[JUNE, 1906.]

BRAIN.

PART II., 1906.

Original Articles and Clinical Cases.

AN ADDRESS ON MENDELIAN HEREDITY AND ITS APPLICATION TO MAN.

BY W. BATESON, M.A., F.R.S.

*Delivered before the Neurological Society of London, on Thursday,
February 1, 1906, Sir Thomas Barlow, President, in the chair.*

MR. PRESIDENT AND GENTLEMEN,—I need not say that I feel it a very high compliment for me, a layman, to be asked to address a professional meeting of this kind. When I received the invitation I hesitated for a moment as to whether anything I could say would have a sufficiently direct bearing on the subjects in which you are interested to justify me in occupying this place. Though I venture to call my paper "Mendelian Heredity and its Application to Man," I ought to say that that application is rather for the future than for the present. We do know cases in man where the rules of inheritance traced in other animals and plants must certainly apply, but those cases are very few. On the other hand, I feel sure that if members of your profession were to take the matter up and study the phenomena of inheritance with due regard to those points which we now know to be critical, the list will be very soon increased.

The advance in knowledge which I am about to describe is the outcome of the work of Mendel. I have not time to tell you who Mendel was, or how it came about that his

paper published in 1865 was completely ignored until 1900, when de Vries and others simultaneously rediscovered it. Nor need I go through the reasoning by which he worked out his discovery. That, I think, will become easily intelligible when you see the practical examples which I shall be able to illustrate by specimens. I will therefore begin at the point we have now reached.

In a very large range of animals and plants we know that bodily characters—points of structure and features of physiological constitution—are treated by the cell divisions in which the germs are found as *units*. This may be made intelligible by a simple demonstration. Here are draughts, white and black. Suppose the discriminating points whose heredity we are to trace are blackness and whiteness.¹ The draughts are the germ cells. When two are united together they represent the soma, or “zygote.” The body-cells, as you know, are double structures, containing twice the number of chromosomes present in the germ cell. A pure black individual is thus represented by two black draughts; a pure white by two white ones. When the two are crossed the hybrid contains both characters—a black draught on a white one. But though the combination of characters in the body of the hybrid may be intimate, yet when that hybrid forms its reproductive cells, the processes of cell division are such that the blackness is segregated from the whiteness. Each germ cell then carries either blackness or whiteness, not both; and an equal number of each kind are formed. Such segregating characters or *allelomorphs* as they are called, are, so far as we know, always constituted in pairs. In respect of each pair, therefore, there are only three kinds of individuals, the pure, or *homozygous*, of each kind, and the impure, or *heterozygous*, containing both.

It is often found that one member of an allelomorphic pair is so conspicuous in the heterozygotes that these impure individuals may pass for pure. The character which thus

¹ Taken as imaginary illustrations. We know, of course, that in man blackness and whiteness do not follow the simple system. In the rabbit, however, they do.

prevails is then called the dominant (D), the other being the recessive (R). The gametes, or germ cells, may be represented by the single letters D, D, D, &c., and R, R, R, &c.; but to represent the zygotes, namely, the individuals resulting from the union of two germ cells in fertilisation, *two* letters, DD, or DR, or RR, are required. In the diagram black is supposed to be dominant, the black draughts lying on the white ones. The results of the various possible unions are then shown. $RR \times DD$ gives all DR, which if

dominance be complete may pass for pure D. Consequently $DR \times DR$ seems to give on an average $3D : 1R$ (fig. 1).

In reality, of the $3D$ two are impure on an average, and one is pure. Similarly $DR \times RR$ gives an equal number of DR and RR (fig. 2), while $DR \times DD$ appears to give all D (fig. 3).

The most striking consequence of allelomorphism is that pure individuals may be bred from impure ones. For

example, whenever an R germ meets an R germ in fertilisation, the individual is pure R, and the same is true for the D germs. Consequently, when an R individual appears in the family, the D element is thrown out of that individual for good and all.

The simplest illustration is that of tall and dwarf ("Cupid") sweet peas crossed together. The first filial generation— F_1 , as we call it—are all tall, for tallness is dominant. In the germ cells the characters, tallness and dwarfness, segregate.

