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EPIDEMIOLOGY OF REINOCULATION TUBERCULOSIS

The Epidemiological Importance of the Course of Bacilli and the Route of Invasion in the Reinoculation Types of Pulmonary Tuberculosis

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In the fight against tuberculosis we have now come to the place where accurate knowledge is more necessary than ever before. The gross measures for prevention which were adopted when every seventh man was dying of the disease were those which were evident to even the casual student, so they were early inaugurated; but the the degree of importance to be ascribed to individual factors now, when the death rate is less than one-fourth as great, is not so clear. However, the knowledge and experience gained in the past sixty years should aid us in determining where greatest stress should be laid.

The intensive study of specific resistance has furnished much valuable information which is necessary to the understanding of tuberculosis, information which may now be used in formulating a more efficient program for its prevention and cure.

To obtain a clear idea of tuberculosis we must understand that the histologic tissue reactions in the foci of disease are partly the specific phenomena associated with the body's protection against bacilli—the complete mechanism being a combination of cellular and humoral elements. The more we study the immunity reaction the better will we understand the various phases of tuberculosis —primary infection and reinoculation, with their varying pathological and immunological reactions; clinical tuberculosis with its varying disturbances in the patient's physiological reactions; and the curative and hostile factors which determine the outcome of the disease.

Physicians have too generally accepted incomplete knowledge of the route of invasion and the source of bacilli of reinfection as though it were final. It is necessary to remember that once infected the host thereafter lives in varying degrees of equilibrium with the bacilli lying within his tissues.

If it were possible to clarify our ideas regarding the action and degree of competency and permanency of the various phases of specific resistance (immunity), we would be on advanced ground for solving the problems associated with reinoculation; for, upon our opinion of this phase of the subject will we base or modify our belief in the relative importance of endogenous and exogenous sources of reinfection; and, accordingly, will we determine what we deem to be the best program for preventing clinical tuberculosis.

FIRST INFECTION VERSUS DISEASE

The source of the bacilli which cause primary infection is nearly always some other human-being who is suffering from open tuberculosis. We still must recognize the possibility of some infection coming from tuberculous cattle but

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in this country the amount is a small and diminishing one. On the other hand, no matter how desirable it is to know, we cannot say with certainty how often the bacilli of reinoculation are from an exogenous and how often from an endogenous source; while bacilli may infect the environment in which many people live, living bacilli may also lie for years in the body of an infected host, in an inactive state, nevertheless capable of taking on activity when the tissues in which they are embedded become favorable to their multiplication and growth. An incompletely healed clinical disease is apt to show repeated reactivations. Even well encapsulated bacilli may now and then become temporarily or continuously active.

During the time between Koch's announcement of the difference in the tissue reactions of a primary infection and a reinoculation, upon which he based the specific therapeutic and diagnostic value of subcutaneous injections of tuberculin, and the discovery of the various local tuberculin tests and the effect of the primary complex upon further implantation of bacilli, much thought was given by clinicians and much experimentation was carried on in laboratories for the purpose of gaining information which would aid in devising effective measures against the disease. Some of this work was erroneous because it was based on the belief that all tuberculosis is of clinical importance.

During this period it was not known that primary infection may take place years before disease is established and that it may be the only evidence of tuberculosis that an individual may ever show. Nor was it known that primary infection is benign, especially in children, and usually limited to the point of implantation and the lymph nodes draining the area, while clinical tuberculosis is a spreading infection due to a series of reinoculations. Yet, when the evidence came to be examined, it could clearly be seen in animal experimentation that first infection changes the tissues and makes them more resistant and causes the defense reaction of the host to be more energetic. There seems to be no satisfactory explanation for the suggestion that what is supposed to be primary inoculation in the adult may frequently extend at once and become a clinical disease. Why should it differ from primary infection in childhood?

