The Co-Brother Method in Clinical Genetics: Tuberculosis Research [1]

Luigi Gedda, Sandro Volta

The genetic aspect of tubercular diseases has been studied for a long time, using the genealogical method, which had forerunners even in the field of narrative, where some Authors, such as Emile Zola, described families in which there was a high frequency of tuberculosis. Then, many Authors gave scientific descriptions of genealogical trees largely stricken by this disease, demonstrating the necessity of stating this problem: Although tuberculosis is originated by a microbe, it can also derive from a particularly receptive, inherited ground. The statistical research, in the hands of Person, Govaerts, Pearl, Ickert and Benze, Geissler and others, indicated that the question was legitimate and that the answer must be positive, because the probability of being affected by tuberculosis is four times higher when the parents, instead of being healthy, both have the disease; because among the ascendants of tuberculous people one finds six times more affected individuals than among those of healthy subjects; and for other similar reasons.

Then, the twin method, used by v. Verschuer, Diehl and Mittschrich, Kallmann and Reisner, by Heilinger and Kunsch, by Vaccarezza and Dutrey, by Kallmann and Jarvik and by others, emphasized the hereditary factor in tubercular diseases.

We, in our turn, intended to tackle the problem of the hereditary component of tuberculosis, but we chose a different way. Among all the patients treated in a Sanatorium in Rome during 23 years, we strove to identify pairs of non-twin brothers. Our project consisted of the study of similarities and dissimilarities of the tubercular process in these pairs of non-twin brothers and in control pairs of random-coupled affected non-brothers.

This research project lasted for about two years and was carried out on the clinical documents of 48,050 tuberculous patients treated in the Forlanini Hospital in Rome, between 1935 and 1938. From this material we drew the data concerning 736 pairs of non-twin brothers: the frequency of the presence of two brothers in the same Sanatorium, in connection with our material, thus being 1.5%.

Moreover, from the same material, we drew the data concerning 200 other patients coupled at random to constitute control pairs.

[1] Presented at the X[th] International Congress of Genetics, Montreal (Canada), August 20 to 27, 1958.

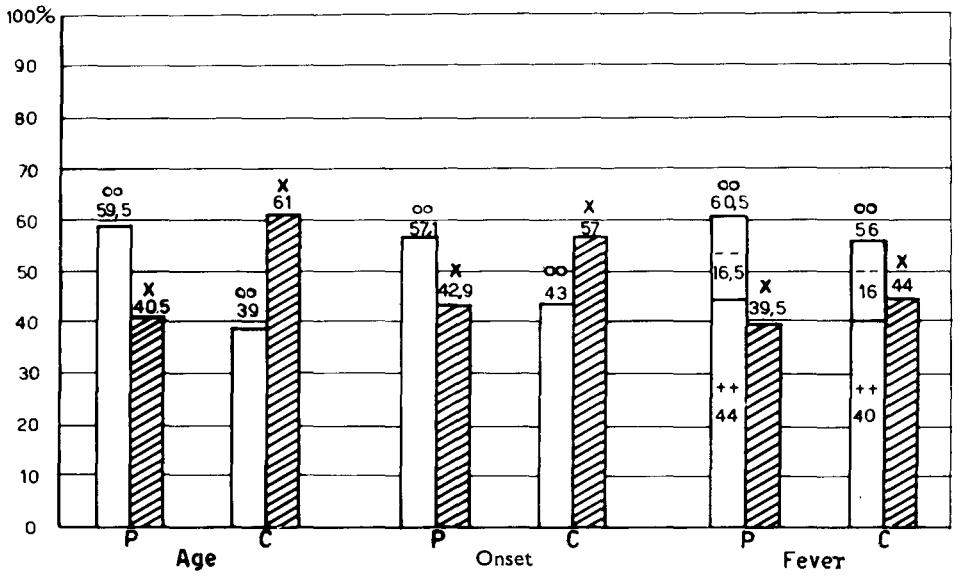

Fig. 1

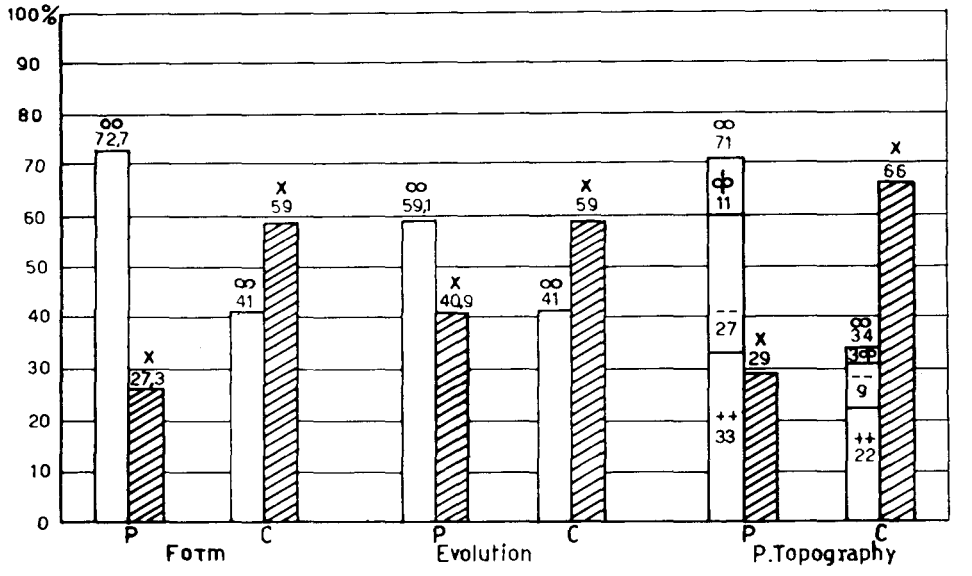

Fig. 2

https://doi.org/10.1017/S1120962300019077 Published online by Cambridge University Press

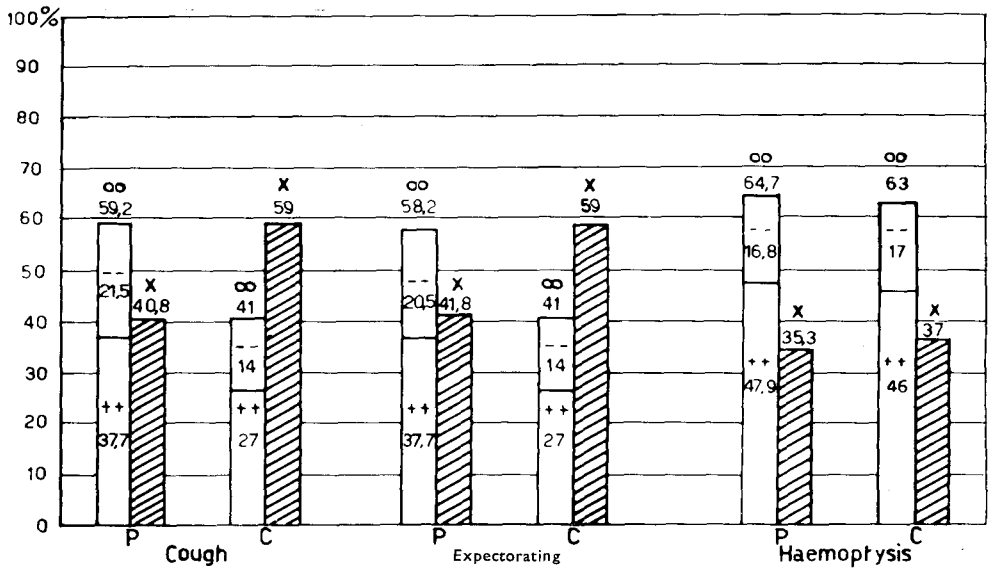

Fig. 3

Concerning each of the patients, we studied the hospital files in order to draw up, in our turn, individual cards, aiming at uniform observation. Our survey was based on the following information:

1. Age of the subject when entering the Hospital;
2. Onset of the disease: acute, mild or deceptive;
3. Symptomatology during first stay in Hospital, namely: presence of fever, cough, expectoration and hemoptysis;
4. Clinical form based on x-ray findings and according to the following pattern: primary process, exhudative process;
5. Course of the disease, according to the following pattern: evolutive type, stationary type, regressive type;
6. Localization of tuberculosis in the lungs based on the side and lobe first stricken.

The research on pairs of tuberculous brothers allowed us to calculate some values of similarity and dissimilarity and to compare them with the same values for non-brother tuberculous patients.

Concerning the *age*, the tuberculous brothers' values (*P* for propositi) are reversed when compared with those of non-brother tuberculous patients (C for controls). Indeed, in the propositi the similarity is 59.5% and the dissimilarity 40.5%, while in the controls the similarity is 39% and the dissimilarity 61%.

We obtained the same results for the *onset* of the disease, where for the propositi

the similarity is 57.1% and the dissimilarity 42.9%, while in the controls the similarity is 43% and dissimilarity 57%.

As for the symptoms (fever, cough, expectoration, hemoptysis), we calculated separately the positive similarity on one part and the negative similarity on the other, but in the graph we gathered together the two percentages in a single column. In *fever*, we do not notice any significant difference in behavior between affected brother pairs (similarity 60.5% – dissimilarity 39.5%) and non-brother pairs (similarity 56%, dissimilarity 44%). Concerning *cough*, a reversal of values as regards the similarity and dissimilarity in the two series of patients is again noticed (propositi: similarity 59.2%, dissimilarity 40.8%; controls: similarity 41%, dissimilarity 59%). The values for *expectoration* as regards similarity and dissimilarity are reversed once more (propositi: similarity 58.2%, dissimilarity 41.8%; controls: similarity 41%, dissimilarity 59%), while for hemoptysis the values are nearly the same in the two groups.

The *clinical form* of the disease presents values of similarity and dissimilarity that are reversed as regards prevalence in the two series of patients; in this case, however, the positive difference between similarity and dissimilarity is the highest among all those we could observe: propositi: similarity 72.7%, dissimilarity 27.3%; controls: similarity 41%, dissimilarity 59%. Also in the evolutive type of the disease we found reversal between similarity and dissimilarity in the two series of pairs (propositi: similarity 59.1%; dissimilarity 40.9%; controls: similarity 41%, dissimilarity 59%).

As for *localization*, we studied the affected side and lobe of pulmonary tuberculosis, obtaining some very significant findings; that is, among propositi the similarity is 71% and dissimilarity 29%, while among controls similarity is 34% and dissimilarity 66%. We also noticed that, while in the propositi the mirror-image similarity is 11%, in the controls it is 3%.

To conclude, it seems that we can expect the genotype to influence tuberculosis as regards age at onset, clinical aspect at onset, classification as to form and to course. Some symptoms, such as fever and hemoptysis, do not reveal much influence of heredity, which seems instead to influence expectoration; we believe that this fact could be related to the demonstrated genotypic influence on pulmonary localization; it appears obvious that the expectoration can be more or less present depending on the affected part of the lung.

It seems to us that the hereditary influence, demonstrated in the localization of the tubercular process, is very important and indicative to explain the other results as well. The topographical similarity in the pairs of affected brothers as compared with those of affected non-brothers indicates that the higher receptivity, on which the genotype has an influence, is, first and certainly, a local fact. Without ruling out the existence of general phenomena obedient to heredity and which may influence the tubercular process, the qualitative and quantitative characteristics of the *locus minoris resistentiae* are enough to explain the high degree of similarity in pairs of brothers concerning the age, the clinical onset, the form and the course of the tubercular process. The action of the local tissue mechanisms can explain the pheno-

genetic mechanism of morbid phenomena which we found to be more similar in brothers than in non-brothers. It is interesting to note that, when we studied phenomena due to mechanisms governed by the central nervous system, such as fever, no hereditary influence could be detected. The same thing happened for hemoptysis, for which, however, the environmental factors are obviously more important.

The pathogenic, clinical and therapeutical consequences to be drawn are many, but we promise ourselves that we shall elaborate on the subject in the final publication. We just want to emphasize here the importance of a methodical study of diseases, comparing pairs of brothers and pairs of non-brothers having the same disease. Such a method is inspired by Kallmann's « Twin Family Method ». It appears to us that this method, applied simply to pairs of brothers, could be very useful in studies of medical and clinical genetics.