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On the Statistical Significance of one Pair of Monozygotic Twins in Clinical Genetics[1]

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A frequent event in Clinical Genetics is that of finding a pair of MZ twins concordant for a given disease. Here is for instance a case of 10-year-old MZ twin girls concordant for congenital dislocation of the hip: this is a hereditary disease " sensu strictiori " (Figs. 1-2). The other case concerns a pair of six-year-old MZ twin boys concordant as to some sequelae of an infectious disease: poliomyelitis (Fig. 3).

The question raised by us was the following: what is the possible statistical significance of such twin cases? The answers were:

1. Proof or confirmation that the propositi are monozygotic.

2. Evidence for the partly or entirely hereditary etiology of the case, specifically excluding phenocopies.

In order to justify these conclusions, it is necessary to consider the twins as two statistical universes rather than as simple statistical units. Such a " partitioning " procedure is concerned with the symptomatology of a disease and duplicates the one which is now being used in diagnostic cybernetics. The method is supposed to prove that a certain number of symptoms cannot occur by chance in both members of a pair: such coincidence must have a cause, i. e. the identicalness of the twins' genotype.

In partitioning the symptoms of a disease into statistical units for our purpose, we have to separate essential clinical manifestations (" sine qua non ") from non-essential ones.

" Sine qua non " symptoms do not present total alternatives since their absence

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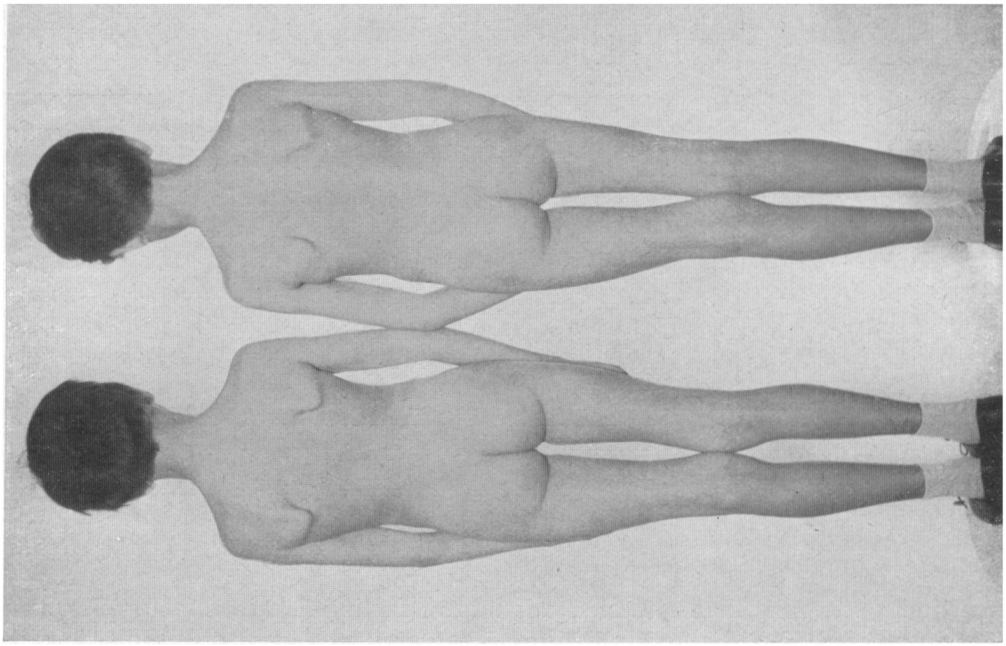

