SOME MODERN VIEWS CONCERNING HEREDITY AND VARIATION.¹

By BREVET-COLONEL R. H. FIRTH.

Royal Army Medical Corps.

In attempting to discuss this subject before you I ask your indulgence for any crudities which my remarks may present. The extreme interest and importance attaching to the problem of heredity and variation of species is the sole excuse I have to offer for discussing the subject at all. Speaking for myself, I may say that from my early student-days the subject has been of absorbing interest, and, as one has grown older and more experienced, the mysteries associated with the problem of the origin of life and the reproduction of somatic units from single germ-cells have lost none of their fascination for me. Doubtless, to more than one here present the same is equally true.

At the outset, let me ask you, what do we mean by inheritance and variation? Limiting ourselves to the conception of organisms only whose offspring develop by processes of growth from a minute fragment detached from the parent organism, we mean by inheritance, the manner by which the nature and characteristics of an organism are handed on to its offspring. On the other hand, variation means the manner or circumstances by which members of the same species differ from each other. Of course, some of the differences may arrive late in life and be the result of education or environment, but the mere fact that offspring may differ at the outset from their parents suggests the possibility, in the course of generations for progressive changes to take place, so that from the offspring of members of the same species entirely new species may arise. It is obvious that we are here face to face with the larger question of organic evolution. It is not my intention to take you into this thorny field of debate, but merely remind you that it has been generally accepted that the various forms of life, with which we are familiar, owe in great measure their present characteristics to the accumulation of a series of changes similar to those which are still in progress. This theory of evolution, as opposed to an hypothesis of creation, is supported by numberless facts familiar to you all, and finds expression in the teaching of Wallace, Darwin,

¹ Being an address given before the Aldershot Military Medical Society, on November 15th, 1909.
Modern Views concerning Heredity and Variation

and Weismann, wherein it is assumed that in the course of generations a steady or continuous change in the characters of a species takes place and follows the direction of best adaptation to new conditions.

This conception admirably covers the case of individual variations which affect every character, or what are termed normal or continuous variations; but it fails to explain satisfactorily abnormal, definite, and discontinuous variations and perpetuation of types arising from them. The view that the evolution of a new species could occur by the help of a mutation or variation of the discontinuous kind dates back to the time of Aristotle, and in recent years has been supported by the work of de Vries, Bateson, and others who maintain that by a single step new forms can arise which have already the definite characters associated with a species adapted specially to particular conditions. From these new forms those best fitted for their environment will survive, while those which are less fitted will disappear by the action of natural selection. While the origin of a new organ is inexplicable by the Wallace-Darwin theory, the explanation of its inception by a mutation theory offers few difficulties, especially as changes of a closely similar nature have been observed actually to take place.

Having, so far, reminded you of the main principles or theories of evolution which are affected by our ideas of heredity and variation, I would next ask your attention to more recent work on these subjects, so that we may see on what lines it has proceeded and how far it has succeeded in making the problem of heredity and variation clearer. To appreciate the drift of this newer work we must bear in mind that the organism is a complex unit, into whose make-up there are concerned somatic plasm and germ plasm, both of these tissues being intimately associated the one with the other. Our conception of the nature of inheritance must clearly be guided or affected by how far we admit the influence of the somatic cells on germinal matter or the effect of germinal plasm on somatic plasm. I question whether any of you seriously entertain the possibility of the former idea or doubt the isolation of the germ cells from the somatic influences. This latter view is the fundamental theme of Weismann's theory, in which he regards the germ plasm as continuous from one generation to another, but endowed with a potentiality for variation, within certain limits, which can be called forth by a suitable environment. In dividing cells, the chromasomes contain the germ plasm of the species, and are identical in male and female reproduction cells, and so
long as their number is complete or sufficient to enable conjugation to take place it is immaterial from which parent they may come.¹ According to Weismann's theory the chromosomes are idants and built up of ids; these again are made up of determinants, which again are composed of biorphors or ultimate units or ultimate molecules of inherited plasm.² As development advances, the ids are disintegrated into determinants and the determinants into biorphors, each group getting smaller and smaller until every biophor ultimately reaches and controls its own cell. To apply Sedgwick's analogy, this conception may be compared to the splitting up of a battalion into half battalions, then into companies, and these, again, into pickets or individual soldiers.

