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Chronon and the Problem of Anticipation

(On two family cases of diabetes)

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In previous contributions our school has already stressed the existence of a temporal dimension of the gene, giving it the name of *chronon* (Gedda, 1961; 1965*a*, *b*, *c*; 1967; Gedda & Brenci, 1966; Gedda *et al.*, 1966*a*, *b*).

This characteristic of the gene is a function of information energy of the gene itself (*ergon*: (Gedda, 1967), expressing the time during which such energy may be released by the gene. The possibility of quantifying this energy by means of the time of duration of its release and the variability of this time, i. e. the variability of *chronon*, were suggested to us by twin data: in fact, the appearance and disappearance of normal and pathological traits reveals a definite chronologic concordance between MZ cotwins and a discordance between DZ cotwins and between pairs.

The *chronon*, which may be also called the " period of the gene ", covers the time lapse between amphimixis and the extinction of the information energy; this phenomenon is reflected phenotypically in the time lapse between activation and extinction of the gene function. In the following context, this latter, phenotypical expression of the *chronon* will be considered.

Along the phenotypical period, potential gene energy may become actual, as a result of ontogenetic requirements and of the gene-environment interactions.

Interesting considerations have also been suggested by Bartalos (1967) about the relationships of the concept of *chronon* with the modern views of molecular genetics, and about the implications of *chronon* in neoplasia.

The *chronon* is a dimension of the gene, exhibiting an original genetic variability, confirmed by the familial chronologic model of ageing. Actually the time of extinction of the gene is genetically conditioned and controlled.

Such hereditary characterization of the *chronon* obviously extends to pathological genes, accounting for the familial chronologic constants of diseases and hereditary dispositions. As a dimension of the gene, the *chronon* exhibits phenotypic aspects that may be analyzed by the standard genetic models. This applies especially whenever the chronologic manifestation of hereditary phenomena exhibits intrafamilial variability.

An interesting phenomenon from this point of view is the one known as "*anticipation*", consisting in the fact that a hereditary disease may appear at an earlier age from generation to generation, i. e. *anticipate* its onset. The phenomenon of *anticipation* in a number of diseases is shown in Tab. 1 (after Penrose).

Tab. 1. Age of onset of various hereditary diseases
(After Penrose, 1948)

Disease	N. of parent-child pairs	Age of onset, mean values (in years)		
		Parent	Child	Difference
Peroneal atrophy (dominant)	86	24.30	19.36	4.94
Muscular dystrophy (dominant)	90	27.44	21.00	6.44
Hereditary glaucoma	113	42.08	30.66	11.42
Huntington's chorea	153	40.80	31.98	8.82
Diabetes mellitus	216	60.29	43.06	17.22
Mental illness (all diagnoses)	1728	50.50	34.20	16.30
Dystrophia myotonica	51	38.48	15.24	23.24

One possible interpretation of this phenomenon is that *anticipation* would tend to produce the disease at an early age in order to make it impossible for the affected individuals to reach the fertile age, thus avoiding retransmission of the morbid genotype.

On the other hand, as reported by Stern (1961), *anticipation* would be due to the modification of the selective forces acting on the human species, i. e. to the easier survival of early affected individuals, by reason of the constant progress of social and

medical sciences. In other words, pathological forms to be considered as lethal for the previous generations, and with a strong selective coefficient, would presently admit the possibility of survival.

In the case of diabetes mellitus, we recall the work by Steinberg & Wilder (1952) attributing most of the differences in the age of onset of the disease in subsequent generations to the method used in the collection of data. These Authors, avoiding any selection and always making use of the same operators, have collected 251 family cases of diabetes mellitus and have analyzed the distribution of frequencies by age of onset both in the parental and filial generations. According to them, there is no real phenomenon of *anticipation*; for any age of onset in the parents, there may be various ages of onset in the offspring: identical, earlier or later.

Medical genetics has all the time to face the problem of translating clinical concepts and data into genetic ones.

This problem is especially felt in the case of diabetes, whose clinical aspects are frequently different and mixed-up. Actually, its clinical classification has been very often discussed upon. On the occasion of the Sixth Congress of the International Diabetes Federation (Stockholm, July 30-August 4, 1967), Marble has confirmed previous views, suggesting the following classification: *prediabetes*, *chemical diabetes*, and *clinical diabetes*.

