On heredity in relation to disease : the Harveian Oration for 1908, delivered before the Royal College of Physicians of London on October 19th, 1908 / by J.A. Ormerod.

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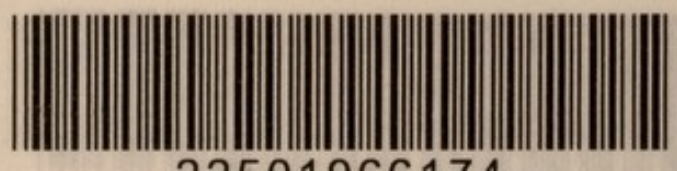

ON HEREDITY IN RELATION TO DISEASE

THE HARVEIAN ORATION FOR 1908

DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON ON OCTOBER 19TH, 1908

BY

J. A. ORMEROD, M.D., F.R.C.P.

ASSISTANT REGISTRAR TO THE COLLEGE;
PHYSICIAN TO ST. BARTHOLOMEW'S HOSPITAL, AND TO THE NATIONAL HOSPITAL FOR THE PARALYSED AND EPILEPTIC, QUEEN SQUARE; FORMERLY FELLOW OF JESUS COLLEGE, OXFORD

London
ADLARD AND SON
BARTHOLOMEW CLOSE

1908

Hon. Or.

TO

SIR RICHARD DOUGLAS POWELL, BART.,
M.D., K.C.V.O.,

PRESIDENT OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON,

THIS ORATION,

DELIVERED AT HIS REQUEST,

IS DEDICATED

WITH SINCERE RESPECT AND ESTEEM

THE HARVEIAN ORATION

ON

HEREDITY IN RELATION TO DISEASE

Mr. President, Fellows of the College, and Gentlemen,—My first duty is to thank you, which I do most sincerely, for entrusting to me the very honourable, though very arduous, duty of delivering the Harveian Oration this year. Such an honour must bring to the mind of any man—it certainly did to mine—first a feeling of pleasure and of pride, which I hope may be pardoned, and next a feeling of much anxiety and misgiving as to one's qualification for the task. For it is indeed a serious thought that ever since 1656, with but few intervals, this

oration has been delivered by a long line of distinguished physicians, who have vied with one another in holding up to admiration the life and work of the illustrious man whom we commemorate to-day. Certainly, had it been possible, I should have wished to bring before you fresh facts about Harvey, or to present some fresh aspect of his genius or his character. But that I cannot hope to do. For have we not already excellent lives of Harvey, two of them, at least, recently written, the work of skilful and sympathetic historians like Dr. Norman Moore and Mr. D'Arcy Power? And have not Harveian orators within our recollection elucidated fully the leading points and bearings of Harvey's work? Dr. George Johnson vindicated the originality of his great discovery; Sir Edward Sieveking brought before the College his re-discovered Lumleian lecture notes; Sir William Church has traced, from Harvey as its source, the rise of physiology in England; Dr. Payne has shown us the influence of Galen upon Harvey; Dr. Norman Moore and Professor Osler have drawn for

us brilliant word pictures of the man, his times, his friends, and his lectures at this College. Alas, that I cannot compete with them! that I have no fresh offering to lay on Harvey's shrine! and that I can only bow my head, as do we all, in memory of this great and good man, of his noble character, his transcendent genius, and his immortal discoveries.

But there are certain definite wishes expressed by Harvey about this oration. One is that there be "an exhortation to the Fellows and Members to search and study out the secrets of Nature by way of experiment." Now, as to experiment in the limited sense of physiological experiment, may we not say that this wish has attained its consummation? No reasonable medical man, certainly no Fellow or member of our College, would deny the greatness of the debt which medicine owes to experimental science. How far would the science and art of medicine have progressed without a knowledge of the circulation?—a knowledge which was obtained, as Harvey himself tells us, by experiment, by the

vivisection of many animals. The interdependence of modern medicine and experimental science was shown by your orator of last year, Dr. Frederick Taylor, so fully that I need not tread that ground again. It is true that we cannot all be experimentalists either in physiology or in other branches of science. But there is no need to place that narrow limit on Harvey's words. Certainly he speaks to each and all of us; but I think he means to emphasise here, as he so often does elsewhere, the importance of independent individual research, whether by experiment or observation, as opposed to a blind or lazy submission to current theory and authority. Knowledge of other men's opinions he certainly did not under-rate, for he was himself a most learned man; but he refused to let learning trammel investigation, and would not look at Nature through the distorting medium of a theory. And this frame of mind is as valuable now as then, and necessary, above all things, in the study of medicine, for of many medical theories one is tempted to say:

"Our little systems have their day;
They have their day and cease to be."

