Annotation

Mendelian inheritance or transmissible agent: lesson of Kuru and the Australia antigen

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The award of the 1976 Nobel prize in medicine to the discoverers of two major forms of transmissible disease—Kuru and the Australia antigen in relation to hepatitis—might seem at first sight to be unrelated to medical genetics. Yet not only was one of the laureates, Baruch S. Blumberg, trained as a geneticist, and the Australia antigen originally believed to be a genetically determined serum protein system, but Kuru itself and some other non-tropical encephalopathies, now known to have a related aetiology, were originally considered to have a hereditary basis.

The development of concepts in these two parallel fields is of great interest in its own right, but for medical geneticists it is of particular relevance, since it raises a number of questions which may have much wider significance. May other disorders now thought to be genetically determined prove in reality to be infectious diseases? May transmissible agents be closely involved in determining the action of specific genes in producing disease? It is worth looking critically at some of the conditions where Mendelian inheritance has been assumed to be the basis for familial aggregation in the light of what has happened to our ideas on the aetiology of Kuru and the Australia antigen.

Kuru

The fascinating story of the discovery and epidemiological documentation of Kuru, and the steps which led to the suspicion and elucidation of a transmissible viral agent as its basis, have been lucidly told in a series of publications by Gajdusek and his colleagues over the past 20 years (Gajdusek and Zigas, 1957, 1959; Gajdusek et al., 1966; Gajdusek, 1973, 1977). The points of special interest to us here are threefold. Why was a hereditary basis of the disorder considered possible initially? Why was this explanation found inadequate, and an infective agent suspected? Is there indeed a hereditary basis for susceptibility to the disease?

Kuru, a subacute, progressive, and invariably fatal neurological degeneration, is and appears always to have been confined to a localised area of the New Guinea highlands, occupied by the Fore people. Gajdusek and Zigas first described the clinical features in 1957, and it was soon clear that the disease was unique both clinically and epidemiologically.

A genetic basis for Kuru was proposed on the basis of its restriction to a particular tribal group and notable familial aggregation, with vertical transmission from generation to generation. Gajdusek and Zigas' original paper concludes:

'The peculiar sex and age distribution of cases, the high familial prevalence in a closely intermarried community, the phenomenon of anticipation (with cases occurring in an earlier age in the second generation) and occasional family histories in which several siblings had died of the disease on reaching approximately the same age, along with the type of clinical picture that the disease presents all support the suspicion that strong genetic factors are operating in the pathogenesis . . .'

Gajdusek and Zigas (1957).

The genetic basis of Kuru was elaborated by Gajdusek and Zigas (1959) and by Bennett et al. (1959) and postulated an autosomal gene, fully penetrant in the heterozygous female, but rarely in the male unless present in homozygous state. Affected children were considered to be homozygotes. Closer study, however, showed discrepancies which were hard to reconcile with Mendelian inheritance: though the Kuru region was a sharply localised one the inhabitants were heterogeneous, showing no special linguistic or physical differences from adjacent areas free of the disease; furthermore the disease was of relatively recent occurrence in the area, having shown a rapid spread over a period of half a century, and subsequently an equally dramatic decline, too rapid to be explained on a purely genetic basis. The sex ratio, though equal in children, showed a distinct female preponderance in adults, while in adults conjugal cases were frequent.
Although an infective aetiology for Kuru had been one of the earliest possibilities to be considered, a combination of failure to isolate an agent and lack of inflammatory changes in the brain had appeared to rule this out until it was realised that the characteristic spongiform changes were similar to those seen in comparable animal disorders such as scrapie in sheep, in which a transmissible agent of exceptionally long incubation time and other unusual properties was known. This led to reinvestigation of a possible infective basis, using transmission experiments of much longer duration than previously.

By 1962 Gajdusek, while still supporting a genetic basis, was clearly having doubts:

‘In spite of all the genetic evidence, both the pathological picture and the epidemiological peculiarities of the disease persistently suggest that some yet-overlooked, slowly progressive, microbrial infection may be involved in Kuru pathogenesis. Similar suspicion prevails in our current epidemiological thinking about a number of less exotic and less rare chronic, progressive, degenerative diseases of the central nervous system. The possibility exists that these may be infections analogous to the slow infections of the nervous system of animals . . .’