By self-fertilisation the second generation— F_2 —is produced, consisting on an average of three tall to one dwarf. The dwarfs are then pure dwarfs, giving no more tall in their posterity; but of the tall, one on an average will be pure tall, and two will be heterozygous, giving the same mixture in the next generation. In the photograph (plate I., fig. 1), members of the F_2 generation are shown. All came from one pod of seed. The dwarfs are now pure dwarfs, though they are the offspring of a tall plant, and though the grand parent was also tall. But of the tall some are pure tall, and some are hybrids of tall and dwarf again, the pure being to the impure on an average 1 : 2.

The next, which is a human case, is exactly similar. It is the case of a family in Pennsylvania described by Farabee [1], many of whose members had a deformity of the digits—the fingers and toes all having two phalanges like the hallux and pollex (plate III., fig. 4). This character was like tallness in the peas, dominant. Every individual that bore the character exhibited it. Those that had normal digits did not transmit the peculiarity, because they were formed from two germ cells not bearing it. Fig. 4 shows the pedigree of the whole family. Though there is even a first-cousin marriage between normals, no abnormal appears in their posterity. Fig. 5 shows the descent from abnormal members, the other parent being in each case a normal person. The fourteen families bred in this way contained thirty-three normals, thirty-six abnormals, a close approach to the expected equality. It is therefore an even chance that the child of one of the abnormals will be normal, or

abnormal; whereas if one of the normals were to consult a medical man and ask what was his chance of having a child with the deformity, he might be confidently assured that the

FIG. 4.

Pedigree of Farabee's family (from his paper). N, normal; A, abnormal, with only two phalanges in fingers and toes.

FIG. 5.

Offspring of abnormal members of Farabee's family¹ (from his paper).

chance was infinitesimal, and no greater for a normal member of this curious family than for any normal person in the general population.

¹ In this and subsequent pedigrees the black symbols represent abnormal individuals.

—which is improbable—the case cannot possibly be brought within our rules.)

Such cases as that shown in fig. 7 suggest a further question which we cannot answer, namely, What is the origin of these variations? As to that we know nothing at all. Whether a variation be dominant or recessive, we cannot form any clear idea as to what is the cause which

FIG. 7.

Congenital cataract from Nettleship after Berry.

The female at the top of the pedigree came of an affected family, but she was probably normal; and her son, from whom the rest descend, is said to have been certainly without cataract. Such descent of the condition through the unaffected is exceptional.

leads it to begin. But having begun, it usually follows the ordinary course. The dominants, viz., the affected have affected and unaffected offspring in equal numbers, and the unaffected have unaffected offspring. This is characteristic of the distribution of dominant characters.

I will now pass rapidly through cases that we know

more about, in plants and animals which are amenable to experiment. The first is a case in the Chinese primrose (*Primula sinensis*). The original species has a palmate leaf (plate II., fig. 2). About 1860 a variety appeared as a sport from seed, having a pinnate or "fern" leaf [fig. 2 (R)]. The palmate form is dominant, and the fern leaf is recessive, breeding true whenever it appears. The deformed sweet pea known as the "Snapdragon" variety is a similar recessive.

In wheat, a long series of characters following these rules has been determined by Biffen [3] and Spillman. Beardless, for instance, is dominant to bearded, and consequently the bearded offspring extracted from a cross-bred are pure to the bearded type.

Another of Biffen's cases has considerable theoretical importance, and is especially interesting as bearing on conceptions of evolution. It occurs in a cross between 2-row and 6-row barley. The difference between them is, briefly, that in the 2-row form certain lateral flowers develop no seed because they are *male* only, having no female organs. In the 6-row all the flowers are both male and female, and all set seed.

When these two are crossed together what should we expect? Certainly I should expect that the positive characteristic, the presence of both male and female parts, would dominate over the negative characteristic, the absence of female organs. But it is not so. It is the negative characteristic which dominates. Though in the "blood" of the cross-bred there is the positive characteristic, yet the negative form dominates and excludes it from appearing. It is as though an inhibitory process had occurred; that there was some substance or arrangement, some peculiarity—we know not what—present in that organism which prevents development of the female organs. Consequently it is 2-rowed, like the 2-rowed parent.

