at least, was similarly affected. Traits, like brachydactyly, inherited in this way, could virtually be wiped out in one generation if affected individuals were prevented from breeding.

In other cases, e.g., some forms of albinism, the trait is inherited in the way characteristic of recessive genes. Here the trait is not shown unless the individual is homozygous for the gene. Heterozygotes are normal and as a consequence affected individuals generally appear in the offspring of two unaffected parents. Clearly such traits could not easily be eradicated even if all affected people were prevented from breeding.

The genes determining other hereditary variations are carried by the sex chromosomes. A woman has two *X* chromosomes, one derived from each of her parents. A man, on the other hand, has an *X* and a *Y* derived from his mother and father respectively. Thus genes carried by the *Y* are handed on from a father to all his sons and are never found in the female members of the family. A number of cases of this type of inheritance are known. The traits in question could be eradicated as easily as those due to dominant genes and by the same means.

X-linked inheritance is rather more complex. Colour blindness is a case to point. It is commoner in males than in females, for if a woman is a carrier of it, though herself having normal sight because she is heterozygous, half her sons will be affected, no matter whether her husband is colour-blind or not. Her daughters, however, will all be normal (though half will resemble the mother in being carriers) unless the father is colour-blind. Thus genes of this kind may be difficult to eradicate for the same reason as are ordinary recessive genes. Hæmophilia is also inherited in this way, and is peculiar in that it is nearly always lethal to the affected males. It would presumably be equally lethal to affected women, but they are rare because affected men generally fail to survive long enough to have families.

So hæmophilia is carried almost exclusively in the female line, though it is shown almost entirely by men.

From a consideration of the lethal action in males, Haldane [1] has shown that one-third of the hæmophilia genes must be lost in each generation, and has been able to calculate the frequency with which, on certain assumptions, new hæmophilia genes must be supposed to arise from their normal counterparts by the process of mutation. This process of mutation would prevent any hereditary traits being eradicated once and for all, since new examples of the genes responsible would always be arising by mutational change. Continued control would, therefore, be necessary in order to prevent the spread of new mutants.

Traits such as we have been discussing are relatively easy to follow in inheritance, because the relation between the trait and its determining gene is a simple one. Variants inherited in these simple ways are, however, generally, of a clearly deleterious or even pathological kind. Their eradication would be, as it were, only a negative step towards improvement in man. We must be interested primarily in the bettering of the best, not merely in the eradication of the worst, and this brings us to the consideration of a further type of inheritance.

Galton, with whom the serious study of human inheritance may be said to have started, showed that characters like stature were inherited even though it is impossible to classify people into distinct categories by means of them. Such variation is said to be quantitative, because every grade of expression is seen between wide limits, as opposed to the qualitative variation discussed above, by means of which individuals are classifiable into sharply distinct classes. Quantitative variation can only be interpreted as depending on a large number of genes, each of small, similar, and supplementary effect. Inheritance of this kind may thus be conveniently described as polygenic.

Single family data seldom suffice to show inheritance of this kind: detailed studies of larger groups are necessary.

The methods of analysis of the data originated with Galton, but have been steadily refined as the science of statistics has grown. It has also gradually become clear that polygenic variation is not confined to morphological characters like stature, but is by way of being universal in occurrence. In particular it appears to be involved in disease resistance and in mental and moral capabilities.

Each of the genes involved in polygenic inheritance must, as we have seen, be supposed to have only a small effect, the large differences sometimes observable between people being due to the joint action of many such genes. Environmental effects may therefore easily simulate or mask the action of small numbers of such genes and special techniques are required to separate the heritable part of quantitative variation from the non-heritable. One powerful means of doing so is by twin analysis.

Twins are of two kinds. First of all there are those which develop from distinct eggs, and which are no more alike genetically than any other pair of brothers or sisters. Such twins will, for example, be of the same and of different sexes in roughly equal numbers of cases. These twins are termed dizygotic or fraternal. Twins of the second kind are termed monozygotic or identical because they develop from a single fertilized egg and hence must be genetically identical. Obviously they must always be of the same sex.

Now a pair of twins, whether identical or fraternal, will enjoy much the same environment. If therefore we can show that identical twins are as a general rule more alike than are fraternals, we may infer that the variation detected in this way is genetic and not environmentally caused. By the use of this method Lange [2] was first able to show that criminality was largely traceable to hereditary causes. Not only were identical twins generally alike in being criminals or in not being criminals, but the type of crime a pair took up was strikingly similar even where they embarked on their criminal careers in different places and presumably unbeknown to one another. Fraternal twins did not show

this marked parallelism of behaviour either in being criminals or in the type of crime.

Many twin researches have been carried out since Lange's time, and all with much the same result. In particular it might be mentioned that twin analyses have shown that susceptibility to tuberculosis is hereditary to a great extent. Kallman and Reisner [3] find, for example, that where one identical twin dies of this ailment the other does too in 87 per cent of cases. The fraternal twin of an affected individual dies in only 26 per cent of cases. Verschuer [4] has found by a similar means that the site in which tuberculosis appears is also hereditarily determined.

While it is as yet impossible to be certain, there seems to be a high probability that criminality and tuberculosis susceptibility would show polygenic inheritance. Intelligence is almost certainly inherited in the same way. Galton devoted considerable time to the inheritance of intelligence, and his results, together with those of later investigators, leave little doubt that it is affected by heritable factors. Furthermore, studies of the distribution of various indices, by means of which we attempt to measure intelligence, show quantitative frequency distributions of the kind encountered with stature and other morphological characters known to show polygenic variation. We must then assume, at least provisionally, that intelligence shows polygenic variation, too, and could be handled genetically only by the methods appropriate to inheritance of this type. This is, however, a question worthy of closer investigation, for of all man's characteristics that of intelligent behaviour, with which is associated, one presumes, ability to learn from others, is outstanding in importance. By this means man has become dominant over other animals and has advanced from savagery to the complexity of modern civilization. Without these abilities he would regress; and we cannot say that he is in no danger of losing them. As Muller [5] has pointed out, the pseudo-inheritance of tradition and culture, by the passing on of information from

individual to individual and from generation to generation, enables man to advance his knowledge and control over nature even in the absence of an advance in actual intelligence. Thus we have no ground for believing that he is any more intelligent now than he was in the Stone Age. The margin of safety which we now have over the lower limit of intelligence, necessary for the continuance of tradition and its corollary of advancing civilization, may well be small.

Now it is a striking feature of polygenic inheritance that stable distributions of the character or characters in question cannot be maintained from generation to generation without some selection. Moreover, some selection will always be in progress. In the wild the level of stability is adjusted by natural selection, but if we alter the direction or rigour of selection a change in the distribution must follow. This is, of course, the basis of improvement by selective breeding, whether of plants or animals, and experiments with species from both living kingdoms have shown that the selective advance, which can be made in characters showing polygenic variation, is very large. We could thus presumably induce in man great increases in average height, intelligence and so on, by appropriate selective breeding.

At present, however, the changes which advancing civilization has wrought in the type of selection to which intelligence is subjected have been of a kind more likely to lead to disaster than to greater success. The distribution of birth seems to be such that those individuals who must be judged less intelligent have on the average larger families than their more intelligent fellows. Fisher [5] considers that this is an inevitable consequence of civilization as civilization has existed up to the present, and that it has led in the past to the collapse of one civilization after another. Our present one may thus go the same way if we do not take positive steps to readjust the selective balance. Whether the collapse of a civilization under this maladjustment of selection would be followed in a percentage of cases by

complete regression to subhuman behaviour, or whether a new and lower equilibrium would always be established under the influence of the readjustment of selection consequent on the removal of those features which in civilization tend to favour undue multiplication of the less intelligent, is a question which we cannot yet answer. But the immediate danger, which is clear, should be sufficient to warn us of the need for positive action.

The means by which the prevailing balance of selection can be adjusted fall into two broad classes. We may, as for example by the system of family allowances which Fisher advocates, attempt to induce a readjustment of the distribution of births. Something of this kind is an obvious first step, and if it proved sufficient no further action would be called for. These further measures, if they proved necessary, would be more difficult to establish since they must presumably involve some direct communal control over the mating and breeding of individuals. Such control would appear repugnant to most people to-day.

The precise form which control should take need not, however, be discussed at present, though a number of suggestions have been or could be made. Two points are, however, worthy of note. Firstly, that such action must be based on sound genetical information, for there is nearly as great a danger in the uncritical increase of selection in an upward direction, consequent on its liability to eradicate the very variability on which selective progress depends, as there is in too timid an approach. Secondly, while positive action to readjust the balance of selection by interference in family life, as we know it, may as we have seen appear repugnant to most people, such interference is, in fact, an established practice. All human communities have in operation to-day their characteristic restrictions on mating, whether they be embodied in the mating lineage system of aboriginal Australia, or the enforced monogamy and prohibited degrees of Western Christendom. Thus we need not view the possibility of establishing new mating

rules with too much pessimism. Indeed, the sterilization laws of certain countries represent a move in this direction, though the advisability and value of these laws raises another issue.

These matters must, however, be for future discussion, if only because at present the pressing need is for a wider realization of the necessity for a genetical approach to the problem of human improvement. Until it is appreciated that genetical questions are involved there can be little hope of any kind of action. The genetical deficiencies in the present structure of society are less obvious than the environmental ones and to most of us are also apparently less pleasant to discuss. Yet it is clear, even from our present knowledge, that the issue facing us is not that of advance as opposed to the *status quo*. Profound influences are continually at work causing changes in the genetical constitution of man, and no amount of ostrich-like behaviour will prevent their action. It is for us to realize the necessity of using selective agencies deliberately to improve the species rather than to shut our eyes to the action of uncontrolled selection in bringing about a decline. Only when this is done can we hope to see undertaken the research necessary for the formulation and implementation of a positive policy for the genetical improvement of man.

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13

GENES

1946

LIKE genetics itself, the idea of the gene springs directly from Mendel's experiments. Each of the seven phenotypic differences which he investigated in his peas turned out to be a unit, in the sense that any plant could show one or other of the contrasting phenotypes, but could never be intermediate. The Mendelian factor, to which the causation of a phenotypic difference was referred, must therefore have consisted of two alternative determinants, which separated cleanly from one another in gametogenesis and which were distinct, though alternative, entities in the hereditary constitution of the organism. Furthermore, where the phenotypes of two parents differed in more than one of these unit characters, the F_2 generation showed every combination of the alternatives by which each unit character was recognized, and showed them in proportions which indicated that the hereditary transmission of one was unaffected by that of another. The various Mendelian factors behaved independently of one another.

Thus two kinds of unit were to be distinguished; first, the alternatives by whose difference a Mendelian factor could be recognized, and second, the Mendelian factors themselves.

The term gene has been loosely applied to both of these units, but it is better restricted to the second type, the alternatives being termed allelomorphs or, more briefly, alleles. On the basis of Mendel's results we thus picture the

hereditary materials as consisting of a number of genes, independent of one another in inheritance, and each consisting of two allelomorphs, alternative to one another in inheritance.

This picture was soon to be modified in two ways. In the first place it became clear that a gene could have more than two allelomorphs, distinguishable by the phenotypes they characteristically determined. Secondly, different genes were found not always to be inherited independently of one another. Sometimes they tended to stick together in inheritance, to show linkage, in that the particular combinations of allelomorphs of two genes present in the parents of a cross re-appeared unduly often in the offspring. Nevertheless, when the parental combinations were broken down, the result was always the appearance of the recombinations which Mendelian theory predicted. The various combinations were not all equally frequent, but the combinations themselves were as expected. The gene was still the unit of hereditary transmission, though additional information was required, in the form of recombination frequencies, for a full prediction of breeding behaviour to be made.

With the study of recombination frequencies, especially in *Drosophila*, it was realized that the genes fell into groups. The different groups were always inherited independently, but inside a group the genes could be pictured as arranged in a straight line, the recombination frequency of any two genes being dependent on their distance apart. The physical basis for the linear groups was provided by the chromosome theory of heredity, and for the recombination of linked genes by the crossing-over of homologous chromosomes at meiosis. A new unit of transmission, the chromosome, was thus introduced, but the validity of the old one was in no way impaired. It was still the "atom of heredity", the brick from which the chromosome was built. When it was found that X-rays could break chromosomes into pieces, it was found that they also separated genes in a

corresponding way. The unit of recombination was reinforced by the unit by X-ray breakage.

At the same time a second means of distinguishing genes had been coming into use. Besides their properties of transmission in heredity, the genes must have properties of action in development. The chain of chemical processes resulting in the production of substance or structure in an organism generally appeared to be long and complex. It might be affected and redirected by a number of gene changes, which might even give end results very similar in appearance. Yet appropriate genetical tests showed that in such cases the genes, although acting on one chain of reactions, could not be regarded as behaving identically. They were not interchangeable. They might act in sequence on a single chain, or in parallel on the joint precursors or joint products of a common chain of reactions, but their actions must be different. Biochemical studies have fully substantiated this genetical conclusion in a number of instances where it has been possible to identify the reaction which each gene is controlling or catalyzing [1]. From these studies, the hypothesis has been advanced that each gene produces one enzyme and that each enzyme is produced by one gene. If substantiated, this principle will allow of an even closer definition of the gene. However this may turn out (and while it seems very likely to be true for major genes, polygenes may very well offer obstacles), it is clear that genes can be recognized as distinct by their inability to replace one another in action. We have a physiological as well as a mechanical or physical gene.

Other properties of the gene may be used in the same way. Mutations, changes from one allelomorph to another, occur. Indeed, the recognition of any gene through the study of hereditary differences must always depend ultimately on mutation. In addition to it being a unit of transmission and of action, the gene may be considered as a unit of mutation. Where two changes can come about independently they would, on this basis, be ascribed to

changes in different genes. Similarly, the gene can be defined as the unit of chromosome reproduction at mitosis or of chromosome pairing at meiosis [5].

We have, therefore, as many ways of defining the gene, as we can recognize properties of the hereditary materials. One qualification is, however, necessary to them all. It must be stipulated that the gene is an ultimate unit. Under special circumstances, segments of chromosomes, whole chromosomes and even whole nuclei may be transmitted as units from one generation to the next. Equally, the whole nucleus is a unit of action in that it contains all that which is necessary, and generally no more than is necessary, for adequate development of the organism. Finally, the whole nucleus, or a set of chromosomes, or single chromosomes, or segments of chromosomes, may also act as units of change in polyploidy, polysomy or structural alteration. In whatever way we look at the genetic materials, therefore, we see levels of organization, each with its own unit. The gene is the smallest of these, found at the final level of genetical subdivision.

At the same time, the gene itself must be subdivisible into chemical radicals and atoms. Our problem is thus that of deciding where subdivision ceases to be genetical and becomes chemical. To define a gene we must decide at what level it is that further subdivision means final loss of the co-ordinated behaviour which binds parts, themselves incapable of initiating and controlling life-processes, into effective wholes.

In view of these considerations, it may seem remarkable that the concept of the gene should have acquired so dominant a place in genetical theory. It is not the only unit with which the geneticist is concerned, and it may be defined, indeed is implicitly defined, in a variety of ways according to the needs of the occasion. Yet few geneticists, in fact until recent years no geneticist, would have appeared to doubt the justification of the notion of the gene. The reasons for this are two-fold, predictive value and consistency.

From Mendel's experiments it appeared that genetical differences could be resolved into a number of parts, each inherited as a unit or gene. Because of this, prediction of breeding behaviour became possible. Later investigations revealed something of the relations and interplay of these genes, but the essential principle of analysis into units for the understanding and prediction of breeding behaviour has never required modification. Whatever the nature of these units may be, their practical value in genetic analysis is indisputably great.

Also, the various ways of distinguishing genes have led regularly to the same units. The genes separated by recombination could be shown to play distinct parts in development, and *vice versa*. The difference resulting from a single mutation was inherited as a unit. Exceptions were, of course, found. Genes such as yellow and scute in *Drosophila melanogaster* were regarded as distinct on grounds of action long before they were shown to recombine. But recombination was eventually observed. Similarly, polymeric genes in wheat and oats were inherited independently of one another, although they appeared to be exactly equivalent in action. The discovery of the allo-polyploid nature of these species showed clearly that such behaviour might reasonably be expected. It was an exception that proved the rule. Confidence in the consistency of the various ways of distinguishing genes has, in fact, grown to be so great that physiological homology, as tested by the phenotype of the hybrid between two mutants, is taken as valid evidence of allelomorphism of the two changed genes.

Thus in the cases where a disparity of inference has arisen, some explanatory special circumstance has generally been clear. With allo-polyploidy we expect some genes separable in inheritance to be of like action. Equally, since separability in inheritance is generally tested by recombination, we must expect to find genes separable in action to be inseparable in inheritance, where the conditions necessary

for recombination are absent. The criterion leading to the fullest sub-division is taken as valid.

Cases have, however, been encountered where the inconsistencies are not easily reconciled in this way. Such cases offer us a means of learning something of the nature of the gene. Take, for example, the yellow gene in *Drosophila*. Many mutant allelomorphs are known. Some of these, like y^1, result in body and bristles having correspondingly changed pigmentation. Others, like y^2, show only the change in body colour. Another, y^N, affects only bristle pigmentation. Now, on a physiological test, both y^2 and y^N are changes in the same gene as y^1, for the heterozygotes are not normal. Yet the heterozygote y^2/y^N is of normal wild type appearance, and we are led to infer that different genes are concerned. It is open to us, of course, to take the view that y^1 really affects two closely adjacent genes, one of which is changed in y^2 and the other in y^N. That recombination of these genes has not been observed is not surprising, since it would be infrequent, more especially as the yellow gene, or gene complex, is situated in a region of low crossing-over. One is, of course, left with the question of why two genes of such related action should be so close to one another, and this question is the more urgent as other genes show the same phenomenon. The difficulty is not, however, a serious one, as an answer might be found in the occurrence of adjacent "repeats", known to exist in *Drosophila* chromosomes.

A more serious conflict arises on this view when the evidence from mutation is taken into account. Were y^1 to be a simultaneous mutation in two distinct though adjacent genes, we should expect it to be rarer than change in either singly. Actually Bridges and Brehme [2] record it, or mutations of closely similar effect, as having recurred on some hundred occasions. It appears to be more common than either of the other types. Thus y^1 seems to be as much a unit change as y^2 and y^N. There appears to be a non-correspondence of the units of action and change. The gene is a com-

pound of parts, each of which may change independently of the others, and each of which plays its special rôle in the working of the whole, as shown by the different results of the different changes; but the actions of these parts are not simply additive. Physiologically they bear a complex relation to one another. They represent a physiological whole, a whole whose action may be altered in various ways by changes in different parts, but ways which bear no simple and easily predictable relation to one another.

In one sense the gene, as viewed in this way, is like a miniature version of the whole genotype, which itself consists of parts, the genes, each playing its characteristic rôle in producing an adjusted phenotype, but which is unitary because a change in any one part destroys this adjustment. The genotype can be broken down for genetical consideration. Can the gene? In so far as the gene is to be the ultimate genetical unit, the answer must be no. It must have parts, but on chemical grounds the behaviour of the whole must depend also on the arrangement of these parts. If this arrangement is changed, then the gene will no longer function in the same way, just as isomers do not have the same properties. We may view it in another way. A chromosome appears to produce not one but a number of major products by which its genetic action results. Within limits, to be discussed later, the region producing one such product does so independently of the rest. The products may interact in various ways later, but this is external to the chromosome. Within one such region, however, we must suppose that the parts act together to give a single major product in a way depending on their arrangement with relation to one another. Such a region would be an ultimate genetical unit. In this way we can arrive at the idea of a gene as a field of co-ordinated activity, the property of full activity being conditioned by internal arrangement, but, within limits, independent of external relations.

This picture is very similar to that reached by Goldschmidt [4] from evidence of the effects on gene activity of

breaks induced in adjacent parts of the left end (yellow-scute portion) of the *X* chromosome in *Drosophila melanogaster*. He concluded that yellow and scute were not so much points, as regions of the chromosome, and that they were not delimited physically from one another in any special way. The parts of one gene (or region) appeared to be as physically distinct as the two genes: in fact, there was some evidence that the regions overlapped by having one or more parts in common. This might well be the case if one original part had some property necessary for the full co-ordination in activity of the other parts on each side of it. Thus each gene would be a physical entity in that on its arrangement depended full physiological activity; but it would be an entity not of necessity separated from neighbouring entities in a special physical way. The apparent physical separation, depending on separability by recombination, would then be due to the fact that two genes can be "marked" by changed physiological properties independently of one another, and hence capable of recognizable re-association, while similar marking of the two ends of one gene would be precluded by the physiological co-ordination of the whole.

A hypomorphic mutant allelomorph, one which is distinguished from the usual allelomorph by reduced efficiency of action on the phenotype, can be as fully efficient in self-reproduction. The unit of self-reproduction is separable from the unit of action on the phenotype. A number of possible relations between the two suggest themselves, of which perhaps the most interesting is, that self-reproducing units of relatively unspecific action may combine in particular ways to give genes of highly specific action. In any case, it is clear that a self-reproducing body can exist without showing the kind of activity associated with the familiar type of gene.

Similarly, since the gene is characterized especially by its physiological co-ordination or integration, it may contain within itself fields of lesser co-ordination. The more complex

the full co-ordination, the greater the possibilities of lesser ones. The gene itself may, therefore, contain lesser genes definable on the same basis, and recognizable according to our method of observing the action of the system. Such a situation would appear as a kind of pleiotropic action, if all the effects were brought under observation. Full co-ordination would be realized in some phases of development. At other times lesser co-ordinations, and hence lesser genes, might appear. Even though recombination must be impossible to observe directly in respect of the greater effect, owing to the physiological limitations on observation, the lesser units might be observed to recombine, granted the necessary crossing-over, because independent "marking" would then be possible. The gene is not wholly definable away from its circumstances.