(Gajdusek, 1962)

The solution to the causative factor in Kuru came both from the experimental approach and from the epidemiological studies which Gajdusek and others had been carrying out concurrently with their clinical and pathological investigations, and illustrates the value of the close familiarity with both the disease and its background which Gajdusek acquired from working and living in the affected communities over a prolonged period. The ritual consumption of the brain of deceased relatives, undertaken by the family, particularly women and children, as an act of mourning and respect, provided the clue that culminated in the successful transmission of the disease to other primates by intracerebral inoculation of the brain tissue from Kuru patients (Gajdusek et al., 1966).

It may asked if genetic factors play a role in susceptibility to Kuru, and thus explain the restriction of the disease to certain family members and to certain communities despite the widespread practice of ritual cannibalism? Despite numerous genetic studies of the Kuru region this question remains unanswered. Early studies of genetic markers done at a time when Kuru was considered a hereditary disorder showed no clear distinction between peoples of the Kuru area and elsewhere, nor did later genetic studies (Gajdusek and Alpers 1972). Kitchin et al. (1972) found a significantly increased incidence of the Gc phenotype Ab in Fore individuals affected with Kuru, but it seems probable that genetic factors have not played a major part in the dramatic spread and later decline of the disease. Whether this will also prove to be the case in other transmissible encephalopathies remains to be seen; the very fact that transmission between different species is possible suggests that genotype is not an absolute determinant of susceptibility.

Kuru, though an intrinsically fascinating disease, would have been of little relevance to medicine in general and medical genetics in particular, had it not been the stimulus for investigation of other chronic degenerative nervous diseases of more general distribution but showing similar neuropathological changes. In at least two of these, Creutzfeldt-Jakob disease and Alzheimer’s disease, there is now firm evidence of a transmissible agent being responsible for the disorder in families previously considered to show Mendelian dominant inheritance.

**Creutzfeldt-Jakob disease**

Most cases of this disorder, characterised by progressive presenile dementia with pyramidal and extrapyramidal abnormalities, and distinctive histological changes similar to those seen in Kuru, are isolated, but a few families have been described with multiple affected members, including transmission over four generations (Jacob et al., 1950). Pratt (1967) considered the disorder to be heterogeneous, with a small proportion determined by an autosomal dominant gene—a reasonable conclusion given the evidence then existing. Such a view is no longer tenable after the demonstration of an agent transmissible to other primates (Gibbs et al., 1968), both in sporadic cases of the disease and in familial cases (Gajdusek and Gibbs, 1975) which would otherwise have been considered compatible with autosomal dominant inheritance (Fig. 1). A particularly high incidence of Creutzfeldt-Jakob disease has been found in Libyan Jews in Israel, and it has been suggested (Herzberg et al., 1974) that this may result from the predilection of this group for consumption of sheep’s brain, rather than from the consanguinity or other genetic properties of the population. Recently direct and disturbing evidence of transmission to humans has come from reports of the disorder developing after corneal graft from an affected donor (Duffy et al., 1974) and from transmission by formalin-sterilised neurosurgical instruments (Traub et al., 1975; Bernoulli, quoted by Gajdusek, 1977).

**Alzheimer’s disease**

This form of presenile dementia frequently occurs in familial aggregations suggestive of autosomal domi-
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Fig. 1 Transmissible virus encephalopathy mimicking autosomal dominant inheritance (after Gajdusek, 1977).
(a) Familial Creutzfeld-Jakob disease. Disease transmitted from brain tissue of proposita to squirrel monkey.
(b) Familial Alzheimer's disease. The proposita showed clinical and neuropathological evidence of Alzheimer's disease, with a course similar to the affected relatives. Intracerebral inoculation of brain tissue produced spongiform encephalopathy in a squirrel monkey.

Fig. 1a

Fig. 1b

niant inheritance, and such families occur with much greater frequency than in Creutzfeldt-Jakob disease. They are, however (as pointed out by Pratt, 1967), selected examples and systematic genetic studies, notably that of Sjögren et al. (1952) in Sweden, give a different picture. In this study an affected parent was found in 10% of cases, with a 4% incidence in sibs, leading Sjögren et al. to postulate multifactorial inheritance. Constantinides et al. (1962) in Switzerland found 12.8% of sibs to show dementia, together with 11.8% of parents, and postulated a single major gene to be responsible, though with reduced penetrance.

These somewhat nebulous explanations for an undoubtedly familial tendency in Alzheimer's disease require total reconsideration after the demonstration that familial Alzheimer's disease can be transmitted to primates by intracerebral inoculation of brain tissue (Gajdusek, 1977; Traub et al., 1977). The agent involved fulfils the criteria for a 'slow virus', with long incubation period, lack of inflammatory response, and pronounced resistance to inactivation by formalin and other agents. Indeed it seems possible that a single agent may be responsible for Alzheimer's disease, Creutzfeldt-Jakob disease, and Kuru in man, and that this in turn may be similar, even identical, to that producing scrapie in sheep and transmissible encephalopathy in mink (Gajdusek, 1977).

The exact mode of transmission of the naturally occurring human disease in the case of both Alzheimer's and Creutzfeldt-Jakob disease remains unknown, and it should be noted that male to male transmission occurs, excluding a solely transplacental transmission. It is equally unknown whether the affected individuals in the pedigrees suggestive of autosomal dominance do in fact have a particular genetic susceptibility. What is beyond doubt is that in both diseases families in which an autosomal dominant mode of inheritance would have been considered almost certain have now been shown to have an infective rather than a primarily genetic disorder. Interestingly no transmissible agent has so far been isolated from non-familial cases of Alzheimer's disease, and whether true heterogeneity exists in aetiology is not clear at present. This situation provides a warning for the uncritical application of 'multifactorial inheritance', for here we appear to have a situation where the more familial a disorder the less genetic its basis!

Huntington's chorea

If our confidence in the recognition of autosomal dominant inheritance has been weakened by the disorders discussed so far, it may seem to strike at the roots of Mendelism itself to suggest a similar origin for Huntington's chorea, yet this has been seriously suggested (Gajdusek, 1977). Transmission of the disease to primates has been attempted but with negative results so far, and though Huntington's chorea shares some clinical and pathological features with other presenile dementias, its pattern of inheritance is so relentlessly regular as to make its Mendelian basis seemingly unassailable, whatever secondary factors may be involved.

There is, however, one feature of this disease which is most un-Mendelian, and which has so far defied explanation: this is the predominantly paternal transmission of cases with juvenile onset, characterised by rigidity rather than chorea as the predominant clinical feature. Merritt et al. (1969) found almost 80% (89 out of 113) of childhood onset cases to be paternaly transmitted. Whether this phenomenon is confined to juvenile cases or reflects a generally earlier onset in all age groups of paternally transmitted cases is still disputed (Brackenridge, 1971, 1973; Bird et al., 1974).

Several ingenious hypotheses have been proposed
to explain these findings, notably a hypothesis by Burch (1973) that the phenotype of Huntington's chorea is modified by other mutations occurring in the germ cells, which are dependent on paternal age. Unfortunately evidence of a paternal age effect in Huntington's chorea is disputed and the juvenile form remains an unexplained feature of the disease. For our present purpose, however, it provides a salutary reminder that even in this most Mendelian of genetic diseases a major non-Mendelian factor is operating. Whether an extrinsic factor such as a virus can be implicated, or whether a developmental effect of the intrauterine environment or the effect of other genetic loci is involved is a matter for speculation at present.

Australia antigen

The other recipient of the 1976 Nobel prize for medicine was Baruch S. Blumberg, for his work on the discovery of the Australia antigen and its relation to hepatitis. The prize was not awarded for studies in genetics, and the citation did not stress that Blumberg's newly discovered antigen was initially considered to be a genetically determined polymorphic protein system rather than an infective agent, nor that his background and original research was in biochemical genetics. Yet it can fairly be argued that without the genetic approach the significance of the findings would not have been recognised.

Any doubts about the origins of this discovery in the science of genetics are firmly dispelled by Blumberg's quotation of E. B. Ford's classical definition of genetic polymorphism in the opening paragraph of his Nobel prize lecture (Blumberg, 1977). Blumberg had in fact studied in Oxford with A. C. Allison in 1957, and thereafter developed his work on haptoglobins, albumin variants, and other protein polymorphisms, leading to the discovery of the lipoprotein polymorphism—the Ag system—in 1962 (Blumberg et al., 1962). Of particular significance in this study was the use of sera from multiply transfused patients and their study by the Ouchterlony immunodiffusion technique, for it was this that led to recognition of a new precipitin resulting from the reaction of the serum of a haemophilia patient with serum from an Australian Aboriginal (Blumberg, 1964; Blumberg et al., 1965).