One of the simplest cases which first attracted attention is that of the cross between the wrinkled sugar-maize and the common or starchy maize with round seeds. In this case the round form dominates. Every "wrinkled" egg

cell fertilised by a pollen grain bearing the "round" character becomes a round seed, developing a starchy endosperm instead of a sugary endosperm. Such a seed, when sown, becomes a plant which, on self-fertilisation, will have a cob containing a mixture of starchy and sugary seeds in the ratio 3 : 1. Every one of the wrinkled seeds would give a plant of pure sugary or "wrinkled" type ; but of the round seeds two would be impure "rounds" for one which was pure (plate II., fig. 3).

The next is the classical experiment of Mendel, which consisted in crossing a wrinkled pea with a round pea, showing that the same series of results follows as in the case of the wrinkled and round maize.

So far all is very simple. From this point various extensions have been made. The first was to find other animals and plants, and other characteristics which followed these rules. Some very interesting ones have been found, for example, a case which will probably have an interest for the medical profession. Biffen has found in wheat that the condition of greater resistance to the rust disease is a recessive character. I have seen myself his wheats growing and can attest that that is so. He crossed a breed of wheat which has comparative immunity, or a greater resistance to rust, with one which has less resistance, whose leaves are yellow with rust. The first generation is affected heavily with rust, like the bad parent. In the next generation one sees the yellowed plants, with green or recessive ones standing among them comparatively immune ; and when the seeds of the resisting plants are saved—they are self-fertilised before the flower opens—the offspring are comparatively disease-resisting. That is the only case of this kind which has been properly attested, but I have no doubt plenty of others will be found when they are looked for. Another case which is rather interesting occurs in the primrose. Most people know from Darwin's books that primroses exist in two forms. In one form the anthers are in the top of the tube, and the style is short. In the other form the anthers are at the point of contraction of the tube, and the style is long. Primroses in Nature exist in about

equal numbers in the two forms. And we find that the thrum, or short style, is dominant over the long style, and these characters are segregated in the ordinary way. Long-styled plants being recessive never produce short-styled offspring unless they are pollinated from a short-styled plant. That is a complete answer to the objection which was made when the Mendelian facts were first discovered, that wild animals and plants might not follow the rules applying to domesticated breeds.

An illustration of interest to neurologists is that of the Japanese "waltzing" mice. The peculiar vertiginous movements exhibited by these creatures are probably connected with malformations of the semi-circular canals. The "waltzing" character is recessive to the normal, for the offspring of normal $\times$ waltzer is always normal, and in F_2 waltzers reappear [4].

Another interesting case, also of a recessive character, is that of sterile anthers in the sweet pea. This curious pathological condition is partially coupled with the absence of colour in the axils of the leaves.

The application of Mendelian rules to mankind has not made the progress that was to have been expected. In particular, we have not clear evidence that these rules apply to the transmission of colour characteristics in man. We know that they do in the rabbit, the mouse, the horse, and many other creatures; but in man there is no clear evidence that the colour characteristics follow the Mendelian rules. There is evidently a complication, probably an important one, in that case. Those who are familiar with the subject will know that though we can work out the simple rules for the blacks, chocolates, and albinos in the mouse and rabbit, we have great difficulty in tracing the rules for yellows and browns. Yellows and browns do not segregate clean when crossed with black. I think that perhaps some difficulty of this kind exists in regard to human pigments, though we should probably be wrong in imagining that there was no segregation.

Even in regard to albinism—usually the most obvious Mendelian recessive in animals and plants—the human

evidence is not yet clear. Albinos have been recorded with some frequency among the offspring of consanguineous matings—a circumstance characteristic of recessive features; but the existence of complications is indicated both by the many degrees in which human albinism may present itself, and by the frequent association of the peculiarity with various forms of disease—an association not usual among domesticated animals.

I now pass to another subject. So far we have only been concerned with the distribution, in their posterity, of characters obviously existing in the original parents from whom the descent is traced. We knew long ago that such original parental types might reappear in F_2 , together with the cross-bred form produced in the first generation. But we knew also that in other cases F_2 might contain a number of *new* forms appearing for the first time. This phenomenon is the “variability” caused by crossing with which all breeders are familiar. Within the last two years this problem has been greatly elucidated. In all the cases which have been properly examined we now know that these new forms are created by simple re-combinations of characters brought in by the original parents.

