An Address

ON

RECENT THEORIES AND EXPERIMENTS ON HEREDITY AND INHERITANCE.*

DELIVERED BEFORE THE DENBIGH AND FLINT DIVISION OF THE BRITISH MEDICAL ASSOCIATION.

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In order to get a clear view of the present aspect of the subject of heredity and inheritance it is desirable to take a review of the principal theories that have been propounded since the beginning of the last century, when Lamarck published his *Philosophie Zoologique* (1809). Up to this time all living things were supposed to have been created in their present condition, and one species was believed to be, genetically, quite distinct from every other species, however closely it might resemble it morphologically and in its relationship to the environment. Though a small oceanic island should possess hundreds of distinct species of beetles, yet they were not related to one another by descent from a common type, but had descended from remote ancestors exactly like themselves, which were specially and separately created, for some inscrutable purpose, for that particular island.

Moreover, the idea was prevalent that animals, whilst still in the germ, were models in miniature of the adult condition, the various parts only requiring expansion and unfolding, a process to which the term "evolution" was applied.

Haller (1708-77), the greatest physiologist of his time, said: "No part of the body is made from another; all are created at once." But the leading apostle of evolution, as then understood, was Charles Bonnet (1720-93), the discoverer of parthenogenesis of *Aphides* (the green fly). Kaspar Friedrich Wolff (1733-94) demonstrated that all the complex organs are formed from simpler structures, and are only developed gradually. To this process he applied the term "epigenesis." He was the true founder of modern embryology.

The first great naturalist who ventured to hint that all the present species have gradually been evolved from ancestral forms of a different type was Buffon. But, however much his own mind was made up on this subject, in his writings he only said that such transformation might have occurred if one were to judge by appearances, and then adds: "But no; it is certain from Revelation that every species was directly created by a separate fiat." "This," a modern writer declares, was "merely as a concession to the Sorbonne, and to the fashionable exegesis of the day." Buffon probably did not like the prospect of spending the remainder of his days in the Bastille, which a too candid expression of his opinion might have involved.

In 1795 Geoffroy St. Hilaire came to the conclusion that all species have descended from a few primitive types. About the same time, and quite independently, Goethe said that all the more perfect organic natures, such as fishes, amphibians, birds, and mammals, with man at their head, were formed at first on one general type. Erasmus Darwin, the grandfather of Charles Darwin, said that animals vary from one another chiefly because they are continually altering their habits and changing their environment.

The most epoch-making speculations, however, were those of Lamarck published in 1809. He propounded two distinct theories: (1) That species are not fixed: those existing at any one time being evolved from earlier, and in most cases less highly organized, forms. This theory has been adopted by practically all subsequent naturalists, for it is apparently the only theory consistent with the facts of morphology, embryology, and palaeontology. (2) His second theory is that this transformation

has arisen as the effect chiefly of use and disuse. Upon this point naturalists are divided into two camps.

The next great landmark was formed by the issue of Charles Darwin's *Origin of Species* in 1859. He laid great stress upon the facts (1) that organisms vary, no two animals or plants being precisely alike, and (2) that they tend to increase to the utmost limits of subsistence. More are born than can come to maturity, and Darwin said there was a "struggle for existence" which resulted in the preservation of those most fitted to the environment, or what Herbert Spencer called "survival of the fittest," the fittest being those with some variation which gave them an advantage in the struggle for life. The inheritance of these beneficial variations, with still further modification in the same direction in the offspring, will account, according to Darwinians, for the origin of species from ancestral forms of a simpler type. And the process may, in imagination, be carried backward until we come to a single speck of living matter. This is the theory of "natural selection," a stimulating and encouraging theory. Afterwards (1868) Darwin supplemented it by his theory of "Pangenesis." Why do offspring bear so close a resemblance to their parents? Put shortly, his idea was that every cell of the body throws off "gemmules," which accumulate in the reproductive germ cells, and, in development, grow into cells like those from which they arose. A much simpler theory was that of "cellular continuity," propounded by Nussbaum in 1884. He drew attention to the early separation, in certain cases, of the reproductive cells from the general body cells. These germ cells remain unchanged, and descend directly from parent to offspring. He could quote some definite facts in support of his theory. Balbiani observed in *Chironomus* that the sex-cells are differentiated even before the blastoderm is complete. The separation of the sex cells has similarly been observed in leeches, polyzoa, certain arthropods, and insects. Generally, however, development is much more advanced before the reproductive cells are separately recognizable, so that one cannot prove cellular continuity in all cases.

