The influence of heredity is sometimes strikingly emphasized by the number of sufferers in a family. In one instance six brothers suffered, their mother, two of her sisters, and both her parents. In another, five sisters, five of their children, the mother, her brother's son, and her own mother.

Such facts might be multiplied almost indefinitely regarding many diseases. But your time may be better employed. We are told we are working on an entirely wrong method. Diem states that he has found neuropathic heredity in nearly 70 per cent. of healthy persons. If he has included every conceivable malady that involves the nervous system, it is quite credible but of no significance.

It has been urged that the essential facts for every member of each generation must be recorded to make observations of value, and we are here to-day to profit by a rare opportunity of learning. We have with us those who have devoted keen ability and a vast amount of time to the study of heredity, and we desire to hear from them the way in which useful observations may be made in the complex range of disease, useful to us, and, if it may be, also useful to them.

Professor BATESON, F.R.S.: Mr. President and Gentlemen,—the object, I suppose, that was intended in inviting a layman like myself to speak to a body of professional men on the subject of heredity was that I should tell you something of the results that are obtained in the study of heredity by the application of experimental methods to animals and plants amenable to those methods. The work that we are able to do is accomplished almost entirely by following the hints that we obtained from the work of Mendel, which I suppose, in outline at least, is familiar to almost everyone in the room. I think I shall have no difficulty in showing you that the conclusions to which Mendel came are applicable, in many cases with considerable precision, to the descent of disease or congenital deformity in man. I think it would be wise to begin by a reference to the simplest possible Mendelian case of inheritance, which we represent in the diagram on p. 23. The result of crossing a tall plant (*Pisum*) with a short plant is shown here. The tall is represented by two long lines and the short one by two short lines. We represent our plant by *two* lines because, as every biologist knows, a plant or animal in all the ordinary cases with which we are concerned is a double structure, having received a series of elements from its father and a series of elements also from its mother. The confusion we used to get into when we tried to trace out rules of heredity in animals and plants

was due largely to the fact that we did not realize sufficiently that the plant or animal is a double structure. The *germ-cell* is a single structure, so when we cross our tall plant with our short plant we imagine the meeting together of a germ-cell which is tall with a germ-cell which is short; and we may represent the result diagrammatically by putting them together—a tall line and a short line. It will be known to most of you, I think, that the pea-plant so produced, as a matter of experimental observation, is not of a height intermediate between the tall and the short, but of about the same height as its tall parent. Now, the discovery which Mendel made was, that in all cases to which his rules applied, when dissimilars meet in one individual there is, on formation of the germ-cells, a separation between the two characters which came

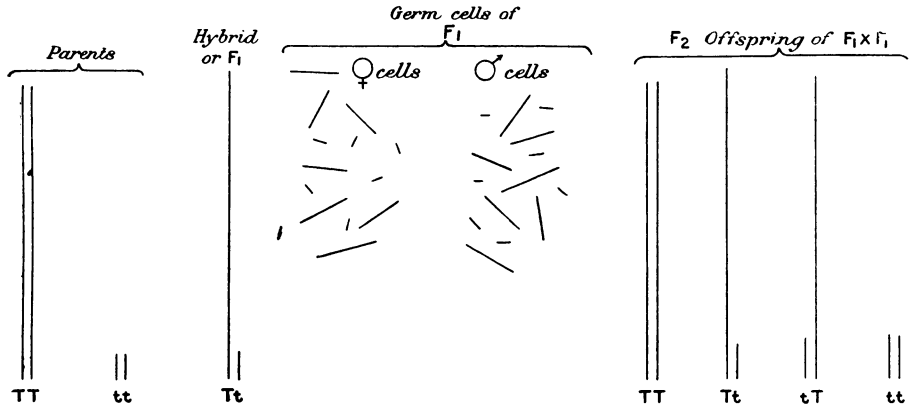

FIG. 1.

A diagrammatic representation of the germ-cells of the tall and short plants, and of their combinations.

in. That may be represented diagrammatically in a crude way by picturing the germ-cells, male and female, as a mixture of long lines and short lines, the long lines representing the germs carrying tallness, and the short lines as the germs destitute of that quality. In ordinary cases the number of each produced is, on an average, equal. That is the phenomenon of *segregation*.