We cross, for example, a red variety of some plant, say a stock, with a cream-coloured variety. The red variety is characterised by red sap, the cream variety is characterised by yellow corpuscles, surrounded by colourless sap. In the red those corpuscles are represented by colourless corpuscles floating in the red sap. What will happen when these two are crossed together? As a matter of fact, we find that the red is dominant. But in the second generation, the F_2 generation, we have nine red, three red with cream, three *white*, and one cream as before. What is the white? White was not put in. Apparently we have produced it *de novo*—an albino by crossing two coloured forms: cream was a corpuscle colour, red was a sap colour, but the white have *colourless* corpuscles floating in *colourless* sap. It is evident what has happened. Which are the factors which segregate in the formation of the germ cells? They are (a) red sap from colourless sap, and (b) white corpuscles from yellow

corpuscles; so that when the possible combinations of those two pairs of characters are made, colourless corpuscles may coincide with colourless sap, and a white flower is the result. I think the answer is quite clear.

The operations may be shown in a tabular form, thus:—

Parents	...	...	...	Red variety	×	Cream variety.
Allelomorphs	{		Red sap (D).	{		Colourless sap (R).
	{		Colourless corpuscles (D).	{		Yellow corpuscles (R).
F 1	...	...	...	{		Red sap.
	{			{		Colourless corpuscles.
F 2	{		Red sap.	{		Red sap.
	{		Colourless corps.	{		Yellow corps.
Appearance	{		9 RED.	{		3 RED-CREAM.
	{			{		3 WHITE.
	{			{		1 CREAM.

Plate III., fig. 5, shows another example of a novelty arising in F_2 by re-combination. In the Chinese primula we have a modern variety with an extraordinarily big yellow eye or flush spreading up the petals, quite different from the small yellow pentagon characteristic of normal types. This variety has the peculiarity that though its pollen and anthers are those of the ordinary pin-eyed type, yet in it the style is short and the stigma is down the tube at the anther level.

Mr. Gregory and I crossed this "homostyle" plant, as it was called by Darwin, with the small-eyed short-styled form. F_2 is short-styled with the small eye. In the F_2 generation we got out four types: (a) Short style with small eye; (b) short style with big eye; (c) *long style* with small eye; (d) homostyle with big eye, in the ratio $9a : 3b : 3c : 1d$. Now, the long-styled or pin type, which apparently was not put in at all, is due to a re-combination of the characters. The two pairs of characters are—

Thrum type (Domt.).	Pin type (Rec.).
Small eye (Domt.).	Large eye (Rec.).

The homostyle is the form which the pin type assumes when the large eye is developed; but when in F_2 the pin type meets the small eye, the ordinary pin, or long-styled, form is produced.

The combinations of two such pairs of characters C.c. and R.r. can be represented diagrammatically as shown in

fig. 8. The figure contains sixteen squares, presenting every combination of the two pairs of characters.

There are therefore four groups of individuals produced in F_2 , viz., nine of the kind that contains C and R; three that contain C only; three that contain R only, and one with neither.

CR CR	cR cR	CR Cr	CR cr
cR CR	cR cR	cR Cr	cR cr
Cr CR	Cr cR	Cr Cr	Cr cr
cr CR	cr cR	cr Cr	cr cr

FIG. 8.

Scheme of distribution of two pairs of factors in F_2 , showing how the F_2 ratio 9 : 3 : 3 : 1 is produced. From the same distribution the F_2 ratio 9 : 3 : 4 results in cases where one factor produces no visible appearance unless the other is present; while, if neither factor can be perceived unless both are present, the F_2 generation is 9 : 7.

The big letter in each case denotes the presence, the small letter the absence, of the given factor.

