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INVITED EDITORIAL
Anticipation: An Old Idea in New Genes

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Anticipation is a concept very much in vogue at present. A recent triumph, the association of intergenerational increase of trinucleotide repeat (TNR) lengths with ever more severe disease progression, has many human geneticists reexamining both pedigrees and DNA sequences of candidate genes to see whether the diseases that they study fit this pattern. Despite the clear success of the TNR-expansion model, this molecular mechanism must be distinguished from the clinical phenomenon of anticipation. Moreover, it is sobering to recall that anticipation was dismissed as a statistical artifact only a few years ago, for reasons that were anything but foolish. In fact, "anticipation" and related terms have been discussed since the mid 19th century. The history of these terms and their popularity at earlier times offer some perspective on our current understanding and may suggest the direction of future research.

Anticipation and the Theory of Degeneration

The notion of anticipation has roots in the social chaos of the French Revolution, as well as in the medical observations of the French "alienist" (an early term for "psychiatrist") Benedict Auguste Morel (1857) and in the theories of atavism advocated by the renowned Italian psychiatrist of the late 19th century, Cesare Lombroso. The present concept of anticipation arises from the theory of degeneration advanced by Morel in his *Traité des Dégénérescences* (1857), the essence of which was the progressive deterioration of illness from parent to child, occurring in a more severe form and at an earlier age with succeeding generations, leading ultimately to extinction of the lineage. The concept of degeneration, renamed "anticipation" in the 20th century, was hotly debated before being temporarily laid to rest when Penrose argued that apparent anticipation arose purely as the result of several classes of ascertainment biases. Fifty years on, with the identification of a molecular mechanism, anticipation is once again in the spotlight of genetic inquiry. However, the influence of Penrose has not been lost. When I first presented my anticipation data on bipolar disorder, I was reminded that, just because Penrose was wrong in myotonic dystrophy, that does not mean that he is always wrong.

Morel established his reputation on the study of goiters and cretinism, the prototypical diseases of degeneration (Freidlander 1973). The popular scientific literature in the mid 19th century regularly discussed these illnesses, often with more enthusiasm than discrimination. Morel cited a variety of causes—environmental, nutritional, and hereditary—that contributed to degeneration. The word "cretin" may be related to *crétine,* referring to alluvial soil, reflecting the belief that prolonged residence on certain types of land soil bore a causal relationship to such illness. Morel wrote in his influential study that offspring of goitrous mothers were much more severely afflicted than the mother, and he claimed that both overuse of alcohol and other nutritional difficulties hastened the degeneration of the individual and the offspring. It is this study in the 19th century that was pivotal in the development of the theory and study of degeneration. The theory of degeneration was an extrapolation from a degeneracy within one disease, cretinism, to a multitude of degeneracies, including illness and social and moral decay.

The environmental influence observed in both cretinism and other states of degeneracy was reflected in ideas about human behavior and social and political change. War and the French Revolution inspired pessimism, resulting in social decay, a form of degeneration. It was observed that "from the peasant, the laborer, and the bourgeois, pacified and tamed by an old civilization, we see all of a sudden spring forth the barbarian, and still worse, the primitive animal, the grinning, sanguinary, wanton baboon, who chuckles while he slays, and gambols over the ruin he has accomplished" (H. A. Taine, as cited in Pick 1989) . From the observations of social degeneracy of the French Revolution sprang the theories of atavism that were propagated by Cesare Lombroso (1911), who suggested that criminality represented a

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form of heritable degeneracy. Lombroso, a student of phrenology and a convincing orator, produced statistical calculations of skull features of criminals to support his ideas and published photos of shady characters and criminals for the benefit of the scientific community (Lombroso 1911). Similar ideas were pursued 20 years ago in the debate over the link between criminal behavior and the XYY karyotype (reviewed in Borgaonkar and Shah 1974).