In its main features, this theory of Weismann's has been universally accepted, but it involves the assumption that all ancestors of the same degree, such as grandparents, make a substantially equal contribution to the hereditary qualities of the offspring. This aspect of the question has been much developed by Karl Pearson and other biometricians,³ who, working purely from the mathematical point of view, have evolved a main generalization known as the law of ancestral inheritance. This law states that the average degree of resemblance between an individual and any particular ancestor is capable of definite numerical expression as co-efficients of correlation. Thus, the mean correlation between the two parents and the offspring, the four grandparents and the offspring, the eight great-grandparents and the offspring and so on are stated to diminish in a geometrical series, which is the same for all characters. The actual amounts of these correlations are calculated by Pearson in the form of the diminishing series 0·6244, 0·1988, 0·0630, &c. He further calculates that, if ancestors be selected in each generation showing a definite deviation from the general mean of the population, after one generation of selection the immediate offspring will show 0·62 of the character selected; after two generations they will show 0·82, after three 0·89, and after a great number of generations 0·92 of the hereditable character.⁴ So that in a few generations the development of a character may be raised to within 90 per cent. of the value selected

¹ Boveri, "Ergebnisse ueben die Konstitution der chromatischen Substanz des Zellkerns," 1904.
³ Galton, "Natural Inheritance," 1889.
but, after this, further selection has little effect. He also calculates that in-breeding of a selected stock is followed by a very gradual return towards the mean character of the original race. It is difficult to say how much reliance can be placed on these theoretical conclusions, as they assume the existence of perfect normal variation, and that the contribution of each ancestor of the same degree to the hereditary endowment of the offspring has been exactly equal. Since both these assumptions are unlikely to be realized in an actual case, it would be wiser to regard the statement as an approximate indication only of what is likely to occur.\footnote{Lock, “Recent Progress in the Study of Heredity and Variation,” 1909, p. 116.}

Whatever may be the precise value to be placed on the work of the biometric school, it suggests the interesting conclusion that, on the basis of a normal continuous variation, selection, as productive of new types, is a diminishing influence. If this be so, how do new varieties arise? Is it possible that Nature makes jumps sometimes and so creates new species? Huxley\footnote{Huxley, “Collected Essays,” vol. ii., p. 77.} writes, “That Nature does make jumps now and then, and a recognition of the fact is of no small importance in disposing of many minor objections to the doctrine of transmutation.” It is in this connection that the work of de Vries and Mendel is so interesting. The former,\footnote{de Vries, “Species and Varieties, their Origin by Mutation,” 1905.} experimenting with \textit{Cenothera lamarckiana}, showed that out of some 50,000 individuals which were grown to a recognisable stage, more than 800 showed mutations, that is to say, they differed specifically from the parent \textit{O. lamarckiana}. When they had once made their appearance, the majority of the new types came true to seed. Time and space do not permit of a full analysis of de Vries’ work, but he formulates the following main conclusions: that new species arise suddenly at a single step, without transitional forms; that the mutations take place indefinitely; that the tendency to mutate recurs periodically. While we cannot accept the whole of de Vries’ theory that all natural species arise in this sudden fashion, there can be little doubt as to the accuracy of his facts, especially as there is confirmative evidence from the experiments of MacDougal.\footnote{MacDougal, various papers published in \textit{Transactions of the Carnegie Institution}, Washington.} In any case, we must admit his experiments go far to support the view “that the origin of species in Nature is a definite process and takes place by steps of considerable amplitude.”
With regard to the causes of mutations, little is known other than that nutrition and environment play the greater parts. Of kinds of mutation we can conceive a *progressive* mutation, as when an entirely new character, or set of characters, may make its appearance; this new character may be hidden, or latent, and only make its visible appearance after several generations. de Vries speaks of *degressive* mutation when characters are only partially latent and exhibit themselves suddenly in rare individuals in the form of sports or abnormalities. The reverse may occur, as when a character previously active may become latent; in this case the mutation is said to be *retrogressive*. Again, the mutation may be *atavistic*, or throw back to a previous ancestor; this would be a case of ancestral character which had become latent, showing itself once more in an active condition.