Prediabetes is a situation with a high genetic probability, but a response within normal limits to glucose tolerance tests. Therefore, the following individuals are to be considered as prediabetic: parents of diabetic offspring, healthy MZ cotwins with a diabetic partner, and, generally, close relatives of diabetic patients; carriers of vascular or neurologic modifications similar to those taking place in diabetes; pregnant women showing phenomena such as fetal macrosomy; subjects showing occasional symptoms of hypoglycemia.

The concept of *chemical diabetes* reflects a situation arising only as a result of a glucose tolerance test (generally, Staub test), and therefore different from diabetes as a disease, which is represented by the well known *clinical* picture.

This is an interesting interpretation from the clinical point of view, which however does not distinguish between the genetic and the environmental variabilities, and is therefore hard to be applied in genetic analysis.

Case histories

Taking advantage by the concrete example of two families affected by diabetes mellitus, we started anew the study of the relationships between a hereditary disease and its age of onset.

Case 1

Propositus

Pierino B., b. 27.III.1956.

Family data (*cf.* Fig. 1)

Paternal grandfather affected by diabetes mellitus at the age of 58; dead at 60.
Father: Staub-negative (*cf.* Fig. 2) at the age of 45.
Mother: Staub-positive (*cf.* Fig. 2) at the age of 37.

Anamnesis

Weight at birth: kg 4.2 (as compared to the Italian average of kg 3.4 for males born alive). At the age of 5: measles. Subsequently: icterus, diabetes mellitus (polydipsia, polyuria, anorexia, loss of weight).

Direct examination (26.X.1966)

Weight: kg 38.2; height: m 1.49
Glycosuria: mg 12%
Glycemia: mg 3%
Azotemia: mg 17%
Cholesterolemia: mg 128%
Diagnosis: diabetes mellitus.