In 1885 Weismann, of Freiburg, propounded his celebrated theory, which is to this effect: "In each development a portion of the germinal plasma which the parental ovum contains is not used up in the formation of the offspring, but is reserved unchanged for the formation of the germinal cells of the following generation." This is what is known as the "continuity of the germ plasma." This germ plasma is situated in the chromosomes of the nucleus. The ovum splits up into two portions:

1. A somatic part from which the body cells are formed.
2. A reproductive part which remains inactive, and, later, gives rise to succeeding generations.

We shall see later on that modifications or variations of organisms are heritable according as they are of somatogenic or of germinal origin.

The chromosomes of the nucleus vary in number in different animals, but are constant in the cells of the same animal. The number of chromosomes in the ovum and in the sperm is half that found in a body cell. The union of the sperm with the ovum raises the number to that of the body cells. Weismann thinks the chromosomes are constituted of an immense number of small parts, which he calls "determinants"; hence the character of the offspring depends upon the adjustment arrived at among the determinants of maternal and paternal origin.

Francis Galton and Professor Karl Pearson have studied heredity by the statistical method, whilst experimentally it has been much advanced by Mendel, Bateson, and De Vries, and at the present time there is quite a small army of observers, including several ladies, who are following their lead.

Mendel experimented with the edible pea (*Pisum sativum*) and "what he sought to discover was the law of inheritance in hybrid varieties." These peas are well suited for such observations, because they are habitually self-fertilized. He studied those conspicuous characters which differ in the several varieties, especially—

- The length of stem, whether tall or short.
- The form of the ripe seed, whether round or angular.
- Cotyledon colour, whether yellow or green.
- The flowers, whether coloured or white.

Thus in each case there is one pair of contrasted characters, tallness contrasted to shortness, etc.

* The address has been slightly condensed for publication; readers interested in the subject may be reminded of the address by Mr. Bateson on Mendelian Heredity and its Application to Man, published in the BRITISH MEDICAL JOURNAL, 1906, vol. ii, p. 61.

Pollen from a flower of a round-seeded variety was transferred to the stigma of an angular-seeded variety (the stamens of the latter flower having been removed before they were ripe in order to prevent self-fertilization), and he noted the shape of the ripe seed produced in the hybrid offspring. Other characters were crossed in a similar way.

The result was striking: the hybrids showed only one of any pair of contrasted characters, to the exclusion of the other one, and no intermediate forms were produced.

A tall and dwarf cross produced only tall.

Coloured flowers crossed with white gave only coloured.

A yellow and a green-seeded cross produced only yellow-seeded plants.

Smooth-seeded plants crossed with angular gave only smooth seeds, and so on.

Thus there was always one character in each cross that always appeared exclusively in the offspring, and to this character Mendel applied the term "dominant," whilst that character which did not appear in the offspring he called "recessive."

Tallness is therefore dominant to dwarfness.

Colour is dominant to absence of colour.

Yellow albumen is dominant to green.

Smooth seeds are dominant to wrinkled.

These hybrids were then allowed to become self-fertilized, and it was found that the characters of both the original parents appeared in the offspring of the hybrids, the tall hybrids resulting from the cross between tall and dwarf plants produced both tall and dwarfs, but there were always 75 per cent. of tall and only 25 per cent. of dwarfs. This proportion of 3 dominants to 1 recessive holds good whatever pair of contrasted characters is experimented with, as shown in the following diagram, where D=dominant and R=recessive.

The recessive character must have been present in the hybrid; so that the hybrid may be represented by D [R]—that is, the recessive character, though present, is latent and unrecognizable; so we must amend the diagram thus:

Mendel assumed that there are two kinds of germ cells produced by such hybrids as he was experimenting with—that is, in D [R]'s one cell possesses the dominant character of the dominant parent, another the recessive character of the other parent; in other words, the dominant and the recessive properties of the parents accumulate or "segregate" in the hybrids in one or other germ cell or "gamete." No gamete can carry both dominant and recessive characters.