Given this background and the finding that presence of the Au antigen appeared to be a permanent feature of the individuals tested, it is not surprising that it was initially considered to be another genetic polymorphism of the serum proteins; epidemiological studies of different populations soon showed a wide variation comparable to that shown by many polymorphic systems, and there was no immediate association with any disease state; the antigen was found to be particularly common in a number of tropical populations, and rare in most parts of Northern Europe and the United States (Blumberg et al., 1965). Within many families the presence of the antigen appeared to follow autosomal recessive inheritance. The complete reversal of these apparently consistent conclusions came, paradoxically, from the study of the Au system in another genetic disorder—Down's syndrome, as well as from the finding of a high incidence of Au +ve individuals with leukaemia. An initial hypothesis that the Au antigen might be related to development of leukaemia (Blumberg et al., 1965) paved the way for the change from a genetic marker to an infective agent, which became firmly established when previously Au negative individuals with Down's syndrome were found to become Au positive during the course of hepatitis (London et al., 1969).

The identification of the Au antigen as an integral part of hepatitis B virus has stimulated an enormous volume of work on the detailed antigenic structure and other properties of this and related viruses which will not be discussed here; it has also had practical consequences in the prevention of hepatitis. In medical genetics it has forced a reappraisal of a number of diseases in which familial aggregation had previously been explained on a hereditary basis; a situation comparable to the current reassessment of degenerative neurological disorders in the light of Kuru.

Familial hepatic disorders and Australia antigen

Apart from disorders of bilirubin metabolism the liver is not notable for an abundance of Mendelian disorders, but a series of remarkable concentrations of chronic liver disease and primary liver cancer had for some years been noted in Japan and elsewhere (Ohbayaishi et al., 1972); they were regarded either as being the result of a rare dominant gene acting in a predominantly non-genetic group of disorders, or as a concentration of genes of additive effect in a disorder determined by multifactorial inheritance. Fig. 2 shows two of the Japanese families: initially investigated before the discovery of the Australia antigen, these families were subsequently reassessed and showed affected individuals to be Au +ve in each case, with numerous Au +ve individuals in the youngest, symptom-free generation. Familial aggregations of this type must clearly be interpreted as resulting from a transmissible agent in the light of an important finding whose significance had not previously been appreciated—transmission of both liver disease and Au antigen is almost exclusively maternal; 16 out of 20 offspring of affected women in the
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**MATERNAL TRANSMISSION OF AUSTRALIA ANTIGEN AND LIVER DISEASE**
(after Ohbayashi et al., 1972)

![Figure 2: Maternal transmission of Australia antigen and liver disease (after Ohbayashi et al., 1972)](http://jmg.bmj.com/)

A series of Ohbayashi et al. were Au +ve, in contrast to 1 out of 8 offspring of affected males. In retrospect this maternal transmission should have alerted investigators to the possibility of a non-genetic basis for the familial clustering.

Subsequent studies on Au antigen have shown direct evidence for perinatal transmission of the virus and have also shown predominantly maternal transmission of Au antigen in apparently healthy high incidence populations (Blumberg, 1977). Persistence of the virus has been shown to be strongly associated with liver cancer in many tropical areas (Blumberg et al., 1975), and it is probable that such neonatal disorders as congenital hepatic fibrosis and biliary atresia may also have a viral origin (Emery, 1974). In both these conditions a genetic basis was formerly considered likely, though in biliary atresia no clear pattern of Mendelian inheritance has been seen. Paradoxically a viral aetiology might imply a higher risk to offspring of carrier mothers than would be the case if the disorder were a rare genetic disorder subject to multifactorial inheritance.

