# Asymptomatic Infections in Leprosy'

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This presentation challenges the basic dogma of leprology that only the "open case" is of concern in the spread of leprosy. Evidence from our field studies in India indicates that the leprosy bacillus spreads more widely in an infected community than is generally believed. We have confirmed the much doubted claims of research workers in Bombay that asymptomatic infections do occur in leprosy. We do not yet have proof, however, that these asymptomatic infections are actually responsible for spread to new cases.

Before presenting our preliminary findings we will evaluate relevant epidemiologic considerations that support the hypothesis that a significant portion of the communicability of leprosy in a community depends on the biologically familiar phenomenon of the "carrier state." In this discussion definitions are particularly important because it is true that the acceptance of a term such as carrier immediately brings with it a whole chain of policy decisions, just as acceptance of the term eradication involves a whole other series of policy implications.

Let me quote the definition of "carriers" given in the most recent American Public Health Association Manual—*Control of Communicable Diseases in Man*, edited by

Dr. John Gordon(<sup>21</sup>). "Carrier—A carrier is an infected person who harbors a specific infectious agent in the absence of discernible clinical disease and serves as a potential source of infection for man. The carrier state may occur with infections inapparent throughout their course (commonly known as healthy carriers), and also as a feature of incubation period, convalescence, and post-convalescence of a clinically recognizable disease (commonly known as incubatory and convalescent carriers). Under either circumstance the carrier state may be short or long (temporary or chronic carriers)." Note the statement "discernible clinical disease;" this requires further clarification, which will be brought out in evaluating existing field information. Most significant is the distinction between incubatory carriers, convalescent carriers, and healthy carriers.

When we started epidemiologic research on leprosy with our first NIH grant some eight years ago we quickly decided that significant advances required new tools. It was apparent that the use of previously available technics had been pushed as far as they could go by epidemiologists of the high professional competence of Doull, Guinto, and others. The clinical recognition of cases that can then be categorized by the nonspecific Mitsuda skin test, and confirmed by relatively insensitive methods of finding bacteria, makes it possible to study only the extreme end of the biologic spectrum of leprosy. It is also important to study the larger proportion of individuals with latent undiagnosed or healed infections and try to define the correlates of resistance.

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FIG. 1. Profiles of epidemiologic features relating to transmission of selected bacterial intestinal infections.

## GENERAL EPIDEMIOLOGY

From the point of view of general epidemiology there are two main reasons for challenging the dogma of the "open case": first, the biologic nature of the leprosy infection, and, second, accumulated information about contact patterns.

Discussion of the biologic nature of leprosy is based largely on analogy with other diseases, since we know so little about leprosy itself. Leprologists have tended to become isolated from the mainstream of medical research almost as much as their patients have been isolated from society. There has been too much thinking that leprosy is different from other conditions, with little attempt to apply general biologic theory and epidemiologic principles.

#### **BIOLOGIC PATTERNS**

Figures 1-4 illustrate a schematic application of six major variables that affect epidemiologic patterns and transmissibility to 12 common diseases. Using the APHA Manual, *Control of Communicable Diseases* in  $Man(^{21})$ , as a guide, profiles were drawn for four groups of three diseases as shown in each of the figures. The specific action of each of the six variables is represented along a vertical spectrum. These diseases were deliberately selected to represent transmission cycles directly from man to man rather than introduce more complicated transmission patterns through intermediate hosts.

Figure 1 shows the profiles for three bacterial infections of the intestinal tract. Cholera is (1) acute, and has (2) a short incubation period, (3) a short period of communicability, (4) a moderately high general susceptibility, (5) a moderate number of inapparent infections and (6) a moderate number of carriers. The profiles for shigellosis and typhoid fever also are essentially similar for the last three variables.

Figure 2 shows a similar group of three acute viral infections. The tendency is clear; they are acute and the profile tends to stay low.

Figure 3 shows three bacterial respiratory infections. They are rather acute, with short incubation and communicability periods, but have a tendency to moderately low susceptibility, many inapparent infections, and a moderate number of carriers. The purpose of these figures is to demonstrate



FIG. 2. Profiles of epidemiologic features relating to transmission of selected acute viral diseases.



FIG. 3. Profiles of epidemiologic features relating to transmission of selected bacterial respiratory infections.



FIG. 4. Profiles of epidemiologic features relating to transmission of selected mycobacterial and treponemal diseases.

that there tends to be a general concordance of epidemiologic variables; diseases with a low general susceptibility, and many inapparent infections also tend to have many carriers. Whooping cough is included because it represents the sole exception encountered of a disease with low general susceptibility and many inapparent infections but relatively few carriers.

