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THE RARE BACILLUS STAGE

For the past thirty years at the Pottenger Sanatorium the dilution-flotation-picric-acid technique (1) has been employed for the examination of sputum.

By examining three day specimens every six weeks, it has not been possible to demonstrate an absence of bacilli for three consecutive examinations in more than four or five per cent of the patients at the time of discharge from the sanatorium. In contrast, many institutions report sputum conversion in fifty per cent or more. Although most of our patients have far advanced tuberculosis, we also have had many who had earlier lesions. Many of these on entering had been classed as having negative sputum, some after many examinations. After admission to the sanatorium, however, examination of the sputum revealed the presence of tubercle bacilli in nearly all of this group.

When these patients with "rare bacilli" are discharged they are physically well and able to walk from one to four or five miles a day. They rarely cough. It is often only with the greatest persistence that specimens of sputum are obtained.

In order to determine the epidemiological significance of "rare bacilli", a comparison might be made between the "rare bacillus" stage and the situation when these patients are expectorating bacilli freely. The Phipps Institute (2) reports on 158 twenty-four-hour specimens from 37 patients. The average twenty-four-hour output of bacilli for white patients was 129,593,000; for Negro patients 894,000,000. The highest count was 20,499,918,000. J. E. Pottenger (3) studied a patient's output of bacilli for several days. The counts were 128, 130, 133, 83, 98, and 131 million. Another patient's count was 30 billion.

In table 1 may be seen the results of bacillary counts of the sputum made at six week intervals in patients now in the sanatorium. The first six have attained the "rare bacillus" stage; the last two are wholly in the acute stage. The figures indicate the number of bacilli expectorated in twenty-four hours. The first six cases were steadily improving, but it will be noted that the decline in numbers of bacilli was not steady. Patients E. T. G., S. D., and J. S. all had cavities which were healing spontaneously. Patients S. A., P. O., and A. H. were minimal cases in whom tubercle bacilli had not previously been found.

J. E. Pottenger (4) made careful comparison of the dilution-flotation-picric-acid and the Ziehl-Neelsen techniques for the examination for tubercle bacilli and found the former 277 times more sensitive in purulent sputum, and 172 times more sensitive in "muco-epithelial" sputum. This sensitive technique may reveal tubercle bacilli when the patient expectorates only a few hundred or a thousand bacilli a day.

[1] Presented before the Epidemiology Section of the American Public Health Association, Atlantic City, October 6, 1947.

[2] Monrovia, California.

How dangerous is sputum which contains a few hundred or a few thousand bacilli in a twenty-four-hour quantity? Frankly, no one knows because conditions differ so greatly, but surely it can not be very dangerous. If the patient knows he has, or has had, tuberculosis, as a rule the sputum is destroyed. In fact, when the sputum decreases to a very small amount it is often swallowed unknown to the patient. If a few hundred or a few thousand bacilli should be expectorated into a room, however, they would be diluted by the air which, if the room is well ventilated, is constantly changing, so the danger would be minimal. Under ordinary conditions of light and ventilation in the average house, most bacilli would be killed in a few hours. It must be admitted, however, that there might be danger in overcrowded, poorly ventilated houses, particularly those occupied by the undernourished.

TABLE 1

Daily output of tubercle bacilli in sputum of patients with pulmonary tuberculosis

	PATIENTS	
1	E. T. G.	3,900,000,000—1,500,000—3,000,000—50,000,000—21,000—500,000—9,300—9,340,000—1,200,000—3,266—0—0—875—892—0—0—0.
2	S. A.	825—0—0—0—586—0—0—0—14,700—0.
3	S. D.	1,700,000—10,600,000—4,200,000—9,250—16,800—12,000,000—40,385—64,100—38,500—3,260—112,700.
4	P. O.	11 days, 0—1,458—13,416—0—13,880—0.
5	J. S.	2,800,000—5,100,000—2,000,000—46,000,000—2,340—5,540—1,106—0—0.
6	A. H.	0—3,266—0—0—0—0—4,375—0—0—0—0.
7	L. G.	80,000,000—5,000,000—47,000—171,000,000—137,000,000—95,000,000.
8	G. H.	190,000,000—267,000,000—64,000,000—385,000,000—240,000,000—7,800,000,000.