The circumstances in which a gene operates are also obviously capable of being affected by its neighbours. The consequences of this are well-known in *Drosophila* under the name of the position effect. A gene acts differently when its neighbours are changed. This might on occasions be due to spatial limitations on the interchange, by paths external to the chromosome, of short-lived products necessary for normal action. This was the original explanation of the position effect, but Ephrussi and Sutton [3] have shown it to be incapable on chemico-dynamical grounds of explaining all the cases. They propose an alternative explanation based on distortion of the physical relations of the chromosome parts. Such a distortion might well lead to a breakdown of the physiological co-ordination by which a gene, as we are discussing it, is characterized. They imagined the distortion to be produced by changed somatic pairing relations, but something similar might also occur in another way. So far as contiguous genes are not separated in any special physical manner, the substitution of a new neighbour could result in co-operation of the marginal part being "stolen" by the new neighbour. The parts of one gene, of one co-ordinated system, adjusted not to co-operate with those of its normal

neighbours, might well be unable to maintain their special relations to one another if new counter-attractions were offered them externally; and when started at one point in the chromosome, the upset of co-ordination might proceed over some distance along its length. The position effect so produced would not be a local one.

Changes of this kind, like internal changes of arrangement would be expected most often merely to be disruptive of the fields of action; but occasionally by chance a new field might be set up, and a new gene thereby come into existence. Normally this would only occur at the expense of the old genes, and the effect would be somewhat cataclysmic. This is not, however, the only way by which new genes can come about. If self-reproducing bodies simpler than the usual genes of major action, in being fields of simpler co-ordination, exist in the nucleus, they could by coming to lie in appropriate arrangement, or by accreting to themselves parts otherwise incapable of self-reproduction, build up new major genes. Do such bodies exist? It would appear that they may do so in the heterochromatin if nowhere else.

Heterochromatin in *Drosophila* has been regarded as inert, because virtually no genes of major effect have been found in it. It obviously has, however, the minimal genetical property of self-reproduction. The evidence on its other activity is less final, though certainly it is less specific than euchromatin. When major genes of the euchromatin are placed in unaccustomed proximity to heterochromatin, they may show a position effect. Whether this is due to the presence of the heterochromatin, or to the mere absence of the former euchromatic neighbours, is not fully clear, but Raffel and Muller [5] regard the effect as due in any case to what they call "invisible genes," *i.e.*, genes not recognized as producing any specific product. It would appear, therefore, at least possible that heterochromatin contains bodies from which major genes can be built, but lacks the co-ordination essential for specific activity, *i.e.*, heterochromatin

might well provide a source of new genes of the euchromatic type. That genic evolution does occur seems difficult to doubt. We can hardly imagine that all the genes of to-day were present fully formed in the first life, and if we admit the evolution of genes in the past, there is no basis available at present for doubting that the process is continuing. To regard the gene as primarily characterized by its properties of co-ordinated physiological actions opens the possibility that materials may regularly be present in the nucleus from which new gene systems can be built up by a process of spatial readjustment.

The theory of the gene is in a transitional stage. The old idea of the chromosome being made up of genes like beads on a string has proved to be too simple. We are reaching a new level of analysis, with new complications, and must expect to modify our ideas accordingly; although for many genetical purposes the older idea will still provide a sufficiently good approximation. What conclusion we shall finally come to is impossible to say. The evidence is not conclusive: indeed, we are still engaged in accumulating the evidence necessary to see our problem in its proper perspective. Any discussion must, therefore, be speculative. Beadle [1] has considered the gene from the biochemical standpoint, and has pointed out that while we cannot yet define the gene in chemical terms with any certainty, we are at least entitled to assume that such a definition will ultimately be possible. He has proposed the hypothesis of one gene giving, at least usually, a single specific product, and a single specific product being given by one gene, as a working basis for the development of biochemical studies to further the biochemical definition of the gene. I have endeavoured to show that to rest a definition of the gene on its physiological or biochemical properties is not unreasonable, and that it leads to a consistent interpretation of existing evidence in terms of an essential co-ordination in activity of gene parts, although the postulation of co-ordination raises the fresh problem of its mechanism. The

discussion has been of necessity both over-brief and speculative, but unless we are prepared to consider the possibilities of the various approaches to the nature of the gene, we cannot see how to set about obtaining the evidence by which our final conclusions must be moulded.

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14

SIGNIFICANCE OF NUCLEAR CHANGE IN DIFFERENTIATION

1948

IN the process of differentiation, cells derived from a common ancestral cell take on different, though mutually adjusted, forms and functions. Some determinants must therefore change during this process in either the cytoplasm or the nucleus, or, of course, both. The genetical problem of differentiation is to discover what the properties of these determinants are, and how they are related to those other determinants, the genes, the permanency of which we recognize by their transmission from generation to generation in sexual reproduction.

There is a growing body of evidence that differentiation is at times, though by no means always, accompanied by changes in the nucleus. These changes appear to be of three main kinds: changes of elimination, replication and manifestation.

Changes of elimination involve specific whole chromosomes or specific parts of chromosomes, in which latter case the process is more commonly called diminution. Elimination is a rare occurrence, most cases being known in the Diptera [1]. In *Ascaris*, where the process is properly diminution, it affects every chromosome at the second to fifth cleavage divisions in those cells ancestral to the soma, the cells of the germ line showing no change. In *Miastor* only whole chromosomes are eliminated, 36 disappearing

out of 48 from the somatic line at the third and fourth cleavages in female, and 42 out of the 48 in males [2]. Other Cecidomyidæ behave in essentially the same way [3]. There is a possibility that this change in the Cecidomyidæ is only one of reducing a polyploid nucleus to a diploid or haploid condition, so being unspecific for members of the basic complement. In *Sciara*, as in the Cecidomyidæ, the elimination again differs according to whether the individual will become male or female; but it goes on over a longer period of development, and at least one chromosome, and possibly more, is eliminated in the germ track. In this fly, too, the members of the basic set are differentially eliminated, and genetical evidence shows further that even homologous chromosomes behave differently, those of paternal origin being eliminated while maternal chromosomes remain. One case of elimination is known in plants, supernumerary chromosomes vanishing from the nuclei of what we may call the root line in *Sorghum*, but remaining in at least part of the shoot line, from which, of course, the reproductive cells develop [4].

It thus appears that elimination essentially brings about a difference between the nuclei of germ line and somatic line, the former obviously retaining the full complement of chromosomes, except in *Sciara*, where the loss in the germ line is offset by later and equally remarkable multiplication. In no case is there evidence that the nuclei of the various somatic tissues characteristically have different chromosome complements as a result of further elimination. The precise function of the eliminated chromosomes or chromosome parts is not clear, but in *Ascaris*, and probably in *Sorghum* too, they are heterochromatic [5], and hence presumably lacking in major genes.

Changes of replication are in nearly every case non-specific, all the chromosomes showing the change equally. The chromosomes divide more often than does the nucleus. This leads to polyploid nuclei where the centromeres divide with the chromosomes, and to polytene nuclei, the

chromosomes of which have multiple strands as in the salivary glands and other tissues of *Drosophila*, where the centromeres do not divide. The difference between polyploidy and polyteny is thus a minor one from our present point of view, and the two are conveniently pooled under one name. Two such names appear to be in use, and of them endopolyploidy is preferable to polysomaty, for the latter might easily become confused with the term polysomy, which has an entirely different meaning. Sometimes, also, the nucleus may divide without the cell doing so, thus giving a third variant, the multinucleate cell or coenocyte [6].

Replication seems commonly to mark the end of active cell division and the onset of differentiation, and White [1] states that the various tissues of insects all have their characteristic degrees of endopolyploidy, some being mosaics of different multiples of the original number of chromosomes. He regards it as likely that the phenomenon is widespread in other animal groups. It is also fairly common in plants, particularly, it would appear, in cortical tissues [7, 8]. Here again mosaicism is frequent, and one of its genetical consequences is the production of a proportion of tetraploid shoots among the diploids regenerated from callus originating in the cortex of decapitated tomato stems. The reverse of replication seems also to occur, though less commonly. Apart from the possibility that elimination in the Cecidomyidæ is a change of this kind, equal reduction, by what must be tantamount to somatic meiosis, has been recorded in *Culex* [9] and in onion and barley roots, especially in the latter case after treatment with growth substances [8].

We have already noticed that changes of replication are generally non-specific or balanced; but in a few cases replication is confined to specific chromosomes. The so-called *X* doubles itself once oftener than any other chromosome at meiosis in normal male *Sciara*, and the *X* of *Drosophila* does the same when the males are carrying the

"sex-ratio" super-gene. In *Sciara* this behaviour compensates for an elimination early in the germ track, and in sex-ratio *Drosophila* the *Y* is eliminated simultaneously [10]. This relation of specific or unequal replication and elimination may well be significant in animals. It has been claimed that similar replication also occurs in the root tissues of certain orchids where no elimination is known, but the evidence for this behaviour cannot be regarded as final [11].

Changes of manifestation strictly involve no alteration in the number or balance of the genes. A typical example is afforded by the different rates of condensation of the chromosomes in the two daughter nuclei produced by the first division in pollen grains. This difference depends in no way on a genetic inequality between the nuclei, for sometimes by either accident or treatment the spindle is formed 90° out of its true line and then the nuclei condense at equal rates. A cytoplasmic gradient must be the cause of the difference [12]. The difference between two daughter nuclei, one destined to divide again and the other not, at the margin of a meristematic region also marks a change of manifestation, as must many differences of chromosome size and contraction. Some of these changes, such as that concerning future division, must affect the chromosomes equally, but in others heterochromatin and euchromatin may behave differently.

Changes of manifestation, though not themselves involving changes of genic number, may be associated with other changes that do. Thus the daughter nucleus, the fate of which it is to divide no further, may undergo a change of replication. Also the chromosome fragmentation which immediately precedes diminution in *Ascaris* would seem properly to be regarded as a change of manifestation, for of itself it involves no change in the genes (apart from a possible change in position effect), but only a partial breakdown of their linear organization. It, too, seems to depend on a cytoplasmic gradient like the difference between the pollen grain nuclei [13].

What is the significance of these various changes for our understanding of differentiation? To answer this question we must see that it consists of two parts, and ask not merely what are the effects of the changes, but also what are their causes.

On the various occasions when it has been recorded that nuclear change accompanies differentiation, there has usually been a suggestion, implicit in the presentation rather than explicit in the statement, that the process of differentiation was an effect of the change in the nucleus. This suggested relation is seldom capable of the direct test of experimental breeding, for the differentiated cells and tissues cannot usually be induced each to regenerate an individual organism sufficiently complete for its genetic constitution to be ascertained. Even in plants, where asexual propagation is possible from roots, shoots and even leaves, regeneration is most often from complexes of different tissues. Nevertheless, when all the myriad examples of asexual propagation afforded by everyday horticulture are taken into account, the conclusion seems inescapable that in plants, with the exception of occasional polyploidy, the cells and tissues are genetically alike. Nor can polyploidy, nor any form of endopolyploidy, be regarded as a type of change intrinsically likely to produce differentiation. Polyploidy is one of the most common differences between individuals in plants, and is also known in a number of animals like flies and newts. Apart from the upsets of sexual development predictable from their detailed chromosome constitutions, the polyploid individuals have a normal structure with all the customary tissues developing and co-operating in the customary fashion. Indeed, it often requires a practised eye to distinguish diploid and polyploid by inspection. Whatever their other significance, changes of replication can scarcely be taken as a cause of differentiation.

