MORBID INHERITANCE IN AN ISOLATED RURAL COMMUNITY*

BY

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It will be generally conceded that a rural community—particularly one which is isolated by reason of its geographical position or by the deliberate choice of its inhabitants, or both—is the ideal locality in which to study the familial incidence of bodily characteristics and morbid processes. Here family trees may be traced for generations, as they can never be in cities, where so often all trace of relatives is lost, and where the population is so constantly shifting. Here, too, with a certain degree of inbreeding necessarily imposed on the inhabitants for generations past—indeed, for centuries—one is bound to come across rare recessive characters, much less likely to occur in communities where random mating is the rule rather than the exception.

For several years I have traced out family trees systematically throughout a village which has a population of about fifteen hundred and collected data concerning numerous morbid conditions. My investigations led me to the conclusion that heredity plays an even more important part in many varied conditions than is generally recognized; and it may be suggested that a careful tracing out of family trees of various patients by observers in different parts of the country might lead to the acquisition of much valuable and helpful information. It would be particularly helpful to have such systematic investigation carried out with special care in isolated rural areas, as the chances of occurrence of recessive traits are much higher in such places. Each year that passes gives greater facilities for travel and so lessens isolation. It would therefore be desirable to study this subject closely before random mating becomes more easy for dwellers in remote country districts.

From my original essay I chose eight of the many conditions studied—namely, hereditary cerebellar ataxia, progressive muscular dystrophy, the lymphatic diathesis, otitis media, hernia, cancer of the bowel, rodent ulcer, and hydramnios—giving pedigrees of representative families, together with detailed medical histories where of interest. A condensed report such as I have had to prepare here necessitates a ruthless cutting down of the material; so I shall omit the medical histories, except in one or two cases, and deal only with the more important points arising in the study. Of the fourteen pedigrees originally presented three of the most interesting are here shown.

Hereditary Cerebellar Ataxia

In the family reported in my original essay twenty-one members had developed hereditary cerebellar ataxia in four generations. The members of the last two generations shown in the genealogical tree are still too young

to reveal signs of the disease. The genealogical tree is unfortunately too large to reproduce here, and it is also impossible to give details of the medical histories of affected members.

One interesting point about the condition is that in several cases the symptoms first developed in a limb which had previously been injured. In one case the ataxia began in an arm which had been damaged in the war; in another in a leg which had been broken a short time before. The condition is a dominant one. Thus a member who died of pneumonia at the age of 30—several years before the average age of onset of the disease—nevertheless transmitted the condition to two daughters.

Five of the six children—all daughters—of an affected mother, who died in 1935, have a very pronounced strabismus. These five, whose ages range from 27 to 19, had "fits" in infancy. No member of any of the earlier generations squinted, so far as can be ascertained, nor is there any relation on the father's side with strabismus. There may therefore be a connexion between the strabismus and the fits. The occurrence of these fits—though convulsive disorders in infancy are of course not uncommon—in five of the six children of a mother suffering from a hereditary nervous disease appears to have some significance, and it would be interesting to see at a later date if these five girls developed the ataxic condition. I cannot discover whether any of the affected members in the previous generations had convulsions in infancy, or any nervous trait prior to the onset of the actual ailment.

Progressive Muscular Dystrophy

From a careful reading of the available literature on the subject it appears that the muscular dystrophies form

a very motley group of conditions, both as regards the muscles affected, the course of the disease, and the type of inheritance. The work of many observers shows that muscular dystrophy may be inherited as a dominant (Landouzy-Dejerine facio-scapulo-humeral type), a recessive (pseudo-hypertrophic type), or a sex-linked recessive trait, as in the present series of cases.

FIG. 1.

It will be seen from a study of the pedigree here given (Fig. 1) that the heredity in this case is sex-linked. As it happens, neither of the brothers of E. B. (II 4) inherited the trait, and in the previous generation on the maternal side there were no males in the family, while neither of E. B.'s sisters married. Thus there is no evidence of the occurrence of the disease prior to generation III, here shown, nor in any other branch of the family than that given here; but the sex-linked nature of the inheritance is clearly to be seen, as it is transmitted by the apparently healthy females in three generations, and contracted by the male members of the family.

The parents, E. B. (II 4) and A. B. (II 8), of the first affected cases were not related in any way, the mother coming from the village thirty miles away where her daughter, M. C. (III 8), now lives. Their two elder sons, R. B. (III 9) and A. B. (III 11), developed the disease at about 14 years of age, and both died at the age of 26. The youngest son, A. B. (III 14), did not show signs of muscular dystrophy till the age of 19, but died of

* A synopsis of the essay awarded the Sir Charles Hastings Clinical Prize, 1937, by the Council of the British Medical Association.

pneumonia at 22. M. C. (III 8), sister of these young men, has had three affected sons, in all of whom the disease developed at about 7 years of age. W. C. (IV 5) died in 1926, aged 14, and R. C. (IV 6) in 1929, aged 15. J. C. (IV 8), who is now 18, is still alive, but has very marked contractures of the legs. The only sister in this family, I. N. (IV 3), has a boy of 5, C. N. (V 3), who for some months has shown pronounced lordosis and waddling gait, and who finds it difficult to rise to an erect position after picking up an object from the ground.