After establishing the fact of the cutaneous reaction it was soon learned that those harboring a primary focus in any phase from an infection of a few weeks' standing to a lesion which had undergone calcification may have the reaction of their cells so changed that any of their tissues when again contacted by bacilli —dead or living— or tuberculin, may respond with inflammation. This discovery was unexpected. It was revolutionary. It called for explanation. Koch's experiments had provided the basis for an explanation, but students of tuberculosis had failed to recognize it. After we had the facts which proved that all who are infected do not have active disease, we were soon to find out by the presence of calcified and partially calcified primary nodes that many individuals suffering from clinical tuberculosis had previously had a primary infection which had modified the course of later inoculations, causing them to assume inflammatory characteristics and aspects of chronicity. The same chronicity was found in case of reinoculation in animal experimentation.

HOW MANY BACILLI WILL INFECT?

Speculation has been engaged in as to how many bacilli are necessary to cause infection. This query is of epidemiological as well as academic interest, but cannot be answered with accuracy. It naturally must vary under different circumstances. Krause was probably correct in stating that one bacillus advantageously placed under extra favorable conditions might infect. But it is probable that such extra favorable conditions are rarely, if ever, present in natural infection.

J. E. Pottenger infected 40 per cent of a group of guinea pigs by 3 ± bacilli isolated from cases of active tuberculosis injected intraperitoneally.

But there is a vast difference between experimental and natural infection, and between infection in a guinea pig and man. In natural infection bacilli which are discharged from the body of one tuberculous patient are injured in various degrees by environmental forces before they enter the tissues of a new host. Then, too, they are not placed directly in the tissues but must run the gauntlet of all the physical, chemical and physiological forces which naturally protect the host from invasion. Furthermore, the guinea pig is known to be very susceptible to tuberculosis. That man's natural protective forces are fairly competent to protect him may be judged by the fact that in past centuries when the bacillus was unknown and no precautions were taken, and when in the environment occupied by tuberculous patients conditions favoring infection were always present, the mortality rate of tuberculosis was fairly constant and even began to decline with improvement in the lot of the workers long before specific precautionary measures were taken. No better assurance can be had that most bacilli which are discharged by patients are destroyed either before or after entering the host; for usually they fail to cause disease. With our present program of earlier diagnosis, isolation of the patient, hygienic care and sanitary disposal of sputum, the chances of bacilli in adequate numbers entering the body from an exogenous source and finding lodgment in the tissues under conditions favorable to growth and multiplication are undoubtedly infinitely smaller than in the past—and these ever diminishing. This should encourage us but not cause us to relax in our precautionary measures. The fact that our program renders the environment in which children live comparatively free from bacilli is shown by the fact that less than one-third of school children now are infected as determined by the tuberculin test, while forty years ago nearly all reacted.

What would be a sufficient number of bacilli to cause primary infection probably would rarely be sufficient to infect an immune host. As proof of the fact that the tissues of an immune host resist bacillary invasion it is only necessary to cite the fact that in far advanced tuberculosis millions of bacilli may pass over the bronchial mucous membranes daily for long periods of time not only without implantation taking place but with healing of the lesion occurring. As the total amount of tuberculosis in the population is now decreasing and the association of the people with the disease is becoming less intimate, and the degree of racial resistance which now exerts a protective influence upon civilized

peoples lessens, susceptibility to infection may increase, thus overcoming some of the advantage gained by reducing the numbers of bacilli in the environment. Then primary infection may become common in adults. It will be interesting to see if it will follow a benign course.

While we may not know the number of bacilli necessary to cause either a primary infection or a reinoculation, it is in accordance with our knowledge that larger numbers of bacilli, or more virulent bacilli, or conditions more favorable to the bacilli must be present for reinfection than for a primary infection. The importance of this from the epidemiological standpoint will readily be appreciated.

Regardless of the specific protection that may be established by previous infection, it is important to remember that both primary infection and each reinoculation establish foci within the body from which bacilli may spread to cause new metastases. This possibility exists even though the lesions become apparently healed.