The case against changes of elimination is a little different. Where they occur, they are commonly associated with a major dichotomy in the fates of the cells, to give soma as

opposed to germ line, or root as against shoot. The soma, or the shoot, has, however, itself a host of differentiated tissues associated with no further elimination. Also, as we have seen, elimination is a rare phenomenon, and its counterpart, unequal replication, even rarer. Thus even if elimination (or unequal replication) should in truth cause the differentiation with which it is associated, another and more general cause must still underlie most tissue differences. Furthermore, genetical experience shows that, like polyploidy, monosomy and polysomy in a wide range of plants and animals can characterize whole individuals, all of the tissues of which differentiate and co-operate sufficiently well for viability (though admittedly with rare exceptions all monosomics and polysomics are somewhat abnormal in form and may even be inviable where the genic unbalance is too great). In these species simple elimination could scarcely account for differentiation.

It might, of course, be argued that these observations should be given little weight, that physical elimination or unequal replication as a cause of differentiation is a phenomenon of individual genes rather than of whole chromosomes or of large segments of chromosomes. To do so would be to postulate a process for which there is no independent genetical or cytological evidence. Nor could it give a complete account of the process, for we should still be faced with the problem of why the genes were eliminated or multiplied differentially just at the appropriate times. Indeed, no hypothesis which makes differentiation the outcome of elimination or multiplication, whether balanced or unbalanced, affecting chromosomes, segments or individual genes, can be regarded as satisfactory, for it leaves unexplained the cause of the nuclear change itself. In adopting such a view we should merely replace one genetical problem of differentiation by another. The answer to our question must be sought in another direction, one to which changes of manifestation point the way.

We now have a wide range of evidence to show that the behaviour of a cell depends immediately not on its nucleus, but on its cytoplasm, which, though ultimately determined by an associated nucleus, may be acting in a manner reflecting the nucleus of a past association rather than that of the present. This persistence of the effect of a nucleus in the cytoplasm shows us that the nucleus, though remaining constant in its genetic content, can have a changing effective action. It is constantly acting on and altering the cytoplasm, so that the circumstances in which it finds itself are altering and with them the future effect of its action [13, 14].

The nucleus itself affords a sensitive test of the constitution of the cytoplasm, so sensitive that it enables us to detect differentiation within the cell, as we have already seen in pollen grains. Indeed, we have several lines of evidence showing us how the fate of the nucleus depends on the cytoplasm. The timing of nuclear processes in great blocks of tissues, like the spermatogonia of animals, must be brought about through the cytoplasmic connexions of

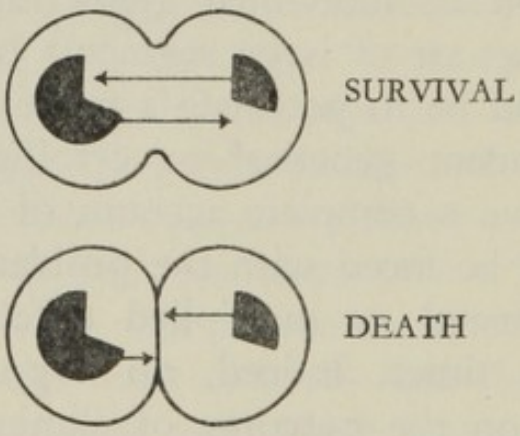

Fig. 11.—Pairs of pollen grains the nuclei of which show complementary unbalance, one carrying in duplicate the chromosomes for which the other is deficient, can survive and the nuclei continue to divide provided that wall formation is not complete so that they enjoy a cytoplasmic connexion. With complete wall formation and loss of the cytoplasmic connexion they die.

the cells. Pairs of pollen grains with nuclei showing complementary unbalance (5 and 7 chromosomes in place of the normal 6 in *Rhœo* [15], and 6 and 8 or 5 and 9, etc., in place of the normal 7 in *Uvularia* [16]) can live and their nuclei

divide so long as they have cytoplasmic connexions through which the products of locally unbalanced gene action can be evened out; but they die when the cytoplasmic connexion is lost (Fig. 11). Furthermore, the cytoplasm can, in its regulation of nuclear processes, reflect the action of a gene no longer contained in the nucleus. This we can see in Beadle's [17] polymitotic maize, where plants homozygous for the gene produce pollen grains all the nuclei of which undergo premature supernumerary divisions. The chromosomes do not show corresponding divisions, so that the nuclei come to contain reduced numbers of chromosomes, some, in fact, having only one. The result is a group of pseudo pollen grains which all die. Plants heterozygous for the gene must produce two genetically different kinds of pollen, one of which will be like the lethal polymitotic pollen borne on the homozygous plants. But none of this pollen shows polymitotic behaviour. Thus polymitosis is like incompatibility in heterostyled plants[18]. The nuclei of the pollen grains do not determine their own fate. Their behaviour, normal or polymitotic, is determined by the cytoplasm transmitted from the parent zygote, where, however, its constitution was determined by the diploid nucleus with which it was then associated (Fig. 12). This principle even applies to the process of elimination, for the loss of one or two *X*'s, to give females or males, depends in *Sciara* on the genic constitution of the mother, from whom the cytoplasm must have been derived, even though the determining gene may not have been passed on to the individual showing the elimination.

Changes of manifestation, which have no direct effect on genic constitution, and so can never of themselves cause differentiation, thus show us how the cytoplasm of one cell can be differentiated so that the fates of the daughter cells will depend, not on which daughter nucleus each obtains (for these will be alike), but on which part of the cytoplasm each inherits. By the aid of these changes we can see how the continuation and adjustment of the processes

of nuclear division depend on the cytoplasm, and hence how endopolyploidy can be a response to the condition of the cytoplasm. We can even see how elimination is but another example of cytoplasmic control. Finally, we can see

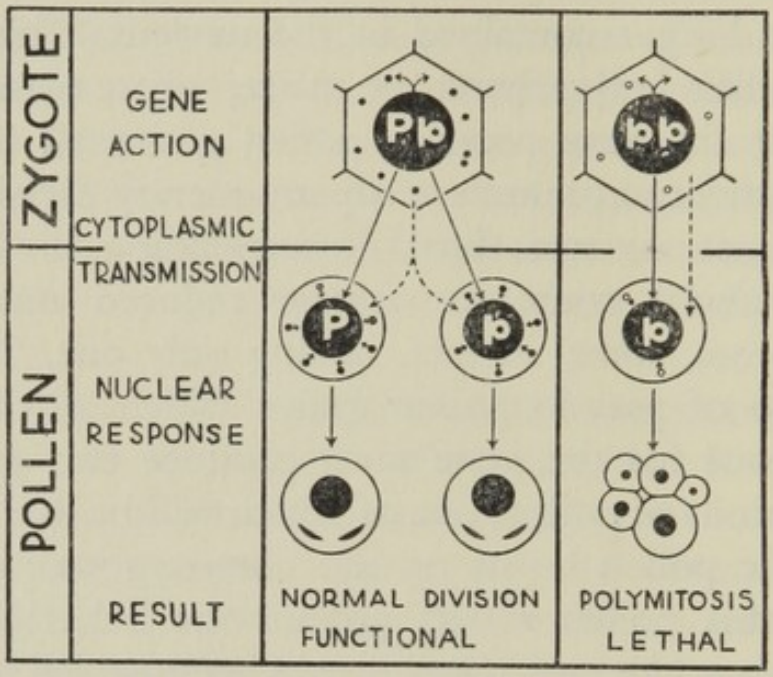

Fig. 12.—Polymitosis of the nuclei in maize pollen grains depends on the action of a recessive gene in the sporophyte. The normal or polymitotic behaviour of the pollen grain's nucleus depends not on the gene it carries, but on the cytoplasm the pollen grain inherited from its parent zygote, where the cytoplasm's constitution was determined by the action of the diploid nucleus with which it was then associated.

how the cytoplasm, in determining these changes of the nucleus, is itself reflecting the past action of that same nucleus or of some other nucleus with which it has been earlier associated.

All these nuclear changes can be interpreted as responses to an accomplished differentiation of the cytoplasm, and many of them, indeed, demand such an interpretation. The nuclear change is but a consequence of the earlier action of the unchanged nucleus. Differentiation is neither generally nor necessarily dependent on the physical elimination or unequal multiplication of the genes and chromosomes to produce what would be seen in a complete individual as a genetic unbalance; it depends on the physiological reduction or enhancement of gene action by the constitution of a cytoplasm itself reflecting the earlier action of

these same genes. The nuclear changes we see are special effects rather than general causes of differentiation. They are special examples of the general process to which all differentiation must be referred.

As an organ the nucleus, like other organs, is part of the phenotype and its behaviour is under the control of its own genes acting in their customary fashion through the cytoplasm. It is true that the phenotypic changes of the nucleus may have a special significance in that some of them might mean changes of the genotype. But this should not blind us to the fact that, even though these secondary changes of genotype may have an adaptive significance in some special cases like *Sciara*, they are, nevertheless, still secondary. They still depend on a previous change of the nucleus acting as phenotype to the genotype it carried in its earlier and unchanged form. Only if we are careful to distinguish between these two aspects of the nucleus, the recently understood phenotypic as well as the long appreciated genotypic, can we hope to assess the true significance of nuclear change in differentiation.

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15

HEREDITY VERSUS DISEASE

1945

NO two individuals are alike. We are quite used to that idea as applied to man. In fact, it expresses what we mean by individuals. We are less used to the idea, however, that in nature this rule holds for almost all sexually reproducing plants and animals. No two mice and no two mayweeds in nature are quite the same. It often happens, to be sure, that plants multiply by runners or bulbs. And when they multiply in this way the products are all the same so that one individual looks like many. But it is only in man's hands that this multiplication of individuals seriously alters the case.

When they are healthy the differences between individuals may be hard to see. But when the mouse or the mayweed is attacked by disease invisible differences come to light. One mouse or one mayweed is more resistant, another more susceptible, to the germ or mildew or insect that attacks it. And the difference is hereditary. In plants this is easily shown by the differences between standard cultivated varieties in resistance to fungus and insect pests. Sometimes this resistance is due to a specific reaction, an over-susceptibility, of the victim. And sometimes, particularly with plants that are being attacked by insects, tougher growth, such as is provided by an extra set of chromosomes, is the means of resistance.

Hereditary differences in the resistance of animals are confused by their own special method of reaction to disease

and by very great differences in susceptibility to such a disease as diphtheria during development. The animal has a defence mechanism which enables it to throw off a light attack and which remains with it to repel a second attack. It acquires immunity. There are, however, hereditary differences underlying this defence mechanism itself. They are revealed by the well-known and characteristic differences in susceptibility to disease amongst different races of poultry, cattle and man. British breeds of livestock fail in different degrees to compete with native breeds in the tropics, as has now been realized at some expense. All breeds are fitted by heredity to their own country or even district and part of their fitness consists in resistance to disease.

In man we have an especially convenient and rigorous way of showing the cause of these differences. There are identical twins which are really the same individual broken into two at the first cell division. Amongst these twins, even when separated in their lives, remarkable agreement is found in the incidence of disease wherever the immediate cause is universal. Thus with tuberculosis, infection is universal but a dangerous attack sporadic. Identical twins are often attacked within a few months of one another. And they are often attacked even in the same part of the same lung. Cancer is not usually due to infection at all but to a kind of internal mutation to which individuals differ in liability. As many as 36 out of 38 cases of cancer in identical twins showed symptoms in both of the twins—and often within a few months of one another. Thus the differences in resistance to tuberculosis and in liability to cancer are hereditary.