From the indubitable evidence of the viral nature of the Australia antigen it might seem that the disorders associated with it have been firmly removed from the field of medical genetics into that of infectious diseases. Paradoxically this is far from being the case, and particularly in high incidence areas it seems that the wheel has come full circle and that genetic factors may indeed be the most important. Over considerable areas of the tropics hepatitis B virus has been shown to be a near ubiquitous pathogen, so that exposure to it must be almost universal. In such a situation host resistance is often a more important factor than presence of the infective agent, and family studies in tropical areas have shown a pattern compatible with autosomal recessive inheritance determining persistence of the Australia antigen (Blumberg et al., 1965; Sutnick et al., 1971). A parallel may be drawn with immune deficiency disorders such as chronic granulomatous disease, where the harmful effects result largely from the effects of specific common pathogens, such as staphylococci, but where the inability to neutralise the environmental agent follows Mendelian inheritance. If a single major gene is indeed responsible for persistence of Australia antigen then this will represent a true genetic polymorphism as was originally believed at its discovery. Whether such a polymorphism exists also in areas of lower exposure, such as Northern Europe and America, remains uncertain since the presence or absence of Australia antigen in such areas is no longer a sufficient indication of resistance or susceptibility. Family studies on Australia antigen carriers in Finland are compatible with autosomal recessive inheritance (Helske and Nevanlinna, 1973), but anomalies occur within a few families, such as discordance of monozygotic twins.

Can the lessons learnt from the studies of Kuru and Australia antigen be extended over a wider range of disorders than those so far discussed? It is worth examining this possibility, and to question which genetic disorders of today might be the infective disorders of tomorrow. The possible conditions appear to fall into two groups—those in which Mendelian inheritance is mimicked by a transmissible agent, and those in which a Mendelian basis is definite, but which show anomalous patterns of inheritance indicating the operation of additional major environmental factors.

**Leber's optic atrophy**

This disorder represents a long-standing enigma for geneticists, and neither its mode of transmission nor its aetiology has been resolved, despite numerous studies (van Senus, 1963; Waardenburg 1963, 1969). The clinical features consist of subacute onset of visual failure in early adult life, often progressing to complete blindness and accompanied by more generalised neurological abnormalities in some cases.

Although males are more frequently affected than females, they never transmit the disorder to their offspring or subsequent descendants, while females may transmit it to both sons and daughters. Most cases are transmitted by asymptomatic females, 50% of sons of such carriers being affected. Autosomal, X-linked, and cytoplasmic inheritance have all been proposed as explanations, but an X-linked gene is
effectively ruled out by the total absence of disease in the descendants of males, and a further factor against Mendelian inheritance is that among the daughters of carrier mothers not 50% but all are either carriers or affected. Such a situation is compatible only with a non-nuclear type of transmission, and on this basis, together with the occurrence of inflammatory changes in neural tissue, a viral aetiology has been proposed (Wallace, 1970). No direct evidence for this has yet been obtained, but transmission to primates via cerebral tissue does not yet appear to have been attempted, possibly because, being a non-lethal disease, necropsies are rare. However the maternal transmission suggests that an infective agent ought not to be confined to nervous tissue—placenta would be a logical choice of material.

A transmissible agent does not explain all the problems of Leber’s disease: in particular the fact that only half the sons of carrier mothers are affected suggests that a major gene may be involved in susceptibility, but this is little different from the situation in chronic liver disease associated with the Australia antigen, where a viral aetiology is a confirmed fact, not just a hypothesis. At present a transmissible agent, whether a conventional or ‘slow’ virus, seems to be the most likely basis for this puzzling disease.

Hereditary nephropathy with deafness (Alport’s syndrome)

This disease, like Leber’s optic atrophy, has been a longstanding puzzle as to its genetic basis, failing to fit precisely any form of Mendelian inheritance, yet showing striking familial aggregations. The uncertainty is illustrated by the variety of hypotheses proposed, which include partial sex-linkage (Perkoff et al., 1951), preferential segregation of an autosome with the X chromosome (Shaw and Glover, 1961), and an X-linked modifying gene (Arnott et al., 1966). Part of the confusion has resulted from undoubted genetic heterogeneity (Tishler et al., 1971), some families with a similar clinical picture showing simple autosomal dominant inheritance, but the existence of data from some large individual kindreds (Preus and Fraser, 1971) allows this to be eliminated as the cause of the anomalous inheritance.

The essential anomaly is a degree of male-to-male transmission (26%) lower than that expected on the basis of autosomal dominant inheritance. Daughters of affected males, and both sons and daughters of affected females show an incidence close to the expected 50% affected, and Preus and Fraser suggested that for the disease to occur in the male both an autosomal gene and a maternally transmitted environmental factor must be present; there is no evidence at present as to whether the factor is viral, or of some other nature.