CASE I

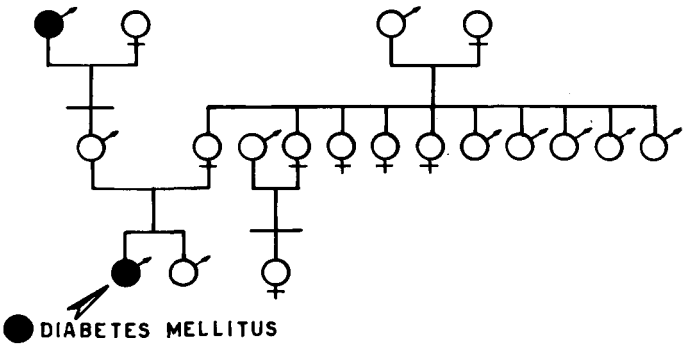

Fig. 1

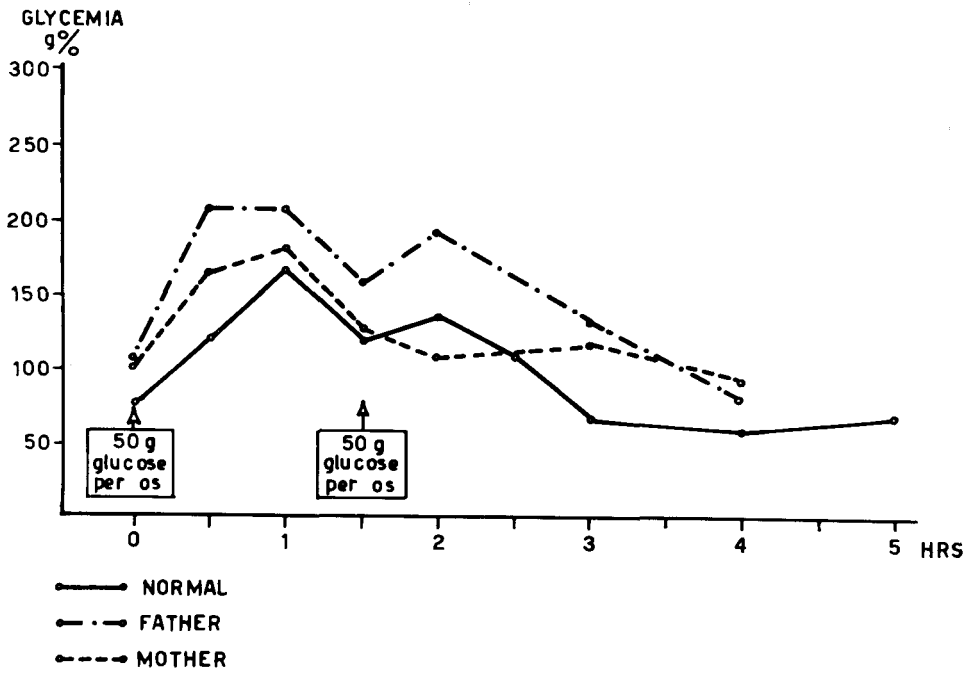

Fig. 2

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Case 2

Propositi

MZ[1] twins Armando and Argante M., b. 22.IV.1932.

Family data (*cf.* Fig. 3)

Paternal aunt: b. 1901, living. At the age of 63: clinical diagnosis of diabetes mellitus.

Anamnesis

Weight at birth: Armando kg 2.5, Argante kg 2.7. At the age of 23, symptoms of schizophrenia in both twins. Hospitalization for 6 months at the age of 25 and for 6 more months at the age of 27 (electroshock and insuline shock). At the age of 34, occasional symptoms of diabetes (hyperglycosuria and hyperglycemia) in Armando.

Direct examination (7.III.67)

Armando: weight kg 68; height m 1.61
Argante: weight kg 76; height m 1.64
Both twins: Staub-negative (*cf.* Fig. 4)
Diagnosis: diabetes mellitus.

[1] **Diagnosis of Zygosity** (For the methodological system, *cf.* Smith *et al.*, 1961; for the frequencies, *cf.* also Parisi & Di Bacco, 1967).

Character	Relative chance of DZ pair
Initial chance	$p_1(D) = 2.3333$
Likeness in Sex (♂♂)	$p_2(D) = .2500$
Likeness in ABO blood group (O-O)	$p_3(D) = .6891$
Likeness in MN blood group (M-M)	$p_4(D) = .6642$
Likeness in Rh blood group (Rh_1rh-Rh_1rh)	$p_5(D) = .5400$
Concordance in Total Finger Ridge Count (157-156)	$p_6(D) = .2300$

