HEREDITY AND ENVIRONMENT

by

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I. Origins of our Ideas

The underlying ideas, the first principles, of Genetics began to be sorted out and put in words nearly a hundred years ago. During the present century they have come to be a little more precisely expressed but otherwise they have changed remarkably little. They have been, and continue to be, so immensely successful that we may well feel it unnecessary or even foolish to question or disturb them. All the more so because those who have in recent years attempted to question them have succeeded merely in making themselves look foolish. It is however the very success of genetics, its dizzy expansion, which makes it necessary to enquire into our first principles, to find out how far they are axiomatic, how far they are unquestionable, or how far, on the other hand, they arise from inference or may at least be corrected or elaborated by inductive and deductive processes. Above all the expansion of genetics to new fields compels us to see to it that our old terms fit the new conditions in which they have to move and work. Otherwise we can neither understand our subject nor safely teach it to others.

II. The Conflict of Notions

The similarities of successive generations of plants and animals we conveniently and popularly ascribe to Heredity. These similarities appear with obscurity or plainness which varies in different families and species. They thus include an element of *uncertainty*. But underneath this uncertainty there appears to lie a principle of uniformity. The theory that there are uniform and inevitable sequences of events, sequen-

ces connected with material particles and extending from generation to generation, this is the theory of genetic determinism.

The ideas of uncertainty and determinism which underlie the theory of heredity run in two separate streams of thought. One stream carries the ancient idea of the *genitalia corpora* of LUCRETIUS, an idea expressed in our own time by a variety of different names as units, elements or particles, determinants, factors or genes. All these refer to the same thing, to the separable parts of the heredity of individuals. It is the distribution, of these parts (recognised by the recombination of their differences) which brings the uncertainty into heredity.

The study of the parts of heredity and their recombinations has been constantly subject to discussion ever since JOHANNSEN introduced the word *gene* in 1911, a term whose axiomatic position I have sufficiently discussed for present purposes at the last Congress of Genetics.

The other stream of thought carries the almost entirely modern idea of the heredity of the individual as a whole. It is this heredity as a whole which carries the principle of determinism and with which I am now chiefly concerned.

Between these two streams of thought there seems to be an inherent opposition, an antithesis, which has resulted in what we may call a split in the personality of genetics. Of this condition the geneticist is naturally apt to be unconscious and may well be surprised to learn. He has been unaware of any restriction to a study which has seemed to enjoy unlimited scope. For example, those who are wrapped up in the immense, and in the case of man, often impossible task of disentangling the parts are inclined to regard with suspicion the easier attempt to define or determine the importance of the whole. How profound is the split arises from the fact that it is a split not only in philosophical assumptions but also, as we shall see, in experimental procedure.

III. GENETICS AND HEREDITY

The two types of procedure as well as the two types of inference arise from MENDEL and GALTON.

Mendel in describing his experiments discussed his principles both of design and inference. He demonstrated the determinism of the whole of heredity by inbreeding. He then demonstrated the uncertainty of the recombination of the parts of heredity by crossing. But he was not thinking of his experiments in this abstract or generalised way. He was thinking of the practical results, especially the uncertainty of re-

combinations, and their material explanation, rather than of the conflict of principle which we can now see between the two steps in his experiment.

GALTON was writing ten years after Mendel, but of course independently of MENDEL. He was not concerned with experiments and could therefore allow himself greater abstraction in dealing with the very same problem. He was also concerned more with the determinism of the whole than with the uncertainty of the parts. This is what he wrote (italics mine):

«*Nature* is all that a man brings with himself into the world; *nurture* is every influence from without that affects him after his birth. The distinction is clear: the one produces the infant such as it actually is, including its *latent faculties* of growth of body and mind; the other affords the environment amid which the growth takes place... Neither of these terms implies any theory; natural gifts may or may not be hereditary...».

I) For the first time he distinguishes between what is inborn and what is, in the popular sense «hereditary».

What is inborn he assumes, or as we might now say, he realises, is genetically determined by the whole character of the particular egg. And what is said to be hereditary is merely an estimate of a similarity in the properties of parent and offspring, a similarity about which Galton did not wish to make any assumption. He was thus turning his attention, away from the uncertainties of transmission of the parts of heredity which we attribute to MENDEL'S recombination (Fig. 1).

