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THE HEREDITARY FACTOR IN THE ETIOLOGY OF TUBERCULOSIS

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THE HEREDITARY FACTOR IN THE ETIOLOGY OF TUBERCULOSIS

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Three factors belong to the etiology of tuberculosis. These are: 1. The *active factor* or *infection*, involving the problems of age at infection, type, strain-virulence of the bacillus and natural and acquired immunity. 2. The *predispositional factor* involving (1) prenatal influences (such as damaging of germ cells by toxins); (2) acquired susceptibility (underfeeding, former diseases, alchoholism); (3) genetic susceptibility or inherited susceptibility. Children become tuberculous because they belong to a stock showing weakness and nonresistance. 3. The *occasional factor* or organic disequilibrium; the cause exciting the development of the disease.

1. THE PROBLEM

Until the last part of the nineteenth century, medical literature attributed tuberculosis to inheritance. Later, it became obvious that the disease itself was not inherited and the general opinion agreed with this latter idea. One cannot maintain that there are tuberculous patients without infection, but the hypothesis may be entertained that different individuals have the power to resist in different degrees and that the families of consumptives have a subnormal power of resistance which is transmitted from parents to children.

What is the relative part of acquired or genetic susceptibility in the predispositional factor in the etiology of tuberculosis? Pearl (1) puts in clear terms the problem. In large cities, says Pearl, there are few persons who escape infection by tubercle bacilli at some time in their lives. Of the infected persons some develop active consumptive tuberculosis and others do not develop the disease in a clinical form. What factors determine the group into which a particular person shall fall, and what is the quantitative influence of particular factors making this determination?

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The problem is complex. It is difficult to separate the case from the influence of the conditions of life. When one goes back a generation the diagnosis is sometimes uncertain. The obscure cases and the question of size, dose and virulence of infection also complicate the problem. Nevertheless, it would be advantageous, in order to reach a clear opinion and to help in the solution of this problem, to make a comparison of the results obtained by different methods and attack the problem by an analytical method. For these reasons I have engaged in this work.

2. EVIDENCE AS TO THE INHERITANCE OF THE TUBERCULOUS DIATHESIS

The special predisposition to contract tuberculosis has been called *diathesis*. It is a constitutional component, possibly functional, chemical and structural, that causes the individual patient to develop, more easily than others, the symptoms of the disease. Evidence that the tuberculous diathesis is inherited is afforded by observations of racial and personal differences, by statistics and by experimental work.

a. Observations

Riffel (Baldwin (2)) observed several generations of tuberculous families where familial infection could fairly be excluded in some descendants who became tuberculous.

Carrière (Baldwin (2)) claimed that the young of animals injected with toxins of tubercle bacilli showed more easily the symptoms of tuberculosis than those of control animals.

Turban (Baldwin (2)) demonstrated that the disease was found to begin in the same lung of the parents and children. Seventy-eight per cent of 28 families where parental tuberculosis existed had children with the corresponding lung affected. In one family the father and four children had the same lung first affected. A. E. Mayer (3) gathered facts from which a fairly correct judgment can be formed. He studied 112 tuberculous families at Davos Dorf, and found that in quite a large proportion of the victims who were related to one another the disease began at the same point in the lungs. Comparing his research with the similar work of Turban, Finkbeiner and others he reckons that in about 72 per cent of the families the starting point of the disease is characteristic.

According to Weinberg (4), of infants of tuberculous parents whose mothers died within one year after labor, 67.9 per cent died likewise within the first year of life, as against a normal death rate of 25 per cent. Of 57 per cent born alive, whose mothers died within four weeks of labor, 78.8 per cent died in the first year.

Among human races there are big differences in the tendency to show signs of active tuberculosis. American Indians, Negroes, and especially mulattoes and Hawaiian Islanders, easily acquire tuberculosis in a fatal form. According to the *Journal of Heredity* (1917, viii, p. 177) tuberculosis was not known in America before the time of Columbus and natives were therefore unselected against it. When the whites and natives lived side by side and, similarly, when whites and negroes live side by side, the white man's disease finds most of its victims among the darker race of natives.

Davies (Baldwin (2)) concluded that consanguineous marriages for many centuries were chiefly responsible for the excessive amount of tuberculosis on the Isle of Man. On the other hand Lundborg (5) enumerates several arguments in support of the theory that racial homogeneity is a powerful factor in preventing degenerative phenomena, including a predisposition to tuberculosis. The pure-bred Jew and Gipsy are comparatively immune to tuberculosis, even when living in poverty, but as soon as they intermarry with other races the immunity disappears. The mortality from tuberculosis in such hybrids is very high. In the south of Sweden, where the population is pure-bred, the incidence of mortality from tuberculosis is very low. Again in Iceland the low incidence of tuberculosis may be correlated with the racial isolation of its inhabitants. The same argument applies to the South of Italy, Sardinia and Sicily where the incidence of tuberculosis is low in spite of defective hygiene. On the other hand, countries, such as Poland and Austria, with a mixed population, suffer greatly from tuberculosis.