It appears that the word "degenerate" evolved in medicine to mean a state of ill health, but, for the most part, degeneracy was the domain of the psychiatrist. Henry Maudsley (1835–1918), the eminent British psychiatrist, addressed degeneration at length over his medical career, initially endorsing Morel's view that degeneration led to extinction. Considerable political and medical debate ensued in the late 19th century, regarding the "outcast London"; writers of the day thought that society was in a state of moral and physical deterioration (Pick 1989). The state of affairs in the nation seemed rather bleak, but, with improving social conditions and increased political confidence around the turn of the century, Maudsley suggested that degeneration also could work in reverse. He noted that "there appears to be at work a silent tendency in nature to restore an insane stock to a sound type, if regeneration be possible, or to end it if its degeneration be such that it is too bad to mend" (Maudsley 1890, p. 57). Degeneration appears to have been euphemized in the first decade of this century and to have been referred to as "anticipation."

Law of Anticipation versus Bias of Ascertainment

By the early 20th century the idea of anticipation had become entrenched in psychiatric thought. In 1911, Mott referred to the "Law of Anticipation," describing the earlier age at onset of disease in successive generations (Mott 1911). In what is probably the first large-scale study addressing anticipation, Mott studied 420 parent-child pairs from London asylums and claimed that "invariably in the case of insane parents and offspring the offspring is affected earlier than the parent, on average approximately at half the age of the parent" (Mott 1911, p. 1256). Although ascertainment biases played no role in Mott's theory, he did appreciate that, with an increasing number of asylums, more insane people were subject to attention. He concluded that hereditary predisposition is the most important factor in the genetics of psychiatric disease and that the presence of anticipation supports the inheritance of a "neuropathic taint," the tendency to mental illness. He claimed that regression to the normal state could occur either through marriage into "normal stocks" or by anticipation terminating the unsound elements of these stocks. These theories were endorsed by the eugenicists, whose popular movement included plans for improvement in the human race (Galton 1909).

An astute German ophthalmologist, Fleischer, is credited with the first observation of anticipation in myotonic dystrophy (DM) (Fleischer 1918). He reported cases of congenital DM in the grandchildren of some of his patients with cataracts and hypothesized a hereditary connection. In subsequent studies it became apparent that no other disease showed anticipation more markedly than did DM (Bell 1947). However, many questions were raised regarding the validity of the theory. The influential geneticist Lionel Penrose noted that "the phenomenon [anticipation] is easy to find in almost any medical data on diseases which commonly occur in two generations of the same family" (Penrose 1948, p. 125). Penrose examined the data collected by Bell and put forth five "causes" of anticipation, the biases of ascertainment. According to Penrose, these biases include selection of affected parents in whom the onset of the disease is late, selection of affected offspring in whom the onset of disease is early, and selection of cases with simultaneous onset in parents and offspring. These biases of ascertainment reflect the cases that will easily come to medical attention, in which the clinicians will pose a question of heredity, or in which families will volunteer this information. A general impression of anticipation will follow when there is either little or weak correlation, in age at onset, between parent and offspring and general variability of age at onset of a disease. Penrose argued generally that random variation in age at onset within the population, coupled with ascertainment biases, was the basis of anticipation.

Penrose's opposition to anticipation was likely not completely free of his own biases. Anticipation at the time was associated with the eugenics movement, which he strongly opposed, and he expended a good deal of effort expunging the term from the science of human genetics (Thom and Jennings 1996). The term "eugenics" was coined by Galton, possibly referring to the Greek *eugenes,* meaning "of noble origin" (Bayertz 1994). Eugenics aimed at the improvement of the human race by both "increasing the best stock" and the "hindrance of marriages and the production of offspring by the exceptionally unfit" (Galton 1909, p. 24). Penrose considered eugenics an ideology, a mixture of propaganda and dreams of a perfect race. He and others worked to free the science of human genetics from accusations of Nazism. Penrose became the editor of *Annals of Eugenics,* changing its name to *Annals of Human Genetics,* and for >20 years influenced genetic discussion. Debate on anticipation seemed to be closed with his conclusion that "the tendency for anticipation to occur in pedigrees of hereditary disease is due to the manner of their selection and is not a phenomenon of direct biological significance" (Penrose 1948, p. 125).

This became the dogma and was to be found in all substantial texts of human genetics as recently as the 1980s (Vogel and Motulsky 1986).