A complication we often meet in the application of the rules of heredity lies in the fact that characters belonging to distinct allelomorphic pairs react on each other. A particular appearance, for instance, may depend on the co-existence of both C and R, and either of these factors alone may be unable to manifest any influence on the individual in the absence of the other. In that case there will be nine showing the appearance in question, say a colour, for seven which

are without it. Or, again, the factor C may produce an effect alone; while R, though imperceptible in the absence of C, may modify the effect of C when C and R co-exist. There will then be nine of the C + R class; three of the C class; and four all alike because C is absent, though their gametic composition is really diverse. This is a result well seen in the colour heredity of mice and rabbits. For example, gray $\times$ albino gives gray F_1 , with in F_2 three gray : one albino. But F_2 may be instead nine gray : three black : four albino. The latter result indicates that the factor which determines the colour to be gray was absent in the albino. The meaning of these occurrences was first pointed out by Cuénot.¹

In illustration of these descents I exhibit skins of some of the remarkable series of rabbits bred by Mr. C. C. Hurst [5], who has kindly lent them for this meeting. Some of his F_2 families were three gray : one albino, while others were nine gray : three black : four albino; in either case, of course, three coloured : one albino. The albinos can give no more coloured. The blacks may be pure blacks, or they may give blacks and albinos. The grays may be pure grays; or they may give grays and albinos; or grays and blacks; or grays, blacks and albinos as before. If in the diagram (fig. 8) C stands for colour, c for albino, R for gray and r for black, the nature of this series will be understood.² Inspection shows that of the four albinos, for instance, which appear on an average in 16 F_2 , one will be carrying the gray determiner, one the black determiner, and two will have both gray and black determiners. By suitable cross-matings the condition of each albino can be exactly determined. For example,

¹ *Arch. zool. exp. et gén.*, 1904; (4) II., *Notes et Rev.*, p. xlv. Cuénot, in his argument, speaks of the determiner for gray as present in the gray mouse, and of the black determiner as present in the albino, regarding the two determiners as allelomorphous to each other. For various reasons, however, it is probably more correct to regard the gray determiner in the gray mouse as allelomorphous to its absence, and to imagine the black determiner as present in both the gray and the albino.

² As implied in the previous note, the account in the text is too simple, though it may suffice as a rough presentation of the phenomena. The case should be expressed thus: The allelomorphs are C, colour; c, albino; G, gray determiner; g, absence of ditto; B, black determiner; b, absence of ditto. The gray rabbit is OGB; the albino is cgB. B is common to both, so that in F_2 the arithmetical result, nine gray : three black : four albino occurs as it would do if G were allelomorphous to B so that the original parents could be expressed as CG and cB.

when bred to a pure black, a G albino will give grays only ; a GB albino will give equal numbers of grays and blacks ; while a B albino will give blacks only. Similarly the exact composition of each coloured rabbit may be determined by experimental breeding.

The particular colour of a rabbit or a mouse is therefore not a simple character depending on the presence of a single factor, but a double one, depending on interaction between one distinct factor and another, each factor being transmitted independently in heredity.

In certain plants we can go beyond this. Two white-flowered sweet peas, for instance, may when crossed give a coloured F_1 , which by self-fertilisation will produce nine coloured : seven white. This result proves that the colour depends for its appearance on the co-existence of two complementary elements or factors. The nine are the nine squares in fig. 8 containing both C and R ; the seven are the three with C, the three with R, and the one with neither. Either factor alone is insufficient to cause colour. C and R are not allelomorphous to each other, but each is allelomorphous to its own absence. This conclusion has been tested and confirmed by an elaborate series of experiments made by Miss Saunders, Mr. Punnett, and myself. A further complication is due to the fact that colour, once formed by the meeting of the two complementary factors, is modified by the operations of distinct determining elements, just as is that of a rabbit. Thus, for instance, the nine coloured : seven white commonly forms the series twenty-seven purple : nine red : twenty-eight white.

In the Stock, which has formed the subject of a long series of experiments by Miss Saunders, a still further complication is met with. Colour in the stock, as in the sweet pea, requires the co-existence of two independent factors, each of which in the germ formation is allelomorphous to its own absence. In addition, the development of the hoariness or felting of hairs upon the leaves is also produced by another similar pair of factors, either of which alone may be present without a single hair being formed.

But in the stocks employed ("ten-week stocks") both these factors for hoariness may be present, but no hairs are developed *unless the flowers are coloured*, that is to say, unless the complementary pair which form pigment are also present. To go through the elaborate steps by which this conclusion has been experimentally established is impossible on this occasion, but I mention it to illustrate the kind of complexity which is to be met with in these investigations, and at the same time the far-reaching precision that may be attained by Mendelian analysis.