$$p(D) = p_1(D) \cdot\ldots\cdot p_6(D) = .0332$$

$$P_{DZ} = \frac{p(D)}{1+p(D)} = .0249$$

$$P_{MZ} = 1-P_{DZ} = .9751$$

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CASE 2

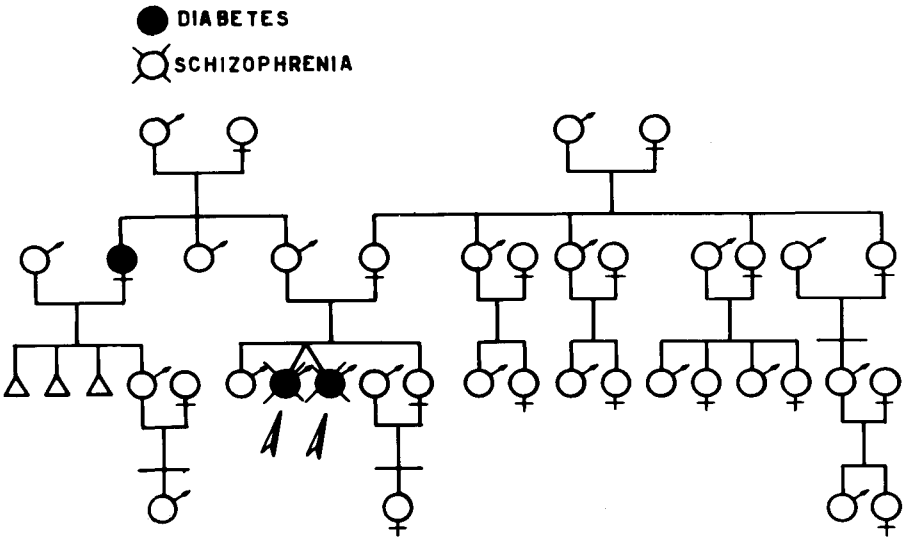

Fig. 3

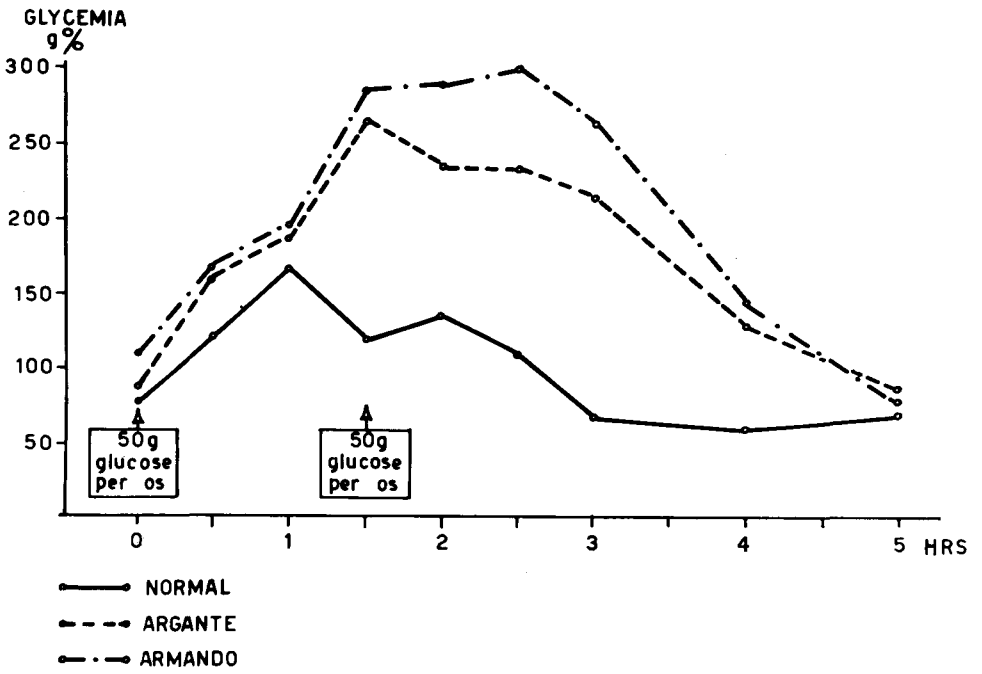

Fig. 4

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Discussion

The two family cases we have described have a complementary meaning, that is to say, they stress the existence of the genetics of the *chronon* both in the presence or absence of *anticipation.*

Our interpretation is based on the following hypotheses:

1) diabetes mellitus is inherited as a simple polyallelic recessive [2];

2) the different alleles represent a different degree of mutational genotypic damage;

3) to each combination of mutant alleles corresponds a reduction of *chronon* proportional to the mutational damage supported.

This interpretation allows attributing to the various genotypic formulae of diabetes mellitus a corresponding clinical interpretation, as shown in Fig. 5.

In the case of the homozygotic combination DD, the resulting individual is genotypically and phenotypically healthy. In the case of the heterozygotic combinations, normal × mutant (Dd_1, Dd_2, Dd_3), the resulting individual is phenotypically healthy and a genetic carrier. In the case of d_1d_1 and d_1d_2 genotypes, diabetes is of the *mild* type, and generally manifests itself in the *late* age. In the case of d_1d_3 and d_2d_2 genotypes, diabetes is of the *moderate* type, and generally manifests itself in the *adult* age. In the case of d_2d_3 and d_3d_3 genotypes, diabetes is of the *severe* type, and generally manifests itself in the *early* age. Many other intermediate types and times of onset might also be suggested, thus increasing the genotypic variability by the introduction of new alleles.

The application of the scheme of Fig. 5 to Case 1 is as follows (*cf.* Fig. 6):

The paternal grandfather of the propositus is considered as a d_2d_2 homozygote. The paternal grandmother is assumed to have been a Dd_1 heterozygote. The father of the propositus (whose diabetes was detected by Staub test) is considered to be a d_1d_2 heterozygote. The mother of the propositus is considered as a Dd_3 heterozygote. The marriage of these latter two individuals may produce various gametic combinations, including d_2d_3, corresponding to a more seriously mutated genotype, and therefore with a more serious damage to the *chronon.* This genotype phenotypically appears as one of the utmost reductions of the time of erogation of the genetic information, i. e. as one of the utmost reductions of *chronon*, which causes early diabetes, as shown by the propositus (and could be possibly indicated by his high weight at birth).

