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The Heredity of Biological Time and Population Genetics

Diabetes, Lupus Erythematosus, and Peptic Ulcer

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SUMMARY

The phenomenon of life, in its individual and collective expressions, develops through a sequence of times resulting from the interference of biological with physical time. While physical time is uniform, the biological one differs from one individual to the other, except for MZ twins.

The problem of biological time has been studied in physiology and informational genetics from the viewpoint of its succession of single times, although irrespective of the individual variability in their duration. This variability has already been shown by the authors to be hereditary, its inheritance being directly connected with the hereditary unit.

Biological time corresponds to the duration of degradation (" chronon ") of the energy of stability (" ergon ") possessed by the gene and, by extension, to the total chronon of the genotypes underlying a given structure or function. Ergon and chronon are correlated index values, thereby constituting a system (" E/C system ").

The individual variability of biological time depends on the A-T/G-C ratio in the DNA molecule, on the different amount of genic redundancy and on the different possibilities of repair of corresponding genes. The variability of these or possibly other causal factors determines the stability with respect to the environment in which the information operates, and especially to mutagenic agents.

The authors apply the E/C model to epidemiologic data concerning diabetes, lupus erythematosus, and peptic ulcer, and verify the consistency of the experimental data with the theoretical model.

The phenomenon of life, in its individual and collective expressions, develops through a sequence of times resulting from the interference of biological with physical time (Szilard, 1959).

Physical time induces many important biological times: e.g., the daily rhythm of the earth's revolution is reflected in the circadian sleep-wake rhythm, as well as in many other organic functions; the monthly rhythm of the moon's rotation is reflected in the woman's menstrual cycle; and the yearly rhythm of the earth's rotation is reflected in the cycle of seasons, in such phenomena as hibernation of certain animal species, in the seasonal rhythm of certain diseases in man, etc. (Pittendrigh, 1960).

Inorganic matter already possessed a physical time when life appeared on our

planet. Life appears and evolves within physical time; i.e., life-responsible molecular structures are faced with an environment which scans uniform and binding times, matching the matter's energy degradation (Strehler, 1962).

Yet, living beings also exhibit an endogenous time characterized by species, population, family, and individual constants (Medvedev, 1966).

The problem of biological time has been studied in physiology and informational genetics from the viewpoint of its succession of single times, although irrespective of their length, i.e., of the individual variability in the duration of times. In a previous study, we succeeded in showing the hereditary character of this variability, its inheritance being directly connected with the hereditary unit (Gedda and Brenci, 1969).

Biological time depends on the duration of the gene's energy of stability, and, by extension, on the bulk of the units of energy and of time involved in a given structure or function of living matter.

The energy of stability of the gene we have called " ergon ", and the duration of information, " chronon ". Having then shown ergon and chronon to be correlated as the terms of a biological equation, we have derived the existence of an " ergon: chronon system " (E/C system).

The individual, hereditary variability of the E/C system depends, in our opinion, on the different A-T/G-C ratio of synonymous codons in the DNA molecule, on the different amount of genic redundancy, and on the different possibilities of repair of corresponding genes (Sonneborn, 1965). This variability is produced by mutagenic agents, and, as any mutation, may be inherited.

The variability of the E/C system (i.e., the different amount of ergon and different duration of chronon, both decreasing with age) is, on one hand, spontaneous, since it depends on the matter's entropic degradation, which is conditioned by its physico-chemical environment, and, on the other, induced by the intensity of the various demands that must be met.

Ecologic factors, since life has appeared on our planet, represent a close sieve of hereditary factors for the genotype, through which selection has been operating both at the quali-quantitative level and at the chronologic one, favouring, with respect to the latter, the philum with the fittest E/C systems. Thus, the species have also evolved with respect to the genetically protected constants of biological time, as already in 1932 Haldane has shown for certain achievements of individual development in different human populations.

The individual is a specimen of the philum in a given moment of its evolution, and produces, in turn, a vital cycle conditioned, with respect to time, by the characteristics of his E/C systems.

