TWIN RESEARCH IN TUBERCULOSIS*

By BARBARA SIMONDS, M.A., M.B.

TUBERCULOSIS has been recognized as a clinical entity since the time of the Greeks. Before Koch's discovery of the tubercle bacillus, however, various theories were put forward to explain its ætiology, but the most widely held view was that tuberculosis was caused by an inherited constitutional predisposition. Thus Hippocrates in the 4th century B.C. considered that tuberculosis affects people with a "smooth skin, blue eyes and of leucophlegmatic habit, with shoulders projecting like wings." The English physician Richard Morton, while recognizing the infectious nature of tuberculosis, also wrote in 1689 "An Hereditary Disposition from the Parents does very often bring on Consumption of the Lungs . . ."

With the discovery of the tubercle bacillus by Koch the problem of the ætiology of tuberculosis appeared to have been solved and efforts were directed to eliminating the disease by an attack on the bacillus. It soon became clear, however, that in natural infection the mere presence of the bacillus is not always sufficient to produce disease; virtually 100 per cent of an industrial community are infected with the tubercle bacillus by the age of twenty, but few of them develop manifest clinical disease.

Factors affecting the development of Tuberculosis

Many factors have since been shown to affect the development of tuberculosis; factors such as the dose of bacillus and particularly the capacity of the individual to resist infection. This resistance to infection may be an acquired capacity, for example, acquired as a result of previous infection with the bacillus, or resistance to infection may be an inherited capacity. The role that individual inherited resistance or susceptibility plays in the development of tuberculosis is still in doubt. It is possible that heredity plays little or no part in the development of tuberculosis and if this is the case it is important that the measures to prevent tuberculosis are directed in the right direction. On the other hand, tuberculosis may be an example of a disease in which it is impossible to distinguish the separate parts played by heredity and environment. Whatever the role of heredity in tuberculosis the part played by environment in the development of the disease is of considerable, if not paramount, importance.

The role of heredity in tuberculosis has been investigated mainly by the study of families and more recently by twin studies. Indirect evidence of heredity factors has been obtained from the apparently different racial reactions to tuberculosis and by the study of animal populations artificially infected with the tubercle bacillus. It is impossible to discuss here the findings of these many investigations. I would just like to mention some of the advantages of twin studies over family studies. Family studies usually rely on the patients having a detailed knowledge of their immediate ancestors and relatives, a knowledge that may be absent or inaccurate. Even if accurate information is obtained in family studies, it is difficult to separate the role of infection and heredity. For example, a child may develop tuberculosis many years after one of his parents has died from the disease. This could be explained either by heredity or by infection in early life which has lain dormant for some time because of the chronicity of tuberculous disease.

It is also invalid to compare some relationship groups, e.g. children and consorts of tuberculous patients. The children are usually exposed to tuberculosis prior to the

* Paper read at a Members' Meeting of the *Eugenics Society* on January 16th, 1957.

development of an acquired immunity, whereas consorts are exposed in adult life.

Twin Studies

The study of tuberculosis in twins removes many of these difficulties. Both partners of a twin pair can be examined and the presence or absence of tuberculosis can be established. The morbidity rate of tuberculosis in the co-twins of monozygotic and dizygotic twins with tuberculosis can then be compared. A large study of this nature was first undertaken by Diehl and von Verschuer[1, 2] in Germany. In 1936 they published the case histories of eighty monozygotic and 125 dizygotic twin pairs. In each twin pair one twin had been reported to them as a case of tuberculosis diagnosed at a chest clinic or sanatorium. They found that 65 per cent of the monozygotic co-twins and approximately 25 per cent of the dizygotic co-twins had a similar tuberculous history to that of their twin.

Kallman and Reisner[3] carried out an investigation in New York and New York State and published their results in 1943. They enlarged the study to include the siblings, parents and consorts of the twin index cases. They reported on seventy-eight monozygotic and 230 dizygotic twin pairs and their families, in which the index case had reinfection tuberculosis. They found that the tuberculous morbidity in the co-twins of monozygotic index cases was 61·5 per cent and in the co-twins of dizygotic index cases was 18·3 per cent. The rate for full siblings was 18·9 per cent, i.e. the rate for dizygotic co-twins and siblings was very similar while that for monozygotic co-twins was higher. From their work, Kallman and Reisner concluded: " The analysis of the morbidity distribution in the sibship groups indicates that resistance to tuberculosis is modified by a heredo-constitutional mechanism which seems to be multi-factorial in its genetic nature."

The use of twins in a study of heredity mainly relies on the assumption that if both partners of monozygotic twin pairs are affected more frequently than both partners of dizygotic twin pairs, then there may be assumed to be some hereditary influence on the disease.

This assumption is, however, unjustified if certain hazards are not avoided. The following are, I consider, the main ways in which errors may be introduced into this type of investigation.

1. By a failure to discover every patient who is a twin, and suffering from tuberculosis, in the hospitals and clinics from which the twin sample is obtained.

2. By incorrectly diagnosing the zygocity of the twins.

3. By ignoring other factors which may account for the difference in the morbidity rate in the monozygotic co-twins from the dizygotic co-twins. For example, in tuberculosis it is known that contact with tuberculosis considerably increases the possibility of contracting the disease. A pair of dizygotic twins living fifty miles apart may rarely see each other, a pair of monozygotic twins living 150 miles apart may visit each other more frequently and be more affectionate when they meet. Such factors are difficult to measure quantitatively, but they must be remembered when assessing the results.

Mistakes in the diagnosis of zygocity are probably not frequent. It is preferable to have a category of twins of doubtful zygocity, but by examining the blood groups these twins of doubtful zygocity will be a very small percentage of the total twins. Using similarity methods it is possible to classify many twin pairs as dizygotic. Other pairs will be thought to be monozygotic on similarity methods and this will be confirmed by doing full blood grouping and finding that all their blood groups are the same. It is now possible, using calculations published by Smith and Penrose[4], to find the probability of these pairs being monozygotic using their blood groups alone. Some twin pairs on examination will be thought to be probably dizygotic but possibly monozygotic. If these are then found to have some different blood group they must be dizygotic. If they have the same blood groups throughout, further studies, such as finger printing,

can be done further to ascertain their zygocity.

To return to the first hazard I mentioned, that is, the failure to collect all the twins. This has, I think, probably produced more errors in twin research in tuberculosis than any other. There is no doubt that all twin studies endeavour to obtain an unselected sample of twins, but the criteria by which the nature of these twin samples are judged are not always sufficiently stringent.

In examining twin samples two methods may be used to decide whether they are an unselected group.

1. The twin sample can be analysed to see if the number of monozygotic twins in it, is similar to the expected number of monozygotic twins in any population of twins.

2. The twin sample can be compared with the population from which it is drawn to see if the total number of twins in it is similar to the expected number of twins in a general population. The expected number of living twins in the population is estimated by taking the number of twin births and correcting for their increased stillbirth rate and neo-natal death rate. There should be approximately 2 per cent of twins in the population.

Though the first of these two methods is useful I do not think that on its own it is an adequate method of judging the representative nature of the twin sample.

The Prophit Survey

I would like to illustrate this point from the work done under the auspices of the Prophit Committee. At first the twins were collected by relying on chest physicians reporting all newly diagnosed patients who were twins. By checking the number of twins reported with the notification rates for tuberculosis it soon became apparent that many twins were not being reported. The method of collection was then improved by arranging a more direct contact with fewer clinics and by finding out the number of new patients in each clinic who were diagnosed as suffering from tuberculosis during the time that twins were being collected. In this way 116 twin index cases were found from a total of 7,633 patients. This is 1·5 per cent and is still less than the expected number.

It was decided that the only way of obtaining all the twins in a given population was to make certain that every patient in the population was asked if they were a twin. Chest physicians in various parts of England co-operated; the full register of tuberculous patients was obtained and each patient was written to directly asking them if they were a twin. Replies were received from 21,251 patients, i.e. 97·3 per cent of those asked. Of these 405 are twins (1·91 per cent). This is very close to the expected 2 per cent.

Thus, in the Prophit Survey three distinct groups of twins have been collected.

A. Twins collected from an unknown population.

B. Twins collected from a population in which the number of twins found is 1·5 per cent.

C. Twins collected from a population in which the number of twins found is 1·9 per cent.

Quite different results are found in these various groups.

TABLE 1

Twins	Total No. of Twin Pairs Investigated	Both with Tuberculosis % Monozygotic	Both with Tuberculosis % Dizygotic
From an unknown population A.	43	50	17·2
From population giving 1·5 per cent of twins B.	73	20	29·2
From population giving 1·9 per cent of twins C.	202	29·6	12·8

From Table 1 it is seen that those twins known to be from an inadequate sample (Group A) show a considerably higher incidence of tuberculosis in the co-twins of the monozygotic index cases than in the co-twins of the dizygotic index cases. In the intermediate group (Group B) the morbidity is higher in the dizygotic co-twins. In the last group (Group C) there is a higher morbidity rate in the monozygotic co-twins.

These findings can be explained by assuming that in Group A the figures are incorrect because nearly all the monozygotic twin pairs who both have tuberculosis are found and some of the twins in the other three categories are not found, i.e. monozygotic twins where only one has tuberculosis, and dizygotic twins where both or only one have tuberculosis. In Group B it is possible that the missing 0·5 per cent of twins are mainly dizygotic twins, only one of whom has tuberculosis and thus the percentage of dizygotic twins both of whom have tuberculosis will be apparently increased. The only group which I consider gives correct results is Group C and therefore I will confine my further discussion to this group.

When questioned, 405 patients with tuberculosis said that they were twins. These twin index cases were collected from various boroughs in London, and from Luton, Suffolk, Birmingham, Warwickshire, Gloucestershire and Oxfordshire.

Further inquiries were made concerning the fate of the co-twins with the results shown in Table 2.

TABLE 2

Fate of Co-twin

Died before 12 months old	110
Died exact age unknown	25
Died from tuberculosis	12
Died after 1 year from non-tuberculous causes	31
Alive	227
TOTAL	405

Of the co-twins who died from a non-tuberculous cause after the age of one year, four died after the index case had contracted tuberculosis. These, together with the twelve co-twins who died from tuberculosis and the co-twins who are alive, are the useful twins to analyse. These 243 index cases are divided as shown in Table 3.

TABLE 3

Untraceable	16
Died before information collected	3
Non-tuberculous	3
Followed up	221
TOTAL	243

The 221 index cases about whom information has been gathered come from 208 twin pairs as in thirteen pairs both twin partners are index cases. Table 4 shows the sex and zygocity of these 208 twin pairs.

TABLE 4

Index Cases	Opposite Sexed	Same Sexed Binovular	Uniovular	Doubtful	Total
Female	52	43	33	4	132
Male	27	26	21	2	76
TOTAL	79	69	54	6	208

There are six pairs of doubtful zygocity, either because it proved impossible to complete the investigations or because the co-twin died before the index case was interviewed and it was not possible to come to a definite conclusion with the information available. These have been omitted from the tables which follow. If the number of opposite sexed twins is taken from the number of same sexed twins, this leaves the number of twins one would expect to be monozygotic. From the above figures one would expect fifty monozygotic twins whereas fifty-four were found. The fifty-four monozygotic twin index cases in this sample are 26 per cent of the total which is about the expected figure in a random sample of twins.

If these twin pairs are classified according to whether both twin partners have tuberculosis or not the results shown in Table 5 are obtained.

TABLE 5

	Monozygotic	Dizygotic
Both with tuberculosis	16	19
	29·6%	12·8%
One with tuberculosis	38	129
	70·4%	87·2%

These results show that more than twice the percentage of monozygotic co-twins compared with dizygotic co-twins have some form of tuberculosis.

Further Analysis

Before any conclusions can be drawn from this result the twin sample must be analysed further.

The monozygotic twin index cases and the dizygotic twin index cases must be examined to see if they are comparable for age, sex, type of tuberculosis and contact with tuberculosis. Perhaps the most important single factor is the type of tuberculosis which the index case contracts. If tuberculosis is contracted in childhood, a primary infection results which is usually localised and clears up completely; it may be a glandular infection alone or it may be associated with a pulmonary infection. Later in life the commonest form of tuberculosis is pulmonary, and solely in order to distinguish it from primary tuberculosis, I shall refer to it as phthisis. However, tuberculosis affects many parts of the body apart from the lungs and these can be classified together as non-pulmonary tuberculosis. Of the 202 twin pairs the index case has phthisis in 152 cases. These 152 twin pairs have been analysed separately and classified into those pairs where only one has phthisis and those where both partners have phthisis. These results are given in Table 6.

TABLE 6

	Monozygotic	Dizygotic
Both with phthisis ..	11	13
	26·8%	11·5%
One with phthisis ..	30	98
	73·2%	88·5%

The percentage of monozygotic co-twins with phthisis (26·8 per cent) is a little lower than the percentage of monozygotic co-twins with all forms of tuberculosis (29·6 per cent) and the same applies to the dizygotic co-twins (11·5 per cent and 12·8 per cent). This might be expected as for various reasons it is commoner for both partners of a twin pair to have primary tuberculosis than it is for both of them to have phthisis.

In the monozygotic twin pairs the co-twins have all forms of tuberculosis 2·31 times more frequently than the dizygotic co-twins; and the monozygotic co-twins have phthisis 2·33 times more frequently than the dizygotic co-twins. That is, both types of twins maintain their pattern of behaviour whatever type of tuberculosis they are suffering from.

In the monozygotic group forty-one of the fifty-four twin index cases have phthisis (75·9 per cent) and in the dizygotic group 111 of the 148 twin index cases have phthisis (75·0 per cent), i.e. the two groups are similar.

Exposure to Tuberculosis

Thus, so far it has been shown that in this group of 202 twin pairs the rate of tuberculosis in the monozygotic co-twins is over twice that in the dizygotic co-twins. Before this finding can be ascribed to an hereditary factor it is important to see if other factors can explain this difference. The only one which will be dealt with here is exposure to a known source of tuberculous infection.

Of the 148 binovular co-twins fifty-six, or 37·8 per cent give a history of exposure to tuberculosis. Of the fifty-four uniovular co-twins twenty-one, or 38·9 per cent give a history of exposure. Thus the co-twins have almost the same history of exposure and the different rates of tuberculosis in the co-twins cannot be explained by an increased exposure rate in the monozygotic co-twins.

It has been suggested by Kallman and Reisner that a history of exposure in the monozygotic co-twins makes little difference to the rate of tuberculosis in the co-twin; i.e. that monozygotic co-twins are likely to develop tuberculosis whether or not they have a history of exposure.

The results from the Prophit series are illustrated in Figure 1.

This shows that there is a considerable difference in the tuberculosis rate in both the monozygotic and dizygotic co-twins depending on their exposure to tuberculosis. This difference is particularly marked in the monozygotic co-twins. In other words, a monozygotic co-twin exposed to tuberculosis is considerably more likely to develop tuberculosis than either an unexposed monozygotic co-twin or an exposed dizygotic co-twin. If a monozygotic twin develops tuberculosis his twin has a 48 per cent chance of developing tuberculosis if exposed but only a 19 per cent chance if unexposed.

As has been mentioned earlier, the amount of exposure to tuberculosis is difficult to

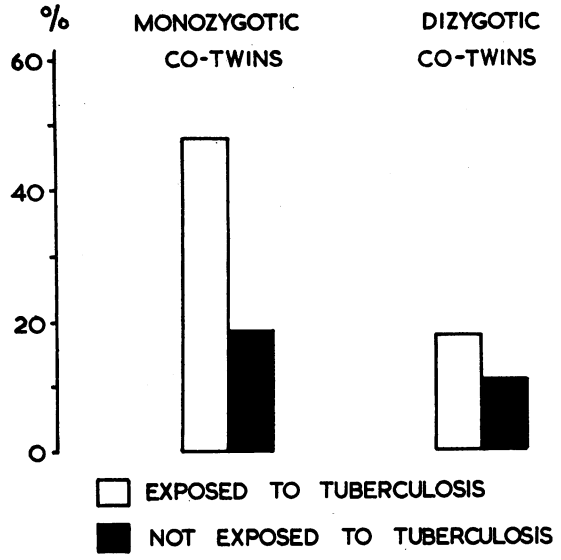

FIGURE 1

The rate of tuberculosis in the co-twins with and without exposure to tuberculosis.

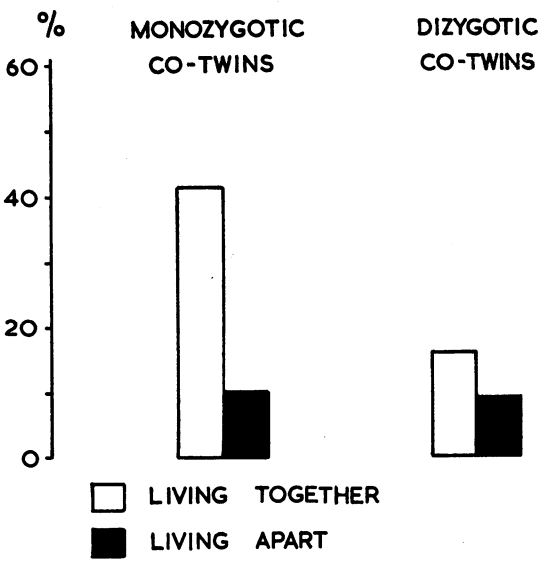

FIGURE 2

The rate of tuberculosis in the co-twins living with and apart from their twins.

measure quantitatively. Twins have been classified as being in contact with tuberculosis only when they have been living in the same house as a patient known to have phthisis. Many people may come into close contact with the disease without being aware of the fact. Whether or not the twins were living together at the time of diagnosis is therefore a check on the history of exposure.

Figure 2 illustrates the number of co-twins who developed tuberculosis while living with or living apart from their twin.

Thus fourteen out of thirty-four (41 per cent) of the monozygotic co-twins living with the index case developed tuberculosis, whereas only twelve out of seventy-five (16 per cent) of the dizygotic co-twins living with the index case developed the disease. The rates for the twins living apart is similar in the monozygotic and dizygotic (10 per cent and 9·6 per cent respectively) co-twins.

This series of twins therefore suggests that monozygotic co-twins are more likely to develop tuberculosis than dizygotic co-twins, but that contact with tuberculosis and living with their twin greatly increases this risk.

It is interesting to note that it is possible for a monozygotic co-twin to live with his twin and to be exposed to tuberculosis either from his twin, or from an outside source, or from both, and still remain healthy. Nine monozygotic co-twins who have lived in these circumstances have remained healthy and nine have developed tuberculosis.

It is, of course, possible that some of the co-twins who are at present healthy will develop tuberculosis in the future. However, for the monozygotic pairs the average time between the diagnosis of the index case and the knowledge that the co-twin is healthy is 6·0 years. The average time between the diagnosis of tuberculosis in the twins when they both have tuberculosis is 4·4 years. It is therefore unlikely that any future cases of tuberculosis will affect the figures to any great extent.

Twin Pairs in which Both Twins have Tuberculosis

So far I have discussed the probability of a co-twin developing tuberculosis if their twin has tuberculosis. A rather different aspect of the problem is the question: if

both twins have tuberculosis, do they react in a similar way to the disease? If it is found that both partners of a monozygotic pair have the same type of tuberculosis more frequently than both partners of a dizygotic pair it would be evidence that the patient's reaction to a tuberculous infection has some hereditary element.

The body's reaction to a tuberculosis infection can conveniently be divided into two aspects.

1. The anatomical site or sites of the disease which results from infection.
2. The clinical development of the infection, i.e. whether the patient recovers, develops chronic disease, or dies. The clinical development of the disease is, of course, modified by treatment.

If the site of tuberculosis in the monozygotic twin pairs is examined: in fourteen out of sixteen pairs in which both twins had tuberculosis the disease was in the same site; in the nineteen dizygotic pairs in which both twins had tuberculosis eighteen had the disease in the same site. Pulmonary tuberculosis has been taken as one site and not divided into the two lungs or lobes of lungs. Thus both twins have tuberculosis in the same site in most of both the monozygotic and dizygotic pairs.

The ability of the patient to recover from tuberculosis is shown in Table 7.

TABLE 7

	Monozygotic	Dizygotic
Similar outcome	12 75%	12 63·1%
Dissimilar outcome	4 25%	7 36·8%

In the monozygotic pairs 75 per cent behave similarly and in the dizygotic pairs 63 per cent behave similarly. Thus the monozygotic pairs do show a slightly higher percentage of twin pairs who behave in a similar manner.

These results, of course, need more detailed analysis because of the effects of treatment, particularly antibiotics.

It is realized that the number of twins who both have tuberculosis is small and few conclusions can be drawn from these figures. They are presented as they do not show the striking difference between monozygotic and dizygotic co-twins which might have been expected from previous studies.

This paper is only meant to give some indication of the results expected from the Prophit Series of twins. Much vital information has been omitted. For example, the data on the families of the twins has not been given at all, and the twins themselves have only been analysed under broad headings.

The results so far, however, do show that the tuberculosis rates in all the co-twins is lower than in previous studies, and that the difference in the rate of monozygotic co-twins and dizygotic co-twins, though appreciable, is not as great as in previous studies.

These results may be interpreted in different ways. The difference between the monozygotic and dizygotic twins suggests that there is some individual inherited resistance to tuberculosis. However, if this inherited resistance plays any great part in the development of tuberculosis it is remarkable that over 50 per cent of monozygotic co-twins exposed to tuberculosis failed to develop the disease. This can only be explained on differences in the exposure and in other features of the environment which it has not been possible to measure.

To me, the results indicate that the attack on the tubercle bacillus, i.e. early case finding in tuberculosis and the prevention of the spread of infection, remain the most important factors in the campaign against tuberculosis. This is, I think, encouraging because while recognizing individual variations in resistance to tuberculosis, it does not mean that some people are born who will almost certainly contract the disease. Given protection from the bacillus and good environmental conditions, anyone can remain free from tuberculosis, including the co-twins of monozygotic twins who already have tuberculosis.

Acknowledgments

I would like to thank the officers and members of the Prophit Committee, under

whose auspices this study is being carried out, for initiating the study and also for their helpful advice and criticism throughout. I would also like to thank Dr. Lawler of the Galton Laboratory who examined all the blood samples. Without the help of the chest physicians in many parts of the country, too numerous to mention by name, it would have been impossible to even contemplate the work. They have suffered considerable disorganization of their clinics in order that this work might be carried out and I thank them most sincerely. Finally to the twins who have most willingly cooperated in the survey, I extend my gratitude.

REFERENCES

1. Diehl, K. and von Verschuer, O. (1933). *Zwillingstuberkulose*. Jena, Gustav Fischer.

2. Diehl, K. and von Verschuer, O. (1936). *Der Erbeinfluss bei der Tuberkulose*. Jena, Gustav Fischer.

3. Kallman, F. J. and Reisner, D. (1943). Twin Studies and Genetic Variations in Resistance to Tuberculosis. *J. Hered.*, **34**, 293-301.

4. Maynard Smith, S. and Penrose, L. S. (1955). *Ann. human Genet.*, **19**, 273-289.