Now, wherever there are hereditary differences affecting survival, selection must alter the character of the population. We must, therefore, suppose that, when a great pandemic, like the plagues that ravaged Europe between 1664 and 1720, wipes out a large part of the population, not only is the surviving population less likely to be attacked by the the same disease owing to direct immunization, but also the

survivors' children by selection are, on the whole, less susceptible. The whole race is altered. It is altered or *adapted*, as we say, to meet the danger it has faced and may have to face again.

The human race itself, as well as crops and cattle, is continually by selection discovering new methods of defence. The results you can see very well when a species is split in two groups which neither mate nor mingle, as mankind was split before the discovery of America. Each half had its own diseases and was separately fitted to deal with them and with them only. When the two halves were rejoined their diseases were added together. Each half suffered. In his ship Columbus brought back from the New World at least one disease, syphilis, which swept Europe, Asia and Africa with a virulence which only many generations of selection for resistance have checked. In the same way, when the South Sea Islands were opened up to trade with us, the usually mild European complaint of measles ravaged those little isolated communities which had never had the opportunity of acquiring resistance by selection and killed off as many as a quarter in one year. The small isolated group suffers from new contact with a large one because it has previously been so well protected. That is one reason, and the main reason, why primitive peoples always suffer from contact with what we call civilization.

It is on this simple Darwinian principle of the selection of the fittest that a great deal of modern plant and animal breeding has been based. Wheats have been bred with the hereditary character of resisting the rust disease. Likewise potatoes which resist blight or wart disease and apples which resist the woolly aphis. It was only when we had done all this that we ran up against a snag. Amongst the millions of rust fungi which had been living on our wheat fields were a few which knew how to attack our resistant wheat. These few had the whole field to themselves and quickly replaced their weaker brethren. Evidently the rusts were individuals also. No two of them were alike and in

Fig. 13.—Sister apple seedlings from the cross Doucin × Northern Spy, raised by Mr. M. B. Crane at the John Innes Institution. The one on the left is resistant to attack by the woolly aphis, whereas the other is susceptible.

breeding tougher wheat we had also been breeding tougher and more effective rusts.

The same kind of warfare is going on all the time in nature. The microbe or the insect is continually by mutation and selection discovering, so to speak, new methods of attack. Bacteria themselves suffer from diseases. They are attacked by still smaller disease organisms, the viruses, or bacteriophages, discovered in 1915. In a culture of bacteria which is being attacked in this way we can get a bird's-eye view of the whole battle. One stroke of mutation by which the bacterium becomes immune to the virus is followed by a counter-stroke when the virus changes to a form capable of attacking the changed bacterium. And so the struggle goes on. Adaptation and counter-adaptation succeed one another in the laboratory culture just as in the wide world.

Man has used this device of setting a still smaller pest on to the larger. Striking victories have been won by getting a red spider to eat down the prickly pear in Australia

and by collecting parasites which will destroy aphids. This weapon, however, will not meet all cases. Of more general use is the chemical killer.

Since the introduction of Bordeaux mixture to kill the blight of the grape vine, the use of insecticides, fungicides and bactericides have spread over the whole world and new types appear every year. Their use is a standard part of the cultivation of most fruit and many arable crops in advanced countries. But even this weapon is liable to break in our hands. Cyanide fumigation and arsenate spraying have been used against scale-insects in lemon groves and codling moths in apple orchards with powerful effects—at least for three or four years. But then something new happened. The parasite seemed to have become resistant to the effects of the poison. New races of parasite had been bred by the resistant survivors which no longer succumbed to the chemical attack.

Every new drug or poison, of course, sweeps all before it. Sulphonamides at first proved fatal to many bacteria, even to the hitherto unconquered *Gonococcus*. But after two years' success new races of this microbe appeared which resisted the drugs and left us as badly off as ever. A little while ago a compound was invented which killed a mould damaging fabric. Its successful application for a couple of years resulted in the appearance of a new mould which lived on the compound that was meant to destroy it. Again, penicillin has marvellous effects on innumerable enemies of mankind. But those bacteria which are not entirely killed by penicillin leave survivors whose progeny resist the drug and multiply in spite of it. When the bacterial world has recovered from the shock of penicillin it will fight back. We must be prepared for a set-back.

How are we to cope with this situation? In man and animals we already know one method of dealing with bacteria and viruses, the method of prophylactic vaccination or inoculation invented by the Turks, improved by Jenner and enormously developed by Pasteur. The method depends

on preparing the defence before the attack is made. The potential victim is given a model attack which enables his blood to manufacture "antibodies" which will put the invader—virus or bacterium—out of action before it has gained a foothold. The strategy works well where the invader is constant. But if the invader is variable his variation enables him to get through with a part of his forces intact. This is probably the trouble with certain virus diseases such as the common cold and influenza.

Virus diseases present us with other special problems. Each virus is usually carried and distributed by a particular species of parasite; there are some even which require a particular race or variant of the tick or the bug to carry them. The strength and the danger of viruses consists in their extreme variability and adaptability (including also their spontaneous origin, by mutation or transplantation, from innocent materials) as well as in their immunity to chemical attack. Moreover, the plants they attack usually fail to form, or at least to distribute, antibodies which will resist them and throw off the infection. In recent years virus diseases of crop plants have become steadily more serious in all advanced agricultural countries. Crops such as raspberries, strawberries and potatoes which 100 years ago in England certainly suffered little if at all from virus diseases now are continually subject to them. The raspberry is being steadily wiped out in England. And potatoes of most varieties cannot safely be grown more than two years without a fresh supply of "seed" tubers from parts of Scotland or Wales where the aphid which carries the virus does not live. Similar precautions are taken over large parts of Europe.

What is the explanation of this spread? All kinds of absurd reasons, such as the modern use of artificial fertilizers, have been suggested. If we examine the spread of a virus we soon get to the root of the trouble. Most viruses are not effectively passed through the seeds. Every new seedling is free from virus. It gets infected from old plants by the

insect which carried the virus. And when it is infected the virus may well be of a strain which does not spread rapidly in this particular seedling. New varieties of sugar cane or raspberry are therefore often thought to be immune to virus. But sooner or later the virus changes and finds them out and another victim falls by the wayside.

Now a remarkable change has come over agriculture in all the more advanced countries of the world during the last 100 years. With seed crops, selected and uniform varieties have been replacing heterogeneous land races. With other crops vegetative propagation has been replacing seed propagation. Cuttings, grafts and tubers give an immense distribution to one identical individual. In former ages (and still to-day in the Balkans and in India) every field of wheat contained thousands of quite different plants, every orchard contained many different trees. To-day there are fewer different kinds of wheat or apples in the whole of England than there were formerly in one field or one orchard. To-day each of these kinds lasts long and spreads far. Uniformity has replaced diversity. This transformation already general in the temperate world is now spreading to the tropics.

This is a wonderful world for the seedsman and the trader, and, at first sight, for the cultivator as well. They all like a standard article. But it is a still more wonderful world for the diseases—and, one might add, for the expert who studies them and discovers new ones every year. The disease organism, whether it is a scale insect, a rust fungus, or a virus, no longer needs by its own adaptations to fit a key to every one of a million different locks. When it fits one, it fits them all. Moreover, the virus no longer needs to infect afresh every year; it remains in the tuber of the potato over winter and is ready for work in the spring. How different is the case as I described it in nature where the plant or animal is continually selected to resist to disease, continually adapts itself, and exists in unlimited variety reproduced anew every year. Now the dice are

loaded against the product of plant breeding. Perfection, multiplied, standardized, and invariable, is bound hand and foot, helpless to defend itself against the variable and resourceful attacker.

The remedy then is clear. We must not seek to select, or even produce, the perfect plant and then trust to our static defences to protect it. We must at once set about replacing it by another and yet another kind. We must restore seed production and we must restore diversity to our crops.

There are many ways of doing this. In potatoes and bananas it is being done by crossing with the wild species from which our cultivated plants were long ago derived. In sugar cane it is being done by providing a regular succession of new varieties as each old one goes down. In maize it is being done by regularly crossing two inbred strains and growing only the hybrid as a crop. In raspberries it is being done by raising each plant from hybrid seed like the maize and replacing the plant by a new seedling after only a few years instead of waiting for the inevitable disaster before doing anything. In animals it is being done by crossing locally adapted races with improved but non-adapted European stocks.

In all these practices we see a sharp change of outlook. In place of the curative methods of human treatment which are necessary for man because he cannot be experimentally bred and which have until now been thought appropriate and sufficient for crops and stocks, we are altering the crops and stocks themselves. In place of cure we have genetic prevention. In place of the older medicine we have a more profound biology. Indeed, we are now reaping the harvest, the long neglected harvest, of Darwinism. It is a kind of Darwinism that would have surprised Darwin. Not least it would have surprised him in showing that the application of his theories of survival was necessary to the survival of agriculture.

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16

THE UNITY AND POWER OF BIOLOGY

1945

WHAT is biology? Is it everything from birdsong to the bacteriophage, from the bright red rose to the methylated and unmethylated anthocyanins? I think not. I think at least we want to find something that looks smaller than that, something more compact. But is there any compact version of biology? Someone has recently been asking (in America) whether such a thing exists. If we go back to the beginning we shall see that it does.

The impulse that set modern science on its feet in 1660 was the belief in its unity and its consequent power. The unity of its method was intellectually gratifying to some. And it gave a power in producing results which was economically gratifying to others. It gave also to a unity of theory. But that unity, achieved by Newton for physics and by Lavoisier for chemistry, was long wanting in biology. Among living things disunity triumphed everywhere. The only universal generalization in biology in its first 200 years was that all living things were different. As Lamarck put it, properly enough, in 1804, "Il n'y a réellement dans la nature que des individus." The whole study was overwhelmed by the diversity of species. Some departments of biology are still overwhelmed by it. As a professor in my university recently told me: "The different branches of biology speak different languages". True enough. "And," he continued, "they always will do so." We shall see about that.

The first great step in bringing biology together was taken by Darwin in 1859. The theory of evolution made possible

a cohesion between every part of the study of living things. The unification was not sudden or complete. The cement is still infiltrating the remote cracks and crevices of the subject and every year witnesses new instances of its effects, instances to which I shall return later.

But even while Darwin was at work the foundations of an entirely new structure were being laid deep down below him. We may represent these foundations by three disconnected discoveries. The first was the discovery by Mendel in 1866 that heredity depended on particles which did not mix or blend, permanent atomic particles, carried by the germ cells. The second was the discovery by Hertwig in 1875 that it was the nuclei of the germ cells which had to fuse if fertilization was to be accomplished, that the nuclei were therefore the essential agents of heredity. And last (in sense, though not in time) there was the discovery by Miescher in 1871 of what we now call nucleoproteins in animal cells.

It has been the work of this century to put these three discoveries together. We can now tell that the particles which Mendel inferred lie inside the cell nucleus whose movements Hertwig followed. And we can show that they consist of the nucleoproteins that Miescher isolated.

These nucleoproteins are so called because they have characteristically in combination with them nucleic acid. This nucleic acid gives them the unique power of reproducing their like which is the essence of growth and reproduction as well as of heredity. These three, always hitherto separated in biology, become at last aspects of the same chemical organization.

Now nucleoproteins exist both inside and outside the cell nucleus. But the dominant part in heredity is taken by those inside the nucleus, that is by the chromosomes. It is only these chromosomes which have the mechanically fixed structure necessary for the control of something so permanent as heredity. Just as a legally fixed constitution is necessary for the government of a country so, it appears,

a mechanically fixed constitution is necessary for the government of a cell and an organism.