ROUTE OF INVASION

The source of the bacilli and the route of invasion are of prime importance in epidemiology. The aerogenous route presupposes that bacilli enter the body via the air passages through droplets of sputum or dust; and, entering with the currents of air, pass directly into the lungs. The fact that the lung is the chief organ affected is given in support of this theory. But this is not conclusive, for, if this is the chief manner in which infection occurs, it is necessary to assume that bacilli enter the pulmonary tissues more or less readily and that they may localize anywhere that they make contact. This might be true in primary invasion and not in reinoculation.

To establish the aerogenous route in primary infection it is necessary to explain how the focus may be situated in any part of the lung with probably a slight preponderance in the upper half, while the more forceful currents of air enter the lower portions of the lung; and, in reinoculation, how the apical and subapical areas are usually involved when localization in these areas is directly opposed by the intrabronchial forces.

To establish first infection through the nasopharyngeal and gastrointestinal route, on the other hand, it must be shown how bacilli so entering may find their way to the pulmonary tissues. Adherents to this theory point out that bacilli which enter the nasal or oral passages in droplets of sputum, or as dust, immediately come in contact with the moist surfaces of the nasal and pharyngeal mucous membranes and that the natural course would be for them to be precipitated upon the surfaces and either pass directly through the walls into lymph spaces or be swallowed. The mechanism of digestion might be one of great protection to the individual.

Infection through the mucous membrane of the nasopharynx was not uncommonly seen as apparently a primary infection in children whose cervical lymph nodes so frequently suppurated in the days when the environment of tuberculous patients was grossly contaminated and when infected milk was commonly used.

Even to-day tonsils and lymph nodes may frequently show mild infection if examined microscopically. The rationale for diagnostic gastric lavage is based on the tendency to swallow sputum in case the quantity is small. Bacilli entering the digestive tract, whether with food or from soiled fingers and utensils, in case they escape the protective action of digestion, may be absorbed along with fats by the lacteals and reach the lung through the thoracic duct, the venous system, the right heart and the branches of the pulmonary artery. When entering through the nasopharyngeal walls, particularly in first infection, they may either be detained in local lymph nodes or pass through these barriers and enter the lungs by the lymph stream and venous blood, and be screened out in any portion of the lung, but especially where the vessels are narrowed.

What we believe regarding the source and route of the bacilli of reinoculation is another thing. It must be modified by our opinion of the degree of specific protection which is aroused in the host by previous infection and the influence which other factors, particularly those of a mechanical nature, may have upon implantation. That bacilli frequently escape into the blood stream from established foci in an immune host and provide the conditions necessary for metastatic invasion is generally recognized.

Certain mechanical factors favor implantation, especially in case of reinoculation. Of these, flattening of the apices as compared with the middle and lower portions of the lung, the direction of the air current and the difference in respiratory movement must be considered. At birth the upper ribs are horizontal and the chest is barrel-shaped, but when the child has assumed the erect posture, after about the third year of age, the sternum and anterior end of the ribs sink downward, compressing and flattening the apices anteroposteriorly, lessening the respiratory movement compressing the tissues and narrowing the lymph spaces and blood vessels. This brings about conditions which facilitate the lodgment of bacilli which may course in the blood stream in these parts. While it is probable that most bacilli which enter the blood stream of an immune host are destroyed by humoral forces, those which resist destruction, and especially clumps of bacilli, might be easily detained in narrowed vessels, especially if assisted by a local inflammatory reaction caused by their contact with hypersensitive cells.

DISCUSSION

My conception of clinical tuberculosis is that it is a disease accompanied by repeated episodes of metastasis and body reaction, each of which, theoretically, according to its relative severity, strengthens or weakens the host's resistance. New infection is prevented or accomplished, and the patient cures or kills himself, according to the sum total of the effects of the multiple invasions.

While it is accepted that bacilli causing reinoculations may come either from without or from within, too many are inclined to base the measures for prevention on the assumption that they come from without and in point of time gain entrance shortly before the disease is discovered. In my experience in history-taking I find that comparatively few patients give a history of known contact

with open cases of tuberculosis, either immediately or even remotely, prior to developing active disease. However, a large percentage give evidence of previous infection either in the form of Ghon's nodes, a history of reaction to tuberculin, or some limited form of the disease, such as perirectal abscess, pleurisy or a mild pulmonary lesion which had shown limited tendency to extend. Any one of these foci could furnish the bacilli for metastatic spread.