Certain obscure points connected with the preceding theory of mutations may appear clearer if we now consider the cognate work of the Abbot Mendel. Originally published in 1866, the works of Gregor Johann Mendel were lost sight of until 1899; since which date their importance has been fully appreciated.\(^1\) The essence of Mendel's discoveries and deductions may be explained by saying that every plant or animal may be regarded as a double structure, having received a series of elements from its male and a series of elements from its female parent. According to Mendel, when dissimilar elements meet in one individual there is, on the formation of the germ-cells, a separation or *segregation* of the two characters which came in. That is to say, the germinal representations of such pairs of characters remain perfectly distinct in the hybrid plant, and separate out at the formation of its gametes in such a way that an equal number of gametes arise containing either character. The members of a pair of characters which behave in this way on crossing are called *allelomorphs*. Further, it may be convenient to explain other terms in common use; the fusion of a pair of gametes during fertilization produces a cell called a *zygote*; if the two gametes are alike the zygote is termed a *homozygote*, while, when the gamete contains opposite members of a pair of allelomorphs the result is called a *heterozygote*. Therefore in respect of any pair of allelomorphic characters, the individuals are of three kinds only. Assume that the gametes are of two kinds \(A\) and \(a\); then the *homozygotes* will be of the forms either \(AA\) or \(aa\), and the *heterozygotes* of the

---

\(^1\) Bateson, Mendel's "Principles of Heredity," 1909. This is a most fascinating book and full of detail concerning this subject.
form \( Aa \). We are now in a position to state the proposition, known as Mendel's law: "The gametes of a heterozygote bear the pure parental allelomorphs completely separated from one another, and the numerical distribution of the separate allelomorphs in the gametes is such that all possible combinations of them are present in approximately equal numbers."

The manner in which characters are actually transmitted has been worked out in the case of many races of animals and plants, and in cases where experimental matings can be carried out and a number of offspring reared it is found that the above rule or law applies and holds good.

It is usual to speak of the respective characters as being either dominant or recessive, that is, potent or non-potent in respective individuals. Assuming we have a tall man and a tall woman, themselves hybrids or offspring of matings between tall and short individuals, then, in combinations of their male and female germ-cells, it is obvious there will be matings of long male with long female, and short male with short female, while in other cases short female will mate with long male or short male with long female germ-cells. On random selection the result would be that three of the offspring will be tall and one short; this latter reappearing because it contains none of the tall element. Of the tall offspring some will have two doses of the tall factor, others will be cross-bred, having only one dose of it. In this hypothetical case the dominant character will have been tallness, and shortness recessive.

\[
\begin{align*}
\text{(Dominant character)} & \quad S. \times W. \quad \text{(recessive character)} \\
S.W. & \quad \text{(heterozygote looking like } S.) \\
\text{on self-fertilisation this yields} & \\
S.S. & \quad S.W. \quad W.S. \quad W.W. \quad \text{(extracted recessive)} \\
\text{(extracted dominant)} & \\
S.S. & \quad S.S. \quad S.W. \quad W.S. \quad W.W. \quad W.W. \quad \text{and so on, breeding true.} \\
S.S. & \quad S.W. \quad W.W. \quad \text{and so on, breeding true.}
\end{align*}
\]
The following case, given by Lock, may make the subject more clear. In Indian corn there are two common varieties, one with smooth starchy grains and one with wrinkled sugary grains. On crossing these two varieties the grains immediately resulting are smooth and starchy, no matter whether the starch strain is used as the seed-parent or as the pollen-parent. This means that the starchy character is dominant, appearing to the almost complete exclusion in the next generation of the corresponding recessive or sugary character. The further behaviour of this cross is shown in the preceding scheme, where S signifies smooth grain and W indicates wrinkled or sugary. In an actual example 5,310 smooth grains were obtained and 1,764 wrinkled, or roughly, 75 to 25, that is, 3 to 1.