The application of the scheme of Fig. 5 to Case 2 is as follows (*cf.* Fig. 7):

The paternal aunt is considered as a d_1d_1 homozygote. The father and the

[2] The genetic interpretation of diabetes mellitus has for a long time been oversimplified. This disease has been generally reported as a simple recessive, which hardly fits its complex clinical features and variability. More recent studies, in fact, have also suggested multifactorial inheritance (*cf.* Neel *et al.*, 1965; Jörgensen, 1966).

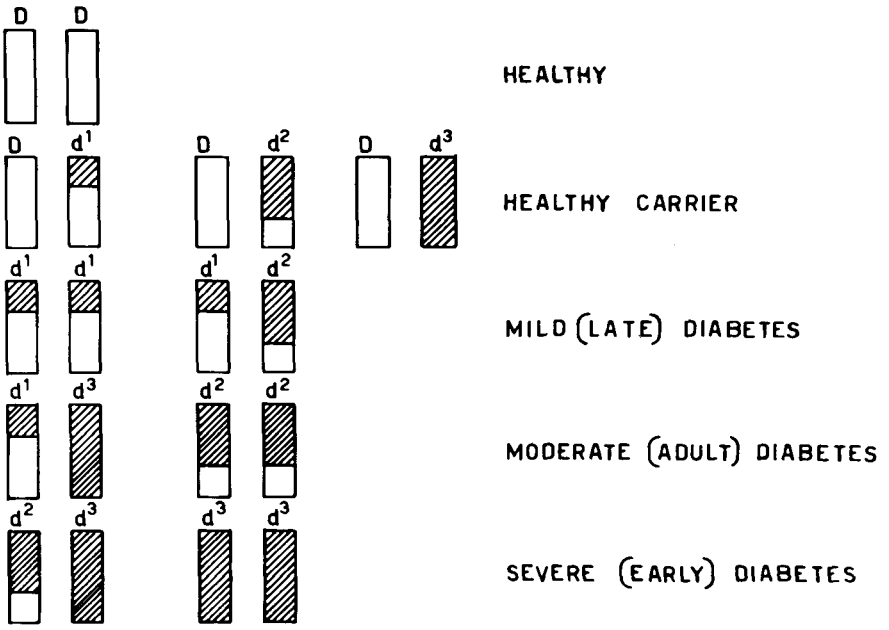

Fig. 5

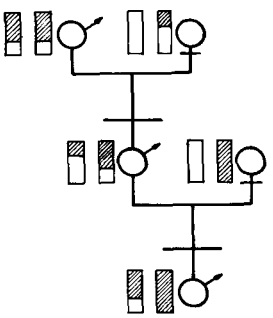

Fig. 6

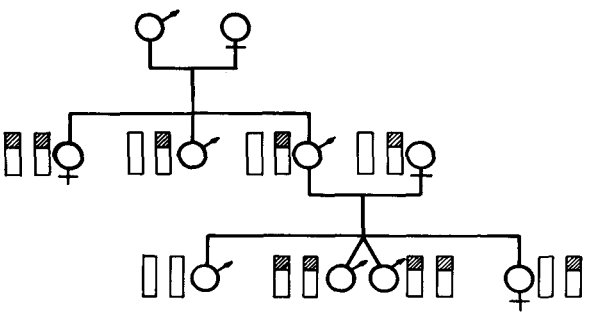

Fig. 7

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mother of the twins, both clinically healthy, are therefore attributed a Dd_1 genotype. Their marriage may give rise to phenotypically healthy offspring, as in the case of the sibs of the propositi, and to affected offspring, as in the case of the twin propositi. The latter may possess a d_1d_1 genotype, identical to the one which is reported in the scheme among the possible genotypes of the paternal aunt.

With respect to these family cases, our interpretation explains the possible changes in the time of onset and the ensuing clinical implications of diabetes.

Summarizing, in the first family a d_2d_2 diabetes becomes a d_1d_2 diabetes in the second generation (*posticipation*) and a d_2d_3 diabetes in the third generation (*anticipation*). In the second family a d_1d_1 diabetes keeps as such in the subsequent generation (*repetition*). The inverse proportionality between mutational damage and *chronon* allows, in the two families, an explanation of the hereditary transformation of *chronon*, not only in the sense of a chronologic *anticipation*, but in the sense of *posticipation* and *repetition*, as well.