These chromosomes we can see under the microscope. As nucleoproteins we can subject them to all the tricks of chemical and physical analysis. And as strings of genes we can change or recombine them in breeding experiments. Never before have three such entirely different methods of attack been brought to bear on one kind of structure. And when you remember that that structure is the material foundation of heredity and development, equally in plants and in animals, you will see what a revolutionary change has taken place. The synthesis which has made plant and animal science into one has also made them one with physics and chemistry.

The theoretical consequences of this change have been quickly appreciated. In a recent book by Professor Erwin Schrödinger, the physicist describes this union as the most "interesting" event in modern discovery. He points out that the chromosome molecules "doubtless represent the highest degree of well-ordered atomic association we know of," and that this property enables the organism, as it were, to live outside the world of increasing entropy around it and to escape to a very large extent the quantum indeterminacy of inorganic matter. We can no longer skip merrily (as some did a short while ago) from quantum mechanics to free will. The organism now has a say in the matter.

This theoretical union is, as always, intellectually gratifying. But what about its practical and technical effects? The wave of advance is moving outwards in all directions. I will give three examples.

Our knowledge of the chemistry and mechanics of heredity is gradually enabling us to control it. With X-rays we can break up the chromosomes and shake up the genes within them. We can combine, separate and modify nuclei by chemical and physical agencies. We can compress a millennium of variation within a few minutes, and by

these means cross species that were once uncrossable and make hybrids fertile that were once sterile. In such ways as these plant and animal breeding have acquired the new strength they need to meet new tasks.

What these new tasks are we find when we take a second direction, that of disease. The study of disease has hitherto been split between medicine and agriculture, between plants and animals, between bacteria and viruses. It is now possible for biology to join together what specialized technology has put asunder. In the normal cell there exists, as we saw, nucleoproteins which reproduce themselves. Now viruses, so far as they are known, are nucleoproteins. They are capable of being extracted from the cell and even crystallized. And, since new viruses can arise spontaneously or in plants by grafting, it seems likely that in general they owe their origin to the introduction of the proteins of one plant (or animal) into the cells of another, or to the mutation of proteins already there. For viruses, like the genes of heredity, undergo mutation, selection, and, therefore, adaptation.

We have thus discovered a secondary source of life and evolution beginning at the molecular level. We have also discovered the evolution of one side of disease. On the other side, that of the victim, there is also adaptation and evolution. We know more of it in plants than in animals or man because plants are more easily experimented with. But the principle is the same everywhere.

Disease has a lock and key mechanism. Every victim is a lock into which the key of disease has to fit. Every species of victim is continually, under pressure of natural selection, changing the design of its lock. And every disease, also under pressure of natural selection, is changing the design of its key. In nature some kind of balance is kept up in this way. But see what happens in modern agriculture. Here the stock or the crops, the potential victims, are standardized for the use of man. In many of our crops a single individual is propagated by grafts or cuttings. The

whole situation is simplified—from the point of view of the disease. A standard lock is provided for the disease organism. For a few years it fumbles with its keys and then, sure enough, it finds one that fits. And when it fits not one victim falls but a million.

This is the recent disastrous history of many crops, such as strawberries, raspberries, and potatoes, with the most advanced agriculture. It has been one reason why people have been telling us to give up advanced agriculture (or at least to give up the use of fertilizers). The remedy of course is to unstandardize our crops, a process which is fortunately not difficult to do if there are enough plant breeders.

For a third example let us turn to man and take what can be regarded as at once the most fundamental and the most practical question in biology, that of cancer. The cancer problem exists at different levels, every one of which is touched by the development of fundamental biology. First, there is chemically induced cancer which can be imitated by a chemically induced mutation, by a genetic change. Secondly, there is virus-induced cancer which can be imitated by grafting in plants. Thirdly, there are the special conditions of rapid cell division, abnormal chromosome behaviour and cell chemistry characteristic of malignant growth which can be imitated both by genetic changes and by chemical treatments in plants and animals. And beyond all these there is the great problem of the treatment of cancer by X-rays and radium—a problem whose solution is being reached by applying the principles derived from normal plants and animals suitable for experimental treatment. New theories and new techniques have sprung up from these foundations, and in consequence the diagnosis and treatment of cancer has been radically improved even in the past year. This improvement in turn will be passed on to many fields of medical practice.

It may well be said that biology as I have described it is not taught to-day in this country. That is true. Fundamental biology does not exist either for the botanist or the

zoologist, either for medicine or for agriculture. Biology teaching and research are thirty years out of date. And for that reason the immense fruits of this unity and power will not be reaped for many years to come. Those who undoubtedly speak different languages may long continue to assert, in the isolation of their innumerable learned societies and research departments, that no common speech will ever be discovered, or ought ever to be discovered, in biology. To quote another professor in my university: "We teach botany to people so that they can teach botany to other people, and there is no point in making it more difficult than it is."

But that point of view is being swept away. From what we see of different modes of activity of proteins common principles are emerging. And these common principles are as useful as they are fundamental. They give a power, both intellectual and material, a power that will, as soon as it is allowed, make life look and feel very different for us all.

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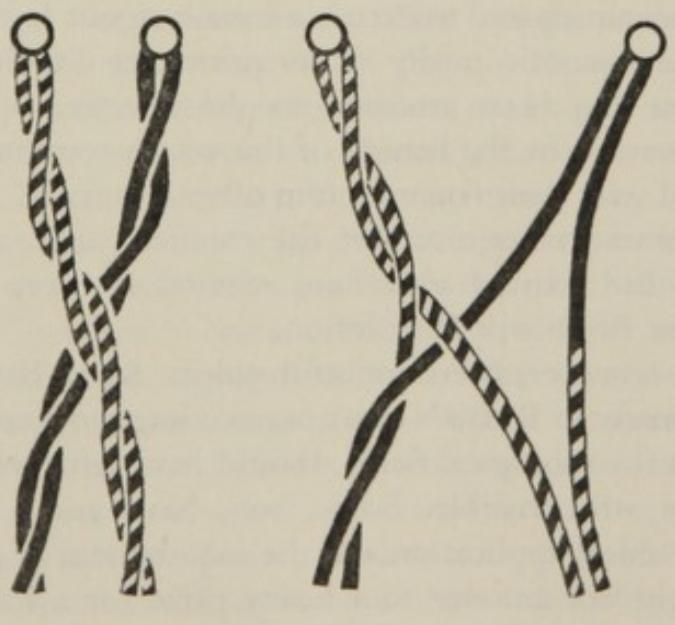

Appendix

THE NEW SOVIET GENETICS

1947

The development of science in Russia since the revolution of 1917 has been made known to the outside world, in spite of a restricted intercourse, in a variety of ways. Scientific publications, usually in the earlier days with foreign language summaries; international scientific congresses and celebrations in Moscow, always well planned and provided; popular publications circulated abroad describing officially the achievements of Soviet Science; finally, numerous articles and books by western writers, some of whom have visited more than one important centre in Russia, have described the work that was being done, and sometimes the work that would be done, by Soviet scientists.

The views of some of these western writers have been coloured, perhaps legitimately, by the proclaimed adherence of Soviet statesmen to a philosophy, the Marxist philosophy, which attributes a pre-eminent importance to science and hence seems to allow scientists a more respectable and even a more authoritative position in society than they enjoy elsewhere. Some visitors, too, like the English geneticist Bateson in 1924, have been prepared to excuse a certain rigour in the regime on grounds of the scientific purity of its principles and its aims. The importance that has been attached to the effective application of scientific discoveries for the benefit of the whole community has also been contrasted with their frustration in other countries. All scientists, indeed, were bound to rejoice that the conflict between science and society which had existed elsewhere seemed to have been finally resolved by the Bolshevik Revolution.

There have, however, been doubtful voices. Some have wanted to know why so many of Russia's most outstanding workers, both in the physical and in the biological fields, should have left their native land when that was still possible. Some, too, have asked whether the pressure for practical application and the requirement of philosophical orthodoxy might not amount to a heavy price for a scientist to pay for seeing his work made use of.

The answer to these questions can now be attempted. The development of one of those sciences lying at the root of present-day advance, namely, the science of genetics which concerns itself with heredity and

evolution, has been fairly fully revealed since the end of the war. It has been described in English by a number of scientific translators, travellers, inquirers and reporters of various races and nations and political opinions. The story can therefore be told and interpreted on sufficient documentary authority.

When Lenin examined the situation of genetics, and the possibilities of its useful application, in the Soviet Union in 1921 he found it comparing not unfavourably with that in the rest of Europe. The confusion of parties and opinions found elsewhere was to be sure enhanced by political controversy. Timiriazev, a leading plant physiologist of radical politics, had been engaged in sustaining Darwinism, which is a necessary part of Marxist doctrine (and by Darwinism he correctly meant to imply evolution by natural selection) equally against anti-evolution and against anti-selection. With this second heresy Bateson had implicated Mendelism and the new science of genetics. In a preface of 1905 we therefore find Timiriazev denouncing Bateson as the "head of clerical Anti-Darwinism." Apparently in the heat of argument Mendel's theory of heredity could be connected with his abominable profession as a monk.

In spite of the emotional views he expressed in his old age, Timiriazev recognized the uses of Mendelian segregation. One of the great difficulties of Darwin's theory of natural selection, in his own opinion, had been that differences blended in inheritance. New characters would therefore be lost before they could be selected for their advantages by nature. To overcome this difficulty Darwin had latterly fallen back on the so-called Lamarckian theory. This was the ancient superstition that a changing environment could directly change heredity and so mould and adapt races and species without the help of natural selection. Mendel, however (unknown to Darwin), had shown that different types did not blend in heredity. On the contrary, they were passed on, unchanged by one another or by the environment, from generation to generation and, in consequence, mixed parents have children, brothers and sisters, different from one another. The process by which they do so is known as Mendelian segregation. It was Timiriazev who first pointed out that this segregation brings out the differences for selection to act upon and hence that Mendelism is not merely consistent with Darwinism but provides its necessary foundation. It is not surprising therefore that, after the death of Timiriazev, Lenin chose a Mendelian to take over the development and application of plant breeding, and indeed of agricultural science generally, in the Soviet Union.

It was in 1921 that Lenin appointed N. I. Vavilov,[1] then aged 36, as President of his new Lenin Academy of Agricultural Sciences and

[1] Brother of the present President of the Soviet Academy of Sciences.

Director of the Institute of Plant Industry. Vavilov was a pupil of Bateson. He was deeply versed in western science and western culture. He was sympathetic to the revolution but, like Darwin, he was of well-to-do origin and was, in any case, a scientist rather than a Marxist. The importance of the distinction will appear shortly.

During the following twelve years the growth of Vavilov's work was one of the most impressive signs of the scientific prosperity of the Soviet Union. Under his control experiment stations sprang up in European Russia, Transcaucasia, Central Asia and the Far East. Under his leadership expeditions went to Afghanistan, Abyssinia, Mexico and Peru. To-day his pioneer exploration of the sources of cultivated plants is being studied and his example followed, both for its practical and for its theoretical value, by Dutch, American and British scientists. In Soviet Russia, however, events took a different course. Under the new Stalin regime, after 1928, Marxist orthodoxy became more important. Party members of research institutes began to find it profitable to intrigue for promotion. Philosophical exegesis began to intrude more frequently into the papers of young scientists. Western influence became suspect. A screen was gradually drawn between Russia and the outside world. English summaries were reduced in scientific papers. Visits abroad became restricted to those who left hostages behind. Too many of the leading Soviet scientists, geneticists as well as others, who went abroad were hesitating to return.

