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HOW PREVENT CHILDHOOD INFECTION FROM BECOMING ACTIVE TUBERCULOSIS LATER IN LIFE *

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THE BEARING OF VON PIRQUET'S AND RÖMER'S WORK ON OUR NEW CONCEPTION OF TUBERCULOSIS

The use of tuberculin in diagnosis dates back to the first tuberculin era in 1890-91. The early method of using the test, however, was by subcutaneous injection, which was not suitable for wholesale testing. It was a great advance when von Pirquet in 1906-7[1, 2] reported the fact that tuberculin could be used as a local skin test; because, as he had found, the skin of those who have been infected by tubercle bacilli is rendered hypersensitive to the bacillus and its products.

The testing of large groups of people revealed a fact wholly unexpected, that children who were apparently in all respects healthy were sensitized to tuberculin. Not only some children but nearly all children, as shown by Hamburger[3], in Table I, reacted by the time they had attained the age of fifteen years. The accuracy of Table I is supported by the statistics from Harbitz,[4] shown in Table II. This surprising prevalence of tubercle infection furnished new problems for solution; for while

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TABLE I

PERCENTAGE OF CHILDREN REACTING TO TUBERCULIN ACCORDING TO AGE PERIOD. TEST REPEATED WHEN NEGATIVE (VIENNA)

46 children in the	2nd year of whom	4	or	9 per cent reacted
56 children in the	3rd year of whom	11	or	20 per cent reacted
75 children in the	4th year of whom	24	or	32 per cent reacted
50 children in the	5th year of whom	26	or	52 per cent reacted
63 children in the	6th year of whom	32	or	51 per cent reacted
46 children in the	7th year of whom	28	or	61 per cent reacted
30 children in the	8th year of whom	22	or	73 per cent reacted
35 children in the	9th year of whom	25	or	71 per cent reacted
26 children in the	10th year of whom	22	or	85 per cent reacted
29 children in the	11th year of whom	27	or	93 per cent reacted
19 children in the	12th year of whom	18	or	95 per cent reacted
17 children in the	13th year of whom	16	or	94 per cent reacted
17 children in the	14th year of whom	16	or	94 per cent reacted
509		271		

these children showed infection and were sensitive to tuberculin, they were not ill of tuberculosis. It will be interesting to note to what degree both total and massive infection will be reduced by the intelligent application of present known methods of preventing the spread of bacilli.

Much experimentation was then carried out to determine the meaning of the tuberculin reaction, and it was found that the formation of tubercle, in others words, infection, is essential to the establishment of the conditions which produce the tuberculin reaction. This means that all children who react to tuberculin when applied to the skin have been previously infected with bacilli. The natural corollary to this is that infection does not mean disease; there is a difference between tuberculous infection and tuberculous disease. This fact is basic to our understanding of not only clinical tuberculosis but the prevention of tuberculosis also.

TABLE II

PERCENTAGE OF CHILDREN SHOWING TUBERCULOSIS INFECTION ON POSTMORTEM EXAMINATION

AGE	Number of those Examined	Free from Tuberculosis	%	Infected with Tuberculosis	%	Died of Tube culosis	Latent Tuberculosis	Latent Tubercle Bacilli
1st year.... 1st quarter	82	76	%	6	%	4		2
2nd quarter	55	46		9		4		5
3rd quarter	36	20		16		10	1	5
4th quarter	28	19	80	9	20	6	2	1
	201	161		40		24	3	13
2 years	65	48	74	17	26	14	1	2
3 years	26	18	69	8	31	4	1	3
4 years	18	12	67	6	33	5	1	....
5 years	16	7	44	9	56	8	....	1
6 years	12	2	20	10	80	8	1	1
7 years	13	7	54	6	46	3	....	2
8 years	20	7	35	13	65	6	6	1
9 years	9	3	33	6	67	3	2	1
10 years	11	3	27	8	73	4	4	....
11 years	14	1	7	13	93	7	4	2
12 years	13	4	31	9	69	6	3	....
13 years	13	4	31	9	69	4	5	....
14 years	13	1	8	12	92	4	8	....
15 years	40	8	20	32	80	19	13	....
	484	286	59	198	41	119	52	27
		484					198	

The interpretation of the meaning of the tuberculin test and the significance of the immunity created by previous infection was studied most carefully by Römer [5,6]. In his phenomenal studies he clarified the nature of the acquired resistance to tuberculosis and greatly advanced our knowledge of the relationship of early infection to clinical disease. He showed that a primary infection often prevented bacilli, which were later injected subcutaneously, from becoming implanted.