Anticipation Reinvented

The most recent stage in the study of anticipation began with the work of Höweler et al. (1989), whose study of systematically ascertained DM families was the first to be prospective rather retrospective. The advantage of a prospective study with systematic ascertainment is that subjects are accepted into the study with set rules—for example, presenting to a clinic and being diagnosed with DM and without bias to the hypothesis to be tested. A subject is ascertained regardless of age or status as parent, offspring, or grandparent. Penrose predicted that families exist wherein the age at onset in the parent is earlier and that in the offspring is later, the so-called complementary pairs of those showing anticipation, claiming that these families would be as prevalent as pairs showing anticipation. Höweler et al. (1989) examined all DM patients presenting to a university neurology clinic between 1970 and 1977 and collected family histories; they identified 14 cooperative families and examined 264 relatives. They found an earlier age at onset in 98% of 61 parent-child pairs and concluded that anticipation may be inherent in the transmission of DM. They addressed the biases set forth by Penrose, by systematic ascertainment of their families and subjects; they specifically sought out information regarding the presence of complementary parent-child pairs and found none. Clearly, not all claims of anticipation could be discarded on the basis of the biases discussed by Penrose.

Within 3 years of the Höweler et al. publication, the molecular basis for anticipation in DM was demonstrated (Brook et al. 1992). My colleagues and I, as well as others, had proposed that anticipation may be common, especially in the neuropsychiatric diseases (Ross et al. 1993). Expanding TNRs are now known to be associated with at least eight other diseases (LaSpada et al. 1991; Verkerk et al. 1991; The Huntington's Disease Collaborative Research Group 1993; Knight et al. 1993; Orr et al. 1993; Kawaguchi et al. 1994; Koide et al. 1994), with the most recently identified being Freidreich ataxia (FA) (Campuzano et al. 1996). In Huntington disease, where anticipation had been considered to be very subtle and controversial, there is significant correlation between the length of the TNR and degree of anticipation in paternal transmission (Ranen et al. 1995).

Anticipation and the Familial Leukemias

In the current issue of the *Journal,* Horwitz et al. (1996) present a retrospective study of familial acute myelogenous leukemia (AML) and chronic lymphocytic leukemia (CLL), using data from the literature over the past 50 years. They apply two criteria to ascertain their subjects. First, in each family at least two individuals must present with the same type of leukemia. Second, the family must include at least one affected parent-child pair. In examining nine AML pedigrees with 10 individuals affected in the grandparental, 20 in the parental, and 19 in the youngest generations, they find the mean age-at-onset difference for parent-child pairs to be 28 years (SE = 3.4 years). The results remain significant when the eight independent parent-child pairs are studied, as well as when those with age at onset <25 years are excluded from study. One family did not meet the second criterion but is definitely of interest, with two affected sib pairs in two generations. In their study of CLL the numbers are low, with 1 affected individual in the grandparental generation (excluded from analysis), 7 in the parental generation, and 10 in the youngest generation. Here, the mean age at onset in the parental generation is 66 ± 12 years, and in the youngest it is 51 ± 9 years (a significant difference). Clearly, in these families the age at onset decreases in successive generations, consistent with anticipation, albeit more so in AML than in CLL.

Horwitz et al. (1996) take several measures to address the inevitable problem of ascertainment biases, recognizing that the optimal design would be to consider only prospective cases, but they note that leukemia is rare and that familial leukemia is even more so, making this design impractical. They exclude from their analysis the index family on which their hypothesis was formulated and include only families with uniform diagnoses. Their sample is thereby independent of the hypothesis and is homogeneous; they do not include in their analyses obligate carriers, which would favor anticipation. Survival curves are based on three generations in six of nine families in AML. Where two generations exist, the younger generation is considered part of the youngest generation, and generational membership is not fixed to a time period. They address the Penrose bias that concerns the preferential ascertainment of young severely affected offspring; if the latter are removed from the analysis and if the findings remain significant (as they do), the hypothesis is supported. Further support for the anticipation hypothesis in leukemia is drawn from a population-based survey that included all types of leukemia, lymphoma, and myeloma and that found a 38-year mean difference in age at onset in parent versus that in child.

Although prospective studies clearly would resolve questions of anticipation, as Höweler et al. (1989) did in DM, they are time consuming and expensive. In the study of anticipation in the families available for analysis, investigators have made many efforts to address biases in analyses of their data. However, the Penrose

biases of ascertainment always will be a factor in the nonsystematic and nonprospective study design. In addition, with each illness there may be unique biases to be considered—for example, substance abuse, if it occurs in the younger generation, tends to hasten the onset of psychiatric illness and thus favors anticipation.