In the gigantic experiment in human genetics which has gone on in the United States from its beginning, one finds the same racial differences among the victims of Koch's bacillus. L. Dublin (6) concludes that several races of foreign born population of New York are variable as to their vigor, measured by their mortality tables. The same races are also variable as to the principal causes of death. Concerning tuberculosis and pneumonia, the ratios are given as in table 1.

Data collected by the War Department of physical examinations of drafted men and compiled by Love and Davenport (7) are not less significant. Tuberculosis gives a rate of 30 per 1000 men examined, constituting over 5.4 per cent of defects found. The higher rates fall in the States of Arizona, New Mexico, Colorado and California. "The reason for this," says Davenport,

is that the described area included so many young men who have gone there because they were already victims of active tuberculosis. Perhaps some of the tuberculous are sons of men who have migrated to these Sates on account of nonresistance to tuberculosis and themselves show the family diathesis. The next most infected territories are the Nothern Pacific States, the New England States, and New York, and the group of States immediately south of the Mason and Dixon line, including Missouri, Louisiana, Mississippi and Georgia.

TABLE 1

Death rate per 100,000 persons born in specified countries

COUNTRY OF BIRTH OF DECEDENT	CAUSES OF DEATH			
	Tuberculosis		Pneumonia	
	Males	Females	Males	Females
United States	227.9	140.1	130.2	115.7
England, Scotland and Wales	182.7	110.2	145.0	156.1
Germany	198.0	102.9	154.9	126.2
Ireland	472.4	248.2	278.4	276.9
Italy	117.2	156.7	217.4	223.7
Russia	123.8	74.7	146.9	175.5

New England has been long known as a region with a high rate of tuberculosis, associated with the large number of recent immigrants. The Southern Appalachians have numerous sanatoria for tuberculosis. The high rate in the Gulf States is probably due to the presence in them of a large proportion of Negroes and mulattoes, who are especially susceptible to tuberculosis. Florida and South Carolina have a low rate for the Southern States, because they have the smallest populations of mulattoes, hybrids that apparently have a special susceptibility. The smallest rate of tuberculosis is found in the Great Plains and the northern part of the Rocky Mountains. This is an area occupied largely by a vigorous people.

In general, where one finds a large incidence of tuberculosis there is found also a high rate of underweight, tonsillitis, defective physical

development and deficient chest measurement. These facts are confirmed in another study by the same authors (8). In 10,701 men found at mobilization camps to have pulmonary tuberculosis, the average stature is 68.07 inches, which is 0.58 inch greater than the average height of the first million of drafted men. The standard deviation of stature is 2.74. The average weight is 130.44 pounds or 11 pounds below the average; and the standard deviation of the mean weight is 14.74. The chest circumference is on the average 32.09 inches or 1.13 inches below the general average. As for robustness, the index of build is 28.15, whereas the Pignet index is 30.27. To summarize, the average tuberculous subject is tall, narrow chested and underweight. This work seems to indicate the presence of a type that is less resistant, and susceptible to tuberculosis, which is mixed in the general population.

b. Statistical studies

Karl Pearson (9) studied the problem of the relative influence of heredity and environment, by use of the method of correlation between parent and offspring in respect to tuberculosis, and he concluded that the positive correlation, 0.50, which is found, is due to inheritance. He has also demonstrated by the same method that the correlation between husband and wife in the matter of tuberculosis is far less intense than that between parent and offspring and is of the order of that correlation between husband and wife which we associate with the selective mating that occurs for physical and mental characteristics in man. The following list of coefficients of correlation between parent and offspring (taken from Pearl (1)) will give some idea of their size in the case of various human traits: stature, 0.51; span, 0.46; forearm, 0.50; deaf mutism, 0.54; insanity, 0.53; phthisis, 0.50. Goring (10), investigating tuberculosis in lower social grades, found the same correlation between parent and offspring as Pearson, but the marital correlation for all the tuberculous is 0.01, and for well to do and prosperous classes, 0.16. It is easy to understand the variation of selective mating, that is, with the grade of intellectual taste. Pearson finds that like mates with like more commonly in the more intellectual classes. It is more likely to occur in middle classes than in poorer classes that both parents are tuberculous. The difference is probably due to a selective influence which does not exist among the poor.

The following list of coefficients of correlation are these calculated with our material: between parents and offspring, 0.449; between father

and offspring, 0.352; between mother and offspring, 0.304; degree of assortative mating between husband and wife, 0.128.

Pearl speaks about his own experiments that are going on and the results of which will be interesting. He finds "that a tuberculous person, chosen at random in the working population of Baltimore, will have nearly six times as many blood relatives tuberculous as will a nontuberculous person."

c. Experimental studies

The subject is checked and verified by direct experimental evidence in the laboratory. Wright and Lewis (11) have studied factors in the resistance of guinea pigs to tuberculosis with special regard to inbreeding and heredity. Their experiments on the effects of inbreeding on guinea pigs have been carried on since 1906; over 30,000 animals have been recorded. The subject of the study was the average vigor, including frequency and size of litters, growth from birth to maturity, mortality at birth and later resistance to tuberculosis. They find that certain families are still vigorous after more than twenty generations of brother and sister matings. The inbreeding cannot be said to have a specific deleterious effect on general vigor. In general, a particular combination of vigor in some respects, with weakness in others, has become characteristic of each of the twenty-three families. The differences are clearly hereditary and due to independent factors. On crossing two inbred families, there is a marked improvement in every respect, either in the first or second generation, according as the character is one which depends on the heredity of the young themselves or on the dam. Other characters depend on both the sire and dam (frequency of litters).