Another essential part of Mendel's theory is that a hybrid possesses these two kinds of gametes in equal numbers—if there are four ovules, two of them will be dominant and two recessive. The same will be true of the pollen grains or sperm cells, as illustrated in the following diagram, in which the black circles represent the dominant and the white the recessive gametes:

There is a marked difference between the first hybrids and their parents. The gametes of each parent are of one kind only; and as those of one parent are dominant, it follows that all the offspring of the first generation must possess the dominant features. The hybrids produce two kinds of gametes; one half bear the dominant properties of the dominant parent, the other half bear those of the recessive parent, and consequently their offspring are not of one kind only.

Let us suppose that a hybrid produces four female gametes (ovules) and four male gametes (pollen grains). What is likely to happen is shown in the following diagram, in which the ovules are shown on the left and the pollen grains on the right:

A dominant sperm cell will unite with a dominant ovule (a). Of the remaining three ovules, two are recessive, and one of these is almost certain to be fertilized by the remaining dominant sperm (b). Then a recessive sperm must fertilize the remaining dominant ovule (c). Now in each of these three cases there is a dominant gamete taking part, and the result will be three "zygotes" or organisms showing the dominant character, for the dominant character comes to the top even when united with the recessive. The fourth zygote will be a pure recessive (d), as both gametes are recessive; a and d will both be pure; one (a) a pure dominant, the other (d) a pure recessive. Such are termed "homozygotes." The other two are called "heterozygotes," because they contain both the dominant and the recessive characters, and, although to the eye they appear like pure dominants, they are not so in reality. We must therefore amend the second diagram as we had to amend the first.

The DD means that the zygote is formed of two dominant gametes, and is therefore pure or homozygous. Similarly the RR is a pure recessive formed of two recessive gametes. Each D [R] is an "impure dominant," or heterozygous organism. The hybrid thus produces not three dominants to one recessive, but one pure dominant, two impure dominants, and one pure recessive.

When breeding is further continued it is found that the dominant DD breeds true to the dominant character; the recessive RR breeds true to the recessive character; and the impure dominants D [R] always produce the same kind of offspring that their parents, the first hybrids, produced—namely, 1 pure dominant, 2 impure dominants, and 1 recessive.

In some instances the hybrid differs very considerably from either parent. An exceedingly interesting example of this fact has been worked out by Mr. Punnett. He says:

Breeders have long recognized the difficulty of obtaining a pure strain of the blue Andalusian fowl. No matter how carefully the blues are selected they always throw "wasters" of two sorts, some pure black and others of a peculiar white with black splashes. Careful breeding shows that, on the average, one half of the offspring from a pen of blue Andalusians come blue, one-quarter black, and one-quarter white. These proportions at once suggest that the blues are heterozygotes. . . . If this is so, it follows that the blacks and splashed whites are homozygotes, and consequently ought to breed true. Experiment has shown that such is actually the case. Further, we should be led to expect heterozygous offspring from a union of the two different homozygotes. Here again the experimental result accords with theory; when a black and white are bred together all the offspring, without exception, are blue. . . . The black and the splashed white are the pure breeds; the "pure" blue Andalusian is, and from its nature ever must be, a mongrel. . . . The black and white are two contrasted characters, and the essential feature of gametic purity could not be shown more clearly.

We may now summarize the laws that appear to me to be established so far as regards a single pair of contrasted characters:

$$\begin{aligned} D \times D &= D \\ R \times R &= R \\ D \times R &= D[R] \\ D[R] \times R &= D[R] + R \\ D[R] \times D &= D[R] + D \\ D[R] \times D[R] &= D + 2D[R] + R \end{aligned}$$

These laws have been confirmed by numerous observers—for example, by Correns on peas, maize, etc.; Tschermak on peas; Lang on snails; De Vries on about fifteen species of plants; Bateson on several plants and poultry; Darbishire on mice; Hurst on rabbits; Mudge on rats; Toyama on silk moths; and by Davenport on poultry.