Biases of ascertainment can be minimized and adjusted for but are likely to remain confounding factors in the study of genetic anticipation, as Horwitz et al. (1996) acknowledge. It is difficult to circumvent the first two biases of Penrose—the preferential ascertainment of late-onset parents and early-onset offspring—which lead clinicians to write (and journals to publish) reports of families with dramatic cases of disease. Horwitz et al. (1996) note, however, that, because the onset of leukemia is sudden and requires prompt medical attention regardless of family history, there may be little bias against reporting families that have the "complementary pairs" (i.e., younger-onset parent and older-onset offspring) postulated by Penrose. The simultaneous onset of the illness in the parent and child attracts medical attention and raises the possibility of an environmental influence, but Horwitz et al. (1996) note that, in larger families, affected individuals are distributed geographically and across time. In addition, few environmental factors have been associated with leukemia. In two of the larger pedigrees, affected individuals presented after the family was ascertained and show anticipation; this provides more direct evidence in support of the hypothesis. However, the families already had been ascertained and carried whatever biases were acting at the time of ascertainment. Although the study limits itself to AML and CLL, Horwitz et al. clearly have reviewed the published literature and pedigrees with hematological malignancies and have found evidence for anticipation in these studies. Indeed, they speculate that anticipation may be a general feature of all inherited hematological malignancies. Certainly they are to be commended for their exhaustive review of the literature; and the data, Penrosian biases notwithstanding, strongly favor the presence of anticipation.

Anticipation and Other Diseases

The significance of anticipation is apparent in the number of diseases that display it and that have been shown to be related to expansions in TNRs. In addition, many reports have been published identifying anticipation in many diseases, with the hypothesis that expanding TNRs are implicated in the etiology.

Anticipation has been reported in bipolar disorder (McInnis et al. 1993; Nylander et al. 1994; Engstrom et al. 1995) and schizophrenia (Asherson et al. 1994; Bassett and Honer 1994; Thibaut et al. 1995), with considerable debate over the ascertainment bias. In the analysis of the bipolar data (McInnis et al. 1993), every effort short of embarking on a prospective study was made to overcome biases. Studies of anticipation in schizophrenia had argued that the degree of anticipation (defined as age at onset in parent minus age at onset in child) correlate with the age at onset in the parent, and this correlation had been interpreted to be regression to the mean. However, later it was shown that this correlation was a statistical artifact: a significant correlation between degree of anticipation and parental age at onset was demonstrated even for randomly generated ages at onset (McInnis et al. 1994). Statistical methods have not been successful in identifying true anticipation, and Hodge and Wickramaratne (1995) conclude that, in psychiatric disorders, bias of ascertainment is pervasive—and that there is no simple way to circumvent it. The reason is related to difficulties of correlation between age at onset in the parent and that in the child. Recent studies have found an increase in the size of TNRs in bipolar and schizophrenic patients, compared with that in controls (Lindblad et al. 1995; Morris et al. 1995; O'Donovan et al. 1995), suggesting that TNR-containing loci may play a role in the etiology of these diseases. If so, it may be possible to demonstrate a molecular correlation even in cases in which the epidemiological correlation is suspect.

The appreciation that TNR expansion can cause increasingly severe disease has investigators once again going back to their pedigrees and examining the pattern of phenotypic inheritance, with the view that anticipation may be operating in the families that they are studying. Neurological disorders produce a large number of reports of anticipation. Familial Parkinson disease shows evidence of anticipation (Bonifati et al. 1995; Plantebordeneuve et al. 1995) with a ~20-year age-at-onset difference between generations. Restless-legs syndrome has a 30-year age-at-onset difference between generations in one large German pedigree (Trenkwalder et al. 1996). An exhaustive search for families with Meniere disease identified 42 parent-child pairs with a mean 17.5-year difference in age at onset, favoring anticipation (Morrison 1995). A newly defined disorder, autosomal dominant Rolandic epilepsy and speech dyspraxia, has been described in one pedigree with nine affected individuals in three generations. The grandfather in this family had evidence of speech dyspraxia with no seizures; his children had identical epileptic syndromes with more obvious speech dyspraxia, and the grandchildren were more severely affected with epilepsy and dyspraxia (Scheffer et al. 1995). The authors of that study have concluded that anticipation exists in the form of increasing disease severity. Similarly, familial adult-onset idiopathic dystonia (Cheng et al. 1996) has been studied in 49 families; the age at onset was 38.8 years in offspring and 59 years in parents. In a study of autoso-