Figure 4 shows the profiles for syphilis, tuberculosis and leprosy. Of the types of diseases presented these are the most chronic, with the longest incubation and communicability periods. Leprosy is at the end of the known spectrum of each of these scales. We have good reason to think that leprosy is high on the scale of general resistance of the population, with many inapparent infections. When we come to the carrier state, however, we find that the dogma of leprology would have us believe that carriers are essentially nonexistent in leprosy; a much more extreme situation than the exceptional situation mentioned with whooping cough. Tuberculosis and syphilis encounter lower general susceptibility of the population, and probably also produce fewer inapparent infections. Syphilis produces a moderate proportion of asymptomatic carriers, especially among females. The carrier state in tuberculosis depends on definition. There are a moderate number of functional carriers, but not many true healthy carriers. In other words there are grandmothers and school teachers who chronically cough bacilli from a "cigarette cough" or chronic bronchitis. With adequate diagnostic attention their disease is "clinically discernible," but they do not come to the attention of clinicians until they happen to produce an epidemic of tuberculosis converters in a school or family circle. This is essentially the sequence seen in classic typhoid carriers who have chronic mild gall bladder symptoms attributed to indigestion.

With increasing refinement of diagnostic skill, something can be found clinically in many carrier states, but in order to get better public health control it is useful to think of people with clinically undiscerned disease as being functional carriers.

This issue can be further clarified by considering the biologic gradient of the leprosy infection. Figure 5 shows a diagrammatic model describing the normal distribution of a disease in an infected population. The prototype is diphtheria.

		_		Per cent o	ontacts trace	ed as source of	infection
Country & observer	Ref.	Total cases	Endemicity rate	Household	Neighbor or other casual contact	Genetic relationship	Total
India Madras-Cochrane	4		20 + /1000	63	37		100
Punjab-Abraham (1897)	ខ្លួន	118	Low	36		30	36
Bengal-Chatterjee Bengal-Muir (1923)	88		$20 \pm /1000$	52 28	3		58
Bengal-Lowe	88	10,000	2227 / 1 24	50+	P 30		80
Andhra-Christian <i>et al.</i> (1963) Madras-George (1938)	4 20	61,584 163	$\frac{15}{1000}$ 20+/1000				70 55
Philippines	66	000.01		00			00
Cebu-Rodriguez (1938)	8 8	321		48	49		61
Cebu-Doull et al. (1936)	15	104	17/1000	26	12.5		38.5
Cebu-Guinto et al. (1941)	22	208		37			37
Cebu-Guinto et al. (1954)	23	273	18/1000	27.5			27.5
Hawaii McCoy (1938) Chung-Hoon (1950)	<u>о</u> , ЗЗ	1,058 316	Low Low	40	4.5	37	44.5 40
Africa Basutoland-Long	8	181	High				80
Cape Colony-Gregory (1905)	33	568	Low	33			33
South America Brazil-Diniz	11	525	High	39	23		62
Japan Kitasato (1903-08)	33			15	ŝ	п	18

1 .... 000 001 TARE 1 Relation of endemicity to

720

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110

onesia ampe & Boenjamin (1949)	29	612	14/1000	23	46	69
mtacts in nonpatients s control group)		(1169)			(30-close) (10-casual) (27)	(27)
ope Icasus-Karevel	33	100				89
ssia-Dehio (1898) way-Lie & Sands	88		Low	18	14	60 21
.A. as-Bovd & Warren	33					60
iisiana-Badger (1964) as-Kluth (1956)	6 28	395	Low	15 21.1	18 6.4	34 27.5

The vertical axis represents the severity of the percentage distribution of types of response among the total number of people infected. To the right are those who die. Moving to the left are the severe forms of the disease, such as toxic neurologic and mycocardial effects, laryngeal and faucial diphtheria, the carriers, and the big group of those who are infected but heal without recognized symptoms.

The next diagram shows a postulated biologic gradient for leprosy. The data are synthesized from the Nauru experience(<sup>35</sup>), from Lara and Nolasco's reports on leprosy rates in exposed children from Culion(<sup>30</sup>), and a similar study from Hawaii that was found among the unpublished papers of Dr. Lloyd Aycock<sup>(1)</sup>. Obviously the specific proportions vary from population to population, especially the lepromatoustuberculoid ratio, and these figures are deliberately selected to represent maximum prevalence. We know death is infrequent. Lepromatous cases are considered more severe although they range down to clinically undetectable cases. Tuberculoid and other nonlepromatous cases also have a wide range of severity. We have included a possible carrier group on the basis of data we will present, and beyond that the large group who heal asymptomatic infections spontaneously.

#### CONTACT PATTERNS

In the older literature on leprosy there are frequent references to laborious efforts to trace contacts. Following the dogma of transmission from the "open case" it was logical to try to find out where cases of leprosy had acquired their infections. It proved to be a discouraging and timeconsuming proposition.

Table 1 summarizes information gleaned from a cursory review of the literature. A more complete review would disclose many more reports, but the pattern seems clear. Many of these reports are taken directly from a tabulation in Rogers and Muir's text(<sup>33</sup>). The erratic and frustrating nature of the observations led to a series of explanations clearly conditioned by efforts to make the data fit into accepted dogma. Some authors have said that if you work carefully enough and have the confidence



FIG. 5. Biologic gradients of diphtheria and leprosy (result of infections as proportion of total persons infected).

of patients you will be able to trace every case to its contact source. These authors, however, worked where endemicity rates were highest. Surveys made in villages where every healthy person has contact with leprosy logically should produce 100 per cent contact rates. More instructive follow-up can be done where leprosy endemicity is lowest. A more common explanation is that because of the long incubation period, the uncertain latent period, chronicity, a general desire to hide cases, and poor recognition, one should congratulate oneself if he succeeds in tracing a third to half of the cases to their sources. From the table it is clear that 30-40 per cent success in tracing contact sources seems to be a rather consistent finding in low and moderate endemicity areas, the bulk of these being home contacts. Only Lampe and Boenjamin(29) seem to have conducted a survey of the number of contacts with leprosy to whom healthy individuals in their survey area had been exposed. Their figure of 27 per cent reduces the contact rate for their leprosy patients from 69 per cent to 42 per cent.

722

How does this relate then to the dogma of "prolonged and intimate contact with an open case?" There is almost no evidence for the word "prolonged," whatever it means. We have only suggestive evidence for "intimate." And "open cases" will need to be redefined to include the possibility of functional carriers.

There is, of course, no doubt about the infectivity of clinical cases. It has been clearly established that the risk of exposure to lepromatous leprosy is greater than the risk of exposure to nonlepromatous, and the latter carries a greater exposure risk than no known exposure. Doull and his colleagues<sup>(14)</sup> analyzed the attack rates following various types of known exposure in a carefully studied endemic population on Cebu. Rather than trace the index case to its source contact, they turned their attention to a sophisticated and remarkably precise prospective analysis of what happened to the family contacts of each index case. The focus was not on where the patient acquired his leprosy, but on the persons to whom he gave leprosy. It was 33, 3 (Pt. 2)

clearly shown that lepromatous leprosy caused four to six times as much leprosy as nonlepromatous. The secondary attack rate from nonlepromatous leprosy was about one and a half times that of the general population<sup>(12)</sup>. Similar data were collected by Lampe and Boenjamin(29). Attack rates were 7.7 per cent in persons exposed to lepromatous leprosy and 0.7 per cent in contacts of nonlepromatous leprosy. From Bankura District in Bengal, Dharmendra(10) reported that over a seven year period there was one new case of leprosy per three families with lepromatous leprosy, per 20 families with nonlepromatous leprosy, and per 40 families with no previous case of leprosy. Kluth(27), in Texas, personally examined 492 contacts to check on completeness of diagnosis and demonstrated an attack rate of only 2.8 per cent in contacts of lepromatous leprosy. The attack rate by person years of exposure was calculated to be about half of that in the Philippines.

This does not answer the main question, however, of where most cases of leprosy acquire their infections. A higher infectivity with lower exposure rate can be less dangerous than a lower infectivity but a higher exposure rate. The point has been made by Doull(<sup>13</sup>) in one of his earlier papers, "For the period under consideration in the present report, although the attack rate for those exposed in the household was some four or five times that for those not so exposed, the former contributed only about one-third of all cases of leprosy."

Brown(<sup>3</sup>) in Uganda and Davison(<sup>8</sup>) in South Africa both worked in areas where the proportion of lepromatous cases was so low that mathematical calculations showed they could not possibly have been responsible for most of the new cases in leprosy. They both attributed the high infection rate to transmission from the more numerous tuberculoid cases. Lampe and Boenjamin(29) calculated from their detailed studies in Indonesia that, on the basis of new cases observed in families, "leprosy will not be able to maintain itself when its extension is limited chiefly to transmission within the leper households." In summary, the epidemiologic data provide no basis for saying

that even as many as half of the cases of leprosy can be considered as having originated from an "open case." The importance of carriers probably increases as general prevalence decreases, just as it does with typhoid fewer.