It is Römer's work especially which established the conception that the chronic form of adult tuberculosis is probably due to metastatic infection from foci which resulted from childhood infection; and further that the chronic nature of the adult type of the disease is a result of the immunity gained by the implantation of bacilli which resulted in tubercle formation in early life.

Koch[7] had observed in some of his very early experiments that primary subcutaneous infection is not accompanied by inflammatory reaction at the site of inoculation, but that such an inoculation in an animal already tuberculous is accompanied by inflammation and sloughing at the point of injection. He further stated that the bacilli in the nontuberculous animal escaped freely from the seat of inoculation and even found their way to the regional lymph glands and into the general bloodstream, while in the tuberculous animal the bacilli were hindered in their passage through the tissues. Something held them at the point of inoculation, and there was even an attempt at ridding the animal of them through a sloughing process. Regional

lymph glands took little part in the defense and the bloodstream was only attained by the bacilli at a late period. Krause[8] has shown that the difference in time of bacilli gaining access to the blood stream is three to four days in the nontuberculous animal, and three to four weeks in the tuberculous.

This observation of Koch was the first recognition of the property of producing a specific inflam-

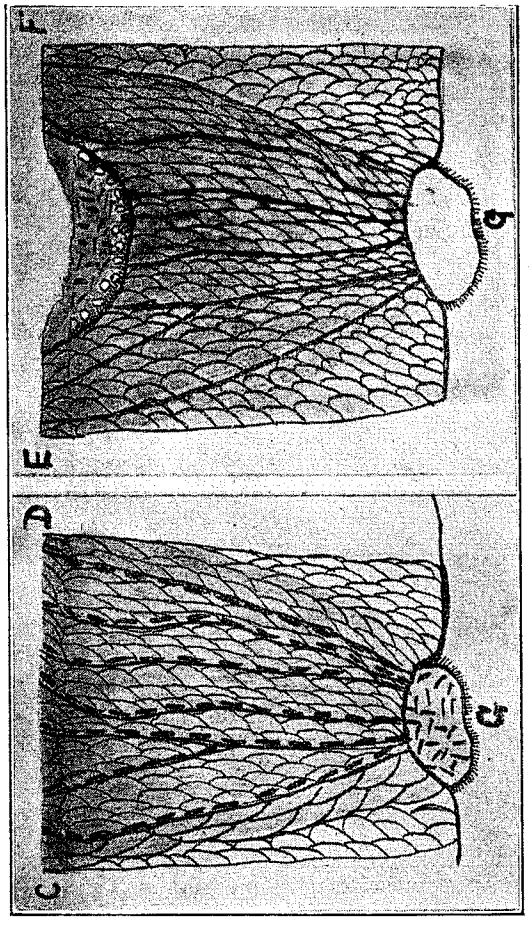

Fig. 1. a, and b illustrate schematically the difference in behavior of tissues towards invading bacilli. In a, specific defense has not been established by previous infection. The bacilli pass through the lymphatic channels to the lymph glands quickly. In b, specific defense has been established by previous infection. Bacilli are held in check immediately under the skin at the point of injection. The tissues between the point of injection and the gland, as well as the gland itself, remain free from infection for a considerable time.

matory reaction which is granted to the body cells by a primary infection, the first observation of allergy, which is now recognized as an essential factor in the body's specific protective mechanism against bacilli.

Fig. 1, a, and b, is a schematic representation of the difference in action of the body in the presence of primary and secondary inoculation of tubercle bacilli. In a, the inoculation of bacilli occurs for the first time and the bacilli readily pass through the tissues to the neighboring lymph glands; while in b, the inoculation occurs in tissues which, because of previous infection, have acquired the specific immunity reaction known as allergy, through which a defensive opposition is at once presented to the invading bacilli, hindering their passage to such an extent that only a few are able, and this only tardily, to pass beyond the point of inoculation and gain access to the neighboring lymph glands and the general circulation.

SOURCES OF INFECTION

Whence comes this all but universal infection? This question cannot be answered too dogmatically. We assume that the bacilli which produce human infection are either of human or bovine origin, but personally I do not believe the last word has been said as to the relative frequency of the two sources.