As a result, it may be assumed that the existence and function of the E/C system should be verified not only by human and medical genetics — through the twin or the genealogical method, as we did before — but by population genetics as well, on account of the frequencies of normal vs. pathologic phenotypes.

We therefore decided to undertake the above verification, and referred to a series of population data concerning different conditions: diabetes, lupus erythematosus, and peptic ulcer.

Epidemiology of Diabetes and the E/C System

The genetics of diabetes is a much debated question. Although there seems to be general agreement on the hereditary character of this disease, its frequency, its penetrance, and especially its mode of inheritance have produced a proliferation of different hypotheses, sometimes based on poor experimental data. The uncertainty is not only due to the difficulties encountered in the experimental verification of the hypotheses, but also to the fact that theoretical models may prove insufficient when only based on static concepts of classic genetics. This inadequacy may be shown by applying the model of the E/C system to sound experimental data.

Mean Glycemic Values in Healthy Adults after Glucose Load

The data of the National Center for Health Statistics (1964) show that in normal males and females, after glucose load, glycemic values increase with age (Tab. I).

Tab. I. Mean glycemic values in healthy adults after glucose load

Age	♂ + ♀	♂	♀
18-24	99.7	94.6	104.1
25-34	105.7	101.5	109.5
35-44	116.7	115.2	117.6
45-54	125.8	118.2	133.1
55-64	137.8	130.1	145.2
65-74	150.7	139.8	159.7
75-79	166.3	154.4	178.7

Source: US National Center for Health Statistics, 1964
Note: The glycemic values (expressed in mg%) have been examined 1 hour after a glucose load of 50 g.

These data therefore indicate that the regulation mechanisms of glucidic metabolism undergo a deterioration which is proportional to life length. This may be due to the fact that the ergon of the genotypes responsible for glucidic homeostasis undergoes a degradation in time, thus producing a quantitative reduction of the specific information available to the organism.

Latent Diabetes by Age

The research into latent diabetes, as carried out by Kent and Leonards (1968) through Staub's test, shows that its frequency undergoes an increase of almost two times for every age class (Tab. II).

Tab. II. Latent diabetes in whites by age

Age	N	Diabetics (%)
20-29	16 423	0.1
30-39	18 629	0.5
40-49	23 632	1.4
50-59	17 140	3.5
60-69	7 654	7.5
70-79	2 498	12.5
80-89	360	20.0

Source: Kent and Leonards, 1968.

These findings are well interpreted, analytically, by an exponential curve. Such a behavior of prediabetes by age reproduces the model of the physical degradation of radioactive atoms, i.e., their random probability of increase in time. Similarly, we are confronted here with a progressive increase in number of the specific genotypes which become exhausted in the subsequent age classes, as a result of the continuous degradation of the ergon of that specific hereditary information. As age progresses, an increasing number of loaded genotypes exhaust their corresponding ergon and chronon, thereby also leading into a preclinical condition (latent diabetes) those obviously more numerous genotypes with a minor hereditary damage.

Familiarity of Diabetes by Age

The research into the familiarity of diabetes has been carried out by Kent and Leonards (1968) in a comparative study of diabetic vs. nondiabetic subjects. Familiarity has been found to decrease with age in the families of diabetic propositi, while remaining more or less constant in those of healthy ones (Tab. III).

The data concerning diabetic propositi may be explained on account of the following two reasons:

1) The chronologic path of diabetes, impressed by the extent of the damage of the E/C system, is shared by practically all diabetic patients belonging to the same family;

2) The more serious the damage, the more the load may be revealed by environ-

Tab. III. Familiarity of diabetes by age

Age	Diabetic subjects		Nondiabetic subjects	
	N	Familiarity of diabetes (%)	N	Familiarity of diabetes (%)
20-29	25	64	18 882	28
30-39	123	56	21 873	32
40-49	409	50	26 679	30
50-59	709	40	18 964	26
60-69	673	39	8 316	25
70-79	373	29	2 586	21
80-89	77	18	359	15
90-99	11	18	18	12
Total	2 400	40	69 561	28

SOURCE: Kent and Leonards, 1968.

mental factors, on account of the increased difficulty of the task of genetic and non-genetic mechanisms of compensation (redundancy, repair, homeostasis).