### BACTERIOLOGICALLY POSITIVE ASYMPTOMATIC INFECTIONS

Definition of a carrier state requires laboratory identification of the organism. The only previous evidence for a carrier state has come from Bombay. A series of publications from the laboratory of Drs. Figueredo and Desai(<sup>9,17,18,19</sup>) and of Dr. Khanolkar(<sup>26</sup>) have claimed to demonstrate leprosy bacilli in asymptomatic family contacts of leprosy patients.

Figueredo and Desai(16) developed a concentration method relying on grinding skin biopsies in chloroform. Over several years they published a series of papers in which leprosy contacts were reported to be positive for acid-fast bacilli in fluctuating percentages, but by 1955, 1,852 contacts showed 32.9 per cent positivity. Up to 38 per cent of these cases eventually developed clinical signs of leprosy. Khanolkar(<sup>26</sup>), in the course of studying the histology of early leprosy, examined biopsy sections from 17 persons from the above series of asymptomatic bacillus-positive individuals. Twenty sections were examined from each biopsy and acid-fast bacilli were found in all, with little or no evidence of inflammatory response except for occasional macrophages. In 1955 Sagher(34) stimulated a symposium in the INTERNATIONAL JOURNAL OF LEPROSY by reporting that he had found five asymtomatic family contacts with positive smears. A few others also said that such individuals were occasionally encountered. Dr. Muir(<sup>31</sup>) concluded the symposium with this classic description of the incubatory carrier, "In many lepromatous cases, I should say possibly in the majority of them when the skin is dark, leprosy bacilli can be found in skin, often in large numbers, before there are any visible clinical signs."

#### ORIGINAL STUDIES

We turn now to presentation of prelimi-

nary results from field work in India. Reasoning as outlined above, we decided that proof of asymptomatic infections depended on better field laboratory methods. Two technics seemed worth working on. First, we have invested a great deal of effort in trying to obtain a purified skin test antigen or leprolin that would permit epidemiologic studies of the kind that tuberculin testing has permitted with tuberculosis. Slow progress is being made in this difficult endeavor.

The other field test is an improved method of identifying mycobacteria in skin biopsies. We use the ear lobe, not only because it is easy but because Dr. Gideon<sup>(24)</sup> of our staff in India analyzed over a thousand reports on "slit and scrape" smears in cases of Karigiri, made under Dr. Job's direction. When slides from eight standardized skin sites were compared, smears from the ear missed less positives than a combination of the next two sites.

The technic is simple enough for mass field use. Figure 6 shows the use of a biopsy instrument that greatly facilitates the taking of skin specimens. It is a corneoscleral biopsy instrument developed by ophthalmologists for glaucoma surgery. It is quick and easy. Pain is minimal so that finger pressure on the ear lobe makes the individual completely unaware of the snip being taken. There are no needles or blades. Villagers, and especially children, are far less apprehensive than when they have blood drawn for malaria smears.

Figure 7 shows how the 1 x 2 mm. skin fragment is dropped into a tiny numbered tube containing 0.4 ml. of 2.0 per cent acetic acid. In one hour the epidermis is easily detached and removed with a long needle. In the laboratory, then, the tissue is ground with a steel rod on a small motor. The acetic acid softens the tissue and permits the bacilli to float into the solution. Two hours' sedimentation removes tissue debris. From the decanted supernatant the bacilli are aggregated by shaking with 10 per cent by volume of chloroform. The centrifuged button is then smeared on a standard sized spot on a slide and examined for five minutes or more.



FIG. 6. Showing use of a corneo-scleral biopsy instrument to take a biopsy from the ear lobe of a patient in Purulia village.

A previous report(<sup>25</sup>) indicated that in trials in guinea-pigs and burnt-out cases the method produced 13-100 x concentration as compared with the standard "slit and scrape" method, or the chloroform concentration method of Figueredo and Desai(<sup>16</sup>).

In testing the hypothesis that there is a bacillus-positive asymptomatic infection, we naturally followed Figueredo and Desai in testing first the family contacts of lepromatous patients, because that is where the highest positivity rates should occur.



FIG. 7. Processing a biopsy during survey in Purulia village.

We made biopsies of the ear of 121 family contacts of lepromatous cases, 80 family contacts of tuberculoid cases, and 50 controls, taken in two series from Punjab villages where there has been no leprosy for many years.