The familial pattern of Alport’s syndrome shows similarities with that of Leber’s optic atrophy, but there are also important differences. In both disorders males are more commonly affected than females and in both transmission by males is reduced compared with females, but the total absence of male transmission in Leber’s optic atrophy effectively rules out orthodox Mendelian inheritance, whereas in Alport’s syndrome any environmental agent seems to be acting in conjunction with a gene showing autosomal dominant inheritance. These two disorders, in which the environmental agents have yet to be identified, are compatible with what has already been firmly demonstrated by Kuru and the Australia antigen, that transmissible environmental agents may both mimic Mendelian inheritance, and may act in conjunction with it. It is in this second category that most of the undetected examples of transmissible agents in genetic diseases are likely to lie.

Environmental agents in established Mendelian disorders

Kuru and the related encephalopathies provide examples of the way in which a transmissible agent can mimic Mendelian inheritance; that the two are not always mutually exclusive has already been shown by the pattern of susceptibility to Australia antigen in high incidence areas, where the genetic properties of the host rather than the ubiquitous virus appear to determine the pattern within families. Huntington’s chorea is another disorder where Mendelian inheritance is beyond doubt, yet leaves room for the operation of important non-Mendelian influences that alter the pattern of transmission under certain conditions. A number of other disorders exist in which similar phenomena are seen, which cannot readily be explained on the basis of Mendelian
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inheritance. The Table summarises some of these; frequently the nature of the environmental agent is unknown, less commonly it can be identified as a specific factor, sometimes metabolic (e.g. maternal phenylketonuria), sometimes immunological (e.g. Rhesus haemolytic disease).

MATERNAL PHENYLKETONURIA
Were the metabolic basis of phenylketonuria still unknown and milder untreated cases more common, we might still be puzzling over the reason for the severe in utero brain damage occurring in almost all offspring of phenylketonuric women (Mabry et al., 1963). With our knowledge of the biochemical defect the explanation for the maternal effect is plain, though the precise mechanism of the brain damage is unknown and it is by no means clear at present whether the fetus is differently affected according to whether it is homozygous or heterozygous at the phenylketonuria locus (Trouche et al., 1974). The rarity of the condition until now has resulted from lack of reproduction of most phenylketonuric females; as a result of successful treatment this is likely to become a considerable problem in management.

MATERNAL HISTIDINAEMIA
Histidinaemia, having started as a disease, has steadily retreated towards being a harmless metabolic abnormality (Neville et al., 1971). It is possible that a maternal effect comparable to that seen in phenylketonuria may exist, for not only is there some evidence of reduced IQ in heterozygous offspring of a histidinaemic mother, but much more severe phenotypic effects may be seen. The family of Bruckman et al. (1970), though reported as showing autosomal dominant inheritance, is likely to represent this situation. In this remarkable family four histidinaemic sisters, all symptomless, had a total of 23 children; 18 (born to 3 of the sisters) were clinically normal, with blood histidine levels suggesting heterozygosity. Three of the 5 children of the fourth sister were histidinaemic; all 3 had severe speech problems and one was mentally retarded. It is not known whether changes in the nervous system comparable to those of murine maternal histidinaemia also occur in the human condition.

CONGENITAL MYOTONIC DYSTROPHY
Although this disorder shows classical autosomal dominant inheritance, a puzzling maternal effect is seen in those cases with onset from birth, now recognised to be much less rare than was previously believed. Almost all such cases reported have shown transmission from an affected mother (Harper and Dyken, 1972), and none has resulted from a new mutation. Only those offspring bearing the myotonic dystrophy gene appear to be affected by the maternal factor; its nature remains unidentified so far, though it is possible that when the biochemical basis of myotonic dystrophy as a whole is understood the basis of the maternal effect will be as clear as it now in maternal phenylketonuria.

RHEUS HAEMOLYTIC DISEASE
The nature of this maternal effect and its dependence on specific genotypes of mother and fetus is so familiar and well documented (see Clarke, 1969, 1975) that it is only surprising that it has not led to similar examples outside the serological field being more thoroughly searched for. Perhaps more than any other example it illustrates the fact that the effects of the Mendelian genotype and maternal environment (in this instance an immunological effect) are complementary, not mutually exclusive.

'HEREDITARY INFECTIONS' IN SPECIES OTHER THAN MAN
While the vertical transmission of infective agents to mimic or to interact with Mendelian inheritance has only gradually become recognised as a major factor in familial disorders of man, several well-documented examples exist in other species which deserve a careful reassessment as potential models for the type of agents which may be involved in those human diseases where the environmental agent is still unidentified.