Therefore, the more serious the damage of the E/C system, the earlier the onset of the disease in the propositus and the larger the presence of clinical diabetes in his relatives. Conversely, the lighter the damage, the later the onset and the lesser the familiarity.

This interpretation is confirmed by the finding of a constant frequency of diabetes among relatives of nondiabetic subjects, showing the frequency of diabetes to be constant in the different age classes of the population. Within such a uniformity of frequency, the different damage of the E/C system induces a discrimination, on account of the different reactivity of loaded genotypes towards environmental factors, according to their hereditary variability with respect to the E/C system.

AGE OF ONSET OF DIABETES

Spiegelman and Marks (1946) have found the mean age of onset of diabetes to be different in the two sexes, i.e., lower and older than 70 respectively in females and males (Tab. IV).

These data, worked out by Burch (1968), show the heterogeneity of the time of onset of the disease to be due to a genotypic heterogeneity. The chronologic heterogeneity of the diabetic genotype might be interpreted on account of a correlation between the chronologic heterogeneity of diabetes and the heterogeneity of the sex genotypes, but may also be interpreted by an E/C model, i.e., on account of different ergons of the genotype responsible for diabetes.

Tab. IV. Onset of diabetes by sex and age

Age	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
♂	—	2.8	5.8	11.0	16.4	24.6	39.6	71.6	101.7	114.8	125.1	113.3	99.0	65.9	20.1
♀	—	3.8	10.0	19.6	31.9	53.7	82.2	130.6	179.5	198.1	201.2	162.4	115.0	66.5	19.7

SOURCE: Spiegelman and Marks, 1946.
NOTE: New diabetics/100 000 (US data for 1935-1936).

Westlund's findings (1966) support the latter hypothesis. In a statistical study concerning the incidence of diabetes in Oslo in the period 1925-1954, he has in fact identified — besides the two characteristic ages of adult's diabetes already referred to — two further characteristic ages (around 10) of juvenile diabetes (Fig. 1). At

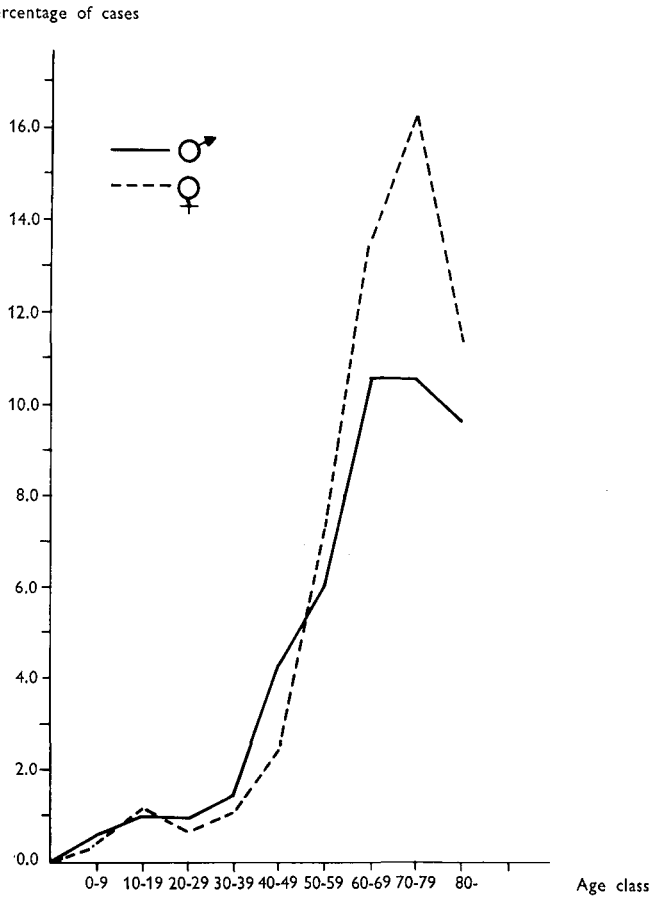

Fig. 1. Distribution of the ages of onset of diabetes (Source: mean values for Oslo in the period 1925-1954 [Westlund, 1966])

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this level of age the two sexes behave in an opposite way with respect to the adult age, the onset being earlier in males than females.