In selecting these cases we went to the houses of patients registered in the group of study villages around our field research center at Jhalda. This town is 26 miles west of Purulia and is the headquarters of the area in which the Purulia Christian Leprosy Mission leprosarium is conducting a case-finding and treatment program. Purulia is 200 miles west of Calcutta, where we have our research laboratory in the All India Institute of Hygiene.

The biopsy specimens are taken in the homes. The epidermis is removed when we return to the field station in Jhalda. The biopsy specimens are then transported to Calcutta without refrigeration, where they are processed. The first 50 contacts of lepromatous patients were processed before the laboratory in Calcutta was established, and were, therefore, shipped by air to Baltimore. This transportation without refrigeration took more than three weeks. The acetic acid was sufficient to prevent the growth of contaminants.

Slides prepared from biopsies of both contacts and controls were read blindly. In other words, the identification numbers were covered with tape and readings were recorded without knowledge of the source of the specimen. One of use (E.P.E.) made all the readings, although another (C.E.T.) has checked most of the positive slides. All questionable bacilli were not included.

Table 2 summarizes the preliminary results. The important point is that we have confirmed Figueredo and Desai's(<sup>18</sup>) and Khanolkar's(<sup>26</sup>) findings. Persons with no clinical manifestations of leprosy may have acid-fast bacilli in skin biopsies. Dr. John H. Hanks and I spent some time a year ago in the villages personally examining many of the positive cases from the first series. Most were completely negative clinically. There were rare individuals with small spots of cutaneous discoloration without sensory loss, such as one might see on any Indian villager. As far as we were concerned, they too were asymptomatic.

The reason I stress the preliminary nature of our results is the fact of marked difference in positivity rates in the Baltimore and Calcutta series. We have spent much time in trying to trace the possible causes for this large discrepancy. We are left with a speculative suggestion that goes back to the findings of Becker and Brieger(2), who showed a bacillary increase in leprosy tissue cultured for several weeks. It is possible that there may have been an increase in numbers of bacilli during the three plus weeks of unrefrigerated transportation from Calcutta to Baltimore. This is suggested not only by the sharp difference in the results of the readings in the two series, but also by the appearance of the bacilli. In the Calcutta series of slides, which were processed soon after biopsy, the bacilli were seen only singly and scattered. Figure 8 shows that in the Baltimore series there were clusters of acid-fast bacilli.

TABLE 2. Acid-fast bacilli found in biopsies from ears of 251 villagers in Bengal and Punjab.

Category	Number	Place	Number positive	Per cent positive
Family contacts- Lepromatous	50	Purulia, Bengal	17	34
(Baltimore series) (Calcutta series)	71	Purulia, Bengal	7	10
TOTAL	121		24	20 (average of above)
Family contacts- Tuberculoid	80	Purulia, Bengal	2	2.5
Controls	50	Ludhiana, Punjab	0	0



We are fully aware that merely finding acid-fast bacilli does not prove they are leprosy bacilli. The following points favor the proposition. We did not find bacilli in controls from the Punjab on blind readings. Although we have not yet made histologic studies of these biopsy specimens, we think the bacilli are in the corium, since the epidermis is discarded before processing. Similar bacilli were found in tuberculoid cases in our previously reported study. Morphologically these acid-fast bacilli resemble *M. leprae*.

Looking to the future, we intend first of all, to further standardize the testing procedure and clarify the above discrepancy between the Baltimore and Calcutta series. It is particularly important, in deciding if these are really asymptomatic cases of leprosy, to follow for a period of time the positive cases already identified. Repeat biopsies will be made periodically to define the distribution of bacilli and determine if they can be related to the development of clinical findings. We will also attempt to develop more precise information on the true prevalence of skin positivity in contacts. We will try to relate these findings to the new skin test antigen we are attempting to develop. We then look forward to undertaking skin biopsy surveys on the total populations of the endemic villages on which we are now accumulating complete epidemiologic information. These new field laboratory tools should provide insight into the natural history of the disease and some understanding of transmission patterns.

FIG. 8. Cluster of acid-fast bacilli following concentration from skin biopsy of lepromatous contact from Belyadi village, stained by the modified Wade-Fite technic.

Acknowledgments. Particular mention must be made of the great amount of help and advice received from Dr. John H. Hanks. He participated actively in planning and organizing the field work, helped to check bacilluspositive contacts, to make sure that they were clinically free from leprosy, and was always available for detailed discussion of the issues raised in this paper.