According to the studies at the Pottenger Sanatorium, it is doubtful whether patients with chronic destructive lesions ever become wholly and continuously free from the discharge of tubercle bacilli under all of the vicissitudes of life; yet they may be able to carry on their work unhampered. Many ex-patients have been followed from five to forty years and it has been found that now and then, particularly following acute respiratory infections, they will cast off a few tubercle bacilli as a result of the stimulation of their old foci. These patients usually become noninfectious soon after recovery from the acute respiratory infection without reactivation of their tuberculous disease and without causing disease in others (5). It is not the controlled patient, but the one who is not cognizant of his disease or the careless one, who is most dangerous to himself and to others.

Our experience is similar to that of Papworth Village (6) in England, which indicates that it takes more than the expectorating of bacilli to cause infection. The report of twenty-five years' experience shows that, of 108 children born in

Papworth Village, not one has developed active tuberculosis, nor has radiologic examination revealed an incidence of pulmonary abnormalities any higher than that found in the general population. Nevertheless, 90 of Papworth's 120 patients suffered from "open" tuberculosis. Of 260 children born before admission to the Village (in the usual city workman's environment), 5.1 per cent had some type of active tuberculosis. These had lived outside the Village in the environment of "open" tuberculosis. Of these children, 8 were over 10 years of age on entering the Village. It is significant that no new cases of active disease developed among them after entering the Village.

This shows the protective value of the control of patients living in a controlled environment, for it must be remembered that all of these children had hereditary susceptibility and many were living in an environment of "open" tuberculosis. Are we to conclude that infection and reinfection can be partly, possibly largely, prevented by living hygienically even in an infected environment? If so, where is the danger line? This is of greater importance than the simple fact of the presence of tubercle bacilli. May this not be interpreted that "rare bacilli" in controlled patients living in a controlled environment are of little danger?

HOW MANY BACILLI WILL INFECT?

The number of bacilli that will cause infection varies according to their virulence and the susceptibility and environment of the host. It is likely that many attempts at invasion are made before infection occurs, especially in hosts of low susceptibility. The important fact is that under conditions which exist many infections do occur. But more important is the fact that there are fewer instances of disease than of infection. This might indicate that the patient protects himself through primary infection.

The host is protected by monocytes and polymorphonuclear leucocytes which engulf and destroy bacilli and conceivably may possess some degree of humoral immunity. The cellular protection is greatly increased in the immune host, making reinfection more difficult, as shown by Lurie (7). Lurie reports that tuberculosis in rabbits removed from an infected environment as soon as sensitization has been acquired pursues the same course as in litter mates which continue in the infected environment.

Whether the bacilli enter the body as dust or droplets is of minor importance. The fact is that bacilli can produce primary infection whenever a sufficient number are able to enter the body, provided they find conditions favorable to growth. Bovine bacilli cause infection by entering otherwise than through the air channels, which is significant. If bovine, why not human? Who knows the portal of entry in chance infection?

EFFECT OF ENVIRONMENT ON BACILLI AND HOST

The infectiousness of bacilli depends largely on the environment in which they are discharged. They do not multiply outside the body, and many are nonvirulent and many are nonviable when discharged. Even virulent bacilli are quickly destroyed by direct sunshine and within a few hours by indirect sun-

light. They live much longer in dark places when protected from drying. Their infectivity is favored by the dead air of nonventilated rooms and is very much reduced by moving currents of air.