These observations show the heterogeneity in the age of onset of diabetes to be determined by at least four genotypes which differentiate on account of the time of onset of the disease.

This variability cannot be accounted for simply on the basis of the heterogeneity of sex genotypes, but requires a model with a larger genetic variability, such as the one defined by the possibility of inheriting different degrees of stability of one and the same morbid genotype.

Further support to the hypothesis of an autosomal genetic conditioning of the age of onset of diabetes is given by the distribution of diabetic deaths by age, as obtained by us on Italian data for 1958-1967 (Tab. V).

Tab. V. Distribution of diabetic deaths by sex and age

Age	0-5	5-10	10-15	15-20	20-25	25-30	30-35	35-40	40-45	45-50
♂	33	22	42	70	104	104	154	207	295	566
♀	24	59	68	78	89	101	129	193	288	500
Total	57	81	110	148	193	205	283	400	583	1 066

Age	50-55	55-60	60-65	65-70	70-75	75-80	80-85	85-90	90→	Total
♂	1 279	2 273	3 519	4 842	5 883	5 419	3 097	1 006	170	29 085
♀	1 301	2 944	5 567	9 214	11 760	10 300	5 806	1 905	332	50 658
Total	2 580	5 217	9 086	14 056	17 643	15 719	8 903	2 911	502	79 743

SOURCE: Italian Institute of National Statistics (ISTAT).
NOTE: Italian data referred to the period 1957-1966.

Using the age at death as an indirect estimate of the age of onset, it may be observed that the cumulative distribution of frequencies (Fig. 2), besides the two branches corresponding to Westlund's two characteristic ages, exhibits a third discontinuity corresponding to age class 65-70. This indicates a further heterogeneity of the data, which is probably the result of the adult's diabetic genotype splitting into two different genotypes, with different ergon, acting in the age ranges 35-65 and 65-95, respectively.

Moreover, with the E/C model the chronologic variability may find an autosomal interpretation in agreement with the results of most genealogical studies.

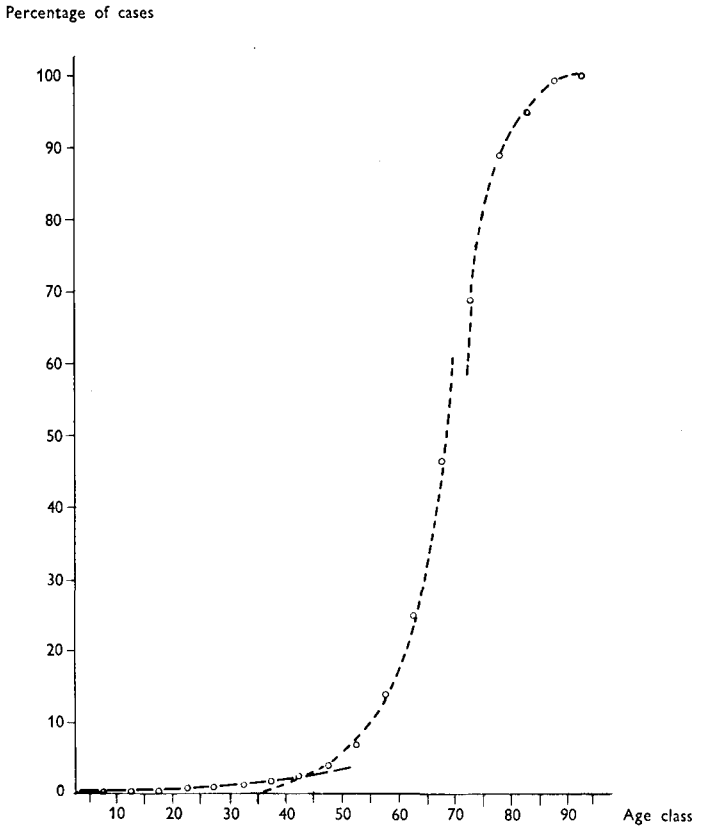

Fig. 2. Cumulative death frequencies for diabetes by age
(Source: Italian statistics for the period 1957-1966 [ISTAT data])