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DISCUSSION

Dr. Cochrane. I am sure that my friend Carl Taylor would be disappointed if I did not get up and say something. Everything he said is true. A person whose interest is in the biologic aspects of disease, who has had no deep clinical experience, is liable to come to conclusions that look alright, but may not be. Any leprologist who has had long experience knows perfectly well that there are carriers in the sense that they are often not recognized either as cases of leprosy or as infective cases. It is perfectly true that lepromatous leprosy is not the only type that is infective. Leprosy is transmitted by the open cases, and this does not necessarily mean the lepromatous case, for nonlepromatous leprosy, e.g., dimorphous macular, infiltrated tuberculoid, and tuberculoid in reaction, can each pass through positive phases, when they would be potentially infective. Three forms must be taken into account. McDonald, along with Davison, some years ago (personal communication), raised the question if there is some factor in the transmission of leprosy other than the lepromatous case. "Look at my area," Dr. McDonald would say; "the lepromatous rate is 5 per cent, but look at the number of cases." The area in which he was working is much like many other areas in the Congo, in which the great majority of cases are what some people call indeterminate macular, and we call dimorphous macular. I once said to Dr. Stanley Browne, "That case was positive." He replied, "Yes, three weeks ago it was highly positive." Some of these macular lesions pass through positive phases, and can be high positive. One can well imagine a child being carried by a mother with one of these lesions, which for three weeks or a month is highly positive, and the child develops a lesion on the forehead. We know perfectly well that the silent leproma is extremely difficult to diagnose. In fact, as I have said to Dr. D'Arcy Hart, the physician has the x-ray to diagnose tuberculosis, but he has just his two eyes in leprosy.

In Karigiri not very long ago I pulled out a case, and Dr. Buker said, "Why did you choose that person for demonstration?" I said, "Because I did not like the look of his skin." We took the patient out in the sunlight and found he was a diffuse lepromatous case.

In Purulia many years ago I gave a certificate like this: "This person is noninfective; he may be employed, but he must not be employed anywhere in the house. He can be employed in the garden, but must have no household contacts. Twenty years later Dr. Archer wrote to me from there, saying, "You remember so-and-so? I was in a missionary's house and looked up and saw this man. I said, 'You had better come and see me.' He was found to be full of bacilli."

Another case: A doctor had a butler who proved to have diffuse lepromatous leprosy. The doctor did not diagnose it—the cook diagnosed it for him. And so we know these cases exist. The point is that leprosy is passed on by M. leprae in a phase where you can find the bacilli, and you find the bacilli under all sorts of conditions. The work of Khanolkar<sup>1</sup> and Figueredo and Desai<sup>2</sup> is perfectly accurate; we have repeated it by biopsies in contacts. The real danger in our attitude toward leprosy is that some people look upon the disease as highly infective and take precautions which I believe only give rise to a hysterical approach to the disease, and thereby cause fear in all those who attend our clinics. If leprosy were as infectious as some people consider it to be, few would escape infection. I am not surprised that persons acquire leprosy. I am surprised that so few people get it. It is largely a matter of susceptibility and contact. If the susceptibility is high, the contact may be less. If susceptibility is low, the contact must be greater. One contact can give a person leprosy-there is no question in my mind about that-if he is highly susceptible.

<sup>&</sup>lt;sup>3</sup>Khanolkar, V. R. Studies in the histology of early lesions in leprosy. Indian Council of Medical Research, No. 19, 1951.

<sup>&</sup>lt;sup>2</sup>Figueredo, N. and Desai, S. D. Positive bacillary findings in the skin of contacts of leprosy patients. Internat. J. Leprosy **18** (1950) 59-66.

I remember a patient in Redhill who said: "I've had leprosy six months." We examined him and learned that he had had anesthesia for much longer. We undressed him and found a macular rash all over his chest. He was a Catholic priest. I said "Father, what about this rash?" He replied, "Oh, that rash. I've had it 20 years; it is only sunburn in East Africa." And so the facts that Dr. Taylor has put forward are absolutely correct. But we must be careful in our conclusions, so that we do not get people scared thinking that leprosy is a highly infective disease.

Dr. Dharmendra. I can understand the subject being discussed, and, because I have done a little work on it myself, I would like to say a few words about it. We know that leprosy bacilli may be found at some place, somewhere in the body, before manifestations of the disease occur. But to presume that all acid-fast bacilli found in all healthy contacts in areas where any number of acid-fast bacilli are present, are leprosy bacilli, is beyond one's understanding. We calculated a little of this work and could not prove a positive relationship between the presence of acid-fast bacilli in healthy persons and a positive lepromin reaction. Even if it were correlated, it would not mean that the acid-fast bacilli seen in healthy persons are leprosy bacilli, because the lepromin test is not specific for infection with leprosy bacilli. Any other acid-fast organism can induce a positive lepromin reaction. Moreover, it might be possible to say that these leprosy bacilli are so numerous, so widespread in the body, that you can cut anywhere-back, arm or thigh-and find the bacilli. That means a state of bacillemia without any symptoms at all.