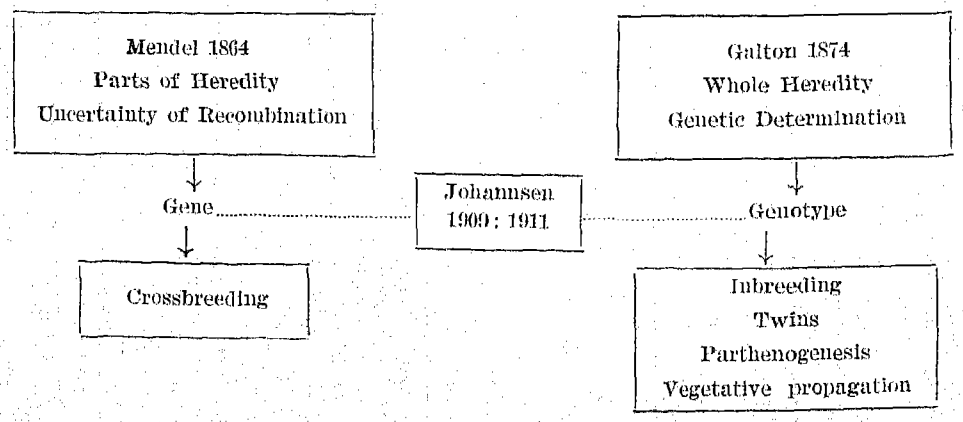

Fig. 1. — The simplified relations of the opposed systems and procedures of genetics.

To-day this distinction between genetic determination and hereditary uncertainty is never understood outside genetic circles. And it is rarely enough understood within them. Biologists are often content to believe that uncertainty is the last term in the genetic argument and that determination has nothing to with the case.

This view, though largely unconscious, is so strongly felt that it has actually led to a restriction of the idea of heredity. It is felt that since uncertainty is virtually excluded in vegetative reproduction we must avoid connecting the name of heredity with any relationship from which sexual processes are absent. This leaves us however with a no-man's land, a *demi-monde* of vegetative or subsexual organisms and processes which ought not to exist, or at least ought to have no heredity.

We may escape from this difficulty in the following way. Uncertainty is evidently a special circumstance. It depends on the occurrence of meiosis or fertilisation (or both). Thus obligatory parthenogenesis largely excludes hereditary uncertainty. Uncertainty also depends on the occurrence of differences which can be recombined at meiosis or fertilisation (or both). With sexual reproduction in pure lines, as Mendel found, complete predictability can be attained. « Heredity » therefore, if it is to have any use at all as a scientific expression, must embrace both determinism and uncertainty, both expressing themselves by way of every kind of reproductive process.

II) Even more fundamental in Galtons's statement is the opposition between nature and nurture. The proverbial expression that « nature passes nurture » was recorded in John Ray's collection of Scottish proverbs in the 17th century. GALTON here, for the first time uses the opposition as an axiomatic basis for the study of life. And he accepts the corollary that what is latent at the beginning is expressed during development in interaction with the environment. Something internal, to which for groups Galton gave the name of *stirp*, reacted with something external, the environment, to determine the appearance of the individual, the *person*.

Since the time of GALTON the idea of heredity as a whole property of the individual has grown from the recognition, variously described, of these kinds of opposition which he foreshadowed:

I. *Inside - Outside*		II. *Determinant - Result.*
Nature - Nurture	Galton 1872-5	Stirp - Person
Heredity - Environment	Weismann 1892	Germplasm - Soma
Genotype - Environment	Johannsen 1909	Genotype - Phenotype

The development of these oppositions has been governed during the present century by the new conditions available for observation and by the new methods available for experiment. These have had divergent, unforeseen, and partly unrealised, effects on the study of plants and animals, microbes and men.

Genetic Determinism as applied to the Whole Heredity of the Individual requires, first, that we distinguish between Heredity and Environment and, secondly, that we standardise one or the other. Both of these requirements have affected the development of genetics.

Consider first the standardisation of heredity. For this purpose vegetative or clonal reproduction, obligatory parthenogenesis and cumulative inbreeding have provided the technique of experiment for successive generations of geneticists from LOUIS de VILMORIN by way of JOHANNSEN to the most modern bacteriologist. Even in animals inbreeding can give genetically uniform populations. In both plants and animals the effects of changes in the environment can thus be easily discovered and separated from the effects of changes in heredity.

It is known that no change of environment can enable us satisfactorily to replace one clone of, say, a potato or an apple by another: nature passes nurture. Attempts to imitate differences of nature by differences of nurture, except in a pejorative direction, are pitifully unsuccessful. In man alone the experimental test of determinism cannot be made by the ordinary processes of experiment. But something very close to an experimental test has been discovered; it was discovered by GALTON; and it presents us with a serious problem of interpretation and theory.