Professor J. Arthur Thomson, in his work, *Heredity* (p. 366), says: "There is as yet no secure evidence of Mendelian phenomena in man, but there has not been time for much investigation." Those who have read my *Account of a Brachydactylous Family* will have observed how strikingly Mendelian laws are there illustrated. I have shown that the normal members are pure recessives, and do not transmit the abnormality, and that the abnormal, being heterozygotes, transmit the peculiarity to 53 per cent. of their offspring, a result which is sufficiently near the theoretical 50 per cent.; for it must be remembered that 50 per cent. is the ideal proportion, but the actual number often exceeds or falls short of it by a small amount.

Thomson's statement, therefore, is no longer true, and, indeed, Mr. Punnett, in a lecture delivered before the Royal Society of Medicine last March, says that the case of brachydactyly "is the most conspicuous example of Mendelian heredity in man." Quite recently Mr. Nettleship has published an account of a family in which congenital sight-blindness has been hereditary through at least ten generations. This family belongs to the neighbourhood of Montpellier, and the disease has been traced back to a man named Jean Nougaret, born in 1637. Nettleship's chart is by far the largest of the kind yet compiled, and embraces 2,121 individuals. The disease has been transmitted solely by the affected individuals. The disease-bearing branches contain 255 members, of whom 53 per cent. were night-blind; so that here again is another example of Mendelism in the human subject.

From the members of my brachydactylous family it would be quite easy, by selection, to produce a short-fingered race, thus:

$$D[R] \times D[R]$$

two affected individuals intermarrying would produce the following offspring:

$$1 D + 2 D[R] + 1 R.$$

The D would be a pure dominant for the brachydactylous character, and if married to another pure dominant would have children all of whom would show the abnormality. It is equally clear that the normal type of individual would be produced by the recessives.

Thus far I have only referred to Mendel's study of a single pair of contrasted characters, but he also observed the result where two pairs of contrasted characters were present in the plants that were crossed. This is called "dihybridism." For instance, he studied height and colour in the same offspring by crossing a tall coloured pea with a dwarf white one, and found that each character acted independently, irrespective of the sex of the plant chosen for any particular character, for tallness and colour are always dominant to dwarfness and absence of colour. He found the first result of the cross to consist entirely of tall coloured plants, that is, the two dominant characters appear, and in the next generation there were three coloured to one white and three tall to one dwarf, and whatever pairs of contrasted characters are experimented with the same proportional numbers are obtained. It is quite clear that Mendel's theory is a good working hypothesis, and by it and it alone are we able to predict, almost with certainty, the kind of offspring which will result from particular crosses.

There are several diseases and peculiarities which seem to be inherited on Mendelian lines; but I can do no more

here than enumerate those which have been chiefly studied in this respect.

Dr. Gossage, in the *Quarterly Journal of Medicine* for April, gives the following instances: Tylosis palmaris, curly hair, congenital lock of white hair, and diabetes insipidus. Nettleship and Berry include congenital cataract.

We must, however, acknowledge that Mendelian laws seem to be inapplicable in certain cases of inherited disease and abnormalities; but if segregation of characters in the gametes is a fact in those cases to which I have already referred, it probably is of universal occurrence, though capable under certain unknown conditions of becoming latent. Mendelian laws, like other natural laws, may be interfered with or disguised in some cases, as in haemophilia, where the males alone as a rule are affected, and yet the fact that unaffected females can transmit the disease to their male children shows that the ova are abnormal, though the body cells escape. Professor J. B. Wood has pointed out a precisely similar phenomenon in the case of crosses between certain breeds of horned and hornless sheep, the male offspring of which are horned, whilst the females as a rule are hornless, though horns were present in the female parent.

Lamarck a hundred years ago combated the idea of the fixity of species. The change of type, Lamarck said, is due to the effects of use and disuse, and the inheritance of parental modifications produced by these means. If the giraffe were evolved gradually in this manner, it follows of necessity that its acquired modifications must have been inherited; in other words, the modification was of somatic and not of germinal origin. On the other hand, the giraffe may have arisen as a "sport" or sudden mutation from some form whose neck and forelegs were of more ordinary proportions. In this case it must have been due to some peculiarity of one or other of the germ cells from which it developed—that is, its origin was germinal.

