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Human genetic polymorphisms and fertility analysis: preliminary data

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Genetica. — *Human genetic polymorphisms and fertility analysis: preliminary data* (*). Nota di LUCIANO TERRENATO e ANDREA NOVELLETTO, presentata (**) dal Socio G. MONTALENTI.

RIASSUNTO. — Le possibili relazioni tra fertilità e polimorfismi genetici nell'uomo sono state analizzate sulla base degli esami effettuati in un campione di famiglie fertili italiane esaminate al momento del parto di uno dei figli. I risultati ottenuti per circa 20 marcatori genetici sono stati confrontati con quelli riportati in letteratura su campioni di famiglie non selezionate per ciò che riguarda misure correlate ai differenziali di fertilità. Nel complesso i dati non rivelano alcun effetto selettivo misurabile. Viene inoltre discussa la possibilità che sporadici errori tecnici, benché rari, abbiano un effetto nel mascherare deviazioni significative dall'equilibrio.

INTRODUCTION

Since the beginning of study of Mendelian inheritance in man, three levels of genetic variability amount have been progressively discovered. Up to the middle forties the genetic variability was thought to be associated mainly with deleterious traits, with few exceptions represented by PTC tasting ability and ABO blood group; therefore, genetic variability was considered at that time to be very low. The rapid discovery of a series of different blood group systems started to change the overall picture, but it was only in the middle sixties that the high level of genetic variability measurable in natural populations, man included, became apparent.

In view of these findings the argument that polymorphisms are mainly maintained by selection is no longer acceptable [see e.g. 1]. In fact, together with the obvious remark that species cannot survive with such a high level of mutational and/or segregational load, one can also consider that the allozymic alleles (by far the vast majority of the newly discovered polymorphisms, with the relevant exception of MCH systems) are good candidates to approach neutrality, in view of the very poor biological effects that can be inferred from their differences in electrophoresis.

Starting from the middle seventies a third level of genetic variability became amenable to investigation, i.e. the nucleic acids. The extent of such a varia-

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bility is turning out to be extremely high and therefore the neutral hypothesis is progressively gaining support, at least for a substantial part of polymorphisms.

Under these circumstances human population studies on selection became less frequent and practically only those cases for which more or less definite selective effects had been suggested (e.g. ABO and Rh blood group systems, not to mention the so called malaric polymorphisms and a few others) continued to be the subjects of this kind of research.

At this point it is useful to make a clear distinction between the two possible approaches: physiopathological studies performed on clinically selected cases (e.g. recurrent abortions) and human population genetic studies performed on stricly non-selected samples.

It clearly follows that the first kind of study uses not only specific materials, but that the specific aim is to discover mechanisms related to some types of reproductive failure. On the other hand studies of the second kind are mainly devoted to the possible discovery of mechanisms relevant to the phenomenon of natural selection.

It is useful to mention that in 1966 Morton *et al.* [2] very comprehensively condensed the seven methods to be followed in order to assess selective forces:

1) Identification of the relevant environmental differences between populations with high and low gene frequencies;

2) Detection of systematic departures of genotype frequencies from Hardy-Weinberg equilibrium;

3) Association between genotype and a specific type of morbidity or response to a specific agent;

4) Analysis of adaptive trends in genotype frequencies with age or among successive generations;

5) Detection of different genotype frequencies in the two sexes;

6) Measurements of fertility and mortality differentials among genotypes;

7) Analysis of departures from Mendelian segregation frequencies.

For example, in a very large scale study, performed in a Brazilian population still exposed to high selection pressure [2], only ABO system appears subject to measurable selection: ABO incompatible matings being associated with a higher rate of prenatal and postnatal deaths. Pre- and postzygotic selection (also working in opposite directions) were already suggested [3] for ABO, MN and P blood groups. On the other hand no distortion was found in two other extensive studies [4, 5], making therefore very likely that previously reported anomalies were simply due to technical problems.

Hp system has a very long story of studies of this kind: an excess of 2-1 children to Hp 2-1 $\times$ 2-2 matings was found [6, 7, 8], but also opposite results were obtained [2]. More recently an excess of Hp 2-1 children of ABO incompatible matings was found [9]. Segregation distortion has been also claimed

for alpha-1 antitrypsin system, but these results have not been confirmed [for a review see 10].

An example of a suspected mother-child segregation distortion has been reported [11]; in 6974 mother-infant pairs Rh (—) mothers were found to produce more Rh (+) infants than expected and Rh (+) mothers to produce fewer Rh (—) infants than expected.

No segregation distortion was found in several researches related to cases of testcrosses for dominant detrimental genetic traits: out of 1033 progeny for several traits 518 affected and 515 normal subjects were found [for a review see 12].

In recent years studies devoted to highly selected cases are more common; for example couples with recurrent abortions of unknown etiology that raise problems associated with a high sharing of HLA B, D/Dr and MT antigens [see for example 13].

In this context it is also worth mentioning those studies devoted to variables associated with electrophoretic mobility that could be evolutionarily relevant, such as in vitro enzymatic activity [14].