Another wish of Harvey's is that there should be "a commemoration of all the benefactors of the College by name," "with an exhortation to others to imitate these benefactors." As a benefactor who has not yet been mentioned in an Harveian oration, I ask you to honour to-day Dr. Charles Coats, a senior Fellow of our College, who has given a sum of £1000 towards providing some hospitable entertainment for our Members and Licentiates; this idea, suggested as I believe, Sir, by yourself, took a tangible form in the successful conversazione of last summer. Such hospitality is entirely consonant with Harvey's spirit, and that entertainment of the Members and Licentiates was the proper complement of the "General Feast" which he instituted for the Fellows to-day.

Now the names of those benefactors who have founded lectures, scholarships and prizes are recorded with all due particulars in the Annual List of the College, and are so well

known to you that I need not recapitulate them. But besides these, and others than these, who have given money, lands, books or other good things to the College, there are those who have devoted their time and talents to its service, or who have shed a lustre upon it by their learning, their discoveries, or their distinguished career. They, also, in the truest sense are benefactors of the College. I look in that invaluable book, Dr. Munk's 'Roll of the College of Physicians,' and I see—first, a long list of Presidents under whose care and devotion the College has thriven, reaching back from yourself, Sir, to our revered founder Linacre; next, men famous in science, physicists like Gilbert, Wollaston, Thomas Young, Arnott; chemists, such as Prout and Alexander Marcet; naturalists and botanists, such as Fothergill, William Pitcairn, Sir Hans Sloane; anatomists and physiologists, at whose head stands Harvey himself, Richard Lower, and such great names as those of Glisson, Havers, William Hunter, Wharton, Willis. There have been famous authors

and men of letters—Sir Thomas Browne, the anniversary of whose birth and death is to-day, Akenside, Arbuthnot, Garth, and (strange contrast) Stukeley the antiquarian, and many others well known for scholarship, learning and literary talent. There are the great masters and discoverers in medicine, such as Sydenham, Matthew Baillie, Bright, Addison. And some have been also known for their simplicity of character, their high ideals, and their life of transparent goodness. Such I think must have been David Pitcairn, of whom Dr. Munk says that he was simple, gentle, dignified, and very kind of heart; and such William Babington, of whom the same authority says, "History does not supply us with a physician more loved or more respected," and such a one was Peter Mere Latham—scholar, physician, inspiring teacher, eloquent writer, high-toned gentleman, devout Christian.

I know that one of our Fellows, whose untimely death we all deplore, took Dr. Latham, though he never saw him, for his model and example.

These are but a few of the many noble figures which fill the great pageant of our past; but need I, Sir, say more? For I am sure that Fellows of the College know so well the lives and works of our illustrious predecessors that for an "exhortation to imitate them" it will suffice to have recalled their names.

Many of my predecessors in this office have varied the theme of their Harveian oration by introducing into it some subject of general medical interest, and I ask your leave, Mr. President, to follow their example. I desire to direct attention to the great subject of heredity, and in particular, heredity in disease. A distinguished German physician has said, "There are no inherited diseases."* We need not argue that, for we should all admit that heredity has much to do with the production of disease. Now of that mysterious thing inheritance I need only say that it lies at the very root of our being both as individuals and as a race, as, indeed,

* Martius, 'Krankheits-anlage und Vererbung,' p. 14, (Leipzig and Wien, 1905).

is recognised in the proverbs and the religions of all nations. "Fortes creantur fortibus," said Horace. "The fathers have eaten sour grapes and the children's teeth are set on edge." The Chinese worship their ancestors; and there are words familiar to ourselves concerning a visitation "unto the third and fourth generation."

This year, too (1908), is the fiftieth anniversary of the paper written by Charles Darwin and Alfred Wallace "On the Tendency of Species to form Varieties, and on the Perpetuation of Varieties and Species by Natural Means of Selection,"* which constituted the inception of that theory of evolution which has since dominated scientific thought, and which has for its basis the facts of inheritance.

But granting the importance of the subject, what has it to do with Harvey? Not much, perhaps, if we limit our thoughts to his great and enduring work on the circulation of the blood. But we know that other problems in

* Read before the Linnæan Society of London, July 1st, 1858 (*vide* 'Times,' June 30th and July 1st, 1908).

physiology occupied his mind. It is true that it was late in Harvey's life when his friend Dr. Ent obtained from him for publication his book 'De Generatione Animalium,' and almost against his will, for he knew that it was incomplete. Yet it seems that he had been patiently collecting facts for it many years before, and one whole section of it, on the generation of insects, had been destroyed by his political enemies as ruthlessly as they might have wrecked a cathedral. One is tempted looking on his two great works to contrast them by saying, that the 'De Motu Cordis et Sanguinis' arose complete, conclusive, victorious, like Pallas from the head of Zeus, while in the 'De Generatione' we witness his painful and laborious searchings after truth. But that would be a superficial contrast, for we know that the truth concerning the circulation was incubating in his mind for some ten years before it found final expression, and we have been taught by the Harveian orator of two years ago that the growth of truth is slow. Granted that in the 'De Generatione' he did not attain to the

full knowledge which he desired (that, indeed, was impossible with the meagre means of observation at his command), yet we cannot but admire his method in the collection and presentation of facts within his reach. I imagine that no better account of the phenomena of development could have been given at that date than Harvey gives in his chapters "On the Inspection of the Egg," and "Of the Order of the Parts in Generation as it appears from Observation." It is only when facts fail him that we fail to follow his conclusions. To give an example: "It is certain," he says, "that no semen reaches the uterus"—he had no microscope wherewith to identify the spermatozoa—"therefore the woman becomes fecundated without the co-operation of any corporeal agent, in the same way as iron touched by the magnet is endowed with its powers and can attract other iron to itself."* A bold analogy indeed, drawn from a branch of science which then was very young; but it shows, like many other passages

* 'Harvey's Works,' translated by Willis for the Sydenham Society, 1847, p. 575 ("On Conception").

from his works, that Harvey, with all his zeal and reverence for facts, had his gaze fixed on the great mysteries of life; on the marvel of conception, on the efficient cause (to use his own phrase) of reproduction, and on heredity in its widest sense. For does he not himself say: "In truth there is no proposition more magnificent or more useful to ascertain than this: How are all things formed by an univocal agent? How does like ever generate the like? And this not only in productions of art (for so house builds house, face designs face, and image forms image), but also in thing relating to the mind; for mind begets mind, opinion is the source of opinion. Democritus with his atoms, and Eudoxus with his chief good, which he placed in pleasure, impregnated Epicurus, the four elements of Empedocles, Aristotle; the doctrine of the ancient Thebans, Pythagoras and Plato; geometry, Euclid. By this same law the son is born like his parents, and virtues which ennoble and vices which degrade a race are sometimes passed on to descendants through a long series of years. Some

diseases propagate their kind, as lepra, gout, syphilis and others. But why do I speak of disease, when the moles, warts and cicatrices of the progenitor are sometimes repeated in the descendant after many generations. Every fourth birth, says Pliny, the mark of the origin of the Dacian family is repeated on the arm."

"Why may not the thoughts, opinions and manners now prevalent return again, after an intermediate period of neglect? For the Divine mind of the Eternal Creator, which is impressed on all things, creates the image of itself in human conceptions."*

I quote these words of the great master in the hope of persuading you that some remarks on heredity may not, after all, be alien to an Harveian oration; and if I invite your attention to that subject for the brief time that remains, it is not, believe me, with any vain-glorious expectation that I shall add to your knowledge, either of facts or of theory, but only that I may perchance—again to quote the words of Harvey—"stir up the

* *Ibid.*, p. 582.

intellects of the studious to search more deeply into so obscure a subject."

It would be interesting, doubtless, to consider what answers modern authors make to the question over which Harvey puzzled, namely, How comes it that the embryo is laid down, with definite parts, in a definite order, and so that it eventually resembles its parent? That would mean a consideration of such theories as the pan-genesis of Charles Darwin, the determinants of Weismann, and the mneme or unconscious memory of Richard Semon—a doctrine set forth, you will remember, by Francis Darwin in his Presidential Address to the British Association this year. But these things I am not competent to expound, neither would time permit me to try. I will therefore only raise such points as seem to have direct practical bearings for us.

And first comes the old question, "Are acquired characters transmissible?" Have those external forces and events, which help to fashion our own life and being, any similar effect, through ourselves, upon our unborn

children? I think that the plain, unlearned man would certainly say "Yes," and so did the learned till a short time ago. Lamarck's views of natural history, and the theory of natural selection as first propounded by Darwin, assumed the possibility of such transmission, and numerous illustrations of it as regards man and his diseases were collected, perhaps in an uncritical fashion, by Prosper Lucas and others. But it is incompatible with Weismann's theory of heredity, which is now so widely held. The central idea of that theory is the "continuity of the germ-plasm." By germ-plasm is meant the formative tissue, out of which, or under the guidance of which, each individual is fashioned. It matters little to the theory whether this germinal plasm is identified with the germinal cells (as formerly), or with the much minuter particles of their nuclei known as "chromosomes." The germ-plasm is continuous, that is to say, it is not manufactured afresh within the individuals of each generation for the purpose of procreating the next, but it is handed on from generation to generation, only changing

in this sense, that as each successive individual is made a portion of the germ-plasm is set aside within him whereby he will carry on the work of generation when his elders have perished. So that we are not links in a chain of life, but rather flowers or leaves which spring from a common stem, the germ-plasm. And in the same way I am not, strictly speaking, my son's father, but his elder brother (to be accurate I should say his half-brother), nor am I my father's son, but his younger brother; the real father of us all is the family germ-plasm, and my duty to that father is to accommodate him in the house he has built—my body—till he has built himself a new one—my son's body. The reason for the resemblance of successive generations to each other is now obvious; it is because they are all brothers, made out of the same stuff on the designs of the same architect. It is obvious, too, that the effects of external conditions on one generation will not be reproduced in another, unless the same external conditions happen to act again. If a caterpillar has gnawed a hole in a leaf

upon a tree, the other leaves will not have holes in them unless the caterpillar has gnawed them too.

Then, do the ills acquired by the parents have no effect on the well-being of their children? Few people, surely, would maintain that. For the germinal plasm is lodged, at any rate, in the parent's body; if he dies, it dies; and if he suffers from any deeply reaching disorder of nutrition, the probability is that it must suffer too. And such nutritional probabilities, I need hardly say, are numerous. We need not suppose, then, that exhausting diseases which may affect the whole organism, such as alcoholism, diabetes, syphilis or phthisis, are without effect upon the health of our children. And is it not also possible that similar far-reaching effects may be produced by other influences not strictly nutritional, say, for example, some nervous shock? May not a violent commotion of the branches of the tree affect its stem?

Still, it is one question whether disease acquired by a parent can produce ill effects

on his children of a general kind (a thesis which to my mind can hardly be denied); it is another question whether, when a patient has acquired a particular disease, disease of the same or of a similar kind is likely to occur in his children? Those who deny this absolutely say, first, that it never happens. Observation must be the test of that. Secondly, that it cannot happen, because it is contrary to theory, and because we know of no mechanism whereby the body-cells could communicate their modifications to the germ-plasm. But ought the door to be slammed in the face of further inquiry? Is there not still here a legitimate field for observation?

At first sight there appears to be a glaring instance of such transmission, that is, syphilis. But this is dealt with as follows: Either the child imbibes the virus *in utero* by the placenta from an infected mother—this is evidently an antenatal infection rather than inheritance; or else the virus is introduced by the sperm-cells of the father at the very moment of conception—this again, whatever

it may appear to us, is to the biologist not inheritance, but an infection of still earlier date than the last. Similarly it is denied that there can be a true inheritance of any microbic disease whatever. Suppose we assent to that, yet susceptibility to such diseases, in either a plus or minus direction, that is, proclivity to them or power of resistance to them, may be inherited. And may not such susceptibility be first acquired and then transmitted? When measles appeared in Fiji for the first time its ravages were far more severe there than among ourselves, with whom it has long been endemic. The simplest explanation of this (I know there are others) seems to me to be, that we have acquired and then perpetuated some degree of resistance to the disease. Suppose that a man of healthy stock acquires phthisis, will his children be more prone to phthisis or no? Our Treasurer, in his 'Treatise on Gout,'* says "the fact of acquired gout must be accepted." Suppose, then, a man of healthy

* 'A Treatise on Gout,' by Sir Dyce Duckworth, London, 1889, p. 129.

stock acquires gout, are his children likely to be gouty? Suppose, again, that a man in consequence of a blow on the head becomes, like Brown-Sequard's guinea-pigs, epileptic, is there any risk that his children will be epileptic? Suppose that a man has syphilis in early life, and later on becomes a general paralytic, ought we to feel more anxious about the mental future of children begotten during his last illness than about that of his earlier ones?

I confess for myself that I do not know the answer to these questions, but I think that there are those among my audience whose experience could supply it, and who are well qualified to "search and study out this secret of Nature," whether acquired diseases are in any degree transmissible to our children or no.

I must now refer, though in the briefest possible way, to the work of Mr. Francis Galton, Professor Karl Pearson, and those others who have enriched the study of heredity by the method of statistics, if only to express my admiration for their arduous

labours. It may be that statistics do not appeal so forcibly as they ought to do to the medical man, because he has principally to deal with individuals. Neither have statistical methods, so far as I know, been largely applied as yet to the subject of heredity in disease. But nevertheless the general principles evolved from them must have their application for us. Thus the "law of ancestral inheritance" reminds us that we are hybrids—mongrels in an extreme degree—or to put it more pleasantly, that our inheritance is very composite, a patchwork or mosaic pieced together from the characters, first of our two parents, next of our four grandparents, and then in a diminishing ratio from an almost infinite number of ancestors, who probably included all sorts and conditions of men. Secondly, the "law of filial regression or correlation" declares that although children resemble their parents in the main, nevertheless, unless constant attention be given to breeding, there is a tendency among the descendants of any individual parent to smooth out any striking

peculiarities he may have possessed and to bring them, whether it be upwards or downwards, to the average level of his multitudinous ancestry. So that the average man cannot hope to escape mediocrity, unless, as the saying goes, he has been very careful in the choice of his ancestors.

But the mention of the word "hybrid" naturally leads our thoughts to the discoveries of Mendel. Now, were romance permissible in an Harveian oration, it might well be evoked by the story of Gregor Johann Mendel, peasant-born, priest by vocation, yet a student of science, and a man of rare scientific insight; whose life was spent as priest and as Abbot at the Monastery of Brünn, and whose leisure was spent in the study of hybridisation of plants. He died in 1884 unknown to scientific fame, and his work, buried in the proceedings of a local scientific society, was like to have died with him; but it has been disinterred in this century by those who recognise in it the hand of genius, and compare it in importance to the work of a Newton or a Dalton.

It is to Professor Bateson that we in this country are chiefly indebted for the exposition and elaboration of Mendel's work. The principles of Mendelism, as it is now called, are admirably summarised in a little book by Mr. Punnett.* I shall borrow from him and not tax your patience long.

Mendel showed that in the study of inheritance it was possible to select certain simple characters whose nature was more or less opposed, such as tallness and dwarfism, roughness and smoothness, colour differences and the like. These could be studied apart from other characters, and were found by him to behave in a definite way, as follows: Suppose a plant which is of a pure tall breed is fertilised from a similar breed, the resultant offspring is of course the same, viz. pure tall; and from a pure dwarf breed treated in the same way the results are pure dwarfs. If a pure tall, however, be fertilised from a pure dwarf, the result must be a generation of hybrids; and one might expect them to be of medium height. But this is not the case;

* 'Mendelism,' by R. C. Punnett (Macmillan, 1907).

they are all tall. It looks as if the tallness had swamped the dwarfism; so that we may call the tallness a dominant character and the dwarfism a recessive character. But though these hybrids are tall in appearance, the dwarf element has not wholly disappeared, it remains in respect of their powers of propagation. For if these tall hybrids be interbred together the dwarfism comes out again in their progeny; so that in the third generation there are some tall, some dwarf. Moreover, there is in this third generation a definite proportion between the two varieties, namely three tall to one dwarf; or to speak more accurately (as can be proved by further interbreeding), one pure tall, two hybrids which appear tall, and one pure dwarf. The theoretical interpretation of these facts is that the pairs of characters which behave in this way (allelo-morphic pairs as they are termed) do not blend in the germ-cells or gametes, but that each gamete carries either one of the characters or the other; and further, that the difference between a pure breed and a half-breed is this, that in

a pure breed all the gametes carry one of the characters, to the complete exclusion of the other, while in a half-breed half the gametes carry one character and half carry the other.

Mendel made his classical experiments on plants; they have been repeated by other observers, not only with plants, but with many forms of animals, *e. g.* insects, snails, poultry, pigeons, rats, mice, rabbits; and many characters have been studied from this point of view. One result may be quoted as specially interesting to physicians. It is that when a certain species of wheat which is very susceptible to the ravages of a fungus which causes "rust," is crossed with another species which is not susceptible, the immunity to rust which reappears in the resulting strains of wheat distributes itself in the Mendelian proportion. This suggests the possibility that something of the same sort may hold with respect to our own susceptibilities to disease, and raises the very questions which interest us most. For we want to know whether Mendelian laws are applicable to

man, to his normal characteristics and to conditions of disease, and how far they are applicable.

This question cannot be answered completely. Observations have been made (many of them, I imagine, under the inspiration of Professor Bateson) on various points, such as the colour of the iris by Mr. Hurst; hereditary diseases of the eye, such as congenital cataract, night-blindness, and colour-blindness by Mr. Nettleship; hæmophilia, albinism, alkaptonuria by Dr. Garrod; hereditary deformities of the limbs by Farabee and others.* Dr. Gossage has rightly drawn attention to the importance of hereditary diseases of the skin, which are easily observed, and has himself investigated the condition known as tylosis of the hands and feet.† It would appear that in some cases the Mendelian proportion works out—in enough, perhaps, to encourage further research; but I do not know whether more can be definitely said. The difficulties are sufficiently obvious. The

* *Vide* Professor Bateson's Address to the Neurological Society, 'Brain,' vol. xxix, p. 157.

† 'Quarterly Journal of Medicine,' vol. i, No. 3, p. 331.

only method of inquiry at present open seems to be the patient collection of pedigrees; experiment is possible with plants and animals, but not with mankind. We cannot pick parents to breed from. The pedigrees, too, must be complete, not only as to the number of diseased people, but also as to the number of the normals, since the proportion between the two is a vital point. A pedigree should embrace at least three generations, therefore the facts can rarely be the result of the physician's direct observation. Again, the numbers in human families are at best so small that a single vitiating instance may make a large error in the proportion of normals to abnormals; and it is difficult to know what to do with still-births, children who die young, or others of whose condition nothing may be known. This numerical difficulty may be partially met by adding up the totals of many families, but that is certainly a method to be employed with caution. And this, too, has to be remembered, that certain modifications have been introduced into the original Mendelian laws which

are, no doubt, necessary and correct, but which tend to mask their simplicity of application. Such, for instance, is the interaction of two sets of characters, whereby the dominance of one member of an allelomorphic pair over the other is rendered conditional on the presence of a third character. Thus it has been supposed, on the analogy of other facts, that hæmophilia is a character which becomes dominant or recessive according as the sex of the person is male or female, and that this accounts for the rarity of female bleeders. Such modifications and complications may make the interpretation of a pedigree as difficult as its construction; and it may be necessary to refer it for its interpretation to someone who knows the business well.

In some diseases, where family pedigrees are not easily obtainable, all that we can say is that the facts agree with some side deduction from Mendel's theory. It appears that first-cousin marriages form one of the causes of alkaptonuria, and it is pointed out that this is just what would happen if alkap-

tonuria were a rare recessive character in the Mendelian sense. The character, being recessive, would not appear on the surface until two similar hybrids—hybrids, that is, possessing the character—intermarried. And since the character is rare, two such hybrids are not likely to meet unless they are of the same family. And that is one thing that may be said, on Mendelian principles, about consanguineous marriages in general. They are a means of bringing to light hidden (recessive) characters. Such characters may be good or bad; we cannot tell beforehand. So that the State of Wyoming, which Lord Rosebery tells us* has forbidden first-cousin marriages, may have prevented evil or may have stifled good.

The study of heredity in disease is likely to be particularly interesting in the sphere of the nervous system. For in the first place heredity is here an agent of great power; it ranks with injuries, infections and intoxications as one of the principal causes of chronic nervous degeneration. Again, in proportion

* 'Times,' July 1st, 1908.

as our civilisation becomes more and more elaborate, so we depend for progress more and more upon our nervous system, upon its flexibility and capacity for adjusting itself to the complication of our surroundings. This suggests the possibility that the ways in which heredity moulds this plastic material may be varied; that just as a young and growing community has to feel its way towards the establishment of its laws or its political system, so here, perhaps, those sequences which we call laws of heredity may not yet have attained a rigid uniformity. However this may be, there are at least two ways in which heredity manifests itself in diseases of the nervous system. The first relates to that common group of maladies known as neuroses. This group includes such affections as epilepsy, insanity, hysteria, neurasthenia, tics, alcoholism, etc., which are characterised, so far as we know them at present, by perverted nervous action rather than by coarse structural disease. They are related together in this way, that they seem to be the expressions, varied and inter-changeable

inter se, of some one underlying nervous defect; we may perhaps call them the ill-timed or inappropriate response of a nervous system which adapts itself badly to its surroundings. This deeply-seated nervous defect, whatever its precise nature may be, is hereditary in a high degree, so that the "neuropathic family" is now notorious in medicine. One member of it may be epileptic, another insane, another eccentric and so forth, but the faulty nervous constitution is the same in all. So much we know, but there is much more that we should like to know. How, asks Dr. Savage, in his Presidential Address to the Neurological Society,* does this instability of nervous system originate? May it have begun through faulty nutrition of some ancestor, so profound that his germinal tissues suffered with the rest of his body? That might suggest a hope that in time it might be rectified by reversing the process. Or may it be that his germinal tissues were old and effete when he undertook the process of procreation? Or is it, after all, some deeply ingrained fault, origina-

* 'Brain,' vol. xx.

ting we know not how, and curable only by extinction of the stock or by repeated crossings with others that are more stable? We cannot answer certainly. Nor can we always tell what determines the special form of neurosis in the different individuals, why some should have epilepsy, some insanity, and so forth; nor why, as sometimes happens, some one of these morbid manifestations should repeat itself, and not alternate with others. Melancholia, Dr. Savage* tells us, is particularly apt to recur in several members of a family, and Dr. Aldren Turner says the same thing, I believe, of epilepsy.† Nor yet do we know why some members of a neuropathic family should appear perfectly normal, and some perhaps even better than their fellow-men. Here we think of the old saying that genius is allied to insanity. Mendelian writers sometimes tell us that we should learn the lesson of the blue Andalusian fowl. That farmyard sermon teaches us, *inter alia*, that from crossing two pure

* 'Brain,' vol. xx, p. 17.

† 'Epilepsy,' by Dr. Aldren Turner, p. 26; Macmillan, 1907.

breeds which are considered undesirable a mongrel may result of a desirable character. May this happen with neurotic stocks? Can two such families atone for their existence by combining to produce a genius? One would hardly care to advise the experiment, and luckily our advice as to pairing is seldom asked and still less often acted on. The science of eugenics is still in its infancy; let us hope that when it becomes an active force physicians will have acquired such knowledge as will enable them to take their proper share in controlling it. Lastly, there is the important inquiry, What relation have these nervous manifestations, and the diathesis in which they have their root, to other diseases of more tangible nature, to gout, rheumatism, tuberculosis, the febrile state, etc.? That there are such relations, and some rather close ones, this we know, but little more.

The second way in which heredity manifests itself as regards nervous disease is different. In this form a certain disease, definite in type, whose identity as a rule is

easily recognised, appears in several members of a family; it may be in successive generations, it may be only in one generation. This class constitutes the group known as family diseases of the nervous system, which was discussed before the College last summer in a most interesting lecture by Professor Raymond. Such family disease is by no means limited to the nervous system, but in that sphere numerous and remarkable examples of it are to be found. Friedreich's ataxia is one of the best-known examples. In this class of disease the precision with which the features of the particular complaint reproduce themselves is generally remarkable, and contrasts strongly with the shifting character of the neuroses which we have just considered. There are, I know, exceptions to this rule, which have been much insisted upon lately, either where the disease is incompletely developed in some individuals, or where different types may appear in different members of the same family; but still, I think that, generally speaking, the reproduction is fairly accurate,

so that the particular disease can be as easily recognised as can tabes, disseminated sclerosis, or other non-family nervous disease. A general neuropathic taint need not necessarily exist in the family, though, of course, it may. The majority and the best known of these diseases present the clinical picture of a slowly progressive incurable paralysis, which may correspond anatomically to an exceedingly definite degeneration of certain nerve tracts. Thus Friedreich's disease affords us an exquisite example of combined system sclerosis beginning in the posterior columns, then affecting the pyramidal tracts, and involving in advanced cases the afferent tracts to the cerebellum as well. Hereditary spastic paraplegia has been shown by Strümpell to depend on a degeneration of the pyramidal tracts.* Yet the patients are not born with these lesions, so that we cannot exactly call them malformations; they are born with an hereditary weakness of

* Combined with a slighter degeneration of certain ascending tracts, *vide* Strümpell, 'Archiv f. Psychiatrie,' vol. x, 1880, and xvii, 1886, and 'Deutsch. Zeitschrift für Nervenheilkunde,' 1893.

these nervous tracts, which break down under the stress of living. The age at which symptoms begin differs largely in the different diseases; the onset may be in early life, in early or late adolescence (instances of all these dates can be given in Friedreich's disease); in middle life or even later, as in Huntington's chorea or the spastic paraplegia just quoted from Strümpell. It is strange to think that a man can develop at that age a disease which must have existed potentially all his life. The date of onset may be influenced, too, within limits, by family proclivity or circumstances; in a series of brothers and sisters it often repeats itself.

Now, though the presence of a definite organic lesion and a progressive downward course are the rule for these complaints, this is not so for all of them. Contrast the hereditary chorea of Huntington, which is fatal, and in which lesions of the cortex have been found by Michell Clarke* and others, with family tremor, which is not necessarily progressive, and for which we know no anatomical

* 'Brain,' vol. xx.

basis. Contrast, too, in this respect, muscular dystrophy, which may slowly reduce a patient to the condition of a living skeleton with the perverted condition of muscular contraction known as myotonia congenita or Thomson's disease.

Notice, too, that most remarkable family disease called "periodic paralysis," in which the patient experiences recurrent attacks of paralysis, so complete that even the electrical reactions of the muscles disappear; yet the attack passes off and he is well in the intervals. This affection has been traced back through as many as five generations. There can hardly be a gross lesion; and the suggestion has been made that some poison is at work, perhaps produced by the patient's own faulty metabolism; an "inborn error of metabolism" like those with which our Croonian lecturer, Dr. Garrod, has made us acquainted.

In these family nervous diseases the curious phenomenon of sex limitation is sometimes seen, and generally in this sort, that females are themselves not affected, yet they transmit the disease. This was pointed out, I think, by

Sir William Gowers,* in pseudo-hypertrophic paralysis; and in the remarkable pedigree of peroneal atrophy published by Dr. Herringham in 1889† it is a striking fact. Yet in peroneal atrophy it is certainly not the rule; and in sundry other family diseases I do not think it occurs at all.

Lastly, as to the essential nature of these diseases. They have been called family diseases, if I mistake not, in order to avoid the distinct assertion that they are hereditary, *i. e.* transmitted from ancestors. But why should we not assert this? It is true that such disease may break out in a family of brothers and sisters without obvious ancestral taint; but in all these instances there is an absence of other sufficient cause; and they can be supplemented by quoting other families in which we know the disease to have been handed down. How, too, when cousins are affected? The common cause must then lie further back than the parents or the upbringing of one particular family. Indeed,

* 'Pseudo-hypertrophic Muscular Paralysis,' pp. 21, 23, Churchill, 1879.

† 'Brain,' vol. xi, p. 230.

if we refuse to call these complaints hereditary because we cannot always trace the heredity, we should on the same ground refuse to call them family affections. For we often meet with isolated instances, sporadic cases where only one member of a family is affected. This is surprisingly frequent in Friedreich's disease. Still, it is a strange thing to witness when a disease, hitherto unknown in a family, arises without apparent cause, and involves in a progressive paralysis one after another of the brothers and sisters. What shall we call it? Is it a "mutation," a biological "sport"? Is the germ-plasm just trying a change, stimulated, it may be, by some untoward circumstance, such, let us say, as alcoholism in the father? Or shall we suppose that the disease has been in the ancestry all along, but hidden away as a "recessive" character, so that if we could push our researches far enough back we might find it? Let us remember the remarkable account given by Rutimeyer,* where no less than four families of cousins

* 'Virchow's Archiv,' Bd. 91.

(in various degrees) were affected by Friedreich's disease—a sure enough indication that there was some ancestral taint. Yet no case could be found among the ancestry till in the fifth generation a record was found of their common great-great-great-grandfather, who, on account of his unsteady gait, had been nicknamed "The Stumbler."

As to the actual pedigrees of these family paralyses, we are beginning now to acquire some tolerably complete ones, and it might be thought that this is just the class of disease which would lend itself to a Mendelian explanation. But I understand that there are considerable difficulties about this, so much, indeed, that it has been suggested that parental infection and not heredity is the real cause. But what infection could pass down for several generations, sometimes skipping a generation, sometimes limiting itself to the male sex? For myself I cannot imagine that, and I think that the key to this lock must be provided by the laws of heredity, whatever those laws may be.

But I fear, Sir, that in pursuing the sub-

ject of heredity I have already wandered too far. How shall I, in conclusion, come back to Harvey and to the College which he loved so well? Harvey himself in the presence of a great subject did not shrink from metaphor. He spoke of bodily conceptions and of conceptions of the mind almost as if they were one, and, in speaking of the generation and inheritance of ideas, he says: "Democritus and Eudoxus 'impregnated' Epicurus, and the four elements of Empedocles, Aristotle." Is it, then, too fanciful to ask, how does this College reproduce itself, and what laws of inheritance are at work within it, from generation to generation? Now, we are told that Nature has reserved the work of reproduction to herself, and left parents little to do in determining the inborn characteristics of their offspring; but we in this College have the privilege of actually choosing our successors. This inestimable privilege we delegate to no one, not even to a body of examiners; and we choose our new Fellows by co-option—the best of methods when well exercised, the worst when exercised badly.

Rightly, then, are we reminded each year of the responsibility which rests upon each of us in this respect, and rightly is that meeting of the Council, in which recommendations for the Fellowship are winnowed out, held to be of supreme importance. Is there, then, no continuity in the successive generations of the College? Does each depend on the mere caprice or individual likings of its predecessor? No; for we, too, have our "germinal plasm," which is continuous and everlasting; I mean the noble principles upon which the College is founded and by which it has ever been maintained—zeal for the pursuit of truth, whether in medicine or in other science; the dedication of knowledge thus acquired to the relief of human sickness and pain; self-effacement in the interests of the profession and of the College to which we belong; and above all, the spirit of unity and amity. For Harvey's last and best exhortation is: "To continue in mutual love and affection among ourselves," an exhortation which he enforces with the weighty words, "Concordiâ res parvæ crescunt, discordiâ magnæ dilabuntur."

ADLARD AND SON, IMPR., LONDON AND DORKING.