Gradually the new conditions began to have their effect. More and more was Soviet science preached as a thing by itself, derived from a canon which included Marx, Engels and Lenin and such as these had spoken well of. Marx had spoken well of Darwin so that Darwinism was sacred. Lenin had spoken well of Timiriazev so that his views were sacred in the second order. Timiriazev had spoken well of the American commercial plant breeder Burbank, so that he enjoyed third-order sanctity. And, again, Lenin had spoken well of an aged Russian plant breeder named Michurin, of whom we shall hear more later.

The application of these apostolic methods began to have more effect as the authority of western science waned and the authority of Moscow philosophy, so-called Marxism, waxed and flourished. A Government which relied on the absence of inborn class and race differences in man as the basis of its political theory was naturally unhappy about a science of genetics which relies on the presence of such differences amongst plants and animals as the basis of evolution and of crop and stock improvement.[2] It was desirable to have a theory of genetics interpreted

[2] Consistency is, however, no longer sought in this respect. According to Ashby, the Soviet school curriculum on Darwinism includes "The inadmissibility of extending the theory of natural selection to human society." Such an extension is classified under heresies as "social Darwinism."

and controlled by Moscow. It was only necessary to go back to the Lamarckian notions that Darwin himself had dallied with and to say that these were Darwinism or at least "Soviet Darwinism." It could then be assumed that better food would breed better wheat and likewise better men. The idea was to be found in the folk-lore of all nations since the ancient Hebrews. It was an idea that had commended itself to Timiriazev in his dotage and to Michurin even in his prime. Their names began to be more and more quoted, and suitably selected passages from their writings more and more frequently published.

With these developments in mind it is worth while looking back on the histories of Michurin, and his American counterpart, Burbank. Both have enjoyed a great name in the popular esteem of their own countries, a name to which statesmen have paid proper posthumous regard. Roosevelt honoured Burbank with a purple postage stamp. Stalin paid his homage to Michurin with a small town, Michurinsk. In both countries societies were formed to advance their work or reputation. Both men had worked for their private profit, collecting useful plants from other countries and breeding from them. Their methods did not include such precautions as are taken by scientific plant breeders, but sometimes, as in all botanical collections, useful seedlings turned up by chance from the seed set by open pollination. In these cases both Michurin and Burbank felt able (as commercial breeders usually do) to attribute the results to "scientific" crossing with particular, and often surprising, parents that happened to be growing nearby. Michurin claimed to have shifted the northward limit of cultivated fruits in Russia. But he made no mention of the fact that Sanders in Ottawa began his breeding work at the same time, in 1887, with the same object and with somewhat better authenticated success, using accepted scientific methods. Michurin merely admitted having received fruit trees from Canada and the United States.

In order to support their prodigious and, by scientific standards, fraudulent claims as creators of new plants, both Burbank and Michurin revived the good old Lamarckian theory of the direct action of a changed environment in changing heredity. They put the theory into a new dress and each probably thought he had invented it. But Michurin went further. He added a few ribbons that were entirely his own. He claimed that by grafting it is possible to *train* a plant for crossing, or to improve the quality of the result of crossing. Moreover, he could modulate or temper heredity by taking pollen from older or younger parents or by grafting older or younger seedlings. These principles a hundred generations of the most skilful and scientific hybridisers and grafters in other countries had failed, and have still failed, to discover.

Armed with such new and powerful instruments with which to change the course of nature the great man's followers at Michurinsk successfully crossed apples with pears, plums with peaches, cherries with plums, and red with black currants. In other countries, if such crosses could be made at all the hybrids would be intermediate between the two parents and completely sterile. The fact that Michurin's "hybrids" were purely maternal and entirely fertile squares perfectly with the evidence of his technical incompetence. They are not hybrids at all. They are, however, good enough material for propaganda when some of the particulars are omitted. The process by which an improbable statement of fact comes to be supported by a still more improbable theory which in turn comes to be supported by impossible statements of fact suggests an analogy with the development of those old religious myths which have fortunately been uprooted in Soviet Russia.

In view of these great successes of a more Marxist science the situation of genetics in the Soviet Union as the first five year plan got under way was becoming what is called "destabilized." Scientific genetics was still officially taught and applied, under Vavilov, to plant and animal breeding, and, under Levit, to medical science. But a strong undercurrent of misgiving was making itself felt in political circles, an undercurrent the possibilities of which were well understood in the more remote and backward provincial universities and research stations.

It was in this situation that a dramatic political change made itself felt. The rise of Hitler to power gave new life to the forces working against western science in general and against genetics in particular. Hitler's doctrine was founded on giving a distorted predominance to a distorted genetics. His theory assumed the permanent, and unconditional, and homogeneous, genetic superiority of a particular group of people, those speaking his own language. The easy retort was obviously to repudiate genetics and put in its place a genuine Russian, proletarian, and if possible Marxist, science. For this purpose very little research was necessary: the classical personalities and achievements of Timiriazev and Michurin were there ready to hand. All that was needed was to discover a new prophet of Marxist genetics or Soviet Darwinism. The prophet was found in Trofim Dennissovitch Lysenko.

The first appearance of Lysenko was in 1928 in connection with special temperature treatments of wheat seed and plants by means of which the plant would come into ear earlier and could therefore be grown farther north. The discovery was based on the work of Gassner in Germany. It was Lysenko, however, a previously unknown worker at an agricultural research station in the Ukraine, who suggested the exploitation of this "vernalization" in Russia. His modest proposals were received with such willing faith that he found himself carried

along on the crest of a wave of disciplined enthusiasm, a wave of such a magnitude as only totalitarian machinery can propagate. The whole world was overwhelmed by its success. Even Lysenko must have been surprised at an achievement which gave him an eminence shared only by the Dnieper Dam.

Perhaps Lysenko also became aware that such an eminence carried with it some vulnerability. For the area of land under vernalized wheat did not grow with the bubble of his reputation. Indeed, at the present day it is a moot point whether true vernalization of cereals is any longer practised in Soviet Russia. The name merely persists as a reminder of past successes in the title of a journal still published by Lysenko.

In these anxious circumstances Lysenko seems to have concluded that the best method of defence was attack, and the people to attack were the geneticists who had been placed in a still more vulnerable position than himself by the rise of Hitler. For this purpose he was lucky enough to fall in with a most astute ally at Odessa; this was a philosophical, that is to say a Marxist, writer of the name of Prezent. The two together apparently took in hand the destruction of the Vavilov school.

The campaign against genetics was built up at a series of national genetic congresses which were held in 1932, 1936 and 1939. The first was mild and hardly noticeable. It was in fact premature. For the second the ground was more thoroughly tilled. Propaganda at all levels from the daily Press to the scientific journal, and in all directions, practical and theoretical, political and philosophical, was brought to bear on genetics. A large and popular audience, to the number of 3,000, was marshalled in the conference hall. With this planned organization Lysenko and his manager launched their attack. They presented their arguments on a correct philosophical and canonical basis which made experiment unnecessary; which was fortunate for the experiments adduced were without controls, without definitions and without numbers. In a word they had no scientific meaning. Before a meeting suitably packed with party men these shortcomings proved to be no disadvantage. H. J. Muller,[3] the leading foreign exponent of the philosophy of the science, replied to the charges that had been brought against genetics, but the official report omitted his remarks. The Lysenko-Prezent programme in 1936 was an almost entire success. At the end the chairman was fully convinced and a resolution was passed that in future genetics and plant breeding were to conform with dialectical materialism. In other words, Moscow was to decide what was right and what was wrong.

Only one more meeting was needed to complete the work. This was

[3] Awarded the Nobel Prize for Medicine and Physiology in 1946.

held in 1939. It took the form less of a conference than a trial. The tone of the attackers became more aggressive and more authoritarian. Darwin himself said it. Timiriazev himself said it. Michurin himself said it. Such was the refrain. But pious quotation was no longer enough. Genetics, or "mendelism-morganism" as it had now become, was connected with fascism and therefore with treason. Clearly no hope was left for the geneticists. Many confessed their errors. But Vavilov could hardly escape the evidence that he had been nominated President of the International Genetics Congress of 1939 in Edinburgh. The Commissar for Agriculture declared for Lysenko in practice and theory. The following year, Vavilov was dismissed from his executive post and arrested, while on duty in Rumania. Later he was condemned to death (on the ground, as it happens, of espionage for Great Britain). On July 31st, 1941, he was taken out of one of the solitary condemned cells in the Butyrki prison and put in a larger cell with nineteen other political prisoners, whether on account of lack of space, or with a view to exile in Siberia, is unknown. When the Moscow prisons were evacuated in December, 1941, he was removed in distressing conditions to a concentration camp near Saratov. There he died.

In Vavilov's place Lysenko was appointed President of the Lenin Academy of Agricultural Sciences and Director of the Laboratory of Genetics (the name still stuck to it) of the Academy of Sciences. He also became a Vice-President of the Supreme Soviet. At the same time the industrious Prezent was rewarded with the chair of "Darwinism" in the University of Leningrad.

This controversy differs in two respects from any other that has been known in modern times. When Roosevelt made the mistake over Burbank the United States Department of Agriculture, the National Research Council and the Carnegie Institution of Washington did not dismiss their very able staffs of geneticists. In Russia, however, Stalin's mistake was part of a plan which included the dismissal of the geneticists and a great deal more besides.

The first victims were in 1932 when G. A. Levitzky the cytologist and his pupil N. P. Avdoulov were sent to labour camps. Vavilov asked Stalin for their release, a request which was temporarily and grudgingly granted. At the same time B. S. Chetverikov the pioneer of population genetics and W. P. Efroimson were sent to Siberia and nothing was heard of them for fifteen years. In 1935 the first two geneticists I. J. Agol and L. P. Ferry were put to death. In 1937 the head of the great institute for medical genetic research in Moscow, S. G. Levit, was put to death and at the same time probably Avdoulov. In 1939 N. A. Iljin, an outstanding animal breeder, disappeared, leaving a posthumous paper to appear in the *Journal of Genetics*. In 1942, not

only Vavilov, but also his closest cytological colleague G. D. Karpechenko, died ("in the fighting" so it was said). At about this time J. J. Kerkis the *Drosophila* geneticist disappeared following a party cell intrigue and Levitzky was finally sent back to a labour camp where he died. At about this time also N. K. Koltzov, the cytologist and doyen of Russian biology, died and his widow committed suicide.

In a word, after thirteen years of persecution, the great fellowship of Russian biological research, formed in the revolution, had been crushed and broken.

The details of this story are covered by secrecy mitigated by rumours and occasional apologies. Enemy action, currency speculation, political unreliability, fascist conspiracy and even, strangest of all, mere nature, have been alleged as causes of death. Presumably Vavilov did not live to know that he had been elected a Foreign Member of the Royal Society in 1942. Those who ask why it was that in the closing stages of the genetics trial he and his devoted followers seemed to have lost their nerve should consider that these men, knowing the methods of the Soviet Government, could foresee their own destruction.