In spite of the danger of infection in massively contaminated environments, those living therein do not all die of tuberculosis. Most of them are infected but do not develop clinical disease. This is a most significant fact in our program of prevention. It should be stressed, for it is the basis of protective vaccination. Throughout the ages not only were precautions rarely taken, but conditions of the premises were most favorable for the bacillus. Nevertheless, only about one new case developed regularly to each death and, wherever the social and economic status of the people improved, the number of deaths decreased. *Immunity and low susceptibility were a little more effective than the bacilli of reinfection.*

Children are most susceptible and are prone to receive a primary tuberculous infection whenever exposure is prolonged. This carries with it an immunity, however, which provides increased protection. But the danger of metastases from primary infection lies in the fact that tubercle bacilli may remain viable and virulent for years in many of these foci and in metastases which form from them. At any time that the architecture of the encapsulating wall is disturbed either mechanically or chemically, endogenous reinfection may be produced. This shows the necessity of knowing every infected child and making it the ward, so to speak, of the Health Department. Such children should be re-examined periodically, according to a plan based upon our knowledge of the significance of primary infection.

The grestest danger is always found among the poor, where from five to seven times as many deaths from tuberculosis occur as among families who live on a higher economic and social plane. This means that the poor patient with tuberculosis is a maximum danger to himself and his associates. Moreover his chances of healing are less, for both his environment and possibly his tissues are more favorable to the life of the bacillus. Public health measures, short of an effective vaccination, will not stamp out tuberculosis among the poor until it solves the problems of nutrition and housing; for poor nutrition and unhygienic homes increase susceptibility. Why let infected children go on to reinfection tuberculosis when a few simple rules of hygiene and a quart of milk a day would probably save many of them and save the taxpayers the expense of caring for well-developed cases of tuberculosis subsequently?

SUSCEPTIBILITY

It must not be forgotten that susceptibility is as important as the tubercle bacillus. Regardless of all public health factors with which people are protected, infection still occurs. Furthermore, it occurs whether or not it can be shown that the host associated intimately with "open" tuberculosis. Two-thirds of the clinical cases at the Pottenger Sanatorium give no history of associating with tuberculous patients. The only reasonable interpretation for this fact is that infection depends much upon the patient's susceptibility. Chance infection is undoubtedly caused by a few tubercle bacilli entering the tissues of a highly

susceptible individual. To be sure, infection of one living with a patient who expectorates hundreds of millions of bacilli a day may occur no matter what the susceptibility of the individual. Probably no one is so resistant that he is able under all circumstances to ward off infection. But, on the other hand, the possibility must not be overlooked that primary infection caused by many bacilli may establish a higher degree of immunity than the few bacilli of chance infection. This is indicated by the Lübeck disaster mentioned below. *May primary infection not have been the protective factor which has preserved the human race throughout the ages?* Does not this suggest vaccination as a way of protecting those nonreactors who live with patients who expectorate rare bacilli, as well as those who expectorate many?

How can all these facts be interpreted and what is their public health significance? Puffer's studies (8) have shown that *hereditary* susceptibility, which probably is similar or the same as general susceptibility, makes the host especially prone to infection. In the families which she studied, the same percentage of children of tuberculous parents who had, and who had not, associated with "open" tuberculosis developed clinical disease by the time they attained the age of fifty. The difference between the two groups was that those who were exposed by intimate association became ill in their earlier years, while those casually exposed developed the disease later. This might suggest that, regardless of the fact that those infected by many bacilli may develop a higher grade of immunity than those infected by a few, yet massive infection doubtless causes larger foci. These larger lesions contain larger numbers of bacilli and become less completely encapsulated and, hence, are more susceptible to injury by the vicissitudes of environment, growth, habits and other infections. Consequently, the patient with such a lesion is more apt to break down with clinical tuberculosis, particularly in the earlier years.

