portal vein can be ligatured and the liver extirpated, without interfering with the circulation through the other abdominal organs. In one recorded experiment, the liver was extirpated after the administration of 25 grammes of dextrose and 25 grammes of starch. During the succeeding 10 hours, 220 cubic centimetres of urine were collected, which, on subjection to alcoholic extraction, yielded an indication of the presence of 0.5 gramme of dextrose. A further 200 cubic centimetres were secreted during the night, and this was found to be free from sugar. In a second recorded experiment, 75 grammes of dextrose were employed. During 12 hours after the operation, 330 cubic centimetres of urine were obtained in which 4.2 grammes of dextrose are stated to have been found, which represent a minute portion only of the dextrose administered. The intestinal contents, it is mentioned, only contained a trace of sugar.

Eck's fistula is the name given to an operative junction of the portal vein with the inferior cava, permitting of the former vessel being tied above the junction and thus cutting off the flow through the liver without interfering with the circulation through the abdominal viscera. The operation is naturally a very delicate and risky one, but it has proved susceptible of being performed upon dogs with survival of the animals in a satisfactory condition for a considerable time afterwards.

Hahn, Massen, Nencki, and Pawlow have published a communication in Schmiedeberg's *Archives*,² containing the results of observations on the effects of the operation upon the system. The operative part of the undertaking was performed by Massen and Pawlow, and the chemical part by Hahn and Nencki. A striking effect noticed was the production of an intolerance of animal food. The dogs subsisted well upon bread and milk, but meat produced a toxæmic state accompanied with various manifestations of nerve disturbance. The authors state that they never found albumin, albumose or sugar in the urine, but there is no indication of any idea of looking for sugar in connexion with carbohydrate food administration as a sequence of the position in which the liver was placed.

A communication entitled "On Carbohydrate Metabolism in Dogs with Eck's Fistula, whereby the Portal Blood passes direct into the Vena Cava without traversing the Liver" has been recently published by F. De Filippi of Rome in the *Zeitschrift für Biologie*.³ A series of observations was conducted upon the toleration of various carbohydrates after recovery from the operation, and finally the actual occlusion of the portal vein was verified by post-mortem examination. The ordinary food administered consisted of bread and milk and wheat-flour porridge, which never, it is stated, produced glycosuria. After the different sugars, however, glycosuria occurred when certain quantities were reached standing below those required to produce glycosuria in the case of dogs in the normal state.

Corresponding results, I perceive, are stated to have been obtained by other experimentalists. For instance, I observe it stated⁴ in connexion with the fate of sugar given to dogs with Eck's fistula, that Popelski, in 1898, found, after feeding with large quantities of saccharose, that against 1 per cent. of the ingested sugar eliminated by normal dogs, 13.5 per cent. was eliminated by the dog with the fistula; and quite recently mention is made by P. B. Hawk⁵ of absence of glycosuria having been observed in a dog with Eck's fistula on a diet of milk, bread, and potatoes. The concurrent testimony seems to be that whilst sugar can lead to the production of glycosuria, starchy matter, on the other hand, fails to do so.

Everything points to the existence of a missing link in the chain of events thus far reckoned to occur in connexion with the passage of carbohydrate from the seat of absorption in the walls of the alimentary canal to that of utilisation in the tissues. We know that small quantities of sugar reaching the circulation by intravenous injection, lead to the production of glycosuria, and why should they not do so when absorbed from the alimentary canal? The liver has been credited with safeguarding the circulation from the entry of sugar in a manner to occasion glycosuria, but how do things stand in the face of the evidence that has been just adduced, founded upon the state observed to exist after the abolition of the influence of the organ?

HEREDITY IN DISEASES OF THE NERVOUS SYSTEM.¹

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

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

Sudden cerebral seizures, apoplexy and the like, depend upon causes that take their heredity far away from the brain in which the lesion occurs. Yet the frequency in which heredity is active is most notable. In some families many members suffer earlier in life than the malady is really common. But we must look to the vessels and the cause of their degeneration for the mechanism by which the disease is produced and through which heredity acts. Toxic states, various in nature and origin, chemical and microbial, are potent causes of disease, but the range of heredity in their occurrence is small. The so-called "inherited syphilis" has, of course, nothing to do with heredity. I do not know of any observations on the children of those who suffer from it and their life-histories. Any influence heredity may have on the liability to suffer from bacterial maladies affecting the nervous system may, perhaps, be suggested by the discussion on the similar facts regarding tubercle. The part it may play in the secondary production of chemical agents from organisms acting on somatic processes is an important problem. It is presented by the paralysis that sometimes follows diphtheria. The experience of our fever hospitals may furnish evidence for or against any family tendency to suffer

² Band xxxii., p. 161, 1893.

³ Band xlix., 1907.

⁴ Maly's Jahresbericht, Band xxviii., p. 369.

⁵ American Journal of Physiology, vol. xxi., p. 259, 1908.

¹ A paper read before the Fellows of the Royal Society of Medicine on Nov. 11th, at the discussion on Heredity, with Special Reference to Cancer, Tuberculosis, and Disease of the Nervous System.

from it. I think the tendency is not directly proportioned to the severity of the primary disease. There must be very many instances of several members of a family suffering from diphtheria and it is most important that the records should be so kept as to facilitate observation of the disease in another generation of the same family. Such search will be necessary in the case of many diseases and will involve a special method of indexing; nothing can be achieved unless it is begun.

It would be wearisome even to enumerate the maladies from which we cannot hope to obtain knowledge but I may mention one class of disease on which we may hope for some facts. Though they are not primarily of the nervous system they often affect it gravely. There are those that consist of deranged chemical processes in the vital laboratory of the human frame giving rise to endogenous toxins. We see it in the nerve disturbance which occurs in diabetes, probably due to other material incidental to that by which the excess of sugar is produced, whether or not it is the same as that which often causes death. The heredity of diabetes is familiar but its thorough study is a difficult task. A child not seldom suffers before a parent. The endogenous poisons of what we call gout are certainly many and some also occur without this constitutional state. Both kinds may cause symmetrical symptoms in the extremities but of their nature we know nothing. It cannot be doubted that the processes of the body are largely influenced by heredity.

The cases of disease of the nervous system in which the influence of heredity is marked seem to fall in certain classes. One of these consists of the early abiotrophies. I proposed this term some years ago¹ as a convenient designation for the cases in which certain systems of structure in the nervous or muscular system have an essential defect of vital endurance, in consequence of which their life slowly fails. A marked example is presented by the hair follicles of the scalp, in consequence of which early and extensive baldness occurs in father and son, a convenient subject for the study of heredity. It is seen in the nervous system, as in hereditary optic atrophy, in which the onset is sometimes excited by some extraneous cause, inadequate alone to cause the enduring effect. Hereditary ataxy, or Friedreich's disease, is another, and so are the various myopathies. By "early" I mean those abiotrophies which begin before the development which coincides with growth is over, and often not many years after birth.

The muscles are not usually considered part of the nervous system although they present a close relation to it in intimate structure and function. We may take the most typical form of pseudo-hypertrophic paralysis as a convenient instance of the heredity of the abiotrophies. The muscular fibres begin to waste during the first seven years of life but the bulk of many of the muscles is actually increased by interstitial overgrowth of fibrous tissue and fat; certain muscles are small and some may seem absent from the first. This disease is due only to heredity, but the heredity is maternal only; it never comes from the father. The tendency to it is thus germinal, a potential defect of development in part of the ovum, that part which will become the muscles. But it is not usually in all the ova; some sons escape. The female children seldom suffer in this typical form, but they inherit the tendency, or some of them do, and their sons are prone to suffer. In the ova from which the daughters develop, the potentiality of the disease is not in the elements that develop into the muscles, but only in that portion of the protoplasm which will become the germinal tissue for another generation. The same facts are true of other early atrophies, in hereditary optic nerve atrophy, &c.; sometimes they are limited to males, but they are only transmitted by females. If the tendency is thus fixed in the germ tissue, and differently fixed, according to the resulting sex, does not the fact make it probable that the sex is also predetermined? Many have held this view and it is not easy to see how otherwise the facts of these diseases can be explained. The disposition to the disease seems seldom to be present in every ovum. Sometimes it apparently is in every male ovum. Every son has died, as in the well-known family described in the "fifties" by Dr. Meryon, but in that one daughter has failed to transmit the disease; another daughter has had two sons and three daughters—both the sons have died from it, all the daughters are free. In an instance which came under my notice long ago four

sons died but the fifth escaped and his sons, of course, are free, but the only daughter, herself free, has her only two sons both affected.

We have many similar instances of the disease in two generations. We have known it just long enough—sixty years—to find it in a second generation, but it is curious how seldom we are able to trace the typical disease in preceding generations, although we are not often able to exclude it from lack of knowledge. But I have met with it in the two sons of a lady (the third and sixth of seven sons) whose lineage and that of the mother of Meryon's cases can be obtained from the Peerage. (I cannot mention the names since members of the families are still alive.) The lineage presents a remarkable fact. Both mothers were descended from a certain duchess who was married in 1774, and in the case of each the descent is solely in the female line. The mother of Meryon's cases I will call Lady A and the other Lady B. Lady A was the granddaughter of the said duchess; Lady B is the great-great-granddaughter. There were sons in both lines, but from their ages at death in Lady A's family there can have been no case of the disease. In Lady B's there is only one that suggests its possibility. A son of her maternal grandmother died at 18, but some other cause is intrinsically more probable. We must, I think, regard it as of definite, though unknown, significance that both these maternal producers of the disease had a single ancestor, and, considering the relation of the disease to sex, their descent by the female line cannot be regarded as an accident. I can offer no suggestion of its meaning. But it is remarkable how free from the disease the ancestors of those who produce it generally seem to be. We may note that isolated cases are more frequent than groups, although the groups comprehend a majority of the actual cases. When females suffer males sometimes escape. Only once have I known the disease to occur in the offspring of first-cousins. There resulted four cases of albinism, one of whom had also pseudo-hypertrophic disease. Neither malady had occurred before. But there had been some previous instances of less close intermarriage during the preceding six generations, and, considering the relation of the disease to the ovum, it can hardly be ascribed to the consanguinity of the actual parents. Of the origin of albinism I hope we shall hear more in the course of the discussion.

Other forms of myopathy have been traced through several generations. The facial form of Déjerine and Landouzy has been traced through five generations. This form often does not begin early; its progress may go on through life, and males may transmit it. The first series of Déjerine and Landouzy, just mentioned, bears a distant but interesting resemblance to Mendel's facts. A man and woman married, the woman being atrophic. They had one daughter who was normal, who married a quite healthy man and bore three daughters, all affected. One of these married a healthy man and had two children, a girl, healthy, and a son in whom the atrophy only showed itself at 26, and did not become general until 50. He married a healthy woman and had nine children, six sons and three daughters. A son and daughter died in childhood; of the remaining seven, four were atrophic, two sons and two daughters. If we regard the normal state as dominant and the atrophy as a recessive state, its absence in the second generation, recurrence in the third, and equality in the fourth and fifth are noteworthy features. I have dwelt on these muscular maladies because they present features that are well defined, and because most, if not all, the early nerve abiotrophies agree with them in origin, even in their maternal heredity.

A second class may include the hereditary maladies which begin later in life, after the period of growth is over. They present persistent disturbance of function and are commonly hereditary, but from either side. In the so-called heredo-ataxy of Marie, the symptoms begin about 30 and are usually fatal in about 20 years. It has been found to depend on atrophy of the cerebellum associated with certain tracts of the spinal cord, at least in one case in which three generations were affected. Huntington's chorea begins usually in the senile period of life, but its heredity is well marked and so is that of the peculiar rigidity called Thomsen's disease, a life-long peculiarity of action of the motor nerve structures, also called myotonia congenita.

I must pass some interesting diseases, paralysis agitans, tremors, Graves's disease, &c., in which heredity can be

¹ THE LANCET, April 12th, 1902, p. 1003.

traced seldom but sometimes remarkably. I think it is probable that we shall hereafter find that special forms of heredity are associated with other characters in a manner that will make it an aid in distinguishing maladies that are now classed together but for this we must wait.

A third class of diseases in which heredity is operative consists of the so-called functional affections. Some of them vary extremely in degree and baffle attempts to group them so as to discover their relation to heredity. Such are hysteria and the defective nerve strength which may manifest itself in varied ways and which we are all drawn, sometimes against our better judgment, to designate "neurasthenia." Other functional disorders, such as chorea and neuralgia, have relations too complex for the clear discernment of heredity; and migraine, defined as it is, is connected with quite different constitutional states than disease of the nervous system. Two forms of functional disease have been much studied in relation to heredity, epilepsy and insanity. I propose to confine myself to epilepsy, leaving the relations of insanity to those who take part in the subsequent discussion.

Some cases of epilepsy are outside our subject. Those that result solely from organic lesions of the brain, from disease, or trauma, or difficult birth are not concerned with heredity. I confess I have always acted on the belief that the tendency to convulsion in such acquired cases, without other evidence of disposition, may be regarded as not transmissible. I have never hesitated, on this ground, to permit the marriage of a sufferer, and I have not had any evidence to show that I was wrong in doing so, however early in life the damage arose. I do not question the guinea-pigs of Brown-Séquard, but I do question an inference from guinea-pigs to men. But such cases of "organic epilepsy" are rare. They constitute so small a proportion of the cases as to have little influence in statistics of heredity. The difficulties in ascertaining the facts of family histories are vast. Among hospital patients genuine ignorance often hinders. A woman brought her son for epilepsy and denied that any of his relations had had fits. As soon as she had gone out of the room she returned with two of his brothers suffering from them. It had not occurred to her that a brother is a relation. In patients seen in private the stigma supposed to attach to some diseases leads to concealment, which produces actual ignorance in another generation. A middle-aged lady, with an epileptic nephew, denied any neurotic antecedents and was indignant when I told her that three great-aunts had been in asylums. But it was so.

In my own inquiries into the heredity of epilepsy I have limited myself to these two maladies, epilepsy and insanity. I find that in the cases seen in private there is a family history of one or both in 47 per cent., in antecedents and present or past collaterals. The difficulties I have just mentioned justify the assumption that at least 50 per cent., and probably more, really present a family tendency. Among hospital patients the number is not more than 35 per cent., so great a difference does ignorance apparently make. In the facts presented the percentage was taken from 2400 cases, of which 600 were seen in private. Heredity was ascertained in 39 per cent. of 1193 males and 43 per cent. of 1207 females. These proportions are much less than have been ascertained by others who have included a larger number of diseases. It may be well to confine myself to the cases in which a parent suffered. Jeremy Taylor tells us in one of his sermons that "an epileptick son doth often come from an epileptick father." Of the total cases in which inheritance was paternal the father himself suffered in 40 per cent., when maternal the mother suffered in only 36 per cent. When epilepsy itself occurred in a parent it was the father who was epileptic in 49 per cent. of the cases, the mother in 51. The cases with insanity in a parent are only one-third the number with parental epilepsy. Of the cases with parental insanity, the father was insane in 37 per cent., the mother in 63. One effect of heredity is to increase the female cases. Where it was absent the excess of males amounted to 4 per cent., but in cases with heredity the same excess was presented by females. This is partly due to the fact that inheritance is more frequently from the mother's side by 13 per cent., and that then females are in excess by 18 per cent. The influence of heredity is sometimes strikingly emphasised 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. 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. We hope to learn much regarding method from those who are here to-day. They have devoted much time and much ability to the scientific study of heredity, and they may tell us how to make our own observations more effective.

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HEREDITY IN CANCER.¹

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THE successful application of the comparative and experimental methods appears to be greatly narrowing the field of inquiry and dismissing many explanations of cancer—previously held with good reason—from further serious consideration. Although this is the case, we still know very little as to its etiology beyond the fact that it manifests itself under the most divergent conditions and in such a way that we may have to entertain the possibility of several etiological factors, some of which are external and some internal to the body. To these factors we are only justified at present in assigning an indirect and mediate etiological significance. The most satisfactory explanation of the causation of cancer will probably be that implied by the accurate description of the nature of the transformation of normal into cancer cells when this advance in knowledge shall have been attained.

In surveying the incidence of cancer in the vertebrate kingdom one has been struck by the fact that certain forms of cancer appear to preponderate in different classes. It is, of course, obvious that the incidence of cancer in representatives of the different zoological classes must differ, since, e.g., structures peculiar to mammals are absent in other vertebrates. But if we consider the mammalia themselves, it appears probable that some species are very liable to forms of cancer, from which others even nearly allied are relatively or altogether exempt, as illustrated, e.g., by the variations in the frequency with which cancer of the uterus or mamma occurs. Cancer of the breast, so common in the human female, is also common in the mouse and dog, but practically unknown in the cow, which, however, suffers quite frequently from primary growths of the liver and adrenal. These tendencies are so constant that it is difficult to escape the conclusion that they depend on innate characters which are hereditarily transmissible, and there can be no doubt as to their etiological importance, although we cannot yet penetrate to their meaning.

Even in the same species we meet with similar idiosyncrasies—e.g., in the greater liability of grey than of other horses to melanotic sarcoma. It may, of course, be argued that these peculiarities in the incidence of the disease are determined by peculiar environment, or by the use to which the organs are put in different species, although this would hardly hold for grey as contrasted with other horses, the disease in question affecting only the pigment cells of the skin. If we compare the tame albino mouse with the wild grey mouse the incidence of cancer is parallel in them, although the two varieties live under very divergent conditions; therefore the liability of the mouse to carcinoma of the mamma appears to be due to an innate tendency.

When we compare the large natural groups of vertebrates, or even the species of the mammalia, the grounds on which we may assume that differences in the incidence of cancer are innate and hereditarily transmitted appear safe. But

¹ A paper read before the Fellows of the Royal Society of Medicine on Nov. 18th, at the adjourned discussion on Heredity, with Special Reference to Cancer, Tuberculosis, and Disease of the Nervous System.