Evolutionists will note that in the stock and the sweet pea we have examples of Darwin's famous "reversion on crossing." Two white-flowered plants crossed may give the wild, purple flower. Two glabrous stocks may reproduce the original hoary, ancestral type. Such reversion is nothing but the meeting of two parted complementary elements, which have somehow been separated by variation.

The various factors, then, which interact to produce what we formerly regarded as a single character, *e.g.*, colour, are *separately* transmitted in heredity. Such interaction constitutes a remarkable phenomenon from the standpoint of general physiology. We cannot doubt that this inter-relationship between these distinct units plays a great part in the determination of bodily features. As these complex inter-relationships are gradually resolved, we shall acquire a new light on the problems of evolution, and especially on the genesis of variation. What the nature of such elements may be we must leave as yet to conjecture. It is natural, however, that we should think of their mutual actions as comparable with that of a ferment acting upon a definite material.

To the student of disease, illustrations of a comparable nature will be familiar in the case of the sex-limited inheritances. In these families the peculiarity is manifested generally, if not always, by members of one sex, say the male; but the females, though unaffected themselves, may transmit it to their male offspring. Hæmophilia and colour-blindness are the most famous examples of this "Knight's move" descent, as it may be called. The possible bearing

of the new ideas upon this curious phenomenon may be shown by an illustration seen in crossing sheep.

Mr. T. B. Wood [6] made a cross between the Dorset Horn and the Suffolks. The Dorsets are horned in both sexes, the Suffolks are hornless in both sexes. In F_1 the males are horned, the females hornless. In other words, horns are dominant in males, recessive in females. But in F_2 there are both horned and hornless males, and also horned and hornless females; because two "hornless" germs have had the opportunity of meeting in presence of "maleness," and two "horned" germs in presence of "femaleness." Un-

FIG. 9.

Pedigree of a family containing colour-blind members observed by Dr. Rivers, among the Todas, an Indian Hill-tribe, illustrating the "Knight's Move" descent of that condition.

doubtedly when these animals have been tested, the hornless F_2 males and the horned F_2 females will be proved to be each pure to their respective characters. (Plate III., fig. 6.)

Though the evidence as to sex-limited descents is imperfect, and in some respects obscure, it is obvious that there is a general resemblance to what we have seen in this case of horns in the sheep. If the affected sex is the male, the unaffected males do not transmit the condition, though the unaffected females¹ may do so. We may suppose that

¹ The popular belief that such a condition is transmitted *only* by females is, of course, a mistake. In hæmophilia, for example, there are many cases of transmission by affected males.

the unaffected males in fact are, by segregation, freed from the peculiarity, just as the hornless rams in F_2 are freed from the horned character. To test the applicability of these comparisons much evidence is required which is not yet obtained, but the tests which must be applied are clear. Supposing the members of the affected family mate with persons not bearing the peculiarity, we should expect that (1) half the sons of (a) *affected males*, and of (b) *unaffected females who had any affected sons*, would be affected. (2) that half the daughters of (a) and (b) would transmit the peculiarity to half their sons. Moreover (3), affected females should be pure in respect of the character, and consequently *all* their sons should exhibit it.

FIG. 10.

Pedigrees of two families containing colour-blind females, from Mr. Nettleship's collection.

We are far from possessing adequate evidence that this simple system holds in any sex-limited descent. The most that can be asserted is that the general course of the inheritance is in rough agreement with some such scheme.

As regards colour-blindness the pedigrees are few, but it is noticeable that the only examples—three—of colour-blind women with sons that are known to me are, so far as they go, in agreement with our hypothesis. Two (fig. 10) are cases observed by Mr. Nettleship. In each a colour-blind woman had one son, who was colour-blind. The other case is that of Burckhardt [7]—a colour-blind woman with three sons, all colour-blind (fig. 11).

As to hæmophilia the evidence is more abundant, and in respect of criteria (1) and (2) is usually not very discordant with expectation. With rarest exceptions unaffected males do not transmit the disease. Nevertheless, many more males are affected than our rule expects¹; and unless it is

Males.			Females.	Sex not given.
Bleeders.	Non-bleeders.	Died young,	Non-bleeders.	Non-bleeders.
188	65	20	177	44

supposed that normal families have been freely disregarded by the recorders, too many of the females transmit. Moreover, of some thirty-five groups of families, at least twelve cannot be brought into line at all. The subject is com-

FIG. 11.