We have been accustomed to talk of the two characters as "dominant" and "recessive," and the terms are useful and applicable. If we consider what is happening to the plant which is made by the union of tall and short germs—why it is tall—I think we are driven to suppose, by examination of a great variety of cases, that its height is due to the introduction into it of some one thing or "factor" from the tall parent,

which factor is absent from the short parent; and that that factor can separate out when the germ-cells are formed, so that some germ-cells possess it and some are without it. The long germs in the diagram possess it and the short ones are without it. The importance of this representation of the dominant as due to a factor present, and the recessive as the condition which results from the absence of that thing, will appear distinctly when I come to speak of the inheritance of disease. The consequence of the combinations of the cells produced by hybrids, females with males, is obviously that in some cases there will be the meeting of long with long, and in some cases the meeting of short with short, and in other cases of short female with short male, or long male with short female. The result will be that where those cells are distributed at random, three of the offspring appear tall and one appears short. The short plants thus reappear because they contain none of the long element. Of the tall plants thus produced some will be pure to tallness, containing two " doses " of the tall factor, others will again be cross-bred, containing only one " dose " of it.

I now put on the screen a photograph which is familiar to many, to show what such a family looks like; they are sweet-peas. These short ones lying on the ground are dwarf plants; they only rise a few inches, while the big ones rise to a height of 5 ft. or more. Here are their tall brothers and sisters, and we know by experiment that the short plants breed pure, just as if they had never come out of the cross at all. They are pure because they have no quality of tallness in them. So some of the talls are pure because they have no shortness in them. The interest of the discovery lies in the fact that it enables us to make analyses of the composition of the animal or plant, in so far as Mendelian principles can be traced. We are able to analyze the plant into its component elements, or, as we call them, units, because they are treated as units when the germ-cells are formed. We must not think of our animal as one thing, but as a combination of a great number of things. The different attributes, such as height, colour, and form, may be, and frequently are, due to distinct factors which are separately transmitted. When we consider the transmission of disease, the application of this principle leads to important results. In a simple case the application of the Mendelian rule to man was traced by Hurst. We know many attempts have been made to discover the descent of eye-colour. The eyes vary in colour between very dark and very light, and it is impossible, by using merely the ordinary names for the colours, properly to define these colours. But

the critical distinction between the dark and the light eye, as Hurst found, turns on whether there is pigment or not on the front of the iris. It is not always easy to see whether the pigment is present or not, but with some trouble it can be made out. The ordinary blue eye is one in which there is no pigment on the front of the iris, while in the brown eye there is pigment on the front. When there is pigment there, it may be transmitted, but when there is none in the parents, the children have none of it. The pigment may be spread over the whole iris, or restricted to some extent, after forming a ring round the pupil. Either type may be pure or impure in respect of eye-colour. The presence of the pigment is a dominant. If a parent is pure dominant, all the children will have colour in the iris; if one parent is impure in the character and the other parent devoid of pigment in the iris, then on an average half the children will have eyes thus pigmented and half have "blue" eyes. Examples of some of these possible matings are shown in the diagrams copied from Hurst (fig. 2, *see* p. 26). One of these shows that a woman who has no colour in her iris, married to a man also without colour, was unable to transmit the colour to children, though her father had colour in his iris. Hurst examined 101 children of such parents, and all were without the pigment. These simple rules so far have been studied only on a small scale. Hurst traced them amongst the people in his own village in Leicestershire, and not until they have been followed out on a larger scale can it be stated with confidence that no exception can be found to them.