It will be apparent, from the above short account, that the Mendelian theory differs from Weismann's and the biometric school's conception of heredity in so far that it does not admit the assumption that all ancestors of the same degree make a substantially equal contribution to the hereditary qualities of the offspring. Its essential doctrine is that the cells of the offspring are of double origin, and in them traits and characters derived from both the father and mother can co-exist side by side. Mendel's experiments and others of the same kind show that although every essential character is represented in each germ-cell, yet each Mendelian character is represented by a maternal or paternal determinant only, and not by both. In this way all immediate ancestors are not represented in the germ-cells in respect of any particular character, but only one of the parents is so represented and apparently to the complete exclusion of the other parent. The Mendelian theory is thus considerably simpler than the germ-plasm theory of Weismann, but at the same time its conceptions are strikingly concordant with the results of recent work in cytology. This will be apparent from the following considerations.

In the process of fertilisation, the two conjugating germ-cells as well as the nuclei which they contain become fused together to form a single cell with one nucleus. The separate chromosomes contained in the conjugating nuclei do not fuse, but the paternal and maternal chromosomes remain separate, so that the nucleus of the zygote or new cell contains twice as many chromosomes as does either of the gametes by whose fusion it arose. This indicates that the chromosomes derived from the two parent cells are present in the nuclei of the offspring cell, and reproduce themselves by bi-partition at each nuclear division. In this way each
somatic cell nucleus of the resulting zygotes contains a double set of chromosomes, half being descended from one parent and half from the other parent. Since the gametes contain only half as many chromosomes as the somatic cells, it follows that during the formation of gametes there must occur a reduction in the number of chromosomes to one-half their former number. In the higher animals we know this does occur during the two cell-divisions which lead directly to the formation of the gametes.

If we consider the case of a cross between parents which differ in respect of two pairs of allelomorphs, and express these pairs as A-a and B-b, then the germ-cells of the heterozygote bear in equal numbers the combinations AB, Ab, aB, and ab, in which the symbols A and a are the particles representing the allelomorphs of one pair, and B and b those of the other. Assuming that one parent shows the characters A and b, and the other one those of a and B, we can plan the accompanying scheme (fig. 1), which
shows the direct line of development and division of the allelo-
morphs at each somatic mitosis. When the formation of germ-cells 
occurs, the members of each pair of allelomorphs must become 
separated from each other in such a way that the particles 
originally derived from parents pass over into different cells. This 
can occur in either of the two ways shown in fig. 2. Experiments 
have shown that this occurs with equal frequency. The actual 
vehicles of Mendelian characters are probably not the chromosomes 
but the minute chromatin granules or chromameres which constitute 
the ultimate structure of the chromosomes. We are indebted to 
de Vries for this conception, who suggests that when the chroma-

![Diagram](https://example.com/diagram.png)

Fig. 2. (After Lock.)

somes fuse together an exchange of allelomorphs takes place 
between the chromasomes. It follows from this that, in a sufficient 
number of cases, there follow all possible chance distributions of 
allelomorphs between the two chromosomes, except that two 
members of the same pair of allelomorphs would never coexist in 
the same chromosome. Since the two chromosomes of a pair pass 
into different germ-cells, that chance distribution is attained which 
the Mendelian theory requires. One cannot within the limits of 
this address discuss all the side issues or the more complicated 
cases which occur; for these reference must be made to the 
standard literature on this subject, but sufficient has been adduced 
to show that the Mendelian theory is concordant with recent 
cytology and throws some light on the minuter features of cell 
structure.

1Lock, op. cit., p. 285.
The application of the Mendelian theory of heredity has been made to a considerable number of diseased or abnormal states in man. Its simplest application is in the elucidation of eye-colour descent. The colour of eyes may vary from the very dark to the light or blue. The distinction turns on whether there is pigment or not on the front of the iris. The ordinary blue eye has no front pigment, while in the brown or dark eye there is pigment in front. The presence of pigment is a dominant factor, it may be much or little; and when it is present it may be transmitted, but when there is none in the parent's eyes the children have none of it. It follows, therefore, from the Mendelian standpoint, that blue eyes, once they separated out, should breed true; also that the recessive blue character mated to the blue breeds true. So, too, in the dark-eyed type, when a dark-eyed person with the blue factor recessive mates with a blue-eyed person, there will be an equal number of dark- and blue-eyed offspring. If a pure dark-eyed person, that is, one without any recessive blue-eye factor in him, mates with a blue-eyed partner, then all the offspring may be expected to be dark-eyed. If we take two dark-eyed parents, the dark element being dominant, three kinds of mating are possible—thus D.D. with D.D., D.D. with

![Diagram](http://militaryhealth.bmj.com/)

**Fig. 3.**

• Signifies Fair European.
• Signifies Black Eurasian
• " Dark European.
• " Chocolate Eurasian
• " Wheat Eurasian
D.B., and D.B. with D.B. In these cases D. is the dominant dark-eyed and B. is the recessive blue-eyed character. So far as visible characters are concerned two results in the offspring are possible; either all the children will be dark-eyed, or some will be dark-eyed and some blue-eyed, the former in the greater number, probably in ratio of 3 to 1.