Epidemiology of Lupus Erythematosus and the E/C System

Lupus erythematosus is an irreversible, usually fatal disease, due to an immunological damage affecting the nonself recognition in the tegumentary tissues (skin and mucous membranes), with different implications of joints, circulation, digestive system, kidneys, etc.

The onset of the disease is generally clearly noted, on account of the presence of the LE factor, and so is the moment of the exitus, which is caused, as a rule, by lupus itself in a short while. (The short interval between onset and exitus may hardly be extended of six more months by the recently introduced cortisone therapy).

Vital and health statistics may therefore be used as a source of epidemiologic data on lupus erythematosus, and a population genetic study may thus be carried out.

Italian statistics (ISTAT data) have in fact been examined with respect to the death rates for lupus erythematosus, by age, in the period 1957-1966 (Tab. VI). As already noted, death rates may be considered to apply to onset as well, the interval between onset and death being very short.

Tab. VI. Death rates for lupus erythematosus by sex and age

Age	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100
♂	—	4	6	7	5	17	7	10	—	—
♀	5	22	41	37	19	15	12	8	3	—
Total	5	26	47	44	24	32	19	18	3	—

SOURCE: Italian Institute of National Statistics (ISTAT).
NOTE: Italian data referred to the period 1957-1966.

The results of the analysis are represented in Fig. 3, showing the cumulative function for every class of age. The curve clearly indicates the existence of four

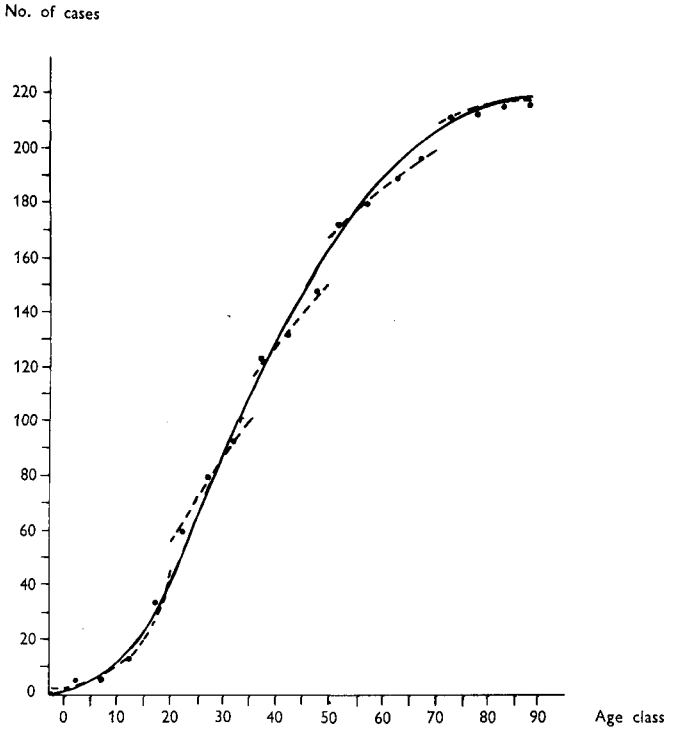

Fig. 3. Cumulative death frequencies for lupus erythematosus (Source: Italian statistics for the period 1957-1966 [ISTAT data])

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modal classes, i.e., the existence of preferential cumulative ages of death at 25, 40, 60, and 80. Such a distribution would reveal lupus erythematosus to be produced by specific genotypes differentiating only at the time level.