We agree on both previously reported interpretations, one attributing the phenomenon of *anticipation* to better environmental conditions, and the other considering *anticipation* as an epiphenomenon of the variability of diabetes mellitus. These hypotheses do not contradict each other, since the survival of patients with anticipating diabetes (*cf.* Stern, 1961) may concern the chronologically minus-variant fraction of the variability considered by Steinberg & Wilder.

Furthermore, both interpretations stand on the actual fact that the manifestation of diabetes at different ages corresponds to a different structure of the genotype with respect to its duration in time. In other words, the genealogical analysis of the temporal transpositions of the age of onset of diabetes shows that the gene does have a temporal dimension, and that this dimension, which we call *chronon*, obviously represents a hereditary trait. In order to interpret the phenomenon of *anticipation* as well as those of *posticipation* and *repetition*, it is sufficient to admit the existence (and genetic variability) of the *chronon*.

From the phenotypic standpoint, *anticipation* may also be explained by means of the new clinical notions on diabetes mellitus. For instance, the presence of metabolites able to repress the action of the activators of haematic insuline, may also explain through an endogenous variability, some cases of *anticipation*. Similarly, dietary factors may determine an exogenous variability in the time of onset of diabetes.

On the other hand, from the genetic standpoint, a basic determination in the time of onset of a hereditary disease must be recognized. This is originated by the variability of a dimension of the gene, called *chronon*, which expresses the duration of erogation in time of the genetic information.

Summary

The Authors analyze the phenomenon whereby, in progressing from generation to generation, a hereditary disease may appear at an earlier, equal or later age (*anticipation*, *repetition* or *posticipation*, respectively). They believe that this represents the phenotypic effect of a temporal dimension of the gene, the " *chronon* ", which may reveal stability, plus-variance or minus-variance according to the standard genetic models. This interpretation provides an explanation of two family cases of diabetes mellitus, respectively exhibiting *anticipation* and *posticipation*, and *repetition*.

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RIASSUNTO

Gli AA. analizzano il fenomeno per cui, da una generazione all'altra, una malattia ereditaria può manifestarsi ad un'età precedente, uguale o più tarda (rispettivamente *anticipazione, ripetizione* e *posticipazione*). Essi ritengono che ciò rappresenti l'effetto fenotipico di una dimensione temporale del gene, il *cronon,* che può rivelare stabilità, plus-varianza, minus-varianza, secondo i normali modelli genetici. Tale interpretazione fornisce una spiegazione di due casi familiari di diabete mellito, i quali presentano, rispettivamente, *anticipazione* e *posticipazione,* e *ripetizione.*

RÉSUMÉ

Les AA. analysent le phénomène par lequel, d'une génération à l'autre, une maladie héréditaire peut se manifester à un âge précédent, égal ou successif (respéctivement, *anticipation, répétition* ou *posticipation*). Ce phénomène vient expliqué comme l'effet phénotypique d'une dimension temporelle du gène, le *chronon,* qui peut démontrer stabilité, plus-variance ou minus-variance, d'après les modèles génétiques courants. Cette interprétation fournit une explication de deux cas familiaux de diabète qui présentent, respéctivement, *anticipation* et *posticipation,* et *répétition.*

ZUSAMMENFASSUNG

Verf. befassen sich mit der Erscheinung, dass eine Erbkrankheit bei aufeinanderfolgenden Generationen in früherem, gleichem oder späterem Alter (d.h. als *Antizipation, Repetition* oder *Postezipation*) auftreten kann. Sie sind der Ansicht, dass diese Erscheinung des Phänotyps Ausdruck einer zeitlichen Dimension des Gens, d.h. des *Chronons* ist, welche den normalen Erbschablonen gegenüber Stabilität oder Plus — bzw. Minus-Varianten aufweisen kann. Diese Deutung würde erklären, wie in zwei Familien mit Diabetes mellitus das Leiden in einem Falle in *Antizipation* bzw. *Postezipation,* beim anderen Falle hingegen in *Repetition* auftrat.

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