Professor Bateson proceeded to show that similar rules can frequently be traced in the descent of certain human diseases and defects. In illustration he exhibited pedigrees of brachydactyly (after Farabee and Drinkwater), remarking that in the three instances in which the descent of a variation apparently meristic had been followed out the *less divided* condition was found to be a dominant. The other two examples were the abbreviated tail of the Manx cat and the aborted coccyx of the "rumpless" fowl (Davenport). Other similar pedigrees were shown relating to keratosis or tylosis palmarum, epidermolysis bullosa, diabetes insipidus, retinitis pigmentosa, irideremia or coloboma, ectopia lentis, and night-blindness. Several of these were taken from the work of Nettleship and from the collections of Gossage. [Other such pedigrees exist for complete abortion of the fingers, split hand and foot, distichiasis, ptosis, certain œdematous conditions of nervous origin, &c.] For most of the diseases named the rule commonly holds that transmission is through the affected

persons only, though exceptions are not unfrequently recorded which call for further consideration. Many of these exceptions were doubtless genuine and as yet inexplicable, pointing, perhaps, to disturbing effects of other factors. Others were attributable to want of opportunity of observing the parents at the right age. Different diseases were sometimes associated under the same name. In retinitis pig-

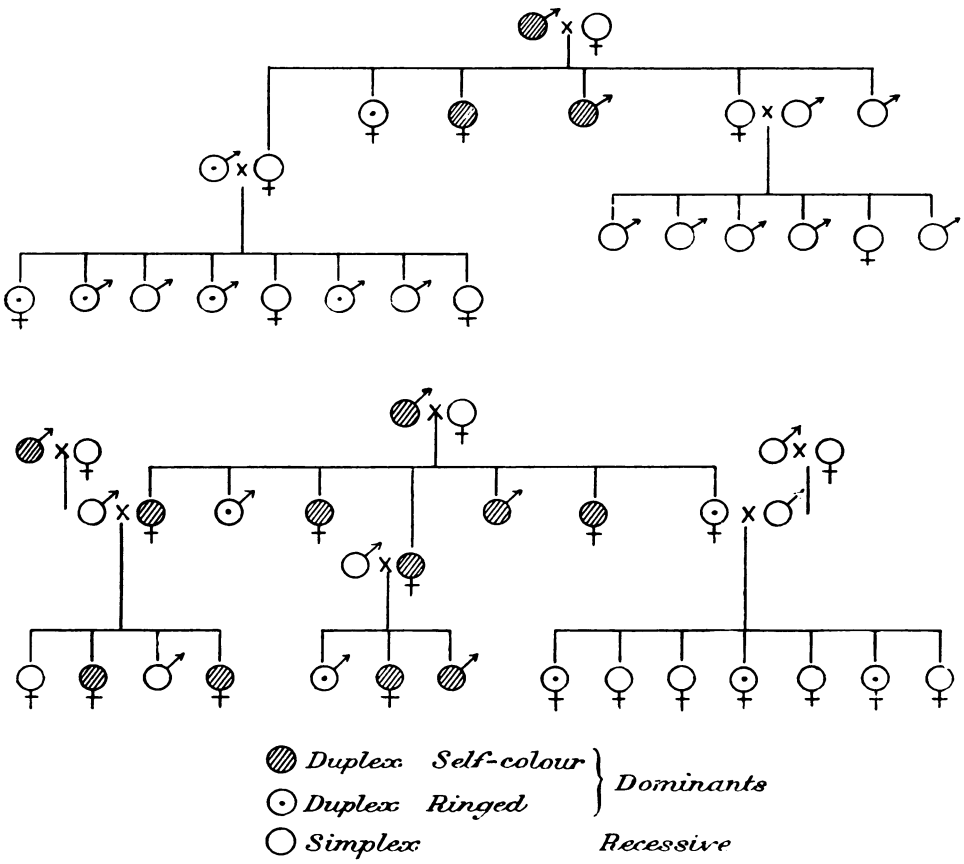

FIG. 2.

Diagrams of descent of eye-colour in two families investigated by Hurst. Copied from *Trans. Leicester Lit. and Phil. Soc.*, 1908, xii, p. 35. See also *Proc. Roy. Soc.*, 80 B, 1908, p. 85.

mentosa, Nettleship's collection of pedigrees showed clearly that the regular descent through the affected was peculiar to certain families. Night-blindness frequently follows the "sex-limited" rule about to be

described; but in the largest pedigree of human defect yet compiled (the work of Nettleship continuing Cunier's materials) the descent had for nine generations followed strictly the rule of transmission through the affected, without exception. Such differences in genetic behaviour probably pointed to differences to pathological nature. As regards numerical results, much irregularity prevailed. Some of the numbers approached fairly closely to the equality expected when cross-bred dominant mates with recessive. Others departed rather widely from expectation. Imperfection of the records was in part, but, he thought, not entirely, responsible for these irregularities, which in some measure he inclined to attribute to physiological causes. In illustration of these numbers the following totals were given. These were of necessity somewhat arbitrarily selected, and for various reasons some families had been rejected. The numbers, however, showed the general course of descent as exhibited by material regarded as homogeneous:—