Fig. 2

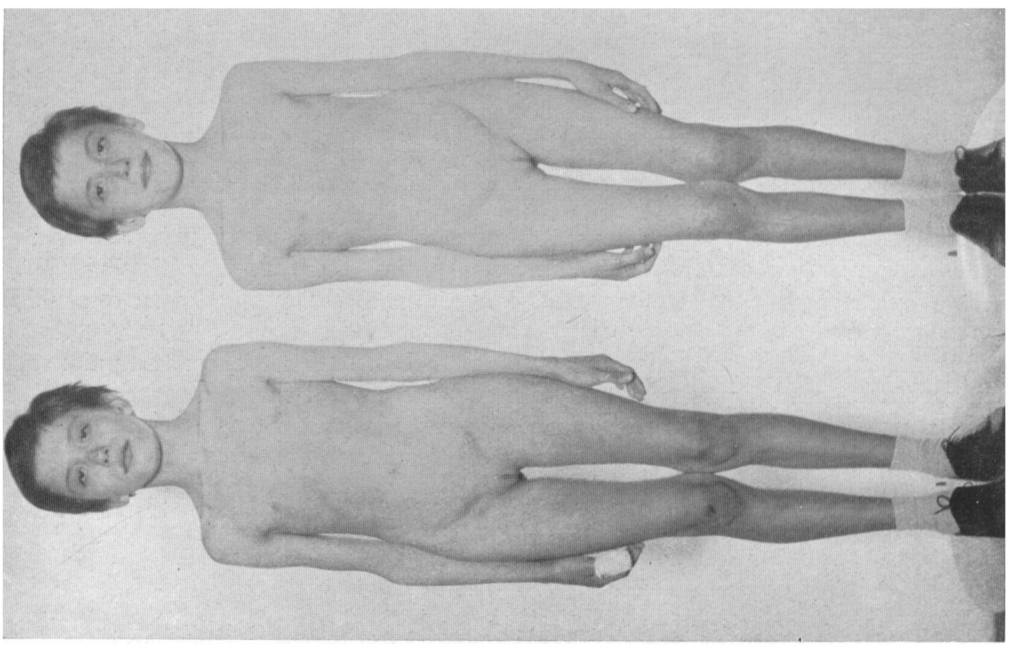

Fig. 1

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precludes the disease: they can be considered only in a quantitative sense: "quoad modum" (For example, in the first pair of twins referred to here with respect to congenital dislocation of the hip, X-ray examination revealed bilateral dislocation in one twin and unilateral dislocation in the cotwin; Figs. 4-5).

On the other hand, non-essential symptoms may be considered either as total alternatives or quantitatively: "quoad praesentiam", or "quoad modum".

Both types of symptom may also be considered chronologically, i. e. from the standpoint of simultaneous or non-simultaneous onset.

In this manner we obtain *n* usable traits with 1, 2, or 3 modalities per symptom.

The significance of the traits observed in either twin is estimated in the following Table (drawn up in collaboration with G. Brenci) which postulates three non-essential traits with one to three possibilities of expression through presumably comparable modalities.

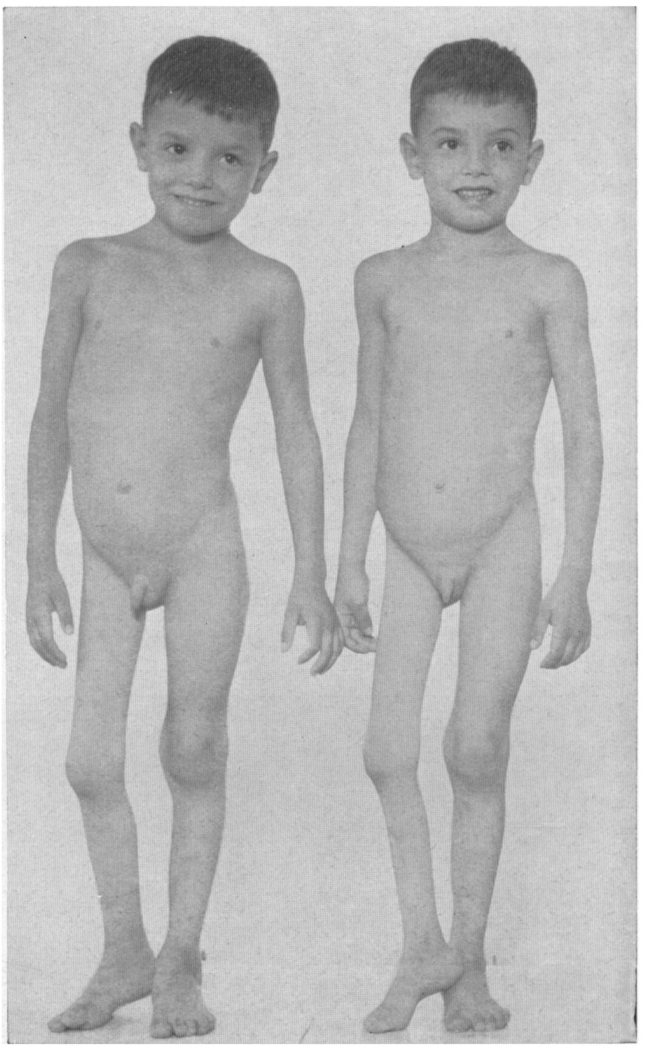

Fig. 3

The first three columns indicate the general population frequencies of the three traits. The second three columns show the probability of observing in a patient a disease with symptoms A-B-C, if each has from one to three modalities of expression.

The last three columns express the probability of encountering, with respect to a given symptomatology, intra-pair concordance as to both symptoms and their modalities by chance.

The asterisk identifies those probabilities of concordance the value of which does not

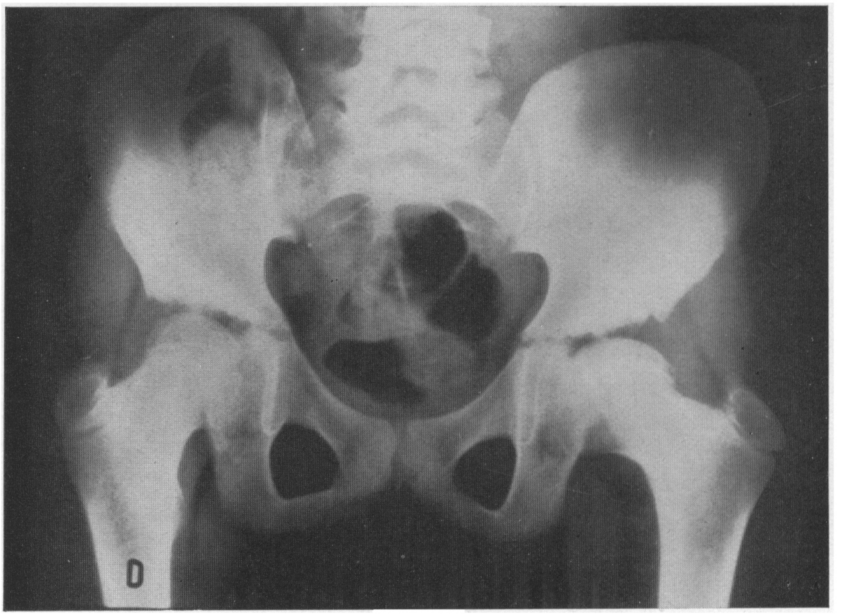

Fig. 4

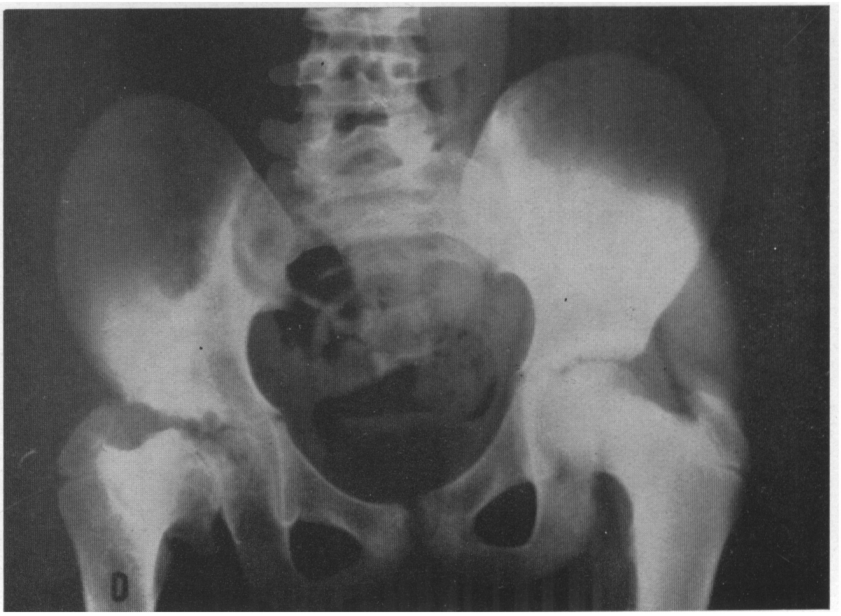

Fig. 5

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Table

Frequency of symptoms			Clinical casual probability of A-B-C			Casual probability of intra-pair concordance for A-B-C symptoms		
A	B	C	With 1 modality	With 2 modalities	With 3 modalities	With 1 modality	With 2 modalities	With 3 modalities
0,90	0,90	0,90	0,7290	0,0911	0,0262	0,5314	0,0083	0,0007*
0,90	0,90	0,80	0,6480	0,0810	0,0233	0,4199	0,0066	0,0005*
0,90	0,90	0,70	0,5670	0,0709	0,0203	0,3215	0,0050	0,0004*
0,90	0,90	0,60	0,4860	0,0607	0,0174	0,2362	0,0037	0,0003*
0,90	0,90	0,50	0,4050	0,0506	0,0145	0,1640	0,0026	0,0002*
0,90	0,80	0,80	0,5760	0,0720	0,0207	0,3318	0,0052	0,0004*
0,90	0,80	0,70	0,5040	0,0630	0,0181	0,2540	0,0040	0,0003*
0,90	0,80	0,60	0,4320	0,0540	0,0155	0,1866	0,0029	0,0002*
0,90	0,80	0,50	0,3600	0,0450	0,0129	0,1296	0,0020	0,0002*
0,90	0,70	0,70	0,4410	0,0551	0,0158	0,1945	0,0030	0,0002*
0,90	0,70	0,60	0,3780	0,0472	0,0136	0,1429	0,0022	0,0002*
0,90	0,70	0,50	0,3150	0,0394	0,0113	0,0992	0,0015	0,0001*
0.90	0,60	0,60	0,3240	0,0405	0,0116	0,1050	0,0016	0,0001*
0,90	0,60	0,50	0,2700	0,0337	0,0097	0,0729	0,0011	0,0001*
0,90	0,50	0,50	0,2250	0,0281	0,0081	0,0506	0,0008*	0,0001*
0,80	0,80	0,80	0,5120	0,0640	0,0184	0,2621	0,0041	0,0003*
0,80	0,80	0,70	0,4480	0,0560	0,0161	0,2007	0,0031	0,0002*
0,80	0,80	0,60	0,3840	0,0480	0,0138	0,1474	0,0023	0,0002*
0,80	0,80	0,50	0,3200	0,0400	0,0115	0,1024	0,0016	0,0001*
0,80	0,70	0,70	0,3920	0,0490	0,0141	0,1537	0,0024	0,0002*
0,80	0,70	0,60	0,3360	0,0420	0,0121	0,1129	0,0018	0,0001*
0,80	0,70	0,50	0,2800	0,0350	0,0100	0,0784	0,0012	0,0001*
0,80	0,60	0,60	0,2880	0,0360	0,0103	0,0829	0,0013	0,0001*
0,80	0,60	0,50	0,2400	0,0300	0,0086	0,0576	0,0009*	0,0001*
0,80	0,50	0,50	0,2000	0,0250	0,0072	0,0400	0,0006*	0,0000*
0,70	0,70	0,70	0,3430	0,0429	0,0123	0,1176	0,0018	0,0001*
0,70	0,70	0,60	0,2940	0,0367	0,0105	0,0864	0,0013	0,0001*
0,70	0,70	0,50	0,2450	0,0306	0,0088	0,0600	0,0009*	0,0001*
0,70	0,60	0,60	0,2520	0,0315	0,0090	0,0635	0,0010*	0,0001*
0,70	0,60	0,50	0,2100	0,0262	0,0075	0,0441	0,0007*	0,0001*
0,70	0,50	0,50	0,1750	0,0219	0,0063	0,0306	0,0005*	0,0000*
0,60	0,60	0,60	0,2160	0,0270	0,0077	0,0466	0,0007*	0,0001*
0,60	0,60	0,50	0,1800	0,0225	0,0065	0,0324	0,0005*	0,0000*
0,60	0,50	0,50	0,1500	0,0187	0,0054	0,0225	0,0003*	0,0000*
0,50	0,50	0,50	0,1250	0,0156	0,0045	0,0156	0,0002*	0,0000*

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exceed 0.001, i. e. pathological conditions with a chance occurrence of less than one in a thousand. The tendency to exceed the probability level of 1 in 1000 may be due to identical symptomatology in cases with:

a) Three symptoms with low probability of occurrence (0.9, 0.5 and 0.5) and two equally likely quantitative expression modalities;

b) Three symptoms with high probability of occurrence (0.9, 0.9 and 0.9) and three comparable quantitative expression modalities.

Obviously, the probability of chance concordance decreases for lower values of symptom frequency.

These statistics apply to symptoms that can be considered to be independent events. If mutual relationships are taken into account and the required data are increased accordingly, our reasoning retains its validity even when symptoms represent subordinate events.

Considering this level of excluding chance occurrence, concordance and sometimes identicalness as to symptomatology may be explained by postulating an equally controlling genotype in both twins, entailing: *a*) monozygosity of the twins; *b*) the entirely or partly hereditary origin of the disease.

Apart from yielding this degree of statistical significance, an MZ pair concordant for a given disease becomes particularly useful in studying its aetiology.

" Cœteris paribus ", in fact, when MZ twin partners differ in their symptomatology, the identicalness of their genotypes points to an interaction with environmental factors as the cause of the different expression modalities of the various symptoms.

This statement acquires absolute validity whenever the disease is known to be hereditary and penetrance either approaches or equals total unit value.

The meaningfulness of concordance in monozygotic twins is not limited to theory. Careful use of such cases affords, for instance, a unique opportunity to appraise the mechanism of action of a given drug or the dissimilar effects of various treatment methods.

The same applies to physiologic phenomena, encountered, for instance, in investigations dealing with the effect of different sports on the individual. For such a purpose only a few MZ twin pairs are needed if the proper experimental conditions are fulfilled.

Summary

A case of one twin pair concordant or discordant as to a given disease is always very important for Clinical Genetics, especially when it is monozygotic. In Clinical Genetics, isolated pairs occur to the physician, and the diagnosis must therefore be based on intra-pair comparison. The statistical treatment of the case must consider the fact that a concordant monozygotic twin pair represents a statistical universe rather than a statistical unit. This entails taking into account many traits concerning the time of onset, the symptoms, development, result of treatment, etc. Suggestions are made for the statistical treatment of such cases.

Literature

GEDDA L.: Twins in history and science. Ediz. Charles C. Thomas, Publisher, U.S.A., 1961.
— BRENCI G.: Lo studio dei gemelli in genetica umana, in «De Genetica Medica», Pars Secunda, Ediz. Ist. G. Mendel, Roma 1962.
FELLER W.: An introduction to probability theory and its application. New York, Wiley, 1960.
LEDLEY and LUSTED: Reasoning foundations of medical diagnosis. Science, 130, 9-21, 1959.
— — Use of electronic computers to aid in medical diagnosis. Proc. Inst. of Radio Engineers, 47, 1970-1977, 1959.
PAYCHA F.: Cybernétique de la consultation. Information et Cybernétique, Gauthier-Villars Editeurs, Paris 1963.

RIASSUNTO

Un caso di coppia gemellare concordante o discordante per una data malattia è sempre molto importante in genetica clinica, in particolare se la coppia è MZ. In genetica clinica il medico si trova di fronte a coppie isolate e deve, quindi, stabilire lo zigotismo, in base al confronto intracoppia. Nel trattamento statistico del caso, va tenuto presente il fatto che una coppia MZ concordante rappresenta statisticamente piuttosto un universo che un'unità. Ciò comporta lo studio di numerosi caratteri, riguardanti l'inizio, i sintomi e lo sviluppo della malattia, i risultati della terapia ecc. Si avanzano suggerimenti per il trattamento statistico di tali casi.

RÉSUMÉ

Un cas de couple de jumeaux concordants ou discordants pour une maladie est toujours très important en génétique clinique, spécialement si les jumeaux sont MZ. En génétique clinique le médecin examine des couples isolés et doit, donc, en établir le zygotisme sur la base de la comparaison intra-couple. Lors de l'étude statistique du cas il faudrait considérer que, statistiquement, le couple représente un univers, plutôt qu'une unité. Ceci implique l'étude de plusieurs traits concernants le début, les symptômes et le développement de la maladie, les résultats de la thérapie, etc. L'on fait des suggestions sur l'étude statistique de ces cas.

ZUSAMMENFASSUNG

Der Fall eines in einer bestimmten Krankheit übereinstimmenden oder nicht übereinstimmenden Zwillingspaares ist für die klinische Genetik immer sehr wichtig, besonders, wenn es sich dabei um ein EZ-Paar handelt. In der klinischen Genetik steht der Arzt einzelnen Paaren gegenüber und muss daher durch Gegenüberstellung der beinden Paarlinge die Eiigkeit feststellen. Bei statistischer Behandlung des Falles ist zu beachten, dass ein konkordantes EZ-Paar statistisch eher ein Universum als eine Einheit darstellt. Daraus ergibt sich, dass zahlreiche Merkmale in Bezug auf Beginn, Symptone und Entwicklung der Krankheit, auf die Behandlungsergebnisse usw. untersucht werden müssen. Es werden Vorschläge für die statistiche Bearbeitung solcher Fälle unterbreitet.