The chronologic, genetic heterogeneity of lupus erythematosus may be easily accounted for, assuming that the epidemiologic subgroups correspond to genotypes with differently efficient E/C system: the more serious subgroup, corresponding to the age of approximately 25, would have a very reduced ergon, thus making the duration of the information, i.e., chronon, become exhausted in an early age. Subsequent classes of later manifestation would then be the result of genotypes with more and more efficient E/C systems. The following considerations may be deduced:

1) Most loaded genotypes underlying lupus erythematosus show a limited reduction of the stability of information, compatible with life until the old age;

2) The E/C system of that genotype underlying the correct information which would exclude lupus, is a *quoad vitam* system;

3) The genetic heterogeneity in the time of onset of lupus does not depend on sexual dimorphism, at least four genotypes having been revealed by formal analysis.

The analytical result obtained through multiple heterogeneity therefore shows that the differentiated onset of lupus is the result of a number of different loaded genotypes, all responsible for one and the same disease, although differentiating at the time level.

Epidemiology of Peptic Ulcer and the E/C System

By peptic ulcer we define similar ulcerative syndromes of stomach and/or duodenum even alternatively present in the same family.

The familiarity of these conditions has been studied by many authors and different genetic models have been suggested, as well as different hypotheses on the possible load actually responsible for the disease.

An epidemiologic study has been carried out in order to ascertain the impact of this load on the chronon of normal hereditary information, i.e., on the duration of good functioning of the mechanisms damaged by the disease. To this end we have traced the pedigrees of 62 cases hospitalized and treated in the period 1966-1969, with special respect to presence or absence of the disease, age of onset, clinical picture, and exitus. The analysis has been limited to the age of onset in the sibships of patients and their parents.

The aim of this research was twofold:

1) To verify whether the distribution of the ages of onset behaves as a constant, when examined after one generation, or is affected by environmental variables (such as diet, for instance);

2) To ascertain the possible existence of responsible genotypes differentiating on account of the age of onset, i.e., to ascertain the genetically determined chronologic heterogeneity of peptic ulcer, defined on account of a variability of the E/C system.

The two series — sibships of patients and sibships of parents — have been examined by age classes of five to five, from birth up to 80 years (Tab. VII). The same data are analyzed in Fig. 4, where the two curves represent the distributions of the ages of onset in the two series: a clearly parallel behavior may be noted.

Tab. VII. Frequency of peptic ulcer compared over two generations

Age	Patients and their sibships	Patients' parents and their sibships	Total
0-5	1	—	1
6-10	2	—	2
11-15	9	1	10
16-20	15	2	17
21-25	15	10	25
26-30	9	5	14
31-35	6	5	11
36-40	18	8	26
41-45	8	4	12
46-50	7	4	11
51-55	1	1	2
56-60	7	4	11
61-65	1	1	2
66-70	1	1	2
71-75	1	—	1
76-80	1	—	1
Total	102	46	148

A χ^2 analysis (Tab. VIII) then shows this behavior to be practically identical, no heterogeneity being noticeable once the age classes grouped into larger ones.

It may be assumed, therefore, that — at least on account of the two generations examined — environmental variables do not significantly affect the manifestation of ulcer.

Moreover, three peaks may be noted on the curves, corresponding to age classes 21-25, 36-40, and 56-60.

The chronological differentiation of onset represents the most peculiar result: it shows, in fact, that the affected population is nonhomogeneous for the age of onset, and that a different chronological behavior of the mutations underlying the syndrome must be accounted for this heterogeneity.

At least three kinds of mutations with different impact on the age of onset may thus be individuated, which does not exclude other discriminating criteria concerning other aspects of the population or other features of the clinical picture.