	Affected	Normal
Brachydactyly (Farabee and Drinkwater) ...	75	65
Abortion of fingers (unpublished)	19	16
Split hand and foot (Lewis and Embleton's collection)	86	64
Cataract, various (selected from Nettleship's collection)	148	155+
Epidermolysis (Gossage's collection) ...	180	209
Keratosis (Gossage's collection)	222	184
Irideremia (various sources)	29	34
Ptosis (various sources)	18	14
Ectopia lentis (various sources)	32	69
Night-blindness (Cunier and Nettleship) ...	130	242[1]
Hereditary chorea (various sources) ...	117	99

[1] Mr. Nettleship gives reasons for believing that the total of normals is here much too high and the number of affected much too low.

There was no reasonable doubt that the descent of these diseases on the whole followed the system of the Mendelian dominant, and that they were due to the presence of special factors, individuals not possessing those factors being unable to transmit them.

As regards tuberculosis, which was due to an infective organism, it was not to be expected that a system of heredity, in the naturalist's sense, should be traceable. The same was not impossibly true in regard to cancer. Special liability to, or special power of resisting, infective diseases might no doubt descend according to Mendelian rules, but no material for testing this in the case of man yet existed.

He continued: The rules for the descent of insanity in general we cannot hope to trace, chiefly because it depends, in so many cases, partly on environmental influences and opportunity for its development. There

is also the difficulty of the diagnosis of different forms, which has not yet been carried sufficiently far for our purpose: we cannot state we are dealing with similar groups. But in hereditary chorea, which is very well defined, it is different. Our numbers are 117 affected, 99 unaffected, which is about as near equality as we can get, or expect to get, in rough data, such as medical records provide.

I have spoken of dominants, and I must now speak of recessives—that is to say, the variations in which something is absent. The albino is an animal which differs from the normal in the absence of something, and, generally speaking, in the case of albinism we have the simplest possible rule which Mendelian analysis can provide. In man albinism is recessive and means that the power of forming pigment is taken out. But in man we cannot get any rule so simple as that which many animals and plants display. These three slides show examples of albinos coming out from normal parents following the converse of that rule which is exhibited by the dominants, and I feel sure that any two of these albinos, if bred together, would have nothing but albino children in all probability. But I have the difficulty exemplified[1] that the number of albinos is far in excess of that which Mendelian rules lead us to expect. I do not think we have evidence sufficient to enable us to discuss the etiology of that.

I should now like to deal with another subject, especially as Sir William Gowers has spoken of it, and that is the descent of sex-limited conditions. The best-known sex-limited conditions are pseudo-hypertrophic muscular paralysis, of which he has spoken, and hæmophilia and colour-blindness. Pseudo-hypertrophic muscular paralysis and hæmophilia are both diseases which are so serious that it is impossible for us to hope to get pedigrees of the descendants of affected persons in sufficient quantity to enable us to investigate them. But colour-blindness is a condition which is not seriously damaging to the chances of

[1] I agree entirely with the remarks subsequently made by Professor Pearson to the effect that the descent of albinism in man is peculiar. As I wrote (*Brain*, 1906, p. 167): "The existence of complication 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 unusual among domesticated animals." Of the slides shown (after Magnus) one exhibited a family from normal parents containing only one normal and *seven albinos*, suggesting a most exceptional behaviour. From various sources I get the totals 197 normals and 126 albinos where the ordinary Mendelian expectation is 242 : 81. Taking all these facts into account, especially the frequency with which albinos have been produced by consanguineous marriage, I think there is no doubt that albinism in man is a Mendelian recessive, but that its descent is complicated by some unascertained disturbance. In the case of alkaptonuria Garrod has shown with great probability that the descent is that of an ordinary recessive. (See especially Garrod, A. E., Croonian Lecture, *Lancet*, July 4, 1908.)

life, and so we can investigate that. The inheritance is well known to be on the lines which Sir William Gowers described, that the sisters of the affected transmitted, or might transmit, to their sons, as, for instance, in a pedigree taken from Nettleship, the affected colour-blind male had a daughter who did not show it, but her son does. The affected, and *sisters* of the affected, transmit.