IV. How One-Egg Twins differ

The distinction between one-egg and two-egg twins was pointed out by GALTON in 1875. The similarities of one-egg twins were due, not to their common environment before birth, as Darwin had supposed, but to their common heredity, their common origin from a single cell with a single nucleus at fertilisation. It was by no coincidence that in this very year OSCAR HERTWIG pointed out the significance of fertilisation which lay, he said, in the fusion of one male and one female nucleus.

Since this time the degree of divergence in form or behaviour between one-egg twins has been supposed to be a satisfactory measure of the effect of differences in the environment. Galton's distinction has been

taken as axiomatic and its application quite simple and unequivocal. For example, NEWMAN and others write (1937, p. 38):

«It is assumed, of course, that the members of a pair of identical twins are genetically identical».

Similarly RIFE (1952, p. 20) writes of one-egg twins:

«all intra-pair differences must be due to non-genetic factors».

These statements must be intended to mean that the internal character if the two cells, or two groups of cells, from which two one-egg twins develop must always be such that the results, under identical external conditions, will be the same. They are, as German workers put it, «erbgleich».

This assumption can be justified by authority, by axiomatic authority; but it cannot be justified by experimental evidence assisted by the usual processes of inference. Various situations are known in which it is groundless and indeed positively false. The two one-egg twins must differ on genetic grounds; that is to say theymust differ internally at the beginning. Such cases may be arranged fairly neatly in three classes, as follows:

1. *Nuclear Differences.*

Individuals are known who are asymmetrical as a result of genetic changes in the chromosomes. These are probably of two main kinds:

1) gene mutations such as give differences of colour between the two eyes of an individual and

2) chromosome errors at mitosis such as give various mosaic markings and occasional structural asymmetries, either small or large, within individuals.

A third situation in which two sperm fertilise the halves of one egg would also cause asymmetry in one-egg twins whose classification might seem uncertain.

The occurrence of these nuclear causes of discordance is largely overlooked. For example, one-egg twins are said to be always concordant in blood groups are not regarded as one-egg twins.
in blood groups. But it would be more correct for an author to say that twins which are not concordant in blood groups are not regarded as one-egg twins.

2. *Nucleo-cytoplasmic Differences.*

Certain new, unadapted and deleterious genes like those affecting ptosis (RENSSEN, 1942) and perhaps hip articulation and a pleiotropic form of hare-lip (GREBE, 1952) act asymmetrically in development.

Presumably they react asymmetrically with the asymmetrical cytoplasm of the egg. However that may be, such genes are bound to react differently in two one-egg twins: one shows the defect and the other shows it less or not at all. The basis of the difference, although it arises from the action of specific genes, is cytoplasmic.

3. *Cytoplasmic Differences.*

The division of the cleaving egg into two is itself inherently liable to asymmetry. NEWMAN *et al* (1937) thought to have excluded this effect when they found that the 20 out of 50 pairs which showed most mirror imagining of physical structure showed least differences in physical and mental structure. But it is now clear that two kinds of unlikeness arise from the splitting of one embryo into two.

One of these unlikenesses is due to the egg cytoplasm which determines the normal asymmetry of development. It appears as a regular mirror-imaging. We mey call it a primary or *cytoplasmic* asymmetry, related in this case to the whole genotype. The other is less regular. It is probably due to errors or inequalities of splitting or to migrations of cells, errors which we may refer to as due to a secondary or *embryological* asymmetry. It includes gross defects of one partner such as those which lead to its death or in less extreme cases to such abnormalities as the local gigantism or asymmetry of one twin as described by LIEBENAM (1938).

Thus, to use other words, differences between one-egg twins are partly like differences between two sides of an individual. They may be due to a reaction, either of an incorrect gene or genotype with a correct asymmetry of the cytoplasm, or of a correct genotype with an incorrect asymmetry of the cytoplasm (or of the young embryo). Neither of these types of difference arise between two-egg twins and it is for this reason that two-egg twins are more alike in birth weight than one-egg, or so called identical, twins. In every cytoplasmic reaction one-egg twins are bound to be, not more but less alike than two-egg twins. And likewise of course in every defect due to errors of splitting.

Both the cytoplasmic and the embryological errors which arise from splitting will no doubt increase, if we are to judge from experiments in

the artifical splitting of amphibian embryos, when the splitting is delayed. But the various types of monsters which arise from imperfect splitting show that splitting can occur in many ways.