During the period between 15 and 25 years of age, the number of cases of clinical tuberculosis takes a rapid rise. This is the period when acute exudative tuberculosis predominates, a type caused by relatively large numbers of bacilli in patients whose cells are highly sensitized. The massive numbers of bacilli which cause this type of disease could well be endogenous in origin, but could hardly come from without. In the experience of the writer, these acute exudative cases are rarely associated with "open" tuberculosis at the time of falling ill. So we must assume, or at least bear in mind, that the source may be the unhealed primary complex, or some metastasis therefrom, whose enveloping walls are subject to injury by both mechanical and chemical factors.

In this connection, it must be remembered that the lung doubles in size from the beginning to the end of puberty. This may be a mechanical factor in reactivating old foci. *Clearly a partly or wholly calcified focus cannot expand and increase in size as the pulmonary and bronchial tissues do. The result might be a weakening or a break in continuity of the encapsulating walls with the escape of bacilli.* Moreover, in this period the tissues must also bear many insults, such as those from malnutrition, unwholesome habits of life, and so forth, just such as will further weaken an already weakened enveloping wall. This is a period of high incidence of clinical tuberculosis, much of it being of the acute exudative

type. The chronic proliferative type, on the other hand, advances slowly, probably because fewer bacilli cause the metastases and gradually immunize and desensitize the patient so that fibrosis predominates over inflammatory processes. This is the predominant form of the disease in later life.

Thus susceptibility seems to be a factor in infection, reinfection, the type of disease, and the outcome of the disease.

VACCINATION AGAINST TUBERCULOSIS

In the future, susceptibility, the protective value of the primary complex, and vaccination, must be given more consideration in providing a program for protecting the people from tuberculosis. Mass roentgenographic studies of the population must be continued, but as susceptibility, both that of a general and hereditary nature, is so important, the finding of those infected will still leave the problem unsolved. Susceptibility must be reduced and preventive vaccination must be generally used among those exposed.

When reinfecting bacilli attempt invasion, the host is able to destroy many more in the case of first invasion. Moreover, if reinfection occurs, it has a tendency to localize and heal, as pointed out by Koch in 1890–1891. Manwaring (9) has shown that, within an hour after tubercle bacilli are injected into the peritoneal cavity of an immune guinea pig, nine-tenths of them have been destroyed. Quite the opposite from the experiment of J. E. Pottenger (10), in which he infected two-thirds of a group of nonimmune experimental pigs by injecting three tubercle bacilli more or less into the peritoneal cavity.

It would seem that the danger to individuals who are protected by a previous infection, either primary or of the reinfection type, in associating with tuberculous patients is negligible, particularly if they are following out the accepted regimen used in treatment. The writer has never recognized an infection transmitted from a patient with active disease to one who was approaching arrestment, although free association of patients in the sanatorium has been observed for more than forty years.

It is possible that the great numbers of bacilli in massively infected environments, by destroying the most susceptible, have kept the tuberculosis mortality high throughout the ages, and by the same process produced a more resistant stock. On the other hand, wherever we have had an improved environment, susceptibility decreased and morbidity and mortality declined.

It must have been decreased susceptibility that reduced the death rate from tuberculosis in England and Wales from 330 per 100,000 population in 1860 to 175 in 1900, for few preventive measures were applied to make the patient's environment safe. In the forty years since 1900, preventive measures have been instituted but, because of war, the decline has been only a little greater than during the years 1860 to 1900, reaching a death rate of 70 per 100,000 in 1936. In Masssachusetts the death rate declined from 444 in 1860 to 254 in 1900, and then, with the institution of preventive measures, the decline, unaffected by war, has been much greater. A death rate of 36 was reached in 1939.

We should develop a more rational attitude toward primary infection. We should show more appreciation of its protective nature. We should likewise appreciate

that it carries with it, unless it heals or remains quiescent, the danger of being the source of endogenous metastases, responsible for much, possibly most, clinical disease.

Were it not for its being the source of acute illness, such as meningitis in small children, and endogenous reinfection later, we might accept it as almost wholly protective. But since it is also a danger, we must, if possible, avoid it.