Regardless of some degree of immunity being present this increased protection might be negatived or at least partially overcome by the more favorable position of the bacilli of reinfection when coming from foci already established within the body. Metastases may take place by bacilli passing from existing foci into contiguous tissue, by being transmitted through the blood and lymph streams or via the natural channels.

The important question to be answered is, how can viable bacilli lying within the tissues become mobilized and how frequently does this occur? That this can occur may be stated unequivocally. How often it occurs we do not know but the conditions for spread may appear at any time as long as viable bacilli are present in the tissues. We (1) have observed many patients for years after discharge from the sanatorium, examining their sputum at intervals using a sensitive technique, and it is surprising to find that ex-patients may be clinically well, showing no demonstrable signs of disease and capable of carrying on their usual work, and still now and then discharge small numbers of bacilli into the bronchi, and probably also into the blood stream had we efficient methods for detecting them. Doubtless this same thing occurs in patients who give a history of having overcome an active disease in the past; also in many who had active lesions without knowledge of their presence. Under extraordinary circumstances we find reactivation in individuals who have recovered from an active disease ten, twenty and thirty years before, and who have lived normal lives in the meantime.

The fact that foci are already within the body and not infrequently within the walls of blood vessels from which they may readily pass into the lumen, and in the pulmonary tissues from which they may readily escape into the air spaces and bronchi when the focal architecture is disturbed from any cause, makes endogenous reinoculation comparatively simple. Endogenous invasion may be precipitated by any factor which will cause increased permeability of the perifocal tissues. This may be caused by other respiratory infections such as measles, whooping-cough, influenza and bronchitis. Diabetes, silicosis and substances irritating to the foci may be responsible for mobilizing bacilli and producing spread, particularly if conditions favorable to the parasite are present. In this, malnutrition, overwork and any prolonged strain producing chronic impairment of health may be readily accepted as disturbing factors. Sudden and marked weather and seasonal changes may do the same by calling out a marked stimulation in and around foci of infection as evidenced by the increase in numbers of cases of active tuberculosis and deaths which occur in the spring and fall as compared with other seasons of the year.

It seems reasonable to assume that the mild proliferative lesions which are so often found at or near the apex of the lung of patients who have previously had a

primary infection in some portion of the body might easily have been established by bacilli, comparatively few in numbers, entering the blood stream from existing foci, escaping the protective forces of the blood, and meeting in the apical tissues conditions usually favorable to their local detention.

Considering these various factors we might with profit reëxamine the premises on which we are basing our present conception of both the route of invasion and the source of bacilli of reinvasion. One hesitates to disturb accepted ideas but, at times, progress can be made only by so doing.

In making plans for the final assault against tuberculosis, these simple problems will loom higher than they have in the past. To establish the exogenous source of reinfection by the aerogenous route, it is necessary to assume that the numbers of invading bacilli are fairly large. Bearing upon the numbers of bacilli contained in droplets which are scattered in coughing, sneezing and talking, it has been shown that only the smaller ones remain suspended in the air for any length of time, while the larger ones, which presumably carry more bacilli, quickly fall to the floor. Moreover, the exogenous source makes it necessary to assume that previous infection establishes either no resistance to the bacilli entering the tissues or an inefficient one; or that reinfection usually takes place when, for some reason, the resistance of the host is low. Then, too, the fact that reinoculation foci are located differently from those of first invasion must be explained. In Ghon's study, the localization of primary single lung foci show no marked predilection for any portion of the lung. On the contrary, early lesions of the reinoculation type are found in the overwhelming majority of instances in the upper part of the lung.