**Dr. Rees.** This time Dr. Dharmendra has almost taken what I was going to say away from me. First of all though, the approach of Dr. Taylor, in my opinion, is basically extremely good, and obviously, from the previous data that he presented, with which many of us are familiar, requires further analysis. What has disturbed me, though, is the fact that, in one respect, a

part of his data seems almost misplaced. If I haven't misunderstood him, his paper should have come earlier in our meeting in the sessions on growth of the human leprosy bacillus. This I find so shattering that I almost feel as if we are wasting our time, and that what we should be doing is collecting material like this and somehow posting it to take three weeks from Calcutta to Baltimore. I don't know if Baltimore is essential, or whether perhaps it could come to London! Because he is presenting data of this type, I feel that he should consider some of the work presented earlier this week, and since apparently this is a bacillary form, I think a number of speakers this week have actually presented methods by which he could identify this organism, as either M. leprae or not M. *leprae*, since apparently what they have been observing is not a protoplastic form. Therefore, may I make a very strong plea that before they consider the data as contributing to the epidemiology of leprosy, they undertake some basic tests to identify the acid-fast bacillus.

Dr. Skinsnes. Dr. Rees, maybe you won't have to transmit them by air from India to London, if you add a little acetic acid to your culture medium! But that is not the basic point I would like to make. Basically leprologists have been saying for many years that there are carriers of this disease. They have pointed to its long incubation period. If there is an incubation period of 3 years or 5 years or 10 years, or more, one must inevitably be carrying bacilli around for all this time, and by defi nition be a carrier. Many have pointed out, and we have written about it ourselves, without adequate figures, however, that probably a large number of such people who harbor the bacilli after contact, cure the disease without it's ever being real disease, i.e., get rid of the bacilli without any overt symptoms whatsoever. What would seem most interesting and really new, would be a many-year follow-up to determine how long this carrier condition can exist, assuming that these are leprosy bacilli, and, without quibbling about that, how long it exists in the same patients and in the same area? Also is it a repetitive

reinfection-type phenomonen or do the bacilli stay there for many years, or will the carriers eventually dispose of their bacilli, develop some form of immunity and not carry them any longer? I think these matters require delineation before one can call for the definition of a carrier state in the sense of, let us say, Typhoid Mary.

Dr. Hanks. I do not believe the discussion this morning is seriously concerned with the question of whether or not there are carriers in leprosy. The real problem is how important they are, and how we can find them. For the lack of more sensitive and specific methods, Dr. Taylor's findings were presented without conclusions. With the methods available, positive microscopic findings were made in contacts of leprosy patients near Purulia, but not in a double blind series from Ludhiana where leprosy does not occur. The microscopic findings after shipment of biopsy specimens have been more frequent than following immediate concentrations. Further work, therefore, seems necessary and justified.

When Dr. Chatterjee arrives in Calcutta, he is going to try a new method of microscopic concentration which should not interfere with bacterial growth. By comparing the immediate results with those obtained after incubation at the designated pH and at room temperature for several weeks, the question of possible bacillary proliferation during transit should be clarified.

**Dr. Sartwell.** I would like to suggest to Dr. Hanks a second form of control, viz., that another group of specimens be shipped to Baltimore, because I am quite unwilling to abandon the hypothesis that Baltimore has something to do with it.

**Dr. Binford.** I enjoyed Dr. Taylor's presentation, and would like to come at the problem from another angle. Dr. Hanks and Dr. Rees have spoken from the standpoint of the bacteriologist. I would like to approach it from the point of view of the pathologist who believes in morphology. If the bacilli in the skin snip are leprosy bacilli, some should be in nerves, and if you could find some way of following up your 9.8 per cent of positives in India or your 34 per cent in Baltimore, and could do formal skin biopsies and examine many more sections, you should, if the 'acilli are M. *leprae*, find a few in nerves. In my opinion, this would establish more or less unequivocally that these are leprosy bacilli. If we, in some way, could work with you on that problem, Dr. Taylor, I think we could help establish the facts.

Dr. Shepard. I would hope that before this material is presented again in a meeting on leprosy, which is our subject this week, the organisms will be identified. It was perhaps permissible ten years ago not to identify the organisms—in Figueredo and Desai's early work (reprinted in *Internat.* J. Leprosy 18 (1950) 59-66; original in Indian J. Med. Sci. 3 (1949) 253-265, the identification was not made at all—but it is not hard any more, and I do not see any reason for not identifying them before results are published as a contribution to the epidemiology of leprosy.

Dr. Latapí. Dr. Taylor told us that his paper would be provocative, and I feel it is. The title is most provocative: "Asymptomatic infections in leprosy." Briefly, I will say that this entails two conditions. One is very frequent. If you find a boy in contact with a lepromatous father, and he gives a very strongly positive lepromin reaction, I say that he is immunized and never in his life will have leprosy as a disease. Of course he does have the infection, just as in tuberculosis. The other condition is the special part he has presented to us. We find another boy in the same condition, make a biopsy in the ear, and find acid-fast bacilli. Of course, I think Dr. Rees and Dr. Shepard are right in thinking of the identification, but that is another point. I believe such cases are initially lepromatous. I think the bacilli are inside the histiocytes, and I believe the real title of the paper should be: "Early diagnosis of leprosy." I think it is a very valuable contribution.

Dr. Reich. Regarding the question of cultivation of the leprosy bacillus, I suggest that perhaps Dr. Taylor might try sending specimens to Cebu. I think that Dr. Taylor did not, nor did Dr. Rees imply, that this was cultivation of the leprosy bacillus. ٦

Dr. Taylor. Let me start by saying that if this conference had not been organized for the purpose of stimulating thinking I would not have made this presentation. We realize completely the preliminary nature of the findings presented. We fully intend to verify and amplify the findings as now presented. We hope to be able to do some of the things that have been suggested—I don't know that we can do them all—but we certainly hope to carry out the obvious needs in terms of identifying as accurately as possible the bacilli we are dealing with. Let me take up just a few of the points that have been made.

In reference to the danger of panic from use of the word "carrier," I know this is a problem. On the other hand, I have been conscious in recent years of a swing in the other direction in leprosy control-people are developing a most unwarranted belief that eradication is possible with the present methods of diagnosis, case finding, and treatment. I have been concerned that we may get ourselves into the position of promising a lot more than we can deliver. I think that until we begin to bring a balance into the total picture of what can and cannot be done in an overall leprosy control program, we are in as much danger from the overconfidence that I see spreading around the world, as in danger of panic. Obviously we have to find a middle course. I do not think it will lead to panic to state clearly that there are carriers. I believe it is time to face the matter frankly, and use a word that has a well recognized biologic, clinical and public health connotation. This term, furthermore, carries with it certain definite implications for additional control procedures.

The classification of carriers is important. Obviously, the point made by several people about incubatory or convalescent individuals carrying bacilli expains many cases. They may only show symptoms for a while, and others may eventually show clinical signs after having carried bacilli. In addition to that, it makes biologic sense also to include the possibility of the healthy carrier. Although Dr. Cochrane has infinitely more clinical experience than most of us, I feel confident that the cases that Dr. Hanks and I saw in the Jlalda villages, which were positive bacteriologically, but did not have clinical findings, would have also been considered clinically negative by Dr. Cochrane. I believe there are incubatory carriers, convalescent carriers and healthy carriers. We won't know what the proportions are until we do more work, and very careful epidemiologic follow-up of individual cases.

Now I turn to the question of whether these are leprosy bacilli. I tried to be careful in my statements and refer to them as acid-fast bacilli. As Dr. Hanks pointed out, these readings were blind and the controls were negative. I labeled the comments I made about the discrepancy between the Baltimore and Calcutta series as speculative. We are obviously in a position now where we can do a great deal about identifying these bacilli and we expect to try. The problem of how long these organisms continue in the skin of these individuals is clearly of great interest. We have started a follow-up on cases that we do find positive, and we expect to follow them over a considerable period of time. Before our claims are considered dramatic, we need much more information and in leprosy work that takes time. On the other hand, it is our hope that other people will be stimulated to work in some of these important epidemiologic issues and especially to use this very simple field procedure, which we feel can make a contribution also to more refined clinical diagnosis. So, let me just say that if this paper stirs other people to active field research, I will be satisfied with this presentation.

Dr. Sartwell. We await the promised next paper with great interest. Now, I should not be introducing the next speaker, for he is well known to all of you. He was associated for many years with Dr. James A. Doull in epidemiologic studies in Cebu, and is still carrying on this work, Dr. Ricardo S. Guinto, who will speak on "Problems requiring solution through field studies."