The resistance to tuberculosis has been tested on over 1100 guinea pigs belonging to five closely inbred families, to the crosses between these families and to a control stock. It has been found that sex and threefold differences in age, rate of gain and weight have only a slight effect on length of life after inoculation. The situation is parallel with respect to fertility, weight and vitality. Though heredity can hardly be demonstrated in the foundation stock, widely divergent strains appear in all cases on inbreeding. That independent hereditary factors are involved, not merely differences in general vigor, is shown by the lack of relation between the rank of the families in resistance to tuberculosis and in other respects. The progeny of crosses is at least equal to that of the better of the two parental families.

Resistance is thus dominant over susceptibility. There is equal transmission by sire and dam, and to sons and daughters. In particular crosses, the average of the progeny is consistently superior to either parental line, indicating that the latter are susceptible for different reasons, each being able to supply what the other lacks. In the total crossbred stock, over 30 per cent of the observed variation is determined by the amount of blood from the best inbred family, 10 per cent is due to age, weight and condition, and 60 per cent due to accidental conditions or unknown causes following inoculation.

3. THE ANALYTICAL METHOD

1. Method of investigation. Now the problem must be attacked by an analytical method. The method employed in this study is that of the Eugenics Record Office. Instead of collecting numerous cases of statistics, a more intensive inquiry is made of special cases. For this purpose, field workers are employed who secure interviews with patients and their relatives and secure data concerning their ancestry. Thus, they collect valuable data about the individuals, correlated with their family and surroundings, considering especially the household, habits, mental and social status. Other data are obtained from the subjects themselves. All of these schedules and records are carefully examined and indexed and preserved by the Eugenics Record Office, which is a valuable clearing house of American family traits. By far the greater number of families studied are scattered through the rural communities or the United States. This population includes people who are able to make adjustments demanded by their surroundings. Some of these are farmers, gardeners, workman, and so on. They live, in general, under good and normal conditions. The questionnaire used for this study is the record of family traits. Some records have been excluded because of incompleteness, doubtful accuracy or various other causes. Each record has been carefully analyzed, and a pedigree charted for it. No special selection has been made among the persons concerned other than the tabulating of those records that included one or more cases of tuberculosis or other respiratory diseases in the offspring, in the parental or grandparental generation. In examining the data, chief reliance has been placed on the answers of the patients to the following questions: birthplace, principal residence, age of marriage, total number of sons and daughters, age of those that died early, occupations at successive

ages, minor diseases to which there was special susceptibility, grave illnesses, if dead cause and age of death, special tastes and peculiarities of mind and body, age when description is given, adult or present height (in inches), and adult or present weight (in pounds). At the same time care was taken to find out the degree and duration of familial contact with tuberculosis of the lungs. Height, weight, and sometimes the index of build and the date of the removal from the town of birth of members of the family, have been very useful in indicating the relative influence of environment and heredity. Each population was classified and subdivided according to tuberculous, nontuberculous, suspect, and respiratory disease (this latter class includes adenoids, hypertrophic tonsillitis, bronchitis, congestion of the lungs, pneumonia and pleurisy). All cases were gathered into different tabulations showing the results in a comprehensive form. These tabulations are:

1. Frequency of tuberculous or nontuberculous in the whole population.
2. Frequency of the same classes in the offspring classified according to close and nonclose contact with tuberculosis of the lungs.
3. Distribution of the offspring according to the pathological character of the parents and grandparents.
4. Distribution of the offspring according to the matings, classified genetically.

2. The results. This study includes 214 families, in which 185 tuberculous matings and 29 nontuberculous matings were found. The whole population represents 5,629 individuals. We call a tuberculous mating one in which the father or the mother, one or both, are tuberculous or whose fraternity and ancestry are tuberculous. Nontuberculous matings are matings in which no member of the family is tuberculous or belongs to a tuberculous stock. Table 2 and chart 1 show the distribution of cases of tuberculosis, nontuberculosis, suspects, and respiratory diseases in the offspring, the parental and the grandparental generations. Reading this table, top to bottom, the striking fact is the unequal proportions from tuberculous matings. The tuberculous stock remains nearly always at the same level while the respiratory class has a tendency to decrease, whereas the nontuberculous is increasing. This depends upon the population which is not the same in each generation. It is obvious that it is easier to know the fraternity of the parental generation than the grandparental generation. This inequality cannot greatly

influence the general results, because, in an eugenical inquiry, the nearness in the degree of kin or connection is more important than the length of the direct line of descent. The striking result of this tabulation is the high proportion of tuberculous children in the defective strain and the high proportion of normal children in the nontuberculous strain. Taking an individual at random, the chances that he may be tuberculous will be higher if he is from a tuberculous family than if he belongs to a healthy family. These differences among the population of two kinds of matings suggest a strong presumption that heredity plays an important part in the etiology of tuberculosis.