In mammals, scrapie is the best studied example, and knowledge of the scrapie agent has played a large part in establishing a similar 'slow virus' basis for Kuru and related diseases in man. Scrapie, like Kuru, is a fatal cerebral degeneration, seen mainly in sheep, but capable of transmission to a variety of other mammals. Both the clinical and pathological findings are similar to those of Kuru, and it has been suggested that they may even be the result of the same agent (Gajdusek, 1977). The transmissible nature of scrapie has been known experimentally for many years; in the natural state transmission is predominantly maternal, and infection appears to be prenatal. There is pronounced variation in susceptibility in sheep, which is genetically determined (Dickinson et al., 1974) while in mice susceptibility and incubation period have been shown to be affected by a specific locus, 'sinc' (Dickinson and Meikle, 1971). This lends support to the existence of genetic factors in human 'slow virus' dementias such as familial Alzheimer's and Creutzfeldt-Jakob disease.

Drosophila provides a particularly striking example of hereditary infection in the form of the 'sex ratio' trait. In certain broods of Drosophila
The 'killer' character of yeasts is perhaps the best documented example of the interaction of a nuclear gene with a transmittable cytoplasmic factor. Cells possessing the 'killer' phenotype produce a toxic polypeptide which kills other sensitive cells. For the 'killer' phenotype to be produced not only must a specific nuclear gene be present, but also a cytoplasmically transmitted factor, which has been shown to be a double stranded RNA (Bevan et al., 1973).

At this point the concept of a 'hereditary infection' can be seen to have merged with that of 'cytoplasmic inheritance', long recognised in plants (Darlington, 1958) and often associated with specific cytoplasmic organelles such as plastids and mitochondria. The pattern of transmission is essentially similar whether the agent is an exogenous 'virus' or an endogenous organelle capable of self replication.

Not all maternally transmitted effects in experimental animals are the result of infective agents. Histidinaemia in the mouse, caused, as in man, by absence of the enzyme histidase, similarly shows no phenotypic abnormalities in the affected individual, but offspring of histidinaemic females show a balance defect caused by abnormal development of the otolith, whereas offspring of histidinaemic males are normal (Kacser et al., 1973). The maternal effect is at least in part dependent on the fetal genotype, since homozygous histidinaemic offspring are more severely affected than are heterozygous offspring (Bulfield and Kacser, 1974).

The mouse provides a further example, comparable to the maternal effect seen in human myotonic dystrophy. The mutation 'hairpin tail' is controlled by an allele at the T locus and shows autosomal dominant inheritance (Johnson, 1974). When the gene is transmitted by the male the phenotypic effect in the offspring is mild, the principal effect being shortening and acute angulation of the tail. When an affected female transmits it, however, not only is the skeletal defect more severe but there is also a high embryonic and neonatal mortality. The mechanism is unknown, but it may be relevant that other alleles at the T locus have an effect on sperm morphology and function.

Conclusions

The diseases which have been described show the ease with which familial environmental factors can be confused with a truly hereditary basis, despite the fact that specific examples of such effects have been well recognised for many years, especially in species other than man. In the case of Kuru and the Australia antigen infective agents have proved to be responsible, and it seems probable that other human familial disorders may prove to have a similar basis. An infective basis is not the only possible explanation for such effects, however; biochemical and immunological mechanisms are equally possible, and have been shown in some of the examples discussed. If we are to ask how may one avoid confusing these effects with the patterns resulting from true Mendelian inheritance one could summarise the major points below:

1. Vertical transmission of a disorder through several generations does not necessarily indicate dominant inheritance.
2. A tendency to familial aggregation without a clear Mendelian pattern does not necessarily imply multifactorial inheritance.
3. Predominantly paternal transmission should raise the suspicion of an intrauterine or comparable environmental factor.
4. The lack of a genetic basis may be irrelevant to practical considerations of genetic counselling—recurrence risk in a family may well be higher if the determining factor is environmental than if it is genetic.
5. The existence of Mendelian inheritance does not exclude the operation of important environmental factors influencing the expression or transmission of the disease.

All of these points are really self evident, yet they have frequently been overlooked. By bearing them in mind we should be able to predict which other genetic diseases of today may perhaps prove to be the environmental diseases of tomorrow.
References


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