In the meanwhile, for each newly discovered polymorphism a certain amount of segregating families had to be collected. Therefore in the last 20 years literature presents several instances of segregation analyses. In the present paper this kind of data have been re-examined from the standpoint of the possible presence of selective forces, together with those obtained in a large scale study carried out in an Italian population sample.

MATERIAL AND METHODS

The available literature was examined with the aim of collecting a representative sample of papers dealing with segregation analysis performed in strictly non-selected families; therefore, no project of exhaustive collection of data was pursued. 33 segregation analyses related to the following polymorphisms were re-examined: PTC tasting [15], ABO [3, 16], MNSs [4, 5] and Rh [16] blood groups, haptoglobins [Hp; 6, 9], adenylate kinase [AK; 17, 18], phosphoglucomutase [PGM1; 19, 20, 21], glyoxalase [GLO; 22, 23, 24], acid phosphatase [ACP; 25], adenosine deaminase [ADA; 26], glutamic-pyruvic transaminase [GPT; 27], esterase D [EsD; 28, 29], phosphoglycolate phosphatase [PGP; 30], delta-aminolevulinate dehydrase [ALADH; 31, 32], S-adenosilhomocysteine hydrolase [SAHH; 33], paraoxonase [ESA 1; 34], alpha-fucosidase [FUC; 35], C 4 [36] and C 8 [37] systems, coagulation factor XIII [38].

Since literature data refer to samples collected in several populations, at different times and for various genetic markers, all the statistical tests were performed mainly to verify intra-sample significant departures from expectations under the appropriate null hypothesis. The results are therefore given in the form of probability distributions of the relative statistics.

As to the Italian sample, it refers to a collaborative study relative to 3432 nuclear families examined for about 20 polymorphisms: ABO, Rh, MN, Kell, PGP, ACP, PGM 1, AK, ADA, GLO, GPT, EsD, 6-phosphogluconate dehydrogenase (PGD), galactose-1-phosphate urydil transferase (GALT), C 3, Hp, HLA—A, —B and —C, placental alkaline phosphatase (ALP), placental phosphoglucomutase-3 (PGM 3) and cytogenetic polymorphisms. The relative detailed papers are either published by the authors of the specific analyses [39-49] or in preparation. Here, only cumulative data are presented in comparison with literature data.

Results

A possible measure of fertility differentials has been adopted for the literature data, according to which a heterogeneity chi-square is calculated for the number of children associated with each genotype.

This was possible since families reported in the literature are always composed of more than one child. The resulting 30 values are reported in fig. 1

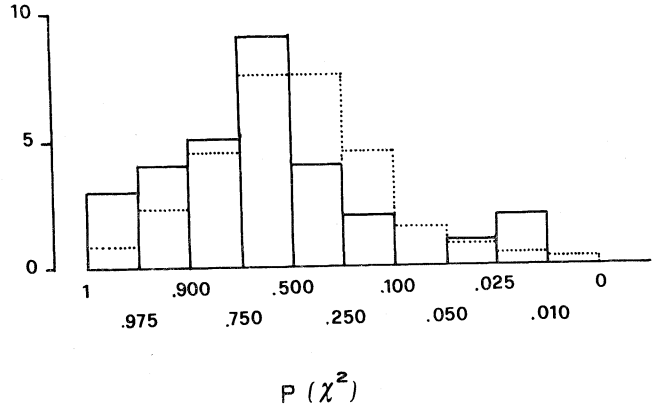

Fig. 1. - Heterogeneity of number of children among genotypes. Original data from literature (see text). On the horizontal axis significance probabilities of the chi square values calculated for each system (dotted line = expected distribution).

subdivided according to a suitable scale of probability. Two points are to be stressed: the excess of low values which could cast some doubts on the randomness of the samples and the excess of significant values (3 against 1.50 expected at $p \leq 0.05$) among which the ABO (data from 16), C 4 and SAHH polymorphisms are present.

A second step of analysis is devoted to the segregation ratios observed in heterozygotes. We tested the hypothesis of equal segregation ratios (even equal or different from 0.5) among the different matings for each genetic system. The obtained results are shown in fig. 2 where both literature data (*a*) and our

data (*b*) are reported. The agreement with the expected is fairly good, with the possible exception of Hp system.