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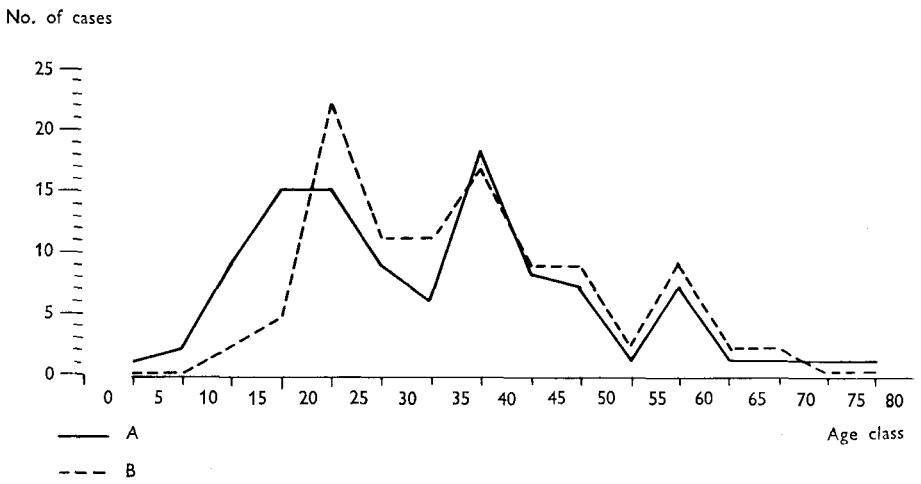

Fig. 4. Age of onset of ulcer in the propositi and their sibships (A) vs. their parents' sibships (B)

Tab. VIII. *Statistical analysis of the frequency of peptic ulcer over two generations*

Age	1-20		21-40		41-60		61-80		Total
Frequency	Expected	Observed	Expected	Observed	Expected	Observed	Expected	Observed	
Patients and their sibships	20.2	27	52.4	48	24.8	23	4.6	4	$\chi^2=3.411$
	$\chi^2 = 2.289$		$\chi^2 = 0.369$		$\chi^2 = 0.675$		$\chi^2 = 0.078$		
Patients' parents and their sibships	9.8	3	23.6	28	11.2	13	1.4	2	$\chi^2=4.123$
	$\chi^2 = 2.759$		$\chi^2 = 0.820$		$\chi^2 = 0.289$		$\chi^2 = 0.257$		
Total	$\chi^2 = 5.048$		$\chi^2 = 1.189$		$\chi^2 = 0.964$		$\chi^2 = 0.335$		$\chi^2=7.536$

3 *df*; $P = 0.055$ ns

SOURCE: Data from Tab. VII.

Heterogeneity may easily be interpreted on account of the E/C system. Of course, mutations have a different impact on the ergon of the genotype underlying normal structure and functioning of gastroduodenal mucous membranes. As a result, normal functioning may continue for a given, proportional period, until chronon and the corresponding specific ergon become exhausted.

The chronological study of ulcer therefore leads to the same conclusions reached in the study of diabetes and lupus, i.e., the E/C system represents a fundamental mechanism for the correct interpretation of morbid phenomena.

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RIASSUNTO

Il fenomeno della vita nelle sue espressioni individuali e collettive si svolge attraverso una sequenza di tempi che risultano dall'interferenza del tempo biologico col tempo fisico. Il tempo fisico è uniforme mentre quello biologico è differente da individuo a individuo, fatta eccezione per i gemelli MZ.

La fisiologia e la genetica dell'informazione hanno studiato il problema del tempo biologico dal punto di vista della successione dei tempi che lo compongono, ma non da quello della variabilità individuale nella durata dei singoli tempi. In precedenti ricerche gli autori hanno dimostrato che questa variabilità è nettamente ereditaria, perché possiede un meccanismo di trasmissione legato al gene.

Il tempo biologico corrisponde alla durata della degradazione (« chronon ») dell'energia di stabilità (« ergon ») posseduta dal gene e, per estensione, al chronon complessivo dei genotipi che operano per una determinata struttura o funzione. Ergon e chronon sono valori-indice correlati e perciò costituiscono un sistema (sistema E/C).