The use of BCG will stimulate immunity, probably not as efficiently as virulent human bacilli, but sufficiently to protect most children from infection. Moreover, it carries no danger of causing endogenous reinfection. Doubtless vaccination should be repeated the same as in case of smallpox. Vaccination should not take the place of other measures but should supplement them.

For those who have inordinate fear of infection or of protective vaccination, I would suggest the study of the Lübeck disaster, where virulent human bacilli were accidentally substituted for BCG. Two hundred and fifty-two children, before they were ten days old, were each given a total of 1,200,000,000 living human bacilli orally in three doses of 400,000,000. According to general opinion, all should have died; but instead 175 were living and well four years after. All were infected, but 70 per cent had developed sufficient resistance to prevent the spread of the disease.

FUTURE PROGRAM

Aside from all the things we are now doing to prevent infection, let us broaden our views. Let us reduce susceptibility both through vaccination and improvement in environment. An effectual program would consist of: (*1*) mass roentgenographic studies until every individual has received the benefits which it offers; (*2*) clearing the slums in which most of our tuberculosis is found; (*3*) teaching people how to live and what to eat, and furnishing food, at least to children, when the breadwinner is ill, so that resistance is kept high; and (*4*) vaccinating children, thus stimulating their immunity without producing a focus of living human bacilli within the tissues from which the disease may spread and produce endogenous reinfection. *We can not take the patient with "rare bacilli" out of society, but we can make him safe by instruction, and those who associate with him safe by vaccination, hygienic living, and adequate diet.*

SUMMARY

1. The "rare bacillus" stage of tuberculosis, with the discharge of a few hundred or a few thousand bacilli per day, is compared with the acute stage in which millions and even billions of bacilli are discharged per day.

2. There is a question whether patients with chronic destructive lesions would ever become continuously and permanently free from the discharge of bacilli, if techniques for examination were sufficiently sensitive, even though the patients might be clinically well and able to carry on their regular work.

3. As about two-thirds of clinical patients give no history of association with "open" tuberculosis, the individual to be infected must be considered as well as the one who scatters infection.

4. The importance of susceptibility is compared with that of environment in causing illness. Mortality from tuberculosis dropped about 50 per cent between

1860 and 1900 before active measures for protecting against infection were instituted in both England and Wales, and in Massachusetts in this country.

5. Vaccination should be used generally, but especially to protect those highly susceptible, those exposed to "rare bacilli" as well as to massive infection. BCG carries with it no danger of providing an endogenous source of reinfection.

SUMARIO

Significación Sanitaria de la Rareza de Bacilos Tuberculosos en el Esputo

1. Compárase la etapa de "bacilos raros" en la tuberculosis, en la que sólo se expulsan algunos centenares o miles de bacilos diarios, con la etapa aguda, en la que se expulsan millones, y hasta miles de millones, al día.

2. Cabe dudar si los enfermos con lesiones detructoras crónicas jamás cesarán continua y permanentemente de expulsar bacilos, si se emplean técnicas suficientemente de licadas para descubrirlos, aun cuando los sujetos estén estén clínicamente bien y puedan desempeñar sus tareas habituales.

3. Dado que dos terceras partes de los enfermos clínicos no comunican antecedentes de asociación con tuberculosis "abierta," hay que considerar al individuo infectable por igual que al infeccioso.

4. Compárase la importancia patógena de la susceptibilidad con la del ambiente. La mortalidad tuberculosa descendió aproximadamente 50 por ciento entre 1860 y 1900, antes de iniciarse medidas activas de protección contra la infección, tanto en Inglaterra como en Gales y en Massachusetts en Estados Unidos.

5. Debe emplearse generalmente la vacunación, pero más en particular para proteger a los muy susceptibles, a los expuestos a "bacilos raros" así como a infección masiva. BCG no entraña riesgo de aportar un foco endógeno de reinfección.

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