There are thus two conceivable ways by which modifications in the type of an organism—a new species—may arise, and Weismann names them

1. Blastogenic or germinal—that is, from the germ cells,
2. Somatogenic—that is, from the body cells,

and for some time naturalists have been divided into two camps, according as they regard one or other of these methods as the means by which new species have arisen. The germ or reproductive cells are formed at a very early stage of development. Any variation starting after these cells have been differentiated are obviously not of germinal origin.

Buffon and Lamarck were the founders of the school which believes in the inheritance of acquired characters, and they have been followed by Charles Darwin, Herbert Spencer, Brown-Séquard, Romanes, and Francis Darwin. The leader and founder of the opposite school is Professor Weismann, and he is supported by Francis Galton, De Vries, T. H. Morgan, Bateson, etc. All these latter authorities maintain that acquired characters, however produced, are *not* heritable, and that only those mutations are heritable which arise as a result of some modification of the germ cell.

From a careful and prolonged study of both sides of the question, it appears to me that the subject is not absolutely settled one way or the other, but there can be little doubt that the most definite facts and precise experimental investigation favour the views of Weismann. How conspicuous has been the failure to produce a short-tailed race of fox terriers by docking the tail generation after generation, or to produce children who inherit the peculiar feet of the Chinese lady! But let a man be born with a peculiarity of germinal origin, such as cataract, brachydactyly, or night-blindness, and about 50 per cent. of his children will show the same defect. Mendel's work is absolutely in favour of Weismannism. Moreover, there are instances on record of the sudden appearance of new species, which still remain, and breed true to their peculiar type, such as

The niata cattle, which first appeared in South America between the sixteenth and eighteenth centuries.

The ancon sheep, which appeared in 1791 (in Massachusetts).

The mauchamp sheep, from a single lamb born in 1828 from merino parents.

Turnspit and pug dogs, short-faced tumbler pigeons, hook-billed ducks, tailless and hornless animals.

These all appeared suddenly, practically in the state we now see them.

If Weismann's theory be true, we shall have to modify our opinions of the rate at which evolution of species has occurred. Darwin taught that animals and plants have a tendency to vary from the parental type, and that by natural selection the advantageous varieties are preserved and those less fitted for the environment are destroyed, and that new species have resulted from the gradual and slow accumulation of minute variations. They have evolved, as it were, on an inclined plane by a sort of continuous process.

A more recent theory, associated especially with the name of De Vries, is that variation has not been continuous, but discontinuous, not along an inclined plane, but by steps, that new forms, completely and sharply separated from the parent species, have frequently if not generally come into existence. "The new species is all at once there" without transitional forms. This is known as "the mutation theory."

According to De Vries there are two kinds of variation:

1. "Fluctuating variation," such as we are familiar with in all animals and plants. These cannot overstep the bounds of the species, and cannot therefore give rise to new species or any new constant character, for they are always indefinite.

2. "Mutation" is a perfectly definite change, which may or may not be as marked as a fluctuating variation, but it is constant, and tends to be repeated in succeeding generations. It produces new species, and is of germinal origin.

The product of fluctuating variations, being of somatic origin, can only be kept at the highest point of development by the most rigid care. If selection ceases for only a few generations, the new form sinks back to the original level, as is well exemplified in the various breeds of pigeons.

According to Darwin's selection theory, only useful characters can survive; according to the mutation theory, useless characters may do so also, and even those that may be hurtful in a small degree, and surely this is in accord with well-known facts.

There are several stumbling-blocks in the way of the theory of natural selection acting on variation as the sole means by which species have originated. I need only mention degeneration and parasitism, dimorphism and trimorphism in plants, exact bilateral and radial symmetry, and especially the extreme perfection of development in certain directions, for instance the hand of man, the development of his vocal organs, his mathematical and philosophical abilities, and keen sense of colour, which seem to go beyond the limit required for the perpetuation of the race or the individual, whereas they are not at all inconsistent with the theory of advance by "mutation." De Vries has proved conclusively that mutations, or "sports" not infrequently occur amongst plants, and give rise to true breeding varieties. If Mendel's law applies to such cases, they are not likely to be swamped by intercrossing with the normal type.