La variabilità individuale del tempo biologico dipende dal rapporto A-T/G-C nella molecola di DNA, dalla diversa quantità della « ridondanza » genica, dalle differenti capacità di « repair » di geni corrispondenti. La variabilità di questi o di altri eventuali fattori causali determina la stabilità rispetto all'ambiente in cui l'informazione opera ed in particolare rispetto agli agenti mutageni.

Gli autori applicano il modello E/C ai dati epidemiologici del diabete mellito, del lupus eritematoso e della malattia ulcerosa, verificando la conformità tra dati sperimentali e modello teorico.

Résumé

Le phénomène de la vie, dans ses expressions individuelles et collectives, se développe à travers une séquence de temps qui résultent de l'interférence du temps biologique et du temps physique. Ce dernier est uniforme, tandis que le temps biologique diffère d'un individu à l'autre, à l'exception des jumeaux MZ.

La physiologie et la génétique informatique ont bien étudié le problème du temps biologique au point de vue de la succession des temps qui le composent, sans toutefois examiner la variabilité individuelle dans la durée de ces temps. Les auteurs, en de précédentes recherches, ont déjà démontré que cette variabilité est clairement héréditaire, son mécanisme de transmission étant directement lié à l'unité génique.

Le temps biologique correspond à la durée de la dégradation (« chronon ») de l'énergie de stabilité (« ergon ») possédée par le gène et, par extension, au chronon total des génotypes qui opèrent pour une structure ou fonction données. Ergon et chronon sont des valeurs-indices corrélées et forment par conséquent un système (système E/C).

La variabilité individuelle du temps biologique dépend du rapport A-T/G-C dans la molécule de DNA, de la différente quantité de « redondance » génique et des différentes possibilités de « repair » de gènes correspondants. La variabilité de ces facteurs causaux, ou d'autres encore, détermine la stabilité vis-à-vis du milieu où l'information opère, notamment vis-à-vis des agents mutagènes.

Les auteurs appliquent le modèle E/C aux données épidémiologiques du diabète, du lupus erythémateux et de l'ulcère, afin de vérifier si le modèle théorique corréspond aux données expérimentales.

Zusammenfassung

Das Phänomen des Lebens in seinen individuellen und kollektiven Äusserungen wickelt sich durch eine Folge von Zeitabständen ab, die sich aus dem Ineinandergreifen von biologischem und physikalischem Tempo ergeben. Das physikalische Tempo ist gleichförmig, das biologische hingegen ist — mit Ausnahme der eineigen Zwillinge — bei jedem Menschen anders.

Physiologie und Informationsgenetik beschäftigten sich mit dem Problem des biologischen Tempos, indem sie die einzelnen Tempi, aus denen es sich zusammensetzt, in ihrer Reihenfolge, nicht aber die individuelle Variabilität ihrer Dauer ins Auge fassten. In ihren vorhergegangenen Forschungen hatten die Verf. bewiesen, dass diese Variabilität deutlich erbbedingt ist, nachdem sie einen gengebundenen Übertragungsmechanismus besitzt.

Das biologische Tempo entspricht der Dauer der Degradation (« Chronon ») der Stabilitätsenergie (« Ergon »), welche dem Gen und demnach auch dem gesamten Chronon der Genotypen innewohnt, die eine bestimmte Struktur oder Funktion bewirken. Ergon und Chronon sind korrelative Indexwerte und stellen daher ein System (E/C-System) dar.

Die individuelle Variabilität des biologischen Tempos bedingen: das Verhältnis A-T/G-C im DNA-Molekül, die unterschiedliche Höhe des Gen-Überschusses », die verschiedenen « repair »-Fähigkeiten der entsprechenden Gene. Aus der Variabilität dieser oder anderer eventueller Kausalfaktoren ergibt sich die Stabilität gegen die Umwelt, in der die Information stattfindet, insbesondere gegenüber den mutagenen Einwirkungen.

Verf. wenden das E/C-Modell auf die epidemiologischen Erhebungen bei Diabetes mellitus, Lupus erythematosus und dem Ulcusleiden an und stellen fest, dass die Versuchsergebnisse mit dem theoretischen Modell übereinstimmen.

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