mal dominant familial spastic paraplegia, three families have been identified (Gispert et al. 1995), and one large pedigree shows evidence for anticipation, on the basis of severity of disease; the age at onset is constant across generations. A study from Brazil has found evidence of anticipation in 34 families with facioscapulohumeral muscular dystrophy (Zatz et al. 1995). The cerebellar ataxias are well known to show anticipation (Holmberg et al. 1995; Lezin et al. 1996; Lindblad and Schalling 1996).

The list of diseases showing anticipation goes on, including many nonneurological diseases, such as Crohn disease (Polito et al. 1996), polycystic kidney disease (Peral et al. 1996), familial primary pulmonary hypertension (Loyd et al. 1995), and familial adenomatous polyposis (Presciuttini et al. 1994). Increased disease severity in successive generations has been identified in Holt-Oram syndrome (Newburyecob et al. 1996), in familial total anomalous pulmonary-venous return (Bleyl et al. 1995), and in a family with Waardenburg syndrome, cleft palate, and Hirschsprung disease (Pierpont et al. 1995). It is likely that more examples will be forthcoming over the next few months.

Mechanisms of Anticipation

Although the list of conditions exhibiting anticipation is growing rapidly, our understanding of the molecular events involved continues to lag. Two recent papers on the FA gene provide one welcome insight that may provide the basis for more detailed mechanistic accounts. Campuzano et al. (1996) have identified two distinct classes of mutations in this gene: point mutations in the open reading frame and expanded GAA repeats at an intronic site. Because these cause similar phenotypes, it appears that alleles with expanded TNRs are functionally equivalent to null or weak alleles. This conclusion is strengthened by a report by Filla et al. (1996) in a recent issue of the *Journal*. This group has shown that, in FA patients with two expanded alleles, the severity of symptoms and the age at onset depend on the length of the shorter of the two alleles. Thus, FA behaves as a simple recessive defect, and expanded alleles apparently become increasingly weak as their repeat length increases. Presumably, alleles with sufficiently great TNR expansions represent true null alleles. It remains unclear, however, why this should be so.

Many models are available to account for the disruption of expression of genes carrying TNR expansions, and there is direct evidence for at least two of these in different genetic diseases. A recent paper by Goldberg et al. (1996) shows that TNR expansion may affect protein stability. In Huntington disease, an expanded CAG repeat leads to a polyglutamine tract in the huntingtin gene product. Goldberg et al. (1996) have shown that, as the length of this tract increases, the protein becomes more susceptible to cleavage by apopain, a cysteine proteinase activated during apoptosis. This class of model may apply whenever a TNR expansion alters an open reading frame in a gene. In cases in which the TNR occurs in an intron or untranslated exonic region, other mechanisms must be acting. Thus, in DM, a CAG repeat is found in the 3′ UTR of the gene (Mahadevan et al. 1992), and primary transcripts with this expansion are found to accumulate at foci within the nucleus (Taneja et al. 1995). This is presumed to reflect aberrant processing of the mRNA, at the level of splicing, polyadenylation, or export from the nucleus. It is also conceivable that, in some genes with TNR expansions, the unusual DNA structure will be found to reduce gene expression at the transcriptional level.

The lack of a general mechanism to explain the correlation between TNR expansion and severe or early-onset forms of disease serves as a reminder that one should not to overgeneralize what has been learned to date. The recent shift in thinking among human geneticists on the subject of anticipation likewise sounds a note of caution. Although, not long ago, we were taught to view claims of anticipation with the greatest skepticism, now anticipation seems nearly ubiquitous. It may be that, as more examples of anticipation are explored at a mechanistic level, we will develop both a broader view of the classes of DNA instability and a deeper understanding of the molecular events involved when the effects of a mutation change as it is transmitted between generations.

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