A question of theory, and also of terms, arises at this point. Are the cytoplasmic and embryological discordances between one-egg twins genetically or environmentally determined? Here we are forced to a surprising, paradoxical and, as some may think, shocking conclusion. It is that the one-egg twin situation by its very nature breaks down, to a limited extent, the distinction between heredity and environment and also between heredity and development. The embryological group of discordances are, it seems, neither genetic nor environmental. They represent inherent defects of the twin experiment as a means of distinguishing genotype and environment. They are irrelevant differences, and must therefore if possible be excluded from consideration, in assessing the relative importance of heredity and environment.

The cytoplasmic group, on the other hand, spring from differences between the parts of the egg. It the egg had not split their effects would have been developmental. They are not derived from differences within the parent's body before the egg was formed. And they are not likely to appear as differences between the offspring of the twins in the next generation. In the popular sense, and indeed in the only possible sense, therefore, they are not hereditary. But since the egg has split they have taken genetic effect. The differences between the two twins themselves must be held to be genetically determined.

It is this cytoplasmic and embryological group of differences which, in its milder manifestations, is probably responsible for a part of the discordances between one-egg twins, for example in such important properties as birth weight, temperament and general intelligence. How great a part we do not know. We know merely that there is a genetic component, or an irrelevant component, in the discordance of one-egg twins. The assumption that it is all environmental is incorrect.

Discordances from all three sources no doubt affect only a minority of one-egg twins. But their total effect, I believe, is sufficient to lead to a gross under-estimate, as well as to specific misunderstandings, of the force of genetic determination in all twin studies. It is the extreme of identity which shows us the truest picture.

Summing up. These considerations do not disparage the authority of twin studies as the crucial means of studying genetic determination in man. Quite the reverse : they are indispensible, for example, in the study of health, education and crime. But they open up another field of

enquiry: the assessment of the nuclear and cytoplasmic components of asymmetry or discordance in regard to each of the properties of twins that are studied.

Meanwhile we must admit that the measurement of genetic determination (which is heavily muffled by the popular observation of « heredity » as the resemblance between parent and offspring in a cross-breeding population) is still obscured in the technical study of one-egg twins by the assumption that they are genetically identical.

V. Environment and the Individual

The world outside us offers as many difficulties to the axiomatic approach as the stuff inside us. But they are difficulties of quite a different kind. To begin with the simplest, the standardisation of the environment to which I have already referred. When we speak of the phenotype as the result of a reaction between genotype and environment we are apt to suppose that we can therefore compare genotypes by fixing one environment for experimental purposes. But this is not so. We do not know that two genotypes have the same optimum, or most suitable, environment or the same possible range of environments. In fact no farmer or gardener would make so foolish an assumption.

Now the laboratory conditions for experimental routine are in this respect entirely different as applied to microbes and to the higher organisms. In the higher plants and animals it is impossible for us to explore the vast range of environments that might be devised for any but the most important of domesticated animals or cultivated plants. Only for man himself, using twins, can we take the experiment seriously. But for microbes, on the other hand, the exploration of new environments has proved to be the key to a new world of genetics. The environment as it is revealed by experiment must therefore be translated into terms of real life in entirely different ways for different kinds of organism. This is not a fault of scientific method: it is part of the nature of life with which scientific method can cope if we take the trouble to understand it.

There is one dominating distinction between organisms in the way in which we have to understand the environment. That is the distinction between stationary and mobile organisms. Animals which can move, as C. B. Davenport pointed out in 1903, are able to select their environments. If a population of animals varies genetically, and if the habitat it can move in varies as an environment, different individuals of the population will choose to live in different parts of the habitat and therefore

under different conditions. This capacity of animals puts their variation, adaptation and evolution on a different footing from that of plants. Choice replaces chance. Nature discovers a new way of passing nurture.

The doctrine expounded by LUCRETIUS (IV: 834-5) that nothing comes into existence in the body in order that it may be used, but having come into existence it acquires a use, the doctrine to which Cuénot gave the name of pre-adaptation, applies, to be sure to both plants and animals. In both it governs above all the evolution of genetic systems since they can evolve only by genetic changes in one generation which benefit later generations. The individual's choice therefore can have no effect in this field. But in the evolution of the form and fuction of the individual, on the other hand, (which is the whole of evolution as popularly understood) choice must have a powerful effect. The member of a variable and mobile species which can find its fittest habitat by exercising choice will reduce the wastage of natural selection and enormously hasten adaptive change. New changes will acquire a use more quickly. This principle should be the chief evolutionary difference between animals and plants.