As bearing upon this question of inherited pigmented features, I call your attention to the accompanying family tree (fig. 3). It represents the results of crossing between the European and native, and was personally investigated by me in India some years ago before I had any idea of Mendel’s work. It commences with the marriage of a fair-haired and blue-eyed Yorkshire man with a pure-blooded Punjabi woman. The two children were Eurasians. The son married a native woman and the offspring were all of the native type, except one who is on the dark side. The daughter married a dark European with light or fair character recessive. The offspring of this union are strikingly concordant with Mendelian principles, for of the seven children two are of the typical fair type. I do not attach any great importance to this particular pedigree, as it is like many others which have been traced, but I introduce it here as suitably illustrative of Mendel’s doctrine of segregation and gametic purity. At the same time I am bound to say that the value of observations of this kind has been seriously challenged, notably by Karl Pearson and those who would judge facts of this nature from a purely statistical standpoint. To my own mind the most serious objection lies in the unavoidable dependence upon personal opinion as to colour or shades of pigmentation in the individuals under review.

One has not time to refer to other pedigrees bearing upon such diverse characters as congenital asthma, keratosis, coat-colour in horses, ptosis, coloboma, squint, brachydactylyism, &c. You will find many of them in the literature on this subject. For most of them the rule holds good that transmission is through the affected person, that is, they follow the Mendelian dominant, individuals not possessing the special factors being unable to transmit them. Conversely, you can get pedigrees showing the influence of a recessive character—albinism, for instance, and alkaptonuria. Difficulties are presented by sex-limited heredities, such as colour-blindness, haemophilia, and pseudo-hypertrophic paralysis, but the difficulties are probably more apparent than real when looked at from the Mendelian standpoint. Take the case of horned and hornless sheep. If a cross be made between...
the Dorset Horned, which have horns in both sexes, and the Suffolks, which are without horns in either rams or ewes, the first generation of male lambs have horns, but the ewes have not. Here this horned character may be said to be dominant in males, but recessive in females. The second generation bred from the first shows four types, horned and hornless males with horned and hornless females. If the generations be carried further the horned ewes of the second generation are found to be pure for horns, and the hornless rams of the same generation are pure for the absence of horns. From this it is apparent that for the female to be horned she must be homozygous in that character; in other words, the factor for hornedness must come in from both parents. Conversely, for the male to be hornless, he must receive the deficiency from both sides of his parentage. As Bateson\(^1\) puts it, this matter of certain characters following certain sexes would appear to be merely a question of dosage.

The facts are similar in the case of man. Thus, in colour-blindness the female appears not to be colour-blind unless she receives two doses of the colour-blind factor, in other words, she must be pure in colour-blindness in order to exhibit it. But the male may be colour-blind if he has but one dose of it. The woman with one dose, though she does not show it, may transmit it to her offspring. We can, therefore, say colour-blindness is dominant in males, but recessive in females, and that a colour-blind female must have had a colour-blind father, and all her sons will be colour-blind. Per contra, the normal male has no colour-blind factor, and unless his wife introduces the peculiarity will have normal children. The male who is not colour-blind cannot pass it on, no matter what his ancestry, and even the male who is colour-blind appears rarely to transmit the affection. Although there are authentic instances of the direct descent of colour-blindness from father to son, it is known that in all of them the affection was introduced by the normal-sighted mother also. Colour-blindness is probably due to the presence of a something conducing to colour-sense paralysis.

