cases of leprosy, returns to the North, stays there and develops leprosy 10 years later, the incubation period is said to have been of 10 years duration. It is assumed that after his return there has been no invasion by the organisms. But can we say with assurance that infection could not have taken place in the North during this 10-year interval?

Infection by invasion of acid-fast bacilli in the soil seems improbable, especially in regions where leprosy is not known to occur. Evidence to the effect that soil injected into rats will give rise to leprosy is rather weak, and yet there is reason to believe that the soil actually contains rat leprosy bacilli. The incidence of human leprosy is constantly a little higher in males than in females, probably because the males of the poorer classes labor more in the fields than do the females, and are more subject to slight cuts and abrasions of the hands and feet which would afford portals of entry for soil organisms.

It is possible that human carriers of infection may exist unrecognized, either because they show no symptoms or because the symptoms they do present are not correctly diagnosed. Our view of the incidence of infectious diseases is expanding at a surprising rate, as is demonstrated in a striking way in McKinley's *Geography of Disease*. A few years ago we believed that poliomyelitis was rare or absent in the tropics. Now, neutralization tests indicate that it is not so limited (Hudson and Lennette 1938), but that paralytic symptoms are less frequent than in the North and epidemics virtually unknown. In the absence of a diagnostic serological or sensitivity test for leprosy, and in consideration of the lack of interest in leprosy shown by most practitioners, any mild cases which might occur would probably pass unnoticed. And perhaps in cold climates the proportion of cases exhibiting inconspicuous lesions to those so marked that they could not be ignored, is greater. Wade has repeatedly pointed out that leprous lesions of the tuberculoid type have been mistaken for simple tuberculosis. Lisi and Sebastiani have described lesions which looked like sarcoids but which contained acid-fast bacilli and later developed into unmistakable leprosy. Reenstierna concludes that

> Leprosy may manifest itself in the form of skin affections which histologically coincide with Besnier's lupus pernio, Boeck's cutaneous sarcoids and Schaumann's erythrodermia.

A critical analysis of the similarity is given in an editorial by Wade and in *Correspondence* in the *International Journal of Leprosy*. But leprosy in the North seems to be less communicable than in the South. In the metropolitan district of New York City there are as many as one

hundred cases of leprosy, which are periodically visited but not isolated; yet in all the years of activity of the health department there is no record of leprosy having been acquired in New York (Pollitzer 1938).

A third possibility is that of infection from an animal reservoir of organisms. Hardly a year passes in which one or more diseases in man are not traced to animals fairly closely associated with man. So-called rat leprosy is geographically quite widely spread. A leprosy-like disease of mice has been reported by Krakower and González. Rats and mice down the ages have lived with man. Before the experiments of Sellards we listed *Macacus rhesus,* rabbits and white mice as resistant to rat leprosy bacilli. He has produced fatal infections in all of them by intracerebral and intraperitoneal injections of the said bacilli. We believe man to be resistant to rat leprosy bacilli and this may ordinarily be the case, just as many adults are fairly resistant to repeated small invasions of human leprosy organisms. But it is safe to say that nobody has yet had enough faith in the prevalent view that the acid-fast organisms of rat leprosy are actually non-pathogenic for human beings to inject them into children at the age when they are most susceptible to human leprosy. Salle and Moser contend that "human and rat leprosy are caused by the same etiological agent," though others emphasize differences.

So much for the chances of infection of John Doe after presumed contact with a case of leprosy in Central America. It is unlikely, but conceivable. The incubation probably begins during his visit. How long after leprous lesions were established was the diagnosis made? If the delay has been considerable, since leprosy is the last disease expected or looked for by his family physician, then the period of incubation as measured is too long. It should be regarded as ending when a competent leprologist could return a positive diagnosis of leprosy.

The only really acceptable evidence as to the length of the incubