CONTROL OF TUBERCULOSIS
IMPORrTANCE OF HEREDITY AND ENVIRONMENT
BY
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INTRODUCTION
From many standpoints, but especially that of
planning public health measures, it is important
to know whether the development of manifest tuber-
culous disease depends principally upon the inherent
susceptibility of the individual, or whether the factors
of dosage of bacilli, exposure to infection, and
fluctuations in resistance determined by environ-
mental conditions outweigh in importance any
influence that may be exerted by heredity. All
physicians treating tuberculosis know of families
with a high incidence of the disease, and it has
seemed probable to them in some instances the
influence of heredity may be decisive. The question
is important because we can do little to influence
heredity whereas it may be possible to control the
other factors.
Animal experiments support the idea that there
is an hereditary resistance to the development of
tuberculosis. Wright and Lewis (1921), working on
guinea pigs, the progeny of brother-sister matings
carried out for many generations, found marked
differences in resistance to experimental infection.
As shown by the length of life after inoculation with
tubercle bacilli, some offspring had a greater
resistance to the disease than did their parents, and
these differences could be maintained for several
generations. This work was continued by Lurie
(1941), who used eight rabbit families all having a
common ancestor. The animals were exposed in
cages to rabbits which had been infected intra-
venously with virulent tubercle bacilli. Such a
procedure produced a chronic type of disease, the
urine being the main source of infection. The lungs
of the contact rabbits were x-rayed every month
and it was found that these rabbit families fell into
three groups:

(1) those developing chronic disease;
(2) those developing rapidly progressive disease;
(3) those developing disease intermediate between
(1) and (2).

In such an experiment the dosage of bacilli
entering the respiratory system is unknown, but
when the resistance to a standard dose of tubercle
bacilli was tested the rabbit families fell into the
same three groups as with natural infection. From
these experiments it appears that families with dif-
ferent degrees of resistance can be created by
inbreeding and that the differences can be main-
tained through several generations. It must be
noted, however, that marked differences in individual
resistance were always present, and that the level of
resistance of a particular family could be gauged
only by the percentage of survivors in each group
exposed to infection. Further, when members of the
various families were exposed to large doses of
bacilli, these differences were obliterated and all the
rabbits succumbed in 5 to 6 weeks.

In human beings, Pearson (1907) found that when
both parents were tuberculous 57 per cent. of the
offspring had pulmonary tuberculosis, whereas only
29 per cent. of the offspring developed pulmonary
tuberculosis when only one parent was tuberculous.
Pearson dealt only with pulmonary tuberculosis and
his selection of families was probably unrepresenta-
tive, since 22 per cent. of the offspring developed
pulmonary tuberculosis when neither parent was
tuberculous. He collected his information by
questioning 383 patients in a sanatorium, all of
whom had pulmonary tuberculosis and were aged
20 or over. Such a method is of dubious value.

Unpleasant facts about one's family may be readily
forgotten and parents sometimes take great care to
conceal from their children that they have ever
suffered from tuberculosis. Pope (ed. and rev.
Pearson, 1908) considered that they had disposed of
the view that infection plays a dominant role in the
aetiology of tuberculosis by comparing the frequency
with which non-tuberculous marital partners con-
tacted tuberculosis from the spouse, with the
frequency with which children contracted the disease
from tuberculous parents. Such a comparison does
not take into consideration the differing incidence
of the disease in different age groups (Springett,
1952), and their conclusions are, therefore, invalid.
The effect on household associates of exposure to sputum-positive cases is well known (Downes, 1935; Grenville-Mathers and Trenchard, 1953; Zeidberg, Dillon, and Gass 1954). Wolff and Ciocco (1942) analysed the death records of 968 husbands and wives and 968 brothers and sisters, one of whom was also a spouse of the former group. They found a distinct association for death from tuberculosis among both groups. They considered that the former was due to infection, but argued that siblings are not in such close contact with the patient and that the association for siblings pointed to the effect of an hereditary factor. Puffer (1944) found that consorts exposed to an open case of pulmonary tuberculosis frequently developed manifest tuberculosis. The risk was greater where the consorts came from families believed to be susceptible because of disease in parents or siblings. In the children of tuberculous persons, the disease was found as frequently in those who had not been exposed to the parent when he had the disease, as in those exposed to risk in the household. She presumed from this that the children of tuberculous parents were susceptible to the disease.

More definite evidence has come from twin studies. Thus Kallmann and Reisner (1943) found that, for monozygotic twins, there was a high probability of both developing tuberculosis. In this context twins cannot be regarded as typical of the population as a whole. Kallmann and Reisner also found that the chance of developing tuberculosis increased in strict proportion to the degree of blood relationship to a tuberculous index case, but their method of analysis is not clear.

We therefore lack definite evidence that an hereditary factor plays a predominant part in the development of tuberculosis in humans. On the other hand, the marked influence of environment in the broad sense, as governed by economic conditions, is now clearly established in the development of the disease. It is more common in poorer-class areas and in over-crowded housing conditions. Benjamin (1953) has shown for the London boroughs a high association of mortality and morbidity with the proportion of occupied and retired men in Social Class V and with the density of housing (persons per room), but he found it impossible to isolate statistically the separate aetiological influences constituting environment. Stein (1954) made a comparison between Birmingham and Glasgow, where the death rates from tuberculosis and housing conditions as indicated by available rooms per household are widely different. She also pointed out that the deaths in Glasgow increased as the rooms per household decreased.

For an evaluation of the relative importance of the soil and the seed in the aetiology of tuberculosis, analyses considering both domiciliary exposure to disease and the family relationship of the members of the household are needed. It seems justifiable to presume that members of the same household usually have approximately the same standard of living. With environment a common factor, heredity and closeness of contact become the main variables. If heredity is pre-eminent in the pathogenesis of tuberculosis, we should expect more cases in the blood relatives of the index case than in the other domiciliary contacts.

Method

At the Edgware and Harrow Chest Clinics great attention has always been paid to the examination of all domiciliary contacts of notified tuberculous cases. These contacts comprise both the blood relatives of the index case and those who are not blood relatives. The former include fathers, mothers, sons, daughters, brothers, and sisters; the latter include brothers-in-law, sisters-in-law, and friends or lodgers living as members of the household. Husbands and wives are not blood relations but stand in a special position so far as contact is concerned and require separate consideration.

For the investigation here reported we have used only those index cases diagnosed as tuberculous in Middlesex, and have excluded already diagnosed patients transferred in from other administrative areas. Altogether there were 2,330 index cases; their ages and type of disease are given in Table I. We have dealt with 6,537 contacts of these index cases. As only 32 grandparents of the index case were available, these were excluded from the analysis. The presence or absence of disease in contacts was determined by clinical and radiological examination of the

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>Pleural Effusion</th>
<th>Non-Respiratory Tuberculosis</th>
<th>Respiratory Tuberculosis</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>3</td>
<td>11</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td>5-9</td>
<td>11</td>
<td>17</td>
<td>34</td>
<td>62</td>
</tr>
<tr>
<td>10-14</td>
<td>18</td>
<td>30</td>
<td>21</td>
<td>69</td>
</tr>
<tr>
<td>15-24</td>
<td>25</td>
<td>258</td>
<td>395</td>
<td>776</td>
</tr>
<tr>
<td>25-34</td>
<td>14</td>
<td>191</td>
<td>338</td>
<td>566</td>
</tr>
<tr>
<td>35-44</td>
<td>12</td>
<td>102</td>
<td>248</td>
<td>372</td>
</tr>
<tr>
<td>45-54</td>
<td>3</td>
<td>60</td>
<td>176</td>
<td>242</td>
</tr>
<tr>
<td>55-64</td>
<td>2</td>
<td>34</td>
<td>101</td>
<td>158</td>
</tr>
<tr>
<td>65 and Over</td>
<td>—</td>
<td>21</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td>Totals</td>
<td>168</td>
<td>747</td>
<td>1,315</td>
<td>2,330</td>
</tr>
</tbody>
</table>

TABLE I

AGE DISTRIBUTION AND TYPE OF DISEASE IN 2,330 INDEX CASES OF TUBERCULOSIS
CONTROL OF TUBERCULOSIS

In comparing the incidence of tuberculosis at first examination in the various groups of contacts, account was taken of their different age structure; the expected numbers of cases were calculated by applying age-specific rates for all contacts combined to those at risk at each age in the different groups. This was done separately for male and female contacts. The following age groups were used for each sex: 0–14, 15–24, 25–34, 35–49, 50 and over.

In the same way annual attack rates were calculated for each age group, and expected cases in the different groups were obtained by applying these age-specific rates for all contacts to those in continued contact with the index case. The results are summarized in Table II. Incidence on and after diagnosis of the index case must be regarded as complementary, since whether the disease develops in a contact before the diagnosis of the index case depends on the length of time that the index case remains undiscovered. Attention should therefore be focused on the final column of Table II, which relates to total incidence.

The observed number of tuberculous individuals did not exceed the expected number to a statistically significant extent for any group of contacts except wives. There is thus no evidence of a greater susceptibility to disease in blood relatives. Moreover, it must be noted that the groups of contacts have been arranged in Table II in an order determined by the degree of infectiousness of the index

### RESULTS

<table>
<thead>
<tr>
<th>Sex of Contact</th>
<th>Relationship of Contact to Index Case</th>
<th>No. of Contacts</th>
<th>Per cent. of Related Index Cases who were ever Sputum-Positive</th>
<th>Number Observed</th>
<th>Number Expected (on overall-age-specific rates)</th>
<th>Ratio of Observed to Expected</th>
<th>Number Observed</th>
<th>Number Expected (on overall-age-specific rates)</th>
<th>Ratio of Observed to Expected</th>
<th>Ratio of Total Observed to Total Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Grandson ...</td>
<td>50</td>
<td>86</td>
<td>3</td>
<td>2.6</td>
<td>(1.2)</td>
<td>0</td>
<td>0.4</td>
<td>(1.2)</td>
<td>(1.0)</td>
</tr>
<tr>
<td></td>
<td>Son ...</td>
<td>958</td>
<td>79</td>
<td>15</td>
<td>12.1</td>
<td>1.2</td>
<td>17</td>
<td>16.5</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>No relative ...</td>
<td>336</td>
<td>66</td>
<td>15</td>
<td>12.1</td>
<td>1.2</td>
<td>1</td>
<td>1.7</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Husband ...</td>
<td>444</td>
<td>64</td>
<td>15</td>
<td>12.4</td>
<td>1.2</td>
<td>5</td>
<td>5.7</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Nephew ...</td>
<td>95</td>
<td>60</td>
<td>15</td>
<td>12.4</td>
<td>1.2</td>
<td>5</td>
<td>0.7</td>
<td>(--)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Brother ...</td>
<td>599</td>
<td>50</td>
<td>30</td>
<td>28.0</td>
<td>1.1</td>
<td>9</td>
<td>4.5</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Father ...</td>
<td>533</td>
<td>41</td>
<td>11</td>
<td>12.0</td>
<td>0.9</td>
<td>1</td>
<td>3.4</td>
<td>(--)</td>
<td>0.8</td>
</tr>
<tr>
<td>Female</td>
<td>Wife ...</td>
<td>668</td>
<td>78</td>
<td>25</td>
<td>15.3</td>
<td>1.6</td>
<td>13</td>
<td>13.9</td>
<td>0.9</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>No relative ...</td>
<td>339</td>
<td>70</td>
<td>12</td>
<td>11.0</td>
<td>1.1</td>
<td>1</td>
<td>1.9</td>
<td>(0.5)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Niece ...</td>
<td>87</td>
<td>64</td>
<td>3</td>
<td>3.4</td>
<td>(0.9)</td>
<td>1</td>
<td>0.3</td>
<td>(3.3)</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Daughter ...</td>
<td>936</td>
<td>63</td>
<td>38</td>
<td>37.9</td>
<td>1.0</td>
<td>8</td>
<td>12.5</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Sister ...</td>
<td>707</td>
<td>51</td>
<td>20</td>
<td>29.8</td>
<td>0.7</td>
<td>15</td>
<td>8.2</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Granddaughter ...</td>
<td>36</td>
<td>47</td>
<td>2</td>
<td>1.4</td>
<td>(1.4)</td>
<td>0</td>
<td>0.2</td>
<td>(--)</td>
<td>(1.3)</td>
</tr>
<tr>
<td></td>
<td>Mother ...</td>
<td>749</td>
<td>43</td>
<td>9</td>
<td>10.0</td>
<td>0.9</td>
<td>3</td>
<td>3.9</td>
<td>(--)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

(Rates in brackets are based on very small numbers of cases)
case as assessed by sputum state. Ignoring the groups with very small numbers (bracketed rates) and considering both sexes together, there is at least a suggestion that the relative incidence of tuberculosis exhibits a similar gradient. In the Figure the ratios of observed cases to expected cases have been plotted against the sputum-positivity of the index cases. The straight line is a "least squares" fit to the whole data of Table II ($y = 0.00423x + 0.742$). The main departures from this gradient are wives, brothers, sons, and daughters, and of these the quality of contact offers partial explanation. It can be presumed, for example, that the probably high degree of contact between spouses increases the effective infectiousness of the index case.

Table III (opposite) gives, by age groups for the main groups of contacts, the percentage in contact with a sputum-positive index case. In general, irrespective of the degree of infection to which they are exposed, females do not often break down after age 35. This Table also shows the relative disadvantages of wives aged 15 to 24 years and husbands aged 25 to 34 years. The closer degree of contact has already been noted as increasing the relative infectivity of the index case. Non-relatives do not appear to have any special advantage over blood relations.

It appeared possible that the effect of any hereditary factor may have been swamped by the great influence of environment, and the data were therefore analysed using only houses in which two or more cases of tuberculosis had occurred (Table IV, opposite). These were chosen as being likely to be biased, since they would probably contain individuals with a
CONTROL OF TUBERCULOSIS

Table III

INCIDENCE OF DISEASE IN MAIN GROUPS OF CONTACTS WHEN FIRST SEEN

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentages Affected with Tuberculosis and in Contact with a Sputum-Positive Case</th>
<th>Relationship of Contacts</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-relatives</td>
<td>Other relative</td>
<td>Male</td>
<td>Non-relatives</td>
</tr>
<tr>
<td>0-14</td>
<td>Affected ... 4.8</td>
<td>5.4</td>
<td>6.3</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>In Contact ... 69</td>
<td>57</td>
<td>62</td>
<td>53</td>
</tr>
<tr>
<td>15-24</td>
<td>Affected ... 18.8</td>
<td>3.4</td>
<td>(2-4)</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>In Contact ... 71</td>
<td>63</td>
<td>36</td>
<td>77</td>
</tr>
<tr>
<td>25-39</td>
<td>Affected ... (1-2)</td>
<td>3.4</td>
<td>4-1</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>In Contact ... 61</td>
<td>58</td>
<td>60</td>
<td>73</td>
</tr>
<tr>
<td>35-39</td>
<td>Affected ... (1-4)</td>
<td>1.6</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>In Contact ... 62</td>
<td>54</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>50 and Over</td>
<td>Affected ... 0</td>
<td>2.7</td>
<td>3.4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>In Contact ... 69</td>
<td>54</td>
<td>70</td>
<td>72</td>
</tr>
</tbody>
</table>

(Rates in brackets based on very small numbers of cases)

lowered resistance to disease. But these households proved to be mainly those in which the index case was sputum-positive. On the whole, Table IV tells the same story as Table II, with the degree of infectivity of the index case and the closeness of contact tending to be more important than blood relationship.

Table IV

HOUSES WITH TWO OR MORE CASES

<table>
<thead>
<tr>
<th>Sex of Contact</th>
<th>Relationship of Contact to Index Case</th>
<th>Number of Contacts</th>
<th>Per cent of Related Index Cases ever Sputum-Positive</th>
<th>Ratio of Total Observed Cases of Tuberculosis to Total Expected during Period of Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Son</td>
<td>171</td>
<td>90</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>Husband</td>
<td>61</td>
<td>86</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Nephew</td>
<td>31</td>
<td>84</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>relative</td>
<td>77</td>
<td>78</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Brother</td>
<td>127</td>
<td>77</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Grandson</td>
<td>8</td>
<td>75</td>
<td>(0.2)</td>
</tr>
<tr>
<td></td>
<td>Father</td>
<td>69</td>
<td>71</td>
<td>0.9</td>
</tr>
<tr>
<td>Female</td>
<td>Grand-daughter</td>
<td>9</td>
<td>100</td>
<td>(0.8)</td>
</tr>
<tr>
<td></td>
<td>Daughter</td>
<td>138</td>
<td>92</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Niece</td>
<td>35</td>
<td>91</td>
<td>(0.4)</td>
</tr>
<tr>
<td></td>
<td>Wife</td>
<td>107</td>
<td>85</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>relative</td>
<td>86</td>
<td>80</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Sister</td>
<td>149</td>
<td>75</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>94</td>
<td>73</td>
<td>1.0</td>
</tr>
</tbody>
</table>

(Rates in brackets based on very small numbers of cases)

Discussion

The results presented here differ from those reported by Puffer, Zeidberg, Dillon, Gass, and Hutcheson (1952) and Kallmann and Reisner (1943), in which the attack rates for close relatives (parents, siblings, and children) were found to be higher than for other contacts. Puffer and others (1952) and Zeidberg and others (1954) also found that the house- hold associates were most liable to develop clinical disease during infancy, early childhood, and early adult life. We found, on the other hand, that the risk of developing clinical disease appears to be related to the degree of infectivity of the index case (except that females do not tend to break down often after age 35). This is in accord with the commonly accepted findings in Great Britain.

Pulmonary tuberculosis in adults may be the result either of a recent primary infection or of a re-infection, which may be either endogenous or, more probably, exogenous (Willis, 1925; Krause, 1926). If the re-infection be mainly exogenous, the degree of exposure of any contacts must clearly be a factor in the development of tuberculosis. The Prophit survey (Daniels, Ridehalgh, Springett, and Hall, 1948) found that only when the degree of exposure to infection was sufficiently great and the number of infections sufficiently high, did the morbidity in the initially tuberculin-negative reactors in the survey begin to exceed that in the initially tuberculin-positive reactors.

Lurie (1941), in his experimental work in rabbit families, found that, although there was an hereditary transmissible factor in resistance to tuberculosis, the differences between the various families were obliterated when exposure to infection was high.

The annual attack rates in our survey were higher than those in surveys reported from the United States of America. It seems probable, therefore, that in the conditions which have prevailed in our chest clinic areas during the past few years the possible influence of any hereditary factor has been obliterated by the high degree of infectivity to which the contacts have been exposed. In this investigation we have dealt only with the household associates of notified cases of tuberculosis (the great majority being respiratory tuberculosis). Our usual criteria for notification of a case of respiratory tuberculosis are the presence of a positive sputum, radiological evidence of cavitory disease, or spreading infiltration on serial films, so that many of our index cases classified as sputum-negative may well have been infectious. Our findings, like those of the Prophit survey, suggest therefore that (in one urban area at least) environmental factors and the degree of exposure to infection are of predominant importance in the development of tuberculosis.
Summary

An investigation into the relative importance of heredity and environment is based on the 6,537 domiciliary contacts of 2,330 cases of tuberculosis. The incidence of disease in blood-relations, spouses, and non-relatives was compared after standardization of age-specific rates. No effective hereditary factor could be found, but the degree of infectivity and the closeness of contact with the index case seemed to be related to the incidence of tuberculous disease in contacts.

We wish to thank the Hendon Group Hospital Management Committee for help towards the clerical expenses.

REFERENCES