Several interesting points arise from a study of the pedigree:

1. The importance of family history in any condition involving loss of power in the limbs. All six cases in generations III and IV have been diagnosed as tuberculous spine, whereas a study of the family history should suggest at least a possibility of one of the familial complaints.

2. Opinion is strongly opposed to the theory of "anticipation" or "antedating" in familial and hereditary diseases. The history of these cases, however, is rather suggestive of something of the sort. In generation III the disease did not develop till about 14 years of age or after, while in generation IV it began at 7 years of age or thereabouts. If the lordosis and waddling gait in V 3 should prove to be the first signs of the condition, we have here an even earlier onset—4 years of age.

3. The most interesting fact of all is that in three cases at least—R. B. (III 9), A. B. (III 11), and W. C. (IV 5)—there is a definite history of failure to bleed when cut, this history being confirmed by several relatives. It is worth considering whether the morbid process here might perhaps be primarily in the vascular system, some peculiarity in the capillaries leading to diminished blood supply to either nerve or muscle tissue, so causing loss of tissue and loss of function. This is a matter rather for the biochemical expert and the neurologist, who might perhaps arrive at some solution of the problem presented by the disease.

I can find no reference to this peculiarity in any reports studied, though Hurwitz (1936) gives extensive blood-chemical investigations in all his cases.

The Lymphatic Diathesis

The so-called lymphatic diathesis is generally admitted to be a hereditary character, but possibly the dominant nature of the hereditary element is not sufficiently recognized. The family trees of all patients in the community found to have unhealthy tonsils have been traced and the conclusion arrived at that the heredity is a dominant one. In one particular family a tendency to enlarged and unhealthy tonsils has been passed down through four successive generations, in each affected sibship the condition appearing in at least one-half of the sibs. In the case of an unaffected member of the second filial generation, however, the three generations following are apparently clear of the condition, though environmental conditions are similar in all branches of the family. It is probable that if family pedigrees were carefully worked out by a large number of observers it would be found that heredity plays the principal part in the production of tonsillitis.

Otitis Media

A study of several family trees has shown that there is a very strong hereditary (dominant) element in otitis media. Stein (1918), indeed, holds that the predisposition to aural infection is more important than the actual infection itself, and suggests that constitutionally susceptible individuals will be likely to fall easy victims to such infection, whether it succeeds tonsillitis, measles, whooping-cough, scarlet fever, or other infection.

In two families in which otitis media is found as an obviously dominant trait it is interesting to note that

there is no coexisting tendency to tonsillar infection. It appears, indeed, as if tonsillitis and otitis media may be—and in the families studied by me actually are—inherited as entirely separate entities. It is obvious, therefore, that, in view of the dominant type of heredity in otitis media, it would be worth while to pay particular attention to the ears in families where this condition occurs, especially in cases of children suffering from catarrhal infections and the exanthemata.

Hernia

In spite of the fact that in an agricultural community the majority of the males and a considerable proportion of the females are farm workers, who necessarily undergo heavy manual labour, the proportion of persons with hernia, either inguinal or femoral, is quite small. I have made very exhaustive research into the incidence of this condition, and have been able to discover not more than twenty cases, of which about half are females. This shows an unusually high percentage of females; but possibly the heavy work undertaken by many of the women may provide the exciting cause of the rupture—less common in women unused to manual work.

On investigating the cases closely a most striking fact at once came to light. Fifteen of the twenty cases occurred in two families, in one of which there was a very high proportion of cases of bilateral hernia. Furthermore, in two instances there was a mating of two affected individuals; in one instance five of the six children being affected, two bilaterally, while the one living child of the other union has a double inguinal hernia. The high incidence of hernia in these two families, when contrasted with the low incidence in the rest of the village, suggests a very strong hereditary (dominant) element in the aetiology of the condition—playing, in fact, an even more important part than that played by direct violence or strain.

Cancer of the Bowel

Cancer of the colon is the one form of malignant disease that is common in this locality, and all the cases which I have been able to trace in the last two generations have occurred in four families, with the exception of one case in which no relatives are known to have died from this cause. Joll (1933) asserts that susceptibility to cancer may be definitely hereditary, and states that polyposis of the colon, which may, and often does, lead to cancer, is inherited as a Mendelian dominant. Piney (1934) suggests that carcinoma coli may be really only a further stage in the development of intestinal polyposis.

From the high proportion of affected members in three of the four families affected it would certainly appear as if the condition were dominant; in the fourth family, however, there seems to be a recessive heredity, if indeed any hereditary element is present. It is certainly possible that polyposis of the colon might be found as a hereditary or familial trait in all four families.