Natural selection and choice of environment of course have a combined effect. The effect is so prompt and so powerful that since ancient times it has favoured a mistaken explanation among men. It has indeed created the illusion that adaptive change in heredity is directly imposed by the environment. The illusion is persuasive insofar as animals are concerned. But in man it is almost overwhelming. Even those who refuse to accept this illusion, in the absence of experimental evidence, find that the enormous diversity of environments in which men (members of the same race and even of the same family) may live, and to which they usually seem so remarkably well-adapted, requires some special kind of assumption. They suppose that in man heredity, although not directly changeable, is so plastic in its expression as to be of very little account except as a basis of agreable amelioration.

Thus genetics is reduced to an absurdity by geneticists! The difficulty however is removed when we admit that men exercise more choice in the selection of environments than any other organisms. And indeed, refusing to rely on a plasticity of which they were unaware, they have gone to infinite trouble in creating new environments to suit their genetically determined needs and desires. The trouble they have taken makes up, indeed, the whole significant record of civilisation.

Summing up: The wonderful mechanism by which sexual recombination imports uncertainty into the relations of parent and offspring has

attracted our attention to heredity and distracted it from genetic determination. When we recognise this distinction and use it in considering the relations of the individual with his environment we see that popular interpretation has turned the whole system upside down attributing causes to effects and *vice versa*. The environment does not determine heredity, or alter or mould heredity, or overwhelm heredity. On the contrary in man heredity to a large extent, although in a very complicated and variable way determines the environment: nature passes nurture.

VI. Conclusion

If geneticists have often misunderstood the reaction of heredity and environment and have underestimated the force of genetic determination, others, social scientists, psychologists and medical workers, are less to be blamed for following their example. Everywhere we look the influence of the environment can be unmistakably assessed. Everywhere we look, too, the influence of genetic determination is concealed by gene recombination. That is except in one-egg twins in man, and even there cytoplasmic errors come in to confuse the simple picture. And the recombination of genes has been adapted throughout evolutionary time to secure a diversity of individuals whose selection shall yield the most effective, and economical, and rapid, evolutionary change.

In a sense, indeed, we may take the process of gene recombination as a prodigious disguise of the permanence of the parts by the changes of the wholes. This deception practised by nature on herself is responsible for the strange opposition between the two streams of genetic thought which, as I said at the beginning, have carried the idea of the whole of heredity and the idea of its separate parts or particles. It is only when we keep both in our mind's eye, and also the third estate of the cytoplasm, that we see what these three have to do with their environment.

The distinctions between heredity, development and infection, as I have pointed out elsewhere, break down in certain circumstances. So also does the distinction between heredity and environment. None of these ideas can be treated as unquestionable or axiomatic. They have to be used dialectically, that is in relation to the changing circumstances of each situation. And when they are used with this rigorous precaution the force of the genetic argument is not weakened, as some have supposed, but strengthened while scientific as well as popular illusions and fallacies are explained.

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DEVELOPMENTAL GENETICS IN THE MOUSE

by

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The field of Physiological Genetics as a whole has, in the past decade, been dominated and overshadowed by the spectacular progress which has been made with the analysis of biochemical mutants in *Neurospora* and other microorganisms. Many investigators have tended to regard the slow-breeding mammals as too unfavourable a material for their attention. Workers have been deterred by the more complex situations encountered on the morphological level which require a much larger expenditure of effort than the simpler biochemical mutants. Criticisms have also been raised against the alleged inadequacy of the «purely descriptive methods» which have to be used in the developmental analysis of mutants in mammalian embryos which, for practical purposes, are inaccessible to the experimental embryologist. As these various sentiments and criticisms have largely gone unanswered, it is perhaps appropriate to deal briefly with these matters here before turning to a review of some of the recent trends in this field.

Biochemical genetics deals with phenomena which are surprisingly uniform throughout the plant and animal kingdoms. The substances which make up the bodies of animals and plants, and their methods of synthesis seem to be largely the same. They clearly trace back to ancestors common to present-day animals and plants which must have lived in the remote pre-Cambrian. Biochemical genetics thus deals largely with the mechanisms of processes which have evolved in the dim «pre-palaeontological» past. While these processes have no doubt been subject to changes in detail in later periods, the fact remains that most of Evolution as known to us through the facts of Palaeontology and Comparative Anatomy is a phenomenon which has taken place on the