Pedigree of colour-blindness, from Burckhardt.

plicated by the circumstance that various pathological conditions have been included under the name hæmophilia, as has been suggested by Legge in reference to female hæmophilia, and a proper analysis of the evidence could only be made by an expert.

Some of these families, especially those in mountain villages, were doubtless much in-bred, a circumstance which may have introduced complications. The excess both of bleeding males and of transmitting females is, however, far

¹ I got the following very rough figures by adding all the published families (containing "bleeder" males) which can be at all supposed to be comparable. Parents non-bleeders in each case.

too large to admit of any simple explanation. (For extreme cases, see Stahel, *Inaug. Diss.*, Zurich, 1880, and Sadler, *Birm. Med. Rev.*, 1898 and 1903). The phenomena could only be brought under the Mendelian scheme by the supposition that a complex system of coupling exists, for which we have as yet no justification. I hope at some time to discuss this subject in more detail.

The same features are presented by another sex-limited disease, peroneal atrophy [8], with the added difficulty that too few of the sons of affected males were affected; while, as before, too many of the women transmit and too many of their sons are affected.¹

A source of complication in understanding these statistics may arise through complete or partial *coupling* between distinct characters. We have proof that in certain cases a character, say of shape, may be so linked or coupled with another character, say of colour, that all or a majority of the germs which carry the one carry the other also. To this fact I can now only refer, but the existence of such coupling constitutes one of the most interesting, as well as one of the most difficult, branches of these inquiries.

Finally, I would say something as to the way in which evidence must be collected if it is to be used in the study of heredity. First, the facts must be so reported as to be capable of analysis. It is for want of such analysis that all examination of the facts by pre-Mendelian methods failed. The tabulations must present each family separately. Miscellaneous statistics are of little use. Secondly, *it is absolutely necessary that the normal or unaffected members should be recorded*, together, if possible, with information as

¹ I have since examined many published pedigrees of nervous diseases to which my attention was called by Dr. Batten and others. In several of these transmission is exclusively, or almost exclusively, through the affected, so the characters may well be dominants, but the ratio of affected to unaffected is nearly always too high. Normals may doubtless have sometimes been omitted, but the deficiency of normals is so persistent as almost to forbid a recourse to this hypothesis. The possibility suggests itself that some of these diseases may be due to actual transmission of a disease germ through the reproductive cells (like pébrine of silkworms studied by Pasteur). I am told that this suggestion is highly improbable; but in view of the statistics for some of these family diseases I feel considerable doubt whether they should be regarded as illustrations of heredity, pure and simple, in the sense in which a naturalist employs the term.

to their offspring. In the records hitherto published these essentials have too often been omitted, the doctor's attention having been more or less exclusively directed to the individuals manifesting the disease. Next, if similar families are to be added together, it is scarcely necessary to insist that the cases added must be in reality similar. For instance, there are abundant genealogies of deaf mutism, but the various families present such inconsistencies in the heredity rules which they follow that there can be no doubt that not one, but many, pathological states are concerned. Accurate diagnosis is the first preliminary in dealing with these phenomena.

When complete information has been obtained, it is to be expected that definite rules of transmission will not rarely be traceable. Suppose the disease dependent on a simple dominant character, the fact will manifest itself in exclusive transmission through the affected; and—if the other parent be unaffected—in the frequent production of affected and normal offspring in equal numbers. The case of dominance limited by sex has already been considered.

Recessive characters may be distinguished by the frequency with which they appear in the offspring of normal parents, and especially as the result of consanguineous marriages. The identification of recessive characters will be less easy, direct experiment being impossible.

One condition probably of this nature may be mentioned—that of alkaptonuria, studied by Dr. Garrod [9]. The high proportion of cases of this rare condition resulting from first-cousin marriages makes it very likely that this peculiar "chemical sport," as Dr. Garrod has called it, is recessive. First-cousin marriages give an opportunity for the meeting of recessive germs. The same element or character, as we may say, meets itself; and thus the hidden characteristic, being brought in by both male and female germs, may appear, though it would still have remained hidden if one of the two germs had not carried it. Think of the tall peas bearing dwarfness as a recessive character. Bred together they give one dwarf on an average in four, though bred with a pure tall individual no dwarf would be given. So when first

cousins marry, it gives a chance for the hidden character to come out, because each parent may be carrying that character derived from the common grandparent. The chance even so, however, is a very small one. I do not suggest it should be considered in practical life. Certainly there is not enough to base advice upon respecting consanguineous marriages. The chance is remote that the hidden character will be present on both sides, and perhaps, too, some recessive characters may be very desirable ones!