In discussing this question in *Clinical Tuberculosis*[9] I quote statistics as shown in Table III from Park and Krumwiede,[10] who analyzed 1,038 carefully studied cases of tuberculosis, and showed that prior to eleven years of age about 75 per cent of cases of tuberculosis were caused by human bacilli

TABLE III—from Park and Krumwiede

Age Period	Per cent of Human Tuberculosis	Per cent of Bovine Tuberculosis
0— 5 years	73.5	26.5
6—11 years	75.	25.
16 years and over	98.69	1.31

and 25 per cent by bovine, and after sixteen years 98.69 per cent were due to human and only 1.31 per cent to bovine bacilli. Also Table IV presents an analysis of 1400 cases studied by the Imperial German Board of Health, showing the number of cases of particular types of the disease with the strain of bacillus responsible for each, in which the percentages in childhood and adult life are compared.

When Koch[11] at the London Congress in 1901 declared that human and bovine tuberculosis were different and that there was no danger to human beings from infected cattle, he called attention to the very important but previously hardly suspected fact that human bacilli differ from bovine bacilli. He was wrong in stating that there was no danger to human beings from bovine bacilli. In fact, there is no way of telling how great this danger is. He was correct in his statement that the bacilli differ.

What seems to me to be the most important fact bearing on the question of transmissibility of bovine bacilli to the human race is that, while we recover bovine bacilli from a considerable number of such childhood forms of tuberculosis as that of the miliary and general tuberculosis, we rarely find them in the adult forms, particularly tuberculosis

TABLE IV

From the Imperial German Board of Health.

	Total Number Investigated Cases	TYPES		Per Cent of all Cases Due to Bovine Type	
		Human	Bovine	In Adults	In Children
Tuberculosis of the lungs	811	807	5	0.66	0.
Tuberculosis of the bones and joints	99	95	5	6.66	4.3
Meningeal tuberculosis	33	30	3	0.	10.34
Generalized tuberculosis	178	147	33	2.5	23.18
Tuberculosis of the cervical glands	167	120	47	5.8	40.7
Tuberculosis of the mesenteric glands	112	78	35	12.0	51.0
Totals	1400	1277	128		

of the lungs. We must assume either that little bovine infection occurs in those who develop clinical tuberculosis in adult life or that the bovine bacilli which are taken into the body during childhood gradually adapt themselves to the human soil, and are transmuted to human bacilli[12]. This assumption seems perfectly reasonable and in accordance with the powers of adaptation to different media which is shown by bacilli in laboratory cultures.

Therefore, we must recognize bovine bacilli as potentially able to produce a considerable but an unknown percentage of clinical tuberculosis during both childhood and adult life. An adequate program of prevention of tuberculosis must recognize childhood as a time when infection occurs very generally and institute protective measures against contact with persons suffering from open tuberculosis and against the use of raw milk from dairy cattle infected with tuberculosis. It is best to use only milk from tuberculin-tested cattle, but where this cannot be had pasturized milk may be used.

The danger of infection is the greater the more intimate the contact. This danger manifests itself in a greater proportion of early infections in children who associate intimately with open tuberculosis, as will be seen by comparing the percentage columns in Table V from Fishberg[13]; and also in infections produced by larger numbers of bacilli, both of which conditions increase the likelihood of the child at once or later developing an active clinical tuberculosis.

RESULTS OF EARLY CHILDHOOD INFECTION

When a child first becomes infected with tubercle bacilli, a very important chain of events ensues.

TABLE V—(Fishberg)

PERCENTAGE GIVING POSITIVE REACTION

Age	Children of Tuberculous Parents		Children of Non-Tuberculous Parents	
	Number of Cases	Per Cent	Number of Cases	Per Cent
Under 1 year....	33	15.15	56	10.07
1 to 2 years.....	49	55.10	39	33.33
3 to 4 years.....	90	68.88	80	41.25
5 to 6 years.....	95	65.26	106	50.00
7 to 10 years....	244	71.31	173	64.74
11 to 14 years...	181	74.58	134	69.40
14 years.....	37	83.79	20	75.00
Total.....	729		608	

The bacilli become enmeshed in the body cells which proliferate and attempt by mechanical means to surround them and wall them off, the same as they would in case of other particles of foreign material.