The western scientist is bound to seek a parallel for these events in his own history. For men who died because they asserted the freedom of scientific inquiry from dogmatic control, nazism and fascism do not offer comparable examples. In Germany and Italy a sound genetics continued as an underground movement under fascism and has survived to-day. Even if we look back as far as Giordano Bruno, who died in 1600 at the hands of the Roman Inquisition, we find only a solitary victim. Never before has science been offered so many martyrs to its cause, men, too, honoured and beloved throughout the world. We must, however, follow the plot further.

Established in his new offices Lysenko was able to develop the theory and the practice of his Marxist "Genetics." The first he described in a small book called *Heredity and its Variability*, published in the stress of war in 1943, and circulated abroad in 1945 and again in 1946. It has now been translated—so far as writing of so transcendental a character can be translated—by one of the three most distinguished Russian geneticists in exile, Professor Th. Dobzhansky, of Columbia University.

Lysenko begins, on page 1, with a definition. Heredity, he says, is not what foreign genetics tries to make us believe, the property by which like begets like. On the contrary heredity is nature; and nature is development. We can, therefore, wipe out the misguided discoveries of bourgeois genetics. They are flat, stale and unprofitable. We can take it as proved without further evidence that, since changes in the environment directly modify the development of a plant or animal, they can also directly modify heredity; that is to say, change the

character of all the descendants of a plant or animal which has been specially treated.

This discovery (which is in keeping with the edited words of the masters already referred to and presumably also with the resolution of 1936) is obviously of great value to the plant breeder. Theory and practice are immediately united. Lysenko's anxieties about the practical failure of vernalization are removed. He can vernalize his wheat once and all succeeding generations will be born ready vernalized. With the wheat "varieties" common in primitive cultivation, consisting as they do, not of one, but of great numbers of pure lines mixed together, selection can quickly sort out types adapted to new and extreme conditions. In this way Lysenko is able to claim that "natural" vernalization has altered the heredity of wheat grown in the far north and thus turn a physiological defeat, the failure of his vernalization programme, into a genetic victory, the transformation of Russian agriculture. On nineteen out of the sixty-two pages of his work on heredity he adumbrates or reflects upon the expectation or promise of this practical achievement. In different countries there are different ways of keeping the wolf from the door.

The essential fallacy in Lysenko's, as in all would-be Lamarckian, experiments depends on starting with a mixture. Lysenko, however, denies the existence of pure lines and assumes that seed samples of all crops are mixtures; he may therefore count himself well protected against this charge. For a few years longer he can continue to hold the carrot of success in front of the donkey's nose and for a few years longer the vicious circle in which the pseudo-scientist, the politician and the philosopher deceive and bribe one another can follow its course.

So much for the serious side of Lysenko's book. There is, however, a comic side. A science must have its dialectical relationships. Lysenko (with the help perhaps of the new Professor of Darwinism) is quite willing to provide them. In order to do so he has to take elements of genuine genetics as his examples. Male and female germ cells do not carry permanent hereditary materials like the chromosomes of western genetics. On the contrary, in fertilisation, they digest one another. This has not been seen under the microscope, and what it would look like nobody knows. The great Russian cytologists in any case are all dead. But it follows directly from the Marxist principle of the interpenetration of opposites. The stronger thus destroys the weaker for the time being. Hence "dominance" is explained although it may seem to us to be less of the kind described by Mendel than that referred to in an unfortunate passage of his fourth book (line 1,209) by Lucretius, when he suggests that children take after the more vigorous partner in the act which begets them. Since 1943 a further advance in theory has been

made. Segregation is due to indigestion. The dominant gene (if one may use that bourgeois expression) with rustic vigour belches the recessive one. This negation of the negation is also strict dialectical materialism as now understood, and does not require vulgar empirical support.

How are we to describe this science or this philosophy ? Anthropomorphism, teleology, animism, and necromancy (which Lysenko modestly calls "Michurinism") are no doubt all dialectically reconcilable with current dogma in Moscow. To the uninitiated, however, their happiest analogy is to be found in the sacred writings and mystical ideas of Hinduism and when Lysenko describes development as due to the "unwinding of a spring wound up in the preceding generation" the Pandits of Benares might well recognize the doctrine of Karma and applaud so correct a philosopher.

In the career of Lysenko there is much of interest for men of science. Some things of course must be in doubt. It may be difficult in such a man to distinguish between the enthusiasm of the charlatan and the frenzy of the fanatic. It may seem that the denial of mysticism must itself become an act of mysticism in the mouths of those whose reason does not itself consent to the denial. It certainly will seem that dialectical processes are as unpredictable in their results as any other political manœuvres. Unity of theory and practice may be achieved (to use the jargon of a decadent science) by the digestion of a recessive theory by a dominant practice and of both by an epistatic politics.

But there can be no doubt that the genetics controversy is in one respect much more serious than any of ours. It means the collapse of an important part of the scientific foundations of an improved agriculture on which the peoples of the Soviet Union depend for their food. Many millions of the more efficient and prosperous peasants have already perished in order to make way for communist improvements in Russian agriculture, that is, for what hopeful and kindly people in foreign parts supposed were scientific improvements. There are few countries in the world in which there is more room for such changes, especially by plant and animal breeding. There is now no ground for hope that such original expectations of Lenin's revolution are going to be fulfilled. And, as for the dialectical materialism in whose name certain branches of science are being crushed, it is neither dialectical nor materialism. It is humbug, humbug fostered and sheltered by a xenophobia, borne of scientific obscurantism and political expediency. Lysenko and his followers are ignorant of foreign languages and no foreign book on genetics or cytology has been translated into Russian since Stalin took control. Their notions of western genetics and cytology are therefore always twenty-five years out of date. Yet the bogus achievements of

Lysenko and Michurin continue to be foisted on us (and still more aggressively on the Russian-occupied zone of Europe) by the Soviet propaganda machine. The window-dresser and the shop-gazer have ceased to be aware of the deception they are propagating, of the dream world they are living in.

The philosophical part of this deception is not the least instructive. Since the early statements of Marxist philosophy great scientific developments have taken place, most of them outside Russia. These developments, particularly in genetics, give a strength and coherence to dialectical materialism which it did not originally possess. Marx knew no more of heredity than Darwin did. Perhaps a little less. But, while Darwin admitted he knew nothing, Marx has to be supposed by Marxists to have known, or to have foreseen, everything. The scholastic method imposed by Lenin, and still more by his successors, thus unfortunately stabilized the official and imperfect doctrine of Moscow in opposition to the highly materialistic and highly dialectical theory of heredity which has been developed since the time of Darwin and Marx in western countries, developed by clerics like Mendel and Janssens, and bourgeois intellectuals like Bateson and Morgan, obeying and using traditional scientific methods.

Why should Marxist philosophy, which was supposed to be founded on science, and to be permanently concordant with it, adopt a scholastic method which was bound to conflict with the later findings of science? The reason for this was that the materialist interpretation of history, which was politically fundamental for the Marxist in Russia, obviously could not be recast from time to time by scientists. Marxism had to be governed by politicians according to their own ideology if it was, like the papal system, to establish the politicians in control. To Marx, heredity was not part of the materialist interpretation because it was immaterial. When science put heredity on a material basis—and with it the basis of class distinction—Marxism was already petrified. We can see therefore how fatal an uncontrolled development of science might be to a political system ostensibly founded on science. To use the Marxist phrase, we can see how the internal contradiction developed in political Marxism.

It is a rule that proselytising religious communities and other missionary bodies forswear, to some extent, the principles and practices on which they have based their claims to political power when in the end they achieve that power. Never has this happened so rapidly as in Soviet Russia. Never certainly has there been so ironical a situation as that in which the authorities in Moscow reproach the rest of the world for an idealism and superstition which are everywhere being supplanted by a materialistic science except in Moscow—and perhaps Madrid.

Once science has been brought under control the change is hardly to be remedied. The further Soviet biology moves away from the natural materialistic development of science the more loudly will its prophets declaim against the wickedness of capitalist or fascist science and the more loudly will they proclaim the mystical merits of Soviet Darwinism or Michurinism. There are, to be sure, several aspirants waiting in Russia to pull Lysenko off his perch by the reintroduction of scientific method. The position of Vice-President of the Supreme Soviet may be envied even if it does not seem enviable to us. Doubtless someone will succeed. But he will not reverse the resolution of 1936. Nor will he bring back the dead to life.

Another question now arises: what bearing has this history on the fate of scientific research in general in the Soviet Union? From time to time other branches of science, less notable in Russia than genetics was, are cleaned up and the survivors, physicists or psychologists, made to understand the correct lines of development until the next change of front. But apart from the caprices of a despotic Government there is something else in the Stalin system equally, although more gradually, fatal to science. The general requirements of secrecy and seclusion would hamstring the scientific research of any country in the long run. In Russia, which has never been above the fifth place in fundamental research, their effect is bound to be more rapid than it would be in any of the first four. But the most serious of all obstacles to Soviet science is the political control of the individual research worker, and of his privileges and promotion, at every stage of his education and training.

Science proceeds very largely by disagreements, controversies, or conflicts, processes which are resolved outside Russia by new dialectical transformations, new syntheses. Inside Russia they are resolved in the scientific, as in the political, field by the destruction of one of the parties to the conflict. The make-believe of free controversy, dressed up as for example in the Genetics Conferences, is pure pantomime. The only difficulty is to understand who is expected to enjoy the illusion. The Marx-Engels Institute in Moscow would be well employed in pointing out defects of this kind in the Soviet system, if such criticism were permissible. All these factors, quite as much as the dramatic open plots, trials and persecutions which have led to the suppression of genetics, are bound to crush fundamental research in Russia into irretrievable ruin. The survivors of the pre-revolutionary generation are still in charge. When that diminishing company has gone we shall see the results of subjecting science to philosophy and philosophy to politics in a totalitarian hierarchy.

Many false conclusions can be, and no doubt will be, drawn from this

history of Soviet science. The principles of the planning of research and its application to social welfare which are officially accepted in Soviet Russia must be applauded by men of science everywhere. We must also acknowledge that these principles are to a limited extent put into practice by the Soviet Government. But we cannot fail to see that three primary evils, by no means necessarily connected with either planning or socialist organization, but undoubtedly connected with one-party government, frustrate the hopes of a scientific civilization in Soviet Russia. The first is the establishment of an officially interpreted orthodox philosophy. The second is the suppression of free speech and of free cultural relations with foreign countries. The third is the use of the death penalty against scientists, and against hostages taken from their families, to enforce this suppression. From these primary evils political intrigue and delation, the pretence of infallibility, the bogus philosophy, and the sweltering authoritarianism, are all derived. No amount of glorification of science, or of what passes for science, will compensate for these evils either in making the good opinion of western nations or, what is more important, in making the happiness and prosperity of the peoples who are ruled from Moscow.

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[4] An account of the Lysenko epic for the instruction of German readers in the Russian zone.

POSTSCRIPT

Ten months after the publication of this article a fourth official conference on Genetics was held in Moscow (July 31—August 7,

1948). Three weeks later Genetics was formally repudiated, its research laboratories dissolved, its exponents dismissed, and its teaching abolished throughout the Soviet Union, by resolutions of the Praesidium of the Soviet Academy of Sciences (26 August, 1948).

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