Now we have been able, I think we may say with confidence, to produce a scheme of descent which represents the facts so closely that there can be no reasonable doubt that we have got very nearly to the actual scheme which is followed by the descent of a simple sex-limited case. I listened with great interest to Sir William Gowers's account of the descent of pseudo-hypertrophic paralysis in the families of those two ladies, and I felt how simply what he said accorded with the principles which we are able to trace by Mendelian analysis. What happens in the descent of sex-limited cases is this. Carry your minds back to the peas. There were peas in which one dose of tallness produces plants of a tall height. There are peas also in which two doses of tallness may be present, but there is no difference in the result. Those that have two doses are tall, and so are those which have one dose. In the descent of colour-blindness there is a difference between these two classes. In the case of females, the female will not be colour-blind unless she has two doses of colour-blindness; she must be *pure* in colour-blindness in order to exhibit it. But the male may show colour-blindness if he has only one dose of it. When the female has only one dose she does not show it, though she may transmit it to her offspring. The colour-blindness is dominant in males, recessive in females. The test of the applicability of these rules is provided by the descent and origin of the colour-blindness in females. According to our rules—to which we are prepared to hear exceptions by-and-by, though they hold so far as we have gone—*the colour-blind female must have had a colour-blind father, and all her sons will be colour-blind.* The normal male has no colour-blindness factor, and will have exclusively normal children unless, of course, his wife introduces the peculiarity. The male who is not colour-blind cannot pass it on, no matter what his ancestry may have been. But the male who is colour-blind can pass it on, and on an average half his sons will be colour-blind and half his daughters will be able to carry on the condition. We have only as yet families of seven colour-blind women available, most of them collected by Mr. Nettleship. They have in all seventeen sons, and all those are colour-blind. We only know the condition of the father of these women in three cases, and in those they are colour-blind.

The importance of this kind of investigation in the physiology of disease is surely this: not only does it enable us to make rules concerning descent (which are liable to all sorts of aberrations owing to various influences), but it gives us an insight into the pathology of these diseases. Colour-blindness, for example, we might have thought was due to the *absence* of something from the body. But from its genetic behaviour we know it is a condition due to the presence of something. It is in all probability due to the presence of some substance which may possibly have an effect somewhat comparable with that produced by nicotine poisoning, producing as this does paralysis of the colour sense.

We have a difficulty in dealing with sex-limited cases other than colour-blindness, that we nearly always find too many persons are affected and too many females carry it on. Herringham's family showing peroneal atrophy is a striking illustration of this difficulty.[1] I cannot yet suggest any real explanation of that discrepancy, and in hæmophilia, where we think we have traced similar rules on these lines, the numbers depart very widely from our expectation. There is, perhaps, a way of dealing even with these exceptions, but I should not be justified yet in suggesting that it is correct. As regards pseudo-hypertrophic muscular paralysis, the pedigrees revealed much irregularity, and it is only in general terms that the descent can be described as following the ordinary sex-limited rule. From a rough tabulation I get the numbers 115 affected, 80 normal where the expectation is equality. When Sir William says no male has been known to carry on the disease I think he must admit we have not yet evidence concerning *affected* males who have lived long enough to have children and show us whether they can transmit it or not. According to our rule, which is not followed with very great accuracy in pseudo-hypertrophic paralysis, the normal males cannot transmit, but abnormal males, if they lived to breed, I think would transmit to their sons.

Dr. G. H. Savage: I feel the responsibility which has been placed upon me, and I feel that it will be difficult in the time allowed to do more than express in general terms my *faith*, which is the result of nearly half a century of experience. First, then, there is a very widely spread feeling that of all the neuroses insanity is the one which is most likely to reappear as the result of parental defect. I at once admit that a very large amount of mental disorder is connected in one way or another with parental weakness; I therefore must admit that some things which

[1] *Brain*, 1889, xi, p. 230.