In the case of some of the other sex-limited heredities there are difficulties still unexplained, notably in hæmophilia and in pseudo-hypertrophic paralysis. The data concerning these diseases, available for analysis, are somewhat heterogeneous, but in respect of the other examples quoted we are on safer ground; so much so that we may assume that sex itself acts as a specific interference, stopping

---

\(^1\) Bateson, *op. cit.*, p. 170.
or inhibiting the effects of a dominant factor. It is curious to note that the inhibition occurs in the female and not in the male, but the inhibition would seem to be limited to cases where the character is heterozygous (single dose) and absent when the character is homozygous (double dose). On the view that femaleness itself is the suppressing factor in the case of some of the pathological states, it is suggestive to recall the circumstance that old or impotent females among the higher animals sometimes assume some of the secondary characters of the male. Can it be that the male character was present in their constitution as a previously latent factor? Doubtless, to some of you, it may have occurred, have these questions thrown any light on the baffling mystery of sex determination? Yes, they have, but only partially so. I can make no pretence to discuss the facts, but would say this, that all Mendelian experiment points to the idea that sex determination is really a matter of gametic differentiation, and the fact that in ordinary cases the two sexes are produced in equal numbers indicates that one sex is heterozygous in respect of sex character, and the other homozygous. In the case of the human family, there is much to suggest that the female is heterozygous for the female factor, whilst the male is homozygous recessive.

Without prejudice as to certain controversial points, I think we can say that recent work, notably that on Mendelian principles, has done much to place the problem of heredity and variation of species upon a better basis, and to render clearer what was formerly very obscure. Of course there is much more to be done. Further, I think you will agree that a prima facie case has been made out for the plea that the hereditary factor can be traced on a scientific basis in regard to simple pathological states. But, you will say, what about the more complex diseases of everyday life? Can we apply any suggested theory of heredity to them? Certainly we can, but in so doing we must have accurate facts, and also bear in mind that in these diseased conditions we are but contemplating variations. In this contemplation of variations, we must be careful not to limit them to mere changes of form, structure, or colour; we must recognise there can be changes or variation in function. Think what a vista of diseased or abnormal conditions this brings up. We are all familiar with the connection which appears to exist between thyroid disease and myxoedema, also between an abnormal condition.

\[1\] For an elaborate analysis of this question, the reader should consult Bateson, op. cit., p. 190.
of the pituitary body and acromegaly. So, too, we know of other
diseases arising from disordered metabolism within the body, or due
to toxins, enzymes, and ferments present in the tissues. Not a few
of these, such as gout, cystinuria, alkaktonurias, tuberculosis, in-
sanity and cancer, appear to run in families, and the practical
question is how far can these diseases be ascribed to heredity, or
are they acquired through forces acting on the individual affected.

Before we can appreciate the true part which heredity plays in
any of these affections, we must have accurate facts as to the indi-
viduals of two, three, or more generations. Much of the evidence
as to ancestral disease is mere hearsay, and consequently unreliable.
We want accurate family medical histories, in which every state-
ment made is verified personally, if possible, by the technical
observer. It need scarcely be remarked that when a disease, such
as tuberculosis, affects certain families with special frequency, the
hereditary factor is either the presence of something which renders
the individual specially liable, or the absence of something which
confers a degree of resistance. From the nature of the case a bare
pedigree will not be of value, unless it be amplified by details as to
what were the relative risks of infection borne respectively by those
who develop the disease and those who escape. Varieties in several
degrees resistant to disease are known in many orders of plants, and
there are indications of a similar character in animals and man.
An attractive field of research is here open, and it is legitimate to
believe that various types of resistance will be disclosed, some
dominant and some recessive. If each medical man would construct
but one such medical pedigree in respect of some disease in one
family, we should have in twenty years all the scientific material
needed to answer these questions as to the inheritance of deformity,
colour, and constitutional tendency to special diseases. We need
to divorce facts from fancies, and only record definite facts, leaving
others to put their interpretations on them. The material is not
available for us in our day to learn or know the truth, but our
work in this field, if we will but do our share, will make much
clear for those who are to follow.

I fear I have allowed myself to be too discursive, and possibly
been none too intelligible. If so, I hope you will make allowances
on account of the inherent difficulties of the subject. I have tried
to take you over ground which is somewhat out of the beaten path,
and I only hope I may have stimulated your interest sufficiently to
tempt you to make incursions on your own account into the same
field of scientific enquiry and observation.