In conclusion, I should warn you that the detection of these systems of heredity is, except in a few cases, not a simple matter, even when experimental breeding is applicable. The rules perceived in the sweet pea and the stock, for instance, have only appeared after five years' careful breeding, and, as these cases show, results which at first seem hopelessly conflicting may ultimately be proved to be entirely consistent. We cannot suppose that the complexities there encountered can be absent in the case of man. We have seen how the presence of one character may either excite or prevent the manifestation of another independent character. Other features are undoubtedly dependent on excitation by external influence—in a wide sense. There are many indications that this is true of some nervous diseases. Lastly, it sometimes happens that two characters, one dominant, the other recessive, to a third character may be scarcely distinguishable from each other. For instance, pure white in fowls (white Leghorns) is dominant to colours; but a white associated with a few minute specks of colour (white rose-comb Bantams) is recessive to colours. Distinctions of this kind are not perceived on superficial examination, and can only be unravelled by most exact and specific investigation.

My object has been to put before you the results of work on lines somewhat remote from your own, though, as you have seen, presenting points of possible contact. If this discourse may lead to a closer study of the hereditary transmission of disease, I am confident that positive results may be expected, and I shall feel that my opportunity has not been wasted.

PLATE I

Dwarf (R).

Tall (D).

FIG. 1.

PLATE II.

Palm (D).

Fern (R).

FIG. 2.

FIG. 3.

PLATE III.

FIG. 4.

FIG. 5.

A.

B.

C.

D.

FIG. 6.

DESCRIPTION OF PLATES.

PLATE I.

F₂ family from the cross tall Sweet Pea × a dwarf procumbent ("Cupid") variety.

The plants, five tall and three dwarfs (on the left of the photograph), came from one pod of seed.

PLATE II.

FIG. 2.—Palm-leaved (dominant) and fern-leaved (recessive) *Primula sinensis* in the F₂ generation from a cross between these two varieties. In F₁ all are like the upper, palm-leaved, plant.

FIG. 3.—A cob of maize produced by Mr. R. H. Lock, in F₂, from the cross round-seed × wrinkled seed.

PLATE III.

FIG. 4.—Skiagraph of hand in Farabee's family copied from his paper.

FIG. 5.—The four types of *Primula* flower in F₂ from the cross large-eyed, homostyle × small-eyed short style. A, small-eyed, long style; B, large-eyed, homostyle; C, small-eyed, short style; D, large-eyed, short style.

FIG. 6.—The four types of Sheep in F₂ from Dorset Horn × Suffolk (hornless) from lambs bred by Mr. T. B. Wood. (For parents and F₁ types, see his paper.) A, horned male; B, hornless male; C, hornless female; D, horned female. In F₁ all males are horned, and all females are hornless.

LIST OF REFERENCES.

- [1] FARABEE, W. C. *Papers Peabody Mus. Amer. Archæol.*, 1905, p. 69.
- [2] NETTLESHIP, E. *Rep. Roy. Lond. Ophth. Hosp.* xvi., pt. iii., pp. 23 and 40.
- [3] BIFFEN, R. H. *Jour. Agric. Sci.*, 1905, i., p. 40.
- [4] DARBISHIRE, A. D. *Biometrika*, iii., p. 20. The fact that waltzers are only about 1 in 6 instead of 1 in 4 in F₂ is without doubt to be ascribed to their great delicacy.
- [5] HURST, C. C. *Jour. Linn. Soc.*, xxix., p. 283.
- [6] WOOD, T. B. *Jour. Agric. Sci.*, 1905, i., p. 364, pl. iv.
- [7] BURCKHARDT, *Verh. Naturf. Ges. Basel.*, 1873, p. 566.
- [8] HERRINGHAM, *Brain*, xi., p. 280.
- [9] GARBOD, A. E. *Lancet*, Dec. 13, 1902, and other papers.