This purely mechanical action, however, does not last long for both bacilli and body cells are living, and vital action comes into play. The bacilli attempt to make conditions congenial to them and favorable for their growth and multiplication. The cells, on the other hand, attempt to destroy the invading bacilli. In order to do this they develop an entirely new property which they had not possessed until they came in contact with bacilli and bacillary products. This is the property of minimizing the activity of, preventing the spread of, and destroying bacilli.

This property constitutes the mechanism of immunity. It is not constant but increases each time that an infection or spread of infection is overcome.

It increases as clinical tuberculosis advances, even though the patient may eventually succumb to the disease. This is evident from the fact that, while a few bacilli will infect an individual who has not previously been infected, a patient with advanced tuberculosis will cast off millions of bacilli from the ulcerated surfaces in the lungs which will pass over the bronchial surfaces without implantation occurring. It decreases during certain infections, such as measles and influenza and also under various stresses of life.

The nature of this immunity is still somewhat obscure. The fact that not only the cells surrounding the tubercle but all cells of the body develop specific immunizing properties shows that the products of the bacillus which stimulate this property gain access to the cells through the circulation.

Of possible properties conferred upon the cells which belong to the immunizing response two stand out very prominently. First of these is the property of producing substances which destroy the bacilli. This is evident from the fact observed particularly after inoculating a tuberculous animal intraperitoneally with bacilli. In a very few minutes the bacilli are degenerated and only a few of them are to be found, suggesting that a destructive action has occurred. The second property is that of reacting with an inflammatory process wherever bacilli are found imbedded in the tissues.

Evidence of the development of a specific immunizing mechanism is shown in the decrease in percentage of mortality and increase in chronicity which follows the advances in age periods, as illustrated in Tables VI and VII from Hamburger[14].

TABLE VI (Hamburger)

MORTALITY OF TUBERCULOUS BY AGE PERIODS

	I			II	III	IV	V	VI
	1 Year							
	0 to 3 months	4 to 6 months	7 to 12 months	2 years	3 to 4 years	5 to 6 years	7 to 10 years	11 to 14 years
Number of cases.....	4	49 13	32	74	102	38	41	31
Fatal cases.....	4	44 13	27	51	69	23	28	16
Percentage of fatality.....	100%	90 100%	80%	70%	67%	60%	68%	50%

TABLE VII (Hamburger)

FREQUENCY OF HEALED TUBERCULOSIS BY AGE PERIODS

	1 Year	2 Years	3 to 4 Years	5 to 6 Years	7 to 10 Years	11 to 14 Years
Total number of cases	49	74	102	38	41	31
Number with signs of healing	0	0	7	4	7	10
Percentage showing healing	0	0	7	10	17	33

Chronicity begins to show markedly in the late years of childhood and after the age of fifteen nearly all clinical tuberculosis is of the chronic type.

It is now generally believed that nearly all clinical tuberculosis met in the adult years of life is due to metastatic implantation from childhood infections. While infections from without are not wholly denied, yet it is difficult to persuade oneself that an allergic reaction which will prevent bacilli from entering the bronchial mucous membrane of a patient with advanced tuberculosis would be unable to ward off bacilli coming in contact with the tissues via the air passages. And it seems almost inconceivable for bacilli to gain access to the lung through other portals of entry, such as the intestinal tract, in the presence of allergy. Infection could take place with comparative ease, however, at times when allergy is temporarily in abeyance.

The important results of childhood infection, then, are two: (1) the development of a specific immunizing mechanism; (2) the establishment of areas of infection, from which bacilli escape to form metastases which may result in future clinical tuberculosis.

HOW PREVENT CLINICAL TUBERCULOSIS

The younger the child when infection occurs the less its chance of overcoming it. Therefore, it is especially desirable to shield children from infection during infancy and early childhood.

All else being equal, infections with large numbers of bacilli are more difficult to overcome than infections with few. Therefore, it is essential to

shield children from intimate association with those suffering from open tuberculosis and also protect them from the use of infected milk.

When infection has once occurred, the possibility of activation with metastasis should be borne in mind. The picture which represents these early spreads of infection should be familiar to all who have care of children. From the time of the primary focus to the development of definite symptoms the chances are that several or many small foci of infection are overcome. If the metastasis is not caused by too many bacilli, or if too many foci do not develop at one time, there is little or no danger; a heightening of immunity only results. But, on the other hand, if a large focus or several foci become established, then clinical symptoms may appear. Whenever tuberculosis is so marked as to make its presence known by symptoms, the individual needs special care if he is to overcome it.

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