In reinoculations implantation could take place by the haematogenous route whenever the bacilli come from a focus already within the body or from without through the digestive tract. In both instances, except in early life, localization in the superior portions of the lung is favored by the relatively compressed apical tissues. In both instances, too, the likelihood of bacilli causing new foci is undoubtedly reduced and often overcome by the heightened protective forces of the body called into action by previous infection. Doubtless there are many instances of bacilli attempting invasion to each infection which occurs.

To account for reinoculation of the apical areas by the aerogenous route, the resistance of the tissues to invasion must be taken into account; and whereas compression of the tissues, especially the vessels, might favor haematogenous spread, compression of the air passages might interfere with bacilli reaching these areas through the bronchi. At least the bacilli should not show a predilection for the apices for the direction of the main current is toward the bases. This fact is cited as an explanation of the difference in localization of pneumonia and tuberculosis. Even the newly studied virus pneumonias seem to show a preference for the nonapical portions of the lung. But we must not lose sight of the fact that the bacilli of aerogenous origin would escape the hostile immune factors in the blood stream and be opposed only by those of the tissues themselves, so smaller numbers of bacilli entering the air passages might be capacle of establishing new foci.

That man does not readily develop clinical tuberculosis on contact, no matter by what route the bacilli enter, is proved, as previously mentioned, by the history of the past. But that he lives during a great proportion of his life in a biological equilibrium with bacilli in his tissues is also evident. This must be evident from the aforementioned facts that with millions of people suffering from active tuberculosis throughout the ages and often living in closed rooms, shunning the open air and sunshine and expectorating promiscuously, the morbidity and mortality remained fairly stable; and that, when the tuberculin test was first put into general use in large groups of the population, it was shown that nearly all people in the cities, and a somewhat smaller number in the country, were infected by the time they attained the age of fifteen years; yet, the proportion which developed active disease was relatively small. Throughout the ages and until recently, the amount of disease among the people remained about the same —one active case replaced each death. We may therefore justifiably assume that limited early infections have protective value. The active measures taken in the past sixty years, in spite of their inefficiency, have reduced the disease by three-fourths, and infection apparently in greater proportion. This promises well for continued success in our program of prevention; yet, reasoning biologically, we must expect the people to lose part of their immunological protection as the disease becomes less prevalent, and primary infection will probably become more common in adolescent and early adult life.

Whether bacilli enter the lung directly by way of the air passages or indirectly through the nasal and oral mucous membranes and the gastrointestinal canal in causing primary infection is of comparatively little epidemiological consequence, for the source of bacilli is the same in either case; but in the reinoculation type of the disease, to know whether the bacilli are of endogenous or exogenous origin is of the greatest importance.

It is rational to believe that both sources may be responsible for infection, but could it be definitely known that most instances of active disease are due to direct contact with active open cases of tuberculosis, our course would be clear. We should spend most of our effort on isolation of the patient and sanitation. The program which we employ to prevent first infection would be ample to prevent reinoculation.

On the other hand, should the chief or a consequential source of bacilli responsible for reinoculation be the foci which are already within the body, then we should, aside from the precautionary measures used to prevent infection in the environment, exert a further effort to secure healing of every infection and to keep the infected individual in a highly resistant state so that his protective mechanism will afford him greatest protection against his own bacilli. To this end, all measures which improve physiological resistance are applicable and should be especially applied to those who have had tuberculosis of clinical importance. Better hygiene, better nutrition, emotional stability and less physical depression should be especially helpful.

Immunity or specific resistance is a labile mechanism. When active, it undoubtedly is competent to ward off or modify the action of many bacilli.

When lowered or in abeyance, it puts the individual exposed to reinfection in a condition approaching that in which he was prior to first infection.

Most of the tuberculous patients who seek medical aid to-day have had many reinoculations with many resultant foci of varying degrees of severity. This makes our problem difficult, for the best that we clinicians can do in a short course of treatment in such a chronic disease is to secure a truce between the patient and his bacilli, a truce which may be broken on either side: by the bacilli in case their environment at any time becomes congenial for their growth and multiplication; by the patient in case he can increase his resistance sufficiently, maintain it continuously at a high level, and thus prevent the bacilli from producing further activity.