Rodent Ulcer

A very striking feature in the list of pathological traits noted in the community is the high incidence of rodent ulcer. In this comparatively small village nine cases have been seen in seven years and histories of several others elicited by inquiry. No environmental causal element can be discovered, nor can any definite hereditary character be found except in one family, shown in Fig. 2.

The occurrence of this striking pedigree of rodent ulcer is at least highly suggestive of a familial element in the aetiology of the complaint. The geographical isolation of the village increasing the tendency for recessive traits to appear, apparently spontaneously, the possibility is that family histories of rodent ulcer might also be discovered in the remaining cases if one were able to go back a couple of generations. The condition being one of later

life, however, it is difficult to trace the family histories back with any degree of accuracy, except in the one case given, as most of the parents of affected individuals have long since died.

An interesting point about the family shown in Fig. 2 is the singling out of the ear by this malignant process in four cases. None of the other six patients with rodent ulcer seen by me in this village had the ear affected. In two cases the ulcer was at the inner canthus of the eye, in one beside the nose, in two on the cheek, and in one on the chin. So far as can be ascertained, no cases of rodent ulcer occurred in any of the sibs of A. F. (I 2) or in any member of the previous generation.

It is possible, therefore, that a tendency to rodent ulcer may depend on a familial character which requires in addition some conjunction of external exciting causes to

FIG. 2.

call it into being. In other words, it may be merely a predisposition to rodent ulcer that is transmitted. Or, what is more likely, it may be that the condition is inherited as a simple recessive, and so remains dormant until two heterozygous carriers of the condition mate, in which case it will appear in a certain proportion of their children. If the mother, M. F. (I 2), were a homozygous recessive and the father, W. F. (I 1), a heterozygous carrier, it would account for the high percentage of children affected.

I can discover no reference in current medical literature to any definite hereditary element in the aetiology of rodent ulcer; but it may be that this is because no attempt has previously been made to trace out pedigrees of this condition in a locality which is geographically isolated, and in which, therefore, recessive characters are most likely to be traced.

Hydramnios

Hydramnios is another condition to the inheritance of which I can find no reference in medical literature; but this may be partly explicable by the fact that this abnormality is associated with a high percentage of stillbirths. One is so apt to associate the terms "hereditary" and "familial" with characters transmitted from parent to child that one forgets the possibility that a malformation affecting a stillborn child may be transmissible from one generation to another. This is emphasized by Baur, Fischer, and Lenz (1931) with regard to anencephaly, which they regard as a familial condition.

The pedigree here given (Fig. 3) is so striking that there must be more than coincidence at work in the production of the cases of hydramnios; and there is at least a strong suggestion of familial tendency. The first case which came to my notice was that of Mrs. R. W. (II 3), to whom I was called by the district nurse in June, 1931, on account of "rapidly increasing size of uterus." On examination the patient was found to have acute hydramnios, the condition having arisen within about forty-eight hours. She was sent into hospital, where labour was induced, resulting

in the birth of a baby, which survived three hours. At necropsy a patent ductus arteriosus was found. The mother has not since become pregnant.

Her sister-in-law, Mrs. B. W. (II 5), was seen by me early in 1933, and on account of difficulty in making out foetal heart sounds or foetal parts I referred her to hospital. There she was examined radiographically, and was found to have an anencephalic foetus—another of the abnormalities often associated with hydramnios. She was sent home, being told to report to hospital again in a month's time (that is, shortly before term). The rough journey down Fen roads, however, brought on labour, and she was delivered at home of an anencephalic child, stillborn.

A neighbour who was present in the room along with the district nurse and myself had also been present at the birth of the child marked II 1 in Fig. 3, the first-born

FIG. 3.

child of the patient's mother-in-law, Mrs. F. W. (I 2). When she saw the baby she remarked that B. W.'s mother had also had "a lot of water and a baby like a frog." This information was entirely unsolicited, and was given so spontaneously on the first sight of the child as to make it certain that II 1 was also anencephalic and that Mrs. F. W. (I 2) had also had hydramnios.

An interesting point about this pedigree is that in each case the mother was a primigravida, whereas the general rule is that in 75 per cent. of cases of hydramnios the mother is a multipara (Ten Teachers, 1922). Another interesting point is that the relationship of the cases is on the paternal, not on the maternal, side. None of the sibs of the three women in question have had a case of hydramnios in their families. It has been suggested by Davenport (1920), in a study of 644 births in families where twins had occurred, that there was a greater tendency for twins to occur among the sibs of the father than of the mother of twins. If this is correct it is equally possible that the paternal element in the production of hydramnios may be an essential feature—a possibility which does not appear to have been suggested up to the present. It is within the bounds of possibility also that the causal element in this condition may be a zygotic lethal factor. Gates (1934) states that, while the evidence for the occurrence of such factors in man is not convincing, there is good reason to believe that they do occur, and that they are perhaps at the root of some miscarriages and monstrosities of various kinds.

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