TABLE 2

Frequency occurrence of tuberculosis among the blood relatives and fraternities of 185 tuberculous matings and of 29 nontuberculous matings

SUBJECT'S HISTORY (SUBJECT AND FRATERNITY)		BLOOD RELATIVES				PERCENTAGES			
		Tb.	S	R. D.	N. Tb.	Tb.	S	R. D.	N Tb.
Filial Generation	Tb.	238	67	260	515	27.0	7.6	28.1	37.0
	N. Tb.	4	1	—	129	2.9	0.9	—	96.2
Parental Generation	Tb.	542	92	166	1320	25.6	4.3	7.8	62.3
	N. Tb.	10	—	—	310	3.1	—	—	96.9
G^d Parental Generation	Tb.	180	5	40	680	12.9	0.6	4.9	81.6
	N. Tb.	8	—	—	270	2.9	—	—	97.1
Totals	Tb.	982	165	466	3224	22.5	3.8	10.9	62.8
	N. Tb.	22	1	—	769	2.8	0.1	—	97.1

Tb. = tuberculous.
S. = suspect.
R. D. = respiratory disease.
N. Tb. = nontuberculous.

The next step is to analyze the elements of this probable heredity. With the aim of eliminating the possibility of the infection factor, it is necessary to control the stock studied. The classes of the filial generation are subdivided into two groups, namely, close contact and nonclose contact with tuberculosis of the lungs. Close contact means a close contact with a case of tuberculosis of the lungs during the whole or a part of life; nonclose contact implies the opposite. Suppose tuberculosis is caused only by poor conditions of life, only by infection; then the percentage of tuberculous will be very high in the close contact subclass and the nontuberculosis percentage will be low in the nonclose contact. It is found, in fact, that the majority of nontuberculous have not been in contact; but, besides this, there is a high percentage of such persons who

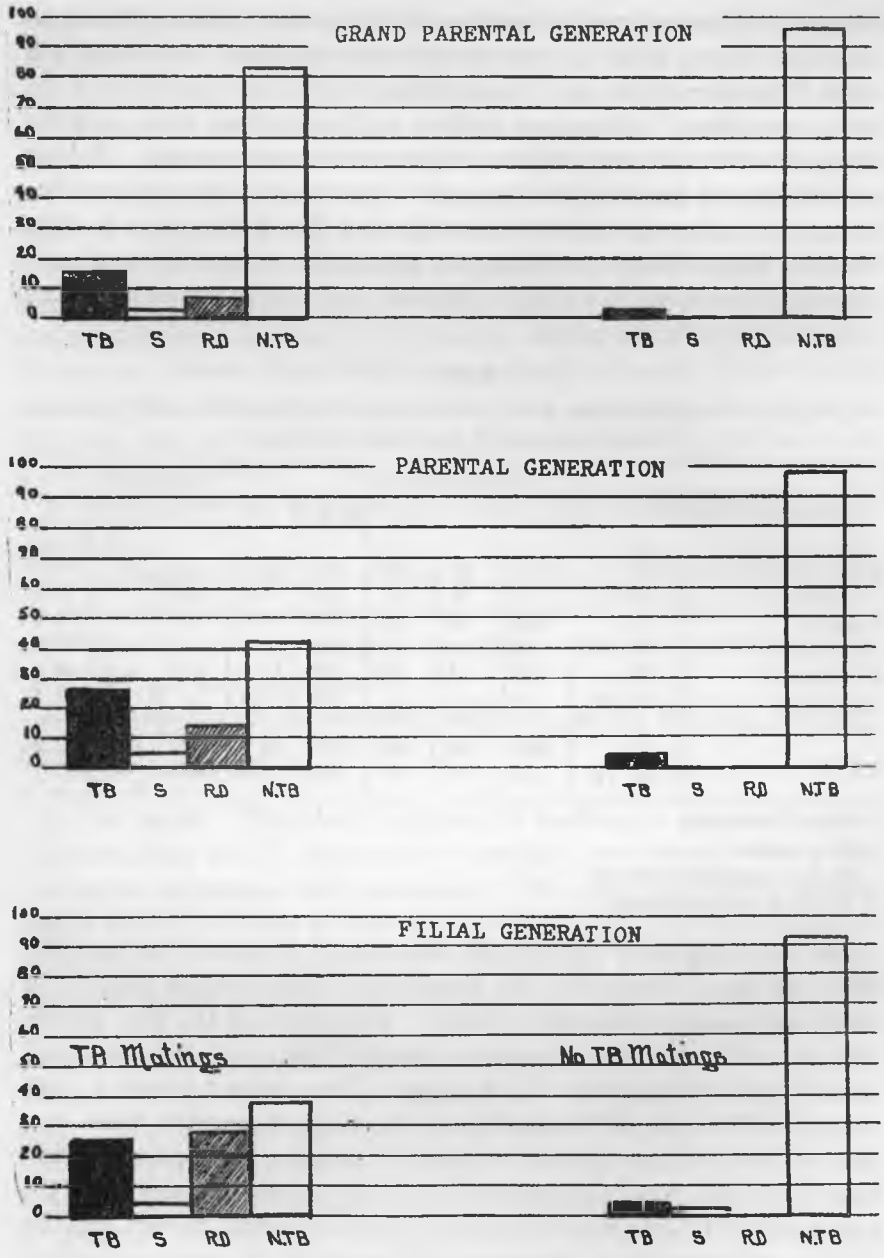

CHART 1. SHOWING AMONG TUBERCULOUS AND NONTUBERCULOUS MATINGS THE PROPORTION OF TUBERCULOUS, SUSPECTS, RESPIRATORY DISEASES AND NONTUBERCULOUS IN THE OFFSPRING

have been in close contact with a tuberculous person. The percentage of cases of tuberculosis and respiratory diseases who have been in nonclose contact is higher than of those who have been in close contact. This is the opposite from the result expected, assuming the contagion to be only the cause of the disease. In this material, it seems, the surroundings and the infection have not played the predominant part. The results and percentages are summarized in table 3 and chart 2. Let us consider now, by hypothesis, that tuberculous and nontuberculous are allelomorphs

TABLE 3

Frequency of cases of tuberculous, suspects, respiratory disease and nontuberculous, according to contact and parentage among the offspring of the family histories

NATURE OF MATINGS	OFFSPRING							
	Tb.		S.		R. D.		N. Tb.	
	c.c.	n.c.c.	c.c.	n.c.c.	c.c.	n.c.c.	c.c.	n.c.c.
N × N	3	1	1	—	—	—	59	70
N × N(T)	4	14	3	3	21	30	33	64
N (T) × N	10	13	2	5	6	10	28	30
N (T) × N(T)	3	7	1	3	10	24	21	31
T × N	29	26	3	7	7	10	19	45
N × T	7	20	2	2	8	17	18	40
N(T) × T	9	11	4	5	3	14	11	40
T × N(T)	5	10	3	—	10	5	25	10
T × T	49	40	10	17	20	26	20	21
Totals	119	143	29	42	85	136	234	351

c.c.: implies close contact with a case of tuberculosis of the lungs.

n.c.c.: means no close contact with a case of tuberculosis of the lungs.

Matings are arranged in accordance with a various combination of two characters, namely, tuberculous and nontuberculous.

and let us arrange the offspring according to the various kinds of parental combinations with one or both of these characters.

There are nine groups as follows:

1. Both parents normal: $N \times N$.

2. Father nontuberculous but of tuberculous strain and mother nontuberculous: $N\ (T) \times N$.

3. Father nontuberculous and mother nontuberculous but of tuberculous strain: $N \times N\ (T)$.

4. Both parents nontuberculous but of tuberculous strain: $N\ (T) \times N\ (T)$.

5. Father tuberculous and mother nontuberculous: $T \times N$

6. Father nontuberculous and mother tuberculous: $N \times T$

7. Father nontuberculous but of tuberculous strain and mother tuberculous: $N\ (T) \times T$

8. Father tuberculous and mother nontuberculous but of tuberculous strain: $T \times N\ (T)$

9. Both parents tuberculous: $T \times T$.

The parents are of tuberculous strain when they have in their families or ancestries tuberculosis or members susceptible to this disease or frequent respiratory diseases. In this order of parentage, the tuberculous influence increases from no. 1 to no. 9. The results are collected in

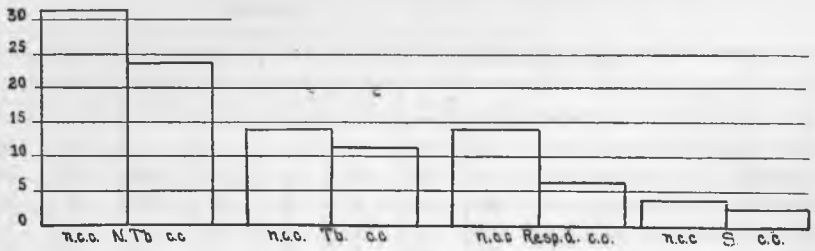

CHART 2. FREQUENCY REDUCED TO PERCENTAGES OF THE OFFSPRING POPULATION, CLASSIFIED AS TUBERCULOUS, SUSPECTS AND RESPIRATORY DISEASES, ACCORDING TO THE PRESENCE OR ABSENCE OF CLOSE CONTACT WITH TUBERCULOUS INDIVIDUALS

N.Tb. = nontuberculous.
Tb. = tuberculous.
R.D. = respiratory disease.
S.S. = suspect.
n.c.c. = non-close contact with a case of tuberculosis of the lung.
c.c. = close contact with a case of tuberculosis of the lung.

tables 3 and 4, and charts 3 and 4. Let us analyze and compare these tables. When both parents are normal there is a high incidence of nontuberculous children; when both parents are tuberculous a high rate of tuberculous is found in the offspring. This confirms the above finding, that is to say, that the tuberculous progeny are less numerous when the parents are normal. But when a tuberculous taint is introduced into normal blood, as in classes 2 and 3, the percentage of defective offspring increases suddenly. As chart 4 shows, this increase is chiefly in the "respiratory" class. When this taint is introduced by the father (mating no. 3) the general proportion of defectives remains at the same level as when introduced by the mother, but there is more active tuberculosis.

TABLE 4

Absolute numbers and percentages of cases of tuberculous, suspects, respiratory diseases, according to the parentage among the offspring of the family histories

CLASSES	MATING	DEFECTS IN THE OFFSPRING								PERCENTAGE AMONG THE DEFECTIVES
		Absolute numbers				Percentages				
		Tb.	S.	R. D.	N. Tb.	Tb.	S.	R. D.	N. Tb.	
1	N × N	4	1	—	129	2.99	0.75	—	96.26	3.74
2	N × N(T)	18	6	51	97	10.46	3.54	29.65	56.40	43.60
3	N(T) × N	23	7	16	58	22.12	6.73	15.38	55.77	44.23
4	N(T) × N(T)	10	4	34	52	10.00	4.00	34.00	52.00	48.00
5	T × N	55	10	17	64	37.24	6.90	11.72	44.14	55.86
6	N × T	27	4	25	58	23.68	3.51	21.93	50.88	49.12
7	N(T) × T	20	9	17	51	20.62	9.28	17.53	52.58	47.42
8	T × N(T)	15	3	15	35	22.06	4.41	22.06	51.47	48.50
9	T × T	89	27	46	41	43.84	13.30	22.66	20.20	79.80

Tb. = tuberculous.
S. = suspect.
R.D. = respiratory disease.
N.Tb. = nontuberculous.
Defectives: implies tuberculous, suspects, respiratory disease among the offspring.

Thus, when the father carries the defect, the tuberculous class increases; when the mother does, the respiratory class increases. Probably, this result is because the defect is carried by the nucleus and not by the cytoplasm of the gamete. This finding is evidence that the result de-

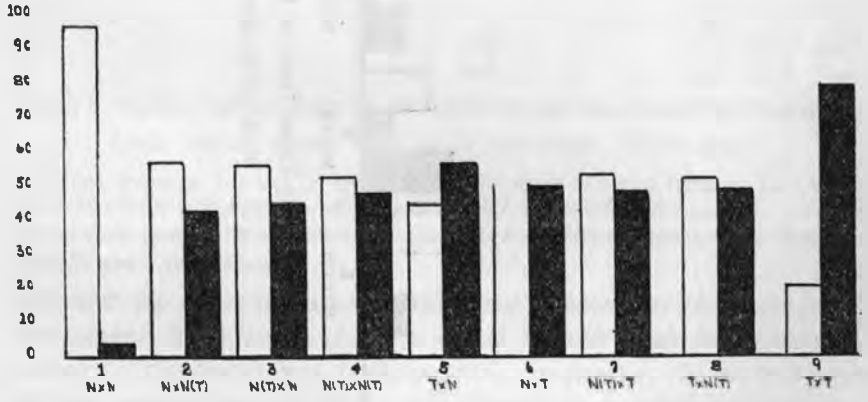

CHART 3. SHOWING THE PROPORTION OF ACTIVE TUBERCULOSIS AND ITS ABSENCE IN THE OFFSPRING, ACCORDING TO THE NATURE OF THE MATING

Black: defective. Clear: nontuberculous

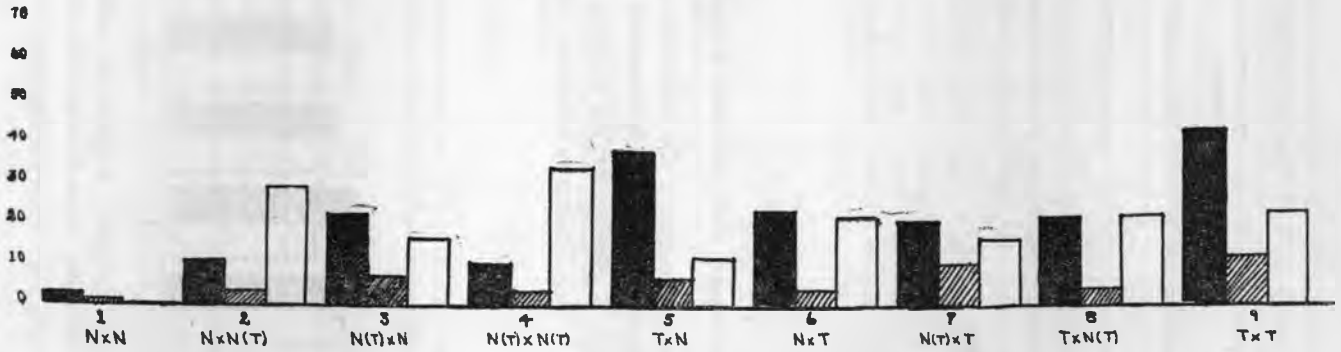

CHART 4. DISTRIBUTION OF THREE TYPES OF DEFECTIVES AMONG THE OFFSPRING OF EACH OF THE NINE KINDS OF MATINGS

Black: tuberculous. Striped: subject. White: respiratory disease

pends on a genetic influence. In class 4, where both parents are tainted, there is a rather high percentage of tuberculous, with a large number of persons suffering from respiratory disease. Let us examine what happens when the tuberculous diathesis is directly transmitted through one or both parents. There is a progressive increase of tuberculous and decrease of nontuberculous offspring. When it is the mother, the increase is found chiefly in the respiratory class. This indicates the same paternal influence as found in class 2. When one parent is tuberculous and the other tainted (mating types 7 and 8) the level of both classes is

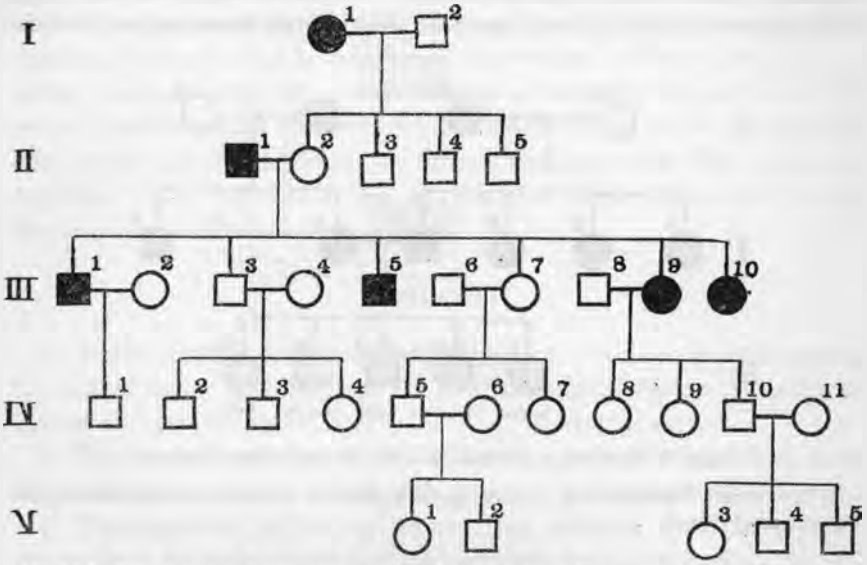

CHART 5. SHOWING THE INFLUENCE OF THE MATING ON THE BEHAVIOR OF THE CHARACTERS

Circle: female. Square: male. Black: tuberculosis. White: normal

The first dysgenical marriage (I) introduces tuberculosis into a strong family. Tuberculosis reappears when a nontuberculous offspring mates with a tuberculous person. The mating of a tuberculous person with a member of a strong family dilutes the defect, which disappears in the IV and V generations.

high and the tuberculous and respiratory diseases are in nearly equal percentage. This means that the defect is more profound when it is carried by the gametes of both parents. In general, the suspect class includes few members. But its variability in numbers is correlated more strongly with that of the tuberculous progeny than with that of the respiratory diseases. From such analysis and comparison two observations follow most clearly, namely,

1. The different percentages of defective or normal offspring are correlated with the quality of their parents.

2. The defect or taint is carried in the parental gametes.

Thus the tuberculous diathesis is not inherited always in the same degree, but in different degrees depending on the gametic constitution of the individual.

One fact stands out clearly in these statistics: that is, that a larger proportion of the offspring are nontuberculous when the mother alone shows active tuberculosis than when the father alone shows it. We should not expect this if active tuberculosis depends on prolonged and repeated contact, because the contact of a child with its mother is generally closer than with its father. Wherever the paternal stock alone is known to be tainted, more of the children show active tubercu-

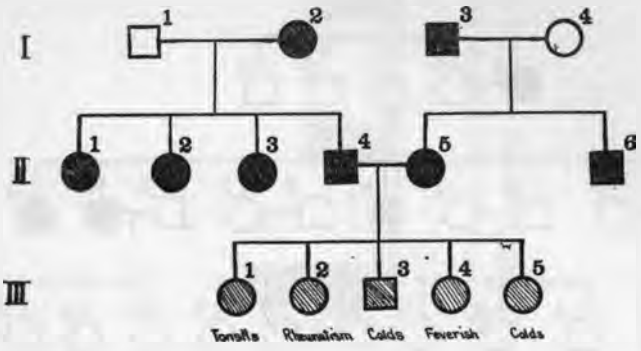

CHART 6. SHOWING A MATING OF TWO TUBERCULOUS PARENTS

Square: male. Circle: female. Black symbols indicate tuberculous and striped symbols respiratory disease.

losis than when the maternal alone is known to be tainted. This suggests that a nonresistant sperm is more injurious to the zygote than a nonresistant egg. On the other hand, when one parent alone is tainted or has active tuberculosis, there is nearly twice as much respiratory disease in the offspring when that parent is the mother as when it is the father. Thus:

Percentage of respiratory disease when father alone is tuberculous:
- Classes 2 and 3.....15.38
- Classes 5 and 6.....11.72

Percentage of respiratory disease when mother alone is tuberculous:
- Classes 2 and 3.....29.65
- Classes 5 and 6.....29.63

The question now arises whether the distribution of active tuberculosis, suspects, and respiratory disease, and nontuberculosis in the offspring agrees at all with Mendelian expectation. It can hardly be expected that it will agree closely, for the following reasons: First, because many of the offspring are still too young to show fully their potentialities. In consequence, the proportion of nontuberculous children will usually be too great. Second, because, as Wright and Lewis point out, there is such a thing as destroying by extremely bad conditions of life a naturally good resistance. This will tend to result in the occasional appearance of tuberculosis where it would not be expected under average conditions. Also, there are undoubtedly errors of classification of parents due to insufficient knowledge. From all of these and other causes, a very close correspondence between calculated and observed results cannot be anticipated. Therefore, if we do not deny the rôle played by environment, we cannot similarly deny that played by heredity. It is improbable that environment alone determines the incidence rate of active tuberculosis.

SUMMARY

1. In the etiology of tuberculosis, three factors are recognized, namely; (1) active factor or infection, (2) predispositional factor including acquired and genetic susceptibility, and (3) incidental factor.

2. Biometrical and statistical studies agree in indicating a high correlation in inheritance of tuberculosis between parents and offspring.

3. Experimental studies on guinea pigs indicate that the resistant character is dominant over the susceptibility to tuberculosis.

4. The analysis of 214 families has established the following facts:

(a) The percentage of tuberculous offspring is higher in tuberculous families.

(b) In the same surroundings, there is a greater occurrence of tuberculous without than with close contact. This holds for the cases of suspects and respiratory diseases.

(c) In the distribution of the offspring according to parental and ancestral combinations, the percentage of the tuberculous increases and that of the nontuberculous decreases with the degree of the ancestral tuberculous influence.

(d) There is a parental influence by which the defect is introduced. Thus the defect is doubtless carried by the gametes.

(e) The maternal influence is very slight and there is no evidence of a prenatal influence.

(f) The variation of tuberculous, suspects, and respiratory diseases among the defectives indicates the presence of an inherited character, which is the constitutional component called *diathesis*. Of these there are biotypes.

(g) Among the biotypes there are those who are more resistant, less resistant and nonresistant.

CONCLUSIONS

One cannot maintain that there can be tuberculosis without infection, but various considerations may still be urged to support the view that different persons have the power to resist the infection in different degrees and that in consumptive families a lack of resisting power is transmitted from gametes to children. The tubercle bacillus is everywhere about us. Some people entirely escape its attacks, while in others the disease may occur in such a slight form that the person attacked recovers from it without being aware that anything has been wrong.

Tuberculosis is not an inheritable character in the sense in which eye color is inheritable. It belongs to a second kind of heredity called *indirect heredity*. Infection and immunity are causes, but they do not exclude inheritance. Biologically speaking, people inherit directly a constitutional make-up, possibly functional, chemical and structural, with a certain amount of power to resist tuberculosis or other related diseases.

From the social and eugenical point of view it is very important that resistance to tuberculosis is transmitted approximately in a Mendelian sense. So it seems possible to establish some principles based on the law of the averages.

From present knowledge no one is able to give advice to normal persons or one apparently normal for a contemplated marriage. Advice is possible only in extreme cases and we need still more minute investigations and studies. Nevertheless, it will be useful to dissuade marriage between two stocks in which the same defect is apparent. In such stocks consanguineous marriages are dangerous. A tuberculous subject will find more advantage for his progeny by marrying a person belonging to a resistant strain. Eugenical marriages should be between normals and those free from defects.

In the future it is necessary that each individual preserve for himself the life book of ancestors, fraternities, and the biological and medical events from birth throughout life. Whenever individuals cannot give a complete account of the members of both the branches of the family, these members should be interviewed by specially trained men. At present the physician cannot content himself with a superficial inquiry as to health of parents, brothers, and sisters of the patient. It is necessary for him to get a complete history. It is hoped that the numerous physicians engaged in the different specialities will collect a larger number of complete pedigrees of those diseases and conditions which are known to be frequently inherited. I believe that a large amount of valuable data can thus be obtained and much light can be thrown on the obscure problem of etiology and help obtained for social and eugenical science.

This work has been done at the Eugenics Record Office, Cold Spring Harbor, Long Island, New York. I owe a large debt of gratitude to Dr. Chas. B. Davenport, Director of the Department of Genetics of the Carnegie Institution of Washington, for many suggestions and a great deal of advice and assistance. I am also indebted to Dr. H. H. Laughlin, Assistant Director, in charge of the Eugenics Record Office, whose sympathy has made possible the present study.

Note: The full tables upon which the summarized tables of this study are based have been deposited at the Eugenics Record Office Cold Spring Harbor, Long Island, New York. Upon request they will be sent for inspection to any qualified student of the subject.

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