Here is where we are making one of our most abject failures in treating tuberculosis. Both physicians and patients are prone to lose interest; or, for other reasons, treatment is often interrupted before healing has been attained. By relaxing measures necessary to complete healing, the patient's defensive powers are allowed to lower, the tissues lose their resistance and new activity starts. Thus are caused the many relapses which plague us and make us almost lose confidence in therapeutic measures. A little longer treatment and a great deal longer extension of the careful life after treatment has been finished, and a full rehabilitation of the patient before he is discharged from observation, and many of the reactivations which we speak of as "breakdowns" would be avoided and many sources of infection would be permanently instead of temporarily elminated.

SUMMARY

1. Now that the morbidity and mortality of tuberculosis are rapidly declining, accuracy in our information regarding infection becomes ever more important.

2. Bacilli entering the tissues for the first time are opposed only by the body's natural physiological defense reactions. Bacilli of reinoculation are opposed not only by these normal processes but by an exaggerated physiological mechanism which we recognize as specific defense or immunity. This is an important fact epidemiologically because it makes reinfection more difficult and the resultant disease more chronic.

3. Our methods of prevention are based upon our opinion as to how the lung becomes infected—the source of the bacilli and the route by which they reach their destination. While bacilli responsible for primary infection must come from an exogenous source, it is not so certain that bacilli causing reinoculation are of the same source. Metastases of endogenous origin seem to be a reasonable explanation of most of the disease that we meet clinically.

4. If the chief source of bacilli responsible for reinoculation is exogenous, then our protective measures must be directed mainly toward preventing the scattering of bacilli in the patient's environment, the same as in case of primary infection. If, on the other hand, the chief source, or any great amount of reinoculation is of endogenous origin, we should not only direct our attention to bacilli which are discharged by patients, but also or even more to the bacilli lying within

the tissues of the individual who has been infected; because so long as there are viable bacilli in the tissues there is a possibility of their reactivation and forming new metastases.

5. The endogenous source of reinoculation calls for more thorough treatment, rehabilitation and more adequate after-care of the tuberculous patient.

SUMARIO

1. Hoy día en que van en rápido descenso la morbidad y la mortalidad de la tuberculosis, se vuelve más importante que nunca contar con datos exactos acerca de la infección.

2. Los bacilos que penetran por primera vez en los tejidos son resistidos únicamente por las reacciones de defensa fisiológica naturales del organismo. Cuando tiene lugar la reinoculación, los bacilos son combatidos no tan sólo por esos procesos normales sino por un mecanismo fisiológico exagerado al que damos el nombre de defensa específica o inmunidad, lo cual constituye un punto importante desde el punto de vista de la epidemiología dado que dificulta más la reinfección y convierte en más crónica la lesión resultante.

3. Nuestros métodos profilácticos están basados en nuestra opinión en cuanto a la manera en que se infecta el pulmón: la procedencia de los bacilos y la vía por la cual llegan a su destino. Aún los bacilos causantes de la infección primaria deben reconocer una procedencia exógena; no es tan seguro que procedan del mismo foco los que ocasionan la reinoculación Las metástasis endógenas parecen ofrecer una explicación lógica de la mayor parte de la enfermedad clínica que encontramos.

4. Si el principal foco de bacilos causantes de la reinoculación es exógeno debemos entonces encaminar nuestras providencias protectoras, principalmente, en el sentido de impedir la dispersión de bacilos en el medio ambiente del enfermo, lo mismo que hacemos en la infección primaria. En cambio, si el foco principal o una gran proporción de la reinoculación son endógenos, debemos no tan sólo fijar nuestra atención en los bacilos expulsados por los enfermos, sino también y hasta más, en los bacilos que restan en los tejidos del individuo infectado, porque en tanto que haya gérmenes viables en los tejidos es posible que se reactiven y formen nuevas metástasis.

5. El foco endógeno de reinoculación exige un tratamiento más completo, reabilitación y asistencia post-sanatorial mas adecuada del tuberculoso.

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