Thus we get a new view of evolution: "Natural selection may explain the survival of the fittest, but it cannot explain the arrival of the fittest" (De Vries).

I submit that the various facts that I have mentioned point out with unmistakable clearness the only way by which hereditary disease can be eliminated. We hear nowadays a great deal about physical deterioration, and a great deal of benefit is expected from education and from improved sanitary conditions; but neither education nor sanitary laws can eradicate hereditary disease except by preventing the marriage of the affected individuals. Just as a purely brachydactylous race might be produced, so it would be equally easy to eradicate this abnormality by preventing the marriage of the abnormal individuals, and there is little doubt that other hereditary defects and diseases can be practically made to disappear by the same means. Unfortunately, modern legislation tends to produce the opposite effect, for everything is done to encourage not only the marriage, but the early marriage, of inferior members of the community, at the same time that the burdens of taxation retard more and more the marriage of the middle classes. Free education, free meals, free clothing, are all very well for a certain class, but they are not remedies, and the net result to this nation will in the long run be detrimental.

HEREDITY

IN

DISEASES OF THE NERVOUS SYSTEM.

INTRODUCTION TO A DISCUSSION ON HEREDITY AT THE ROYAL SOCIETY OF MEDICINE.

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MR. PRESIDENT AND GENTLEMEN.—The scientific study of heredity, which has undergone so wonderful a development since the mists were swept away which for long had hidden Mendel's work, cannot be applied to the diseases of man. The human race is not open to Mendel's essential methods, and its mere complexity of development involves innumerable differences from lower forms of life, the effects of which may be greater than we can well realize. Potential fallacies surround almost every inference that can be drawn. We can seldom look back far at preceding generations, and the future we must leave to those who may follow us. The difficulties of precision and fullness of knowledge are great, and the chance fertilization, from which the flowers of Mendel were guarded by his paper bags, is the rule in the human race, unalterable by us, however we may wish. Hence it seems useless even to apply the hereditary terminology to facts that are in general inconsistent with its grounds. I can only hope to present a few of the more salient facts of heredity in diseases of the nervous system, well known as they are, and I trust that they will be supplemented by others. We are only in the stage of random observation.

Among diseases of the nervous system are commonly included many that are not of it but merely in it, and this can scarcely be justified. Tumours of the brain and spinal cord are allied to morbid growths in general, for the most part. Yet many of them have a special relation to nervous tissue, such as gliomata, composed of the special interstitial elements of the nerve centres. Endotheliomata, growing from the lining tissue of the cavities and surface of the brain and spinal cord, we do not know how to class, whether with the centres in which they are found or with growths of the same character elsewhere. But all such affections are so rare that they have not yet justified any suggestion of heredity. This is also true of another condition in which heredity might reasonably be expected—the defect in the coarser formation of the spinal cord which leads to the cavities, and undeveloped embryonic tissue adjacent, of syringomyelia. It is often found after death when there have been no symptoms to suggest it. When the causal arrest of development has occurred earlier and involved the enclosing structures, it constitutes a state often conspicuous in infancy—*spina bifida*. Heredity in these affections may be thought likely, but no ground for it has been, I think, discerned, and may not be until every member of the family can be scrutinized after death. Insular sclerosis is another affection in which heredity might be expected, according to one view of its nature, but no facts have suggested it.

Sudden cerebral seizures—apoplexy and the like—depend upon causes that take their heredity far away from the brain in which the lesion occurs. Yet the frequency in which heredity is active is most notable. In some families many members suffer earlier in life than the malady is really common. But we must look to the vessels, and the cause of their degeneration, for the mechanism by which the disease is produced and through which heredity acts.

Toxic states, various in nature and origin, chemical and microbial, are potent causes of disease, but the range of heredity in their occurrence is small. The so-called "inherited syphilis" has, of course, nothing to do with heredity. I do not know of any observations on the children of those who suffer from "inherited syphilis," and their life histories. The question is important, and possibly some Fellows may be able to furnish facts. Any influence heredity may have on the liability to suffer from bacterial maladies affecting the nervous system may perhaps be suggested by the discussion on the similar facts regarding tubercle. The part it may play in the secondary production of chemical agents through an