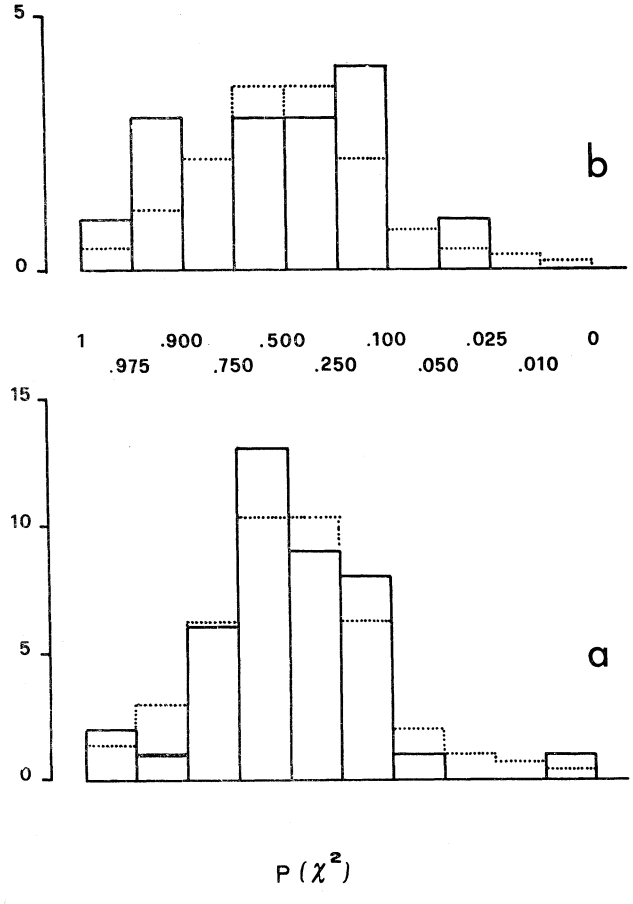

Fig. 2. – Testing equality of segregation ratios among matings. Original data from literature (*a*) and an Italian sample (*b*) (see text). Segregation ratios variability within each system was tested by contingency table chi squares. On the horizontal axis significance probabilities (dotted line = expected distribution).

The overall effect of a segregation ratio different from .5 would result in a shifting of allelic frequencies in the filial generation as compared to the parental one. We tested the equality of these frequencies in the two generations for the data reported in the literature and ours. The distributions reported in fig. 3 refer to normal deviate statistics calculated from the two generations for the most common allele of each system. As to the literature data (*a*) no relevant departures of filial vs. parental gene frequencies can be observed, with the exception of ABO system in the study of Hiraizumi [3]. It is worth noting however that the strong excess of values closely clustered around 0 is a variation lower than expected. A question arises about the effective consistency of the collected data. On the other hand, in our family sample (*b*)

in 12 out of 15 instances a further increase of the most common allele can be observed. Here the intrinsic differences between the two samples must be stressed: 1) whereas our distribution is obtained from a single population sample sectioned according to several genetic systems, in the literature data each system is studied in a different group, and 2) whereas in the literature families different

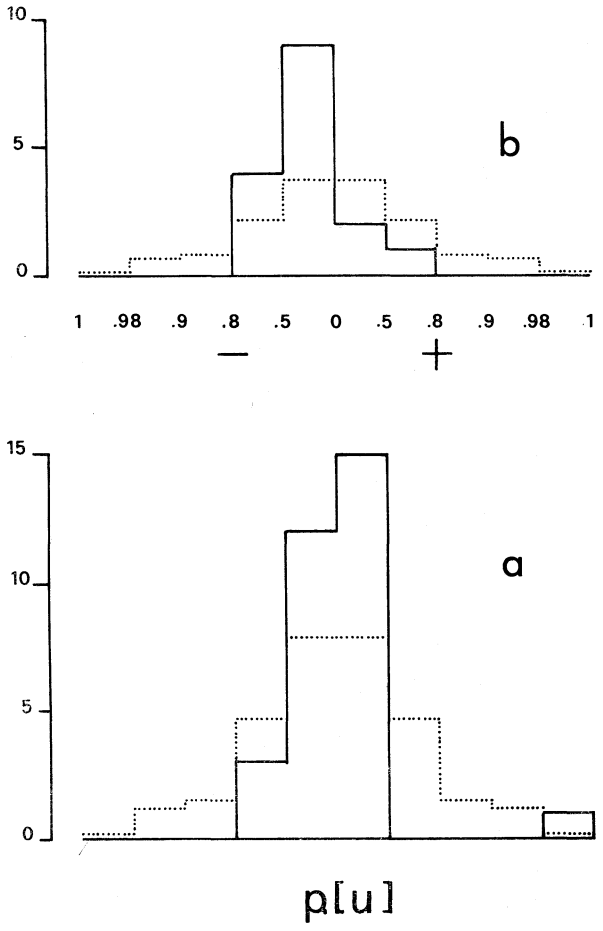

Fig. 3. – Testing gene frequencies constancy between generations. Original data from literature (*a*) and an Italian sample (*b*). A normal deviate value was calculated for the most common allele of each system as the difference in frequencies between parents and children divided by its standard error. On the horizontal axis symmetrical significance probabilities (negative and positive values correspond to frequencies in children higher and lower than parents, respectively) (dotted line = expected distribution).

orders of birth are included, our families have only one child each, in about 50% of cases a first born one. Therefore, in the literature data the hypothetical effects of the birth order would be averaged. In this context the well-known effect of birth order should be remembered, for instance on the sex-ratio [see for example 50].

To see whether our data could be the result of a biased sample, we also tested the equality of gene frequencies between fathers and mothers. The results are shown in fig. 4 where a perfectly symmetrical distribution around 0 value clearly appears.

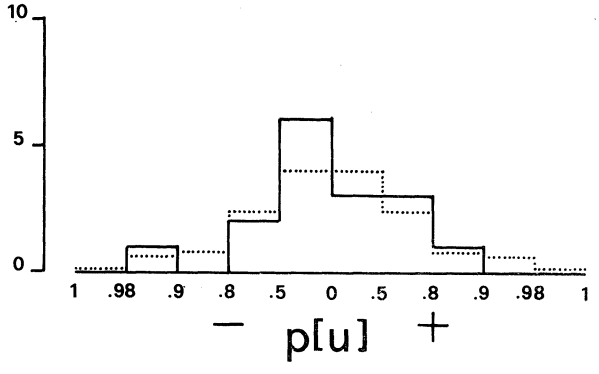

Fig. 4. – Testing gene frequencies differences between fathers and mothers in the Italian sample. See legend to fig. 3 for details (dotted line = expected distribution).

As a futher source of information about the randomness of our sample, possible departures from Hardy-Weinberg equilibrium were tested by estimating an F value [51]. The relative *t* distribution is shown in fig. 5, where the accord between the observed and the expected can be appreciated. The testing of the Hardy-Weinberg equilibrium in the literature data should comprise not only family data and is therefore beyond the scope of the present paper.

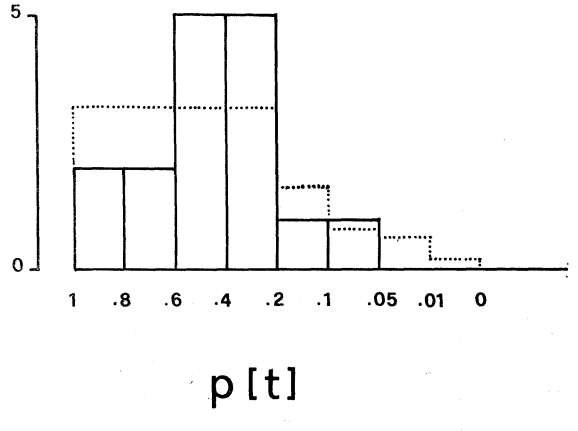

Fig. 5. – Testing departures from Hardy–Weinberg equilibrium in the Italian sample. F values and variances calculated according to [51], eqs. 13 and 14. On the horizontal axis significance probabilities of the relative *t* statistics (dotted line = expected distribution).

The genetic structure and fertility performance of our families were further examined. The panmittic condition is clearly demonstrated in fig. 6 where chi-square distribution closely matches the expected values.

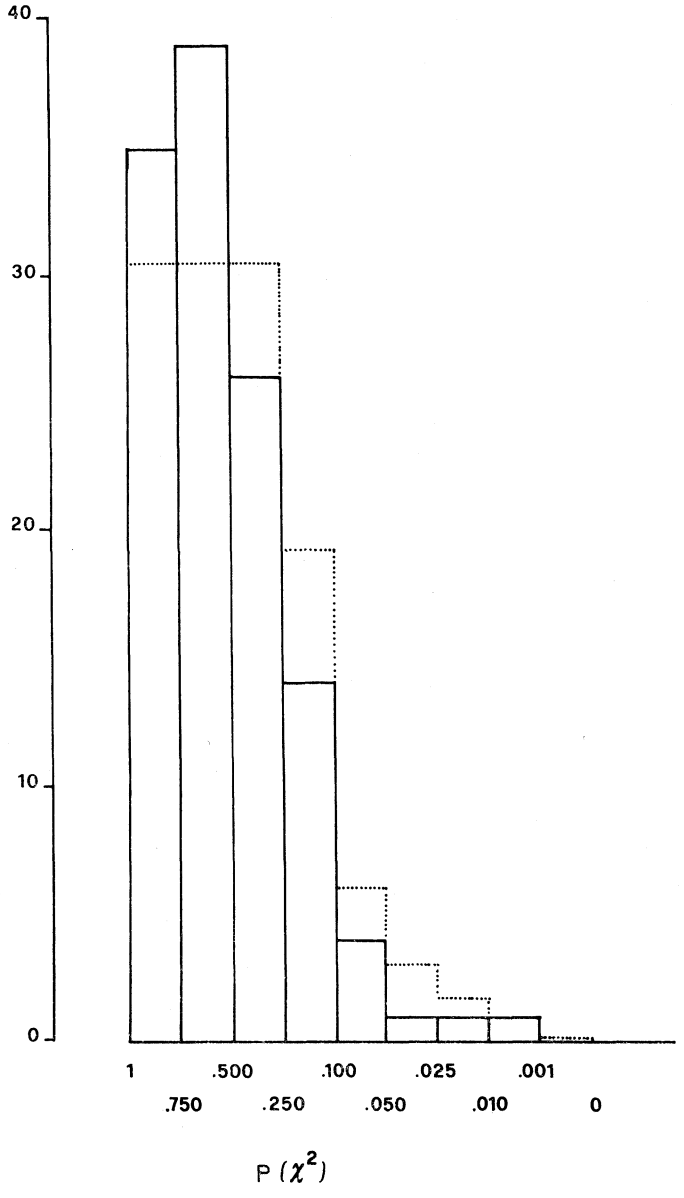

Fig. 6. – Testing the panmittic hypothesis in the Italian sample. On the horizontal axis significance probabilities of chi square values calculated from observed matings and expected ones on the basis of phenotype distribution. For each genetic system all but one of the matings have been considered (dotted line = expected distribution).

In view of the previous results, according to which no clear sign of selective effects measurable with our sample size can be detected, the direct approach of fertility analysis was attempted. The information collected for our sample allows the study of the following three putative covariates: number of pregnancies and natural abortions of the mother prior to the birth of the proband, and

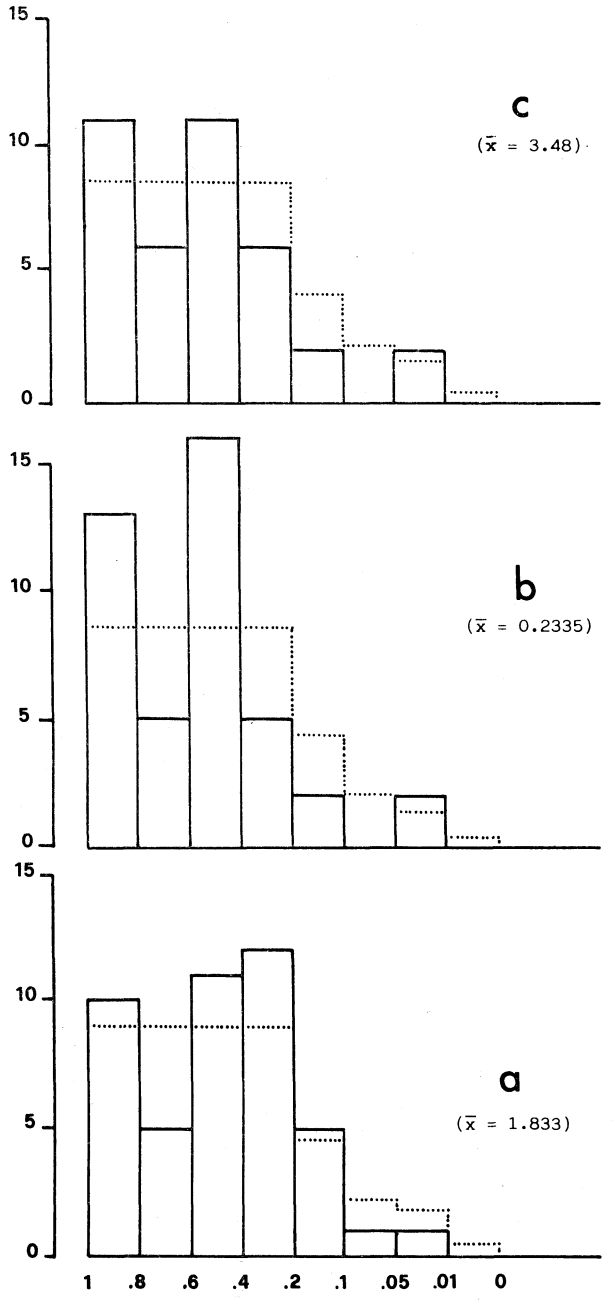

Fig. 7. – Analysis of fertility in the Italian sample. A normal deviate statistics was calculated from the average number in each genotype and the general mean. On the horizontal axis significance probabilities. (*a*) Number of previous pregnancies referred by proband's mother. (*b*) Number of previous natural abortions. (*c*) Number of grandmother pregnancies (dotted line = expected distribution).

overall number of pregnancies of the maternal grandmother of the proband. Fig. 7 (*a*) shows the distribution of mothers' previous pregnancies in the different genotypes; the average number of pregnancies (1.833) closely matches the value (1.793) reported by official statistics for the whole population of the area. The heterogeneity among different genotypes was tested against normal standardized deviate: the observed distribution was in good agreement with the expected one. Fig. 7 (*b*) shows the previous natural abortions distribution. The overall good agreement with the expected, with the possible significant exception of ABO and EsD systems which plot at a p value lower than 0.05, appears clear. Fig. 7 (*c*) shows the total number of pregnancies of the maternal grandmother of the proband. Once again the observed and expected distributions closely fit each other. Moreover, as expected on the ground of random fluctuation around the respective means, the correlation between the average number of pregnancies of mothers with given genotype and their mothers turned out to approach 0.

Conclusions

Preliminary data presented here, agree with the vast majority of selection studies performed on randomly selected families for several polymorphisms, in that they do not show measurable deviation from the expected under the null hypothesis, with the possible exceptions of ABO and Hp systems. On the other hand, even if many details are still to be clarified, there are genetic systems for which evidence of selective effects are being accumulated, for example the ABO, Rh, Hp and HLA systems.

A specific result obtained in our sample deserves a brief discussion: in 12 out of 15 instances the frequencies of the most common allele in the filial generation showed an increase compared to those of the parental generation. As already stressed, the differences between the characteristics of our sample and those collected in the literature make the comparison not completely feasible and therefore the absence of the above mentioned phenomenon in the published data does not invalidate *per se* our finding. Further analyses on fully comparable samples are likely to be useful.

On the other hand, the results presented for apparently " neutral " polymorphisms show, more or less systematically, an excess (of variable intensity) of values approaching expectations. The explanation of this quite unexpected finding is not straightforward; however, it should be stressed that hypothetical biases in typing or technical errors favouring the most likely result (for example the most frequent phenotype, the most frequent filial phenotype given the parental ones and so on) could produce the observed phenomenon. More so if one considers that a bias of the order of magnitude of a percent of the gene frequencies under measure is sufficient to give a substantial effect, with the sample sizes usually attained.

On the whole the present difficulty in carrying on selection study in our species cannot be understated. Selection intensity is very likely to be highly variable in our species, both in space and in time, not to mention the possible racial differences. In particular, Europeans, by far the most commonly studied group, are now experiencing reduced levels of variances in fertility and mortality, the two components of opportunity for selection [52]. Under these conditions homogeneous samples of several thousand families would be necessary to show any measurable effect, at least as far as fertility differentials are concerned, a task hardly achieved. In any case, the methodological approach here presented appears to be suitable for a comprehensive segregational analysis of samples examined for different genetic systems in different populations. A further and more complete analysis is in progress, which will also take into account all the literature data collected in Becker's Humangenetik [53, 54].

Moreover one has to consider that in the family sample discussed here (and the same applies to most literature data) families without progeny are not included. However if, on one side, these infertile couples would contribute to fertility differentials of the whole populations, on the other side our data on Hardy-Weinberg equilibria and frequencies of matings can exclude relevant specific effects.

As to mortality variability the residual perinatal mortality is the best candidate to search for genetic effects. The search for hypothetical selective effects on Mendelian traits exerted through perinatal mortality seems therefore more reasonable. Some variables known to be associated with this kind of mortality, including the birth weight [55], perhaps will afford more chances of detecting such effects, even if contradictory results have been reported [56]. In fact, dealing with continuous traits, a higher amount of information is likely to be gathered from population data, as compared to " yes/no " variables, mostly when the trait is very rare, as is the case with perinatal mortality. Some of these variables have been measured in our family sample on the newborns themselves together with some others examined during a 1-year follow-up. The data are still being analyzed, not only with reference to single gene markers, but also to extended haplotypes as in the case of HLA system and linked genes. The relative results will be reported elsewhere.

REFERENCES

[1] FORD E.B. (1940) – *Polymorphism and taxonomy*. In « The new systematics » (J. Huxley, ed.) Oxford, The Clarendon Press.

[2] MORTON N.E., KIEGER H. and MI M.P. (1966) – *Natural selection on polymorphisms in Northeastern Brazil*. « Am. J. Hum. Genet. », *18*, 153-171.

[3] HIRAIZUMI Y. (1964) – *Prezygotic selection as effector in the maintenance of variability*. « Cold Spring Harb. Symp. Quant. Biol. », *29*, 51-60.

[4] CHOWN B., LEWIS N. and KAITA H. (1967) – *The inheritance of the MNSs blood groups in a Caucasian population sample*. « Am. J. Hum. Genet. », *19*, 86-93.

[5] WIENER A.S., GORDON E.B. and WEXLER J.P. (1963) – *The M–N types, with special reference to the mating MN × MN*. « Expl. Medicine and Surgery », *21*, 89-100.

[6] GALATIUS-JENSEN F. (1957) - *Further investigations on the genetic mechanism of the haptoglobins.* « Acta Genet. », *7*, 549-564.

[7] HARRIS H., ROBSON E.B. and SINISCALCO M. (1959) - *Genetics of the plasma protein variants.* In « Biochemistry of human genetics », G.E.W. Wolstenholme and C.M. O'Connor, eds. Boston, Little, Brown and Co., pp. 151-173.

[8] KIRK R.L. (1968) - *Haptoglobin groups in man.* « Monogr. in Human Genet. », 4 Karger, Basel.

[9] MACDONALD J.L. and PAPIHA S. (1974) - *A segregation analysis of the association of haptoglobin types and ABO blood groups.* « Hum. Hered. », *24*, 45-52.

[10] SUAREZ B., PIERCE J.A., RESTA R., HARLAN F. and REICH T. (1982) - *Alpha-1-antitrypsin allele Pi(S) fails to show segregation distortion.* « Hum. Hered », *32*, 246-252.

[11] VALENZUELA C.Y. and HARB Z. (1982) - *A mother-child segregation distortion for the the Rh system. New evidence for another compatibility system associated with Rh.* « Am. J. Hum. Genet. », *34*, 925-936.

[12] LEVITAN M. and MONTAGU A. (1971) - *Textbook of Human Genetics*, Oxford Univ. Press.

[13] BEER A.E., QUEBBEMAN J.F., HAMAZAKI Y. and SEMPRINI A.E. (1985) - *Pregnancy outcome in human couples with recurrent spontaneous abortions: the role(s) of HLA antigen sharing, ABO blood group antigen profiles, female serum mlr blocking factors, antisperm antibodies and immunotherapy.* Expl. clin. Immunoget. in press.

[14] BATTISTUZZI G., SCOZZARI R., SANTOLAMAZZA P., TERRENATO L. and MODIANO G. (1974) - *Comparative activity of red cell adenosine deaminase allelic forms.* « Nature », *251*, 711-713.

[15] SNYDER L.H. (1932) - *The inheritance of taste deficiency in man.* « Ohio J. Sci. », *32*, 436-440.

[16] WIENER A.S. (1943) - *Blood groups and transfusions, 3rd ed.* Thomas, Springfield Ill.

[17] FILDES R.A. and HARRIS H. (1966) - *Genetically determined variation of adenylate kinase in man.* « Nature », *209*, 261-266.

[18] RAPLEY S., ROBSON E.B. and HARRIS H. (1967) - *Data on the incidence, segregation and linkage relations of the adenylate kinase (AK) polymorphism.* « Ann. Hum. Genet », *31*, 237-242.

[19] SPENCER N., HOPKINSON D.A. and HARRIS H. (1964) - *Phosphoglucomutase polymorphism in man.* « Nature », *204*, 742-745.

[20] ERIKSSON A.W., KIRJARINTA M., LEHTOSALO T., KAJANOJA P., LEHMANN W., MOURANT A.E., TILLS D., SINGH S., BENKMANN H.G., HIRTH L. and GOEDDE H.W. (1971) - *Red cell phosphoglucomutase polymorphism in Finland-Swedes, Finns, Finnish Lapps, Maris (Cheremisses) and Greenland Eskimos, and segregation studies of PGM (1) types in Lapp families.* « Hum. Hered. », *21*, 140-153.

[21] KUHNL P. and SPIELMANN W. (1978) - *Investigations on the PGM (a1) polymorphism by isoelectric focusing.* « Hum. Genet. », *43*, 57-67.

[22] KOMPF J., BISSBORT S. and RITTER H. (1975) - *Red cell glyoxalase I: formal genetics and linkage relations.* « Humangenetik », 28, 249-251.

[23] KUHNL P., SCHWABENLAND R. and SPIELMANN W. (1977) - *Investigations on the polymorphism of glyoxalase I in the population of Hessen, Germany.* « Hum. Genet. », 38, 99-106.

[24] ERIKSEN B. (1979) - *Human red cell glyoxalase I in Denmark and its application to paternity cases.* « Hum. Hered. », *29*, 265-271.

[25] HOPKINSON D.A., SPENCER N. and HARRIS H. (1963) - *Red cell acid phosphatase variants: a new human polymorphism.* « Nature », *199*, 969-971.

[26] HOPKINSON D.A., COOK P.J.L. and HARRIS H. (1969) - *Further data on the adenosine deaminase (ADA) polymorphism and a report of a new phenotype.* « Ann. Hum. Genet. », *32*, 361-367.

[27] CHEN S.H., GIBLETT E.R., ANDERSON J.E. and FOSSUM B.L.G. (1972) - *Genetics of glutamic-pyruvic transaminase: its inheritance, common and rare variants, popula-*

tion distribution, and differences in catalytic activity. « Ann. Hum. Genet. », *35*, 401-409.

[28] HOPKINSON D.A., MESTRINER M.A., CORTNER J. and HARRIS H. (1973) – *Esterase D : a new human polymorphism.* « Ann. Hum. Genet. », *37*, 119-137.

[29] RITTNER C. and MULLER G. (1975) – *Esterase D : some population and formal genetical data.* « Hum. Hered. », *25*, 152-155.

[30] BARKER R.F. and HOPKINSON D.A. (1978) – *Genetic polymorphism of human phosphoglycolate phosphatase (PGP).* « Ann. Hum. Genet. », *42*, 143-148.

[31] BATTISTUZZI G., PETRUCCI R., SILVAGNI L., URBANI F.R. and CAIOLA S. (1981) – *Delta-aminolevulinate dehydrase : a new genetic polymorphism in man.* « Ann. Hum. Genet. », *45*, 223-229.

[32] EIBERG H., MOHR J. and NIELSEN L.S. (1983) – *Delta-aminolevulinatedehydrase : synteny with ABO–AK 1–ORM (and assignment to chromosome 9).* « Clinical genetics », *23*, 150-154.

[33] BISSBORT S., BENDER K., WIENKER T.F. and GRZESCHIK K.H. (1983) – *Genetics of human S–adenosylhomocysteine hydrolase. A new polymorphism in man.* « Hum. Genet. », *65*, 68-71.

[34] ECKERSON H.W., WYTE C.M. and LA DU B.N. (1983) – *The human serum paraoxonase/arylesterase polymorphism.* « Am. J. Hum. Genet. », *35*, 1126-1138.

[35] TURNER B.M., TURNER V.S., BERATIS N.G., and HIRSCHHORN K. (1975) – *Polymorphism of human alpha-fucosidase.* « Am. J. Hum. Genet. », *27*, 651-661.

[36] OLAISEN B., TEISBERG P., JONASSEN R. and GEDDE-DAHL T. Jr. (1979) – *The C4 system.* « Hum. Genet. », *50*, 187-192.

[37] RITTNER C., HARGESHEIMER W. and MOLLENHAUER E. (1984) – *Population and formal genetics of the human C81 polymorphism.* « Hum. Genet. », *67*, 166-169.

[38] GRAHAM J.B., EDGELL J.S., FLEMING H., NAMBOODIRI K.K., KEATS B.J.B. and ELSTON R.C. (1984) – *Coagulation factor XIII : A useful polymorphic genetic marker.* « Hum. Genet. », *67*, 132-135.

[39] FELICETTI L., URBANI C., COLOMBO B., BENINCASA A., NOVELLETTO A. and TERRENATO L. (1981) – *Hb A2 levels at birth.* 6th International Congress of Human Genetics. Jerusalem.

[40] LUCARELLI P., SCACCHI R., CORBO R.M., SCOZZARI R., FORTUNA G., ELEUTERI P., NOVELLETTO A., SAMPIETRI E. and TERRENATO L. (1981) – *Human glyoxalase I and phosphoglucomu-mutase–3 polymorphisms in 850 italian families.* 6th International Congress of Human Genetics. Jerusalem.

[41] NOVELLETTO A. and TERRENATO L. (1981) – *Morphological variables through three generations.* 6th International Congress of Human Genetics. Jerusalem.

[42] SANTOLAMAZZA C., NOVELLETTO A., SAMPIETRI E., MENNUCCI M., PETRUCCI R., SCOZZARI R., DE ANGELIS L., MODIANO G. and TERRENATO L. (1981) – *Human phosphoglycolate phosphatase polymorphism : gene frequencies, mating types and segregation analysis in Italian families.* 6th International Congress of Human Genetics. Jerusalem.

[43] SCOZZARI R., TRIPPA G., SANTACHIARA–BENERECETTI A.S., TERRENATO L., IODICE C. and BENINCASA A. (1981) – *Further genetic heterogeneity of human red cell phosphoglucomutase–1 : a non–electrophoretic polymorphism.* « Ann. Hum. Genet. », *45*, 313-322.

[44] SIMI S. and TURSI F. (1981) – *The segregation of C band polymorphism of human chromosomes 1, 9, 16, Y.* « Clinical Genet. », *20*, 392.

[45] SIMI S. and TURSI F. (1982) – *Polymorphism of human chromosomes 1, 9, 16, Y : variations, segregation and mosaicism.* « Hum. Genet. », *62*, 217-220.

[46] SIMI S., TURSI F. and TOMMASEO D. (1981) – *Cytogenetics survey of two unselected populations from central Italy.* « Clin. Genet. », *20*, 392-393.

[47] BELLONI G., BENINCASA A., BOSI A., DE CAPOA A., DI CASTRO M., FERRARO M., LOMBARDI D., MOSTACCI C., PELLICCIA F., PRANTERA G. and ROCCHI A. (1983) –

Screening for cytogenetic polymorphisms in a random sample of liveborn infants from Italian population. « Acta Antropogenetica », *7*, 205-217.

[48] FELICETTI L., NOVELLETTO A., BENINCASA A., TERRENATO L. and COLOMBO B. (1984) - *The HbA/HbA2 ratio in newborns and its correlation with fetal maturity.* « Br. J. Haematol. », *56*, 465-471.

[49] VACCARO A.M., MANDARA I., MUSCILLO M., CIAFFONI F., DE PELLEGRIN S., BENINCASA A., NOVELLETTO A. and TERRENATO L. (1984) - *Polymorphism of erythrocyte galactose-1-phosphate uridyl-transferase in Italy : segregation analysis in 693 families.* « Hum. Hered. », *34*, 197-206.

[50] NOVITSKI E. and SANDLER L. (1956) - *The relationship between parental age, birth order and the secondary sex-ratio in humans.* « Ann. Hum. Genet. », *21*, 123-131.

[51] ROBERTSON A. and HILL W.G. (1984) - *Deviations from Hardy-Weinberg proportions : sampling variances and use in estimation of inbreeding coefficients.* « Genetics », *107*, 703-718.

[52] CROW J.F. (1958) - *Some possibilities for measuring selection intensities in man.* « Hum. Biol. », *30*, 1-13.

[53] BECKER P.E. (ed.) (1975) - *Humangenetik - Ein kurzes Handbuch in funf Banden.* Band I/3. Georg Thieme Verlag, Stuttgart.

[54] BECKER P.E. (ed.) (1972) - *Humangenetik - Ein kurzes Handbuch in funf Banden.* Band I/4, Georg Thieme Verlag, Stuttgart.

[55] KARN M.N. and PENROSE L.S. (1951) - *Birth weight and gestation time in relation to maternal age, parity and infant survival.* « Ann. Eugenics », *16*, 147-160.

[56] WARD R.D., SARFARAZI M., AZIMI-GARAKANI C. and BEARDMORE J.A. (1985) - *Population genetics of polymorphisms in Cardiff newborn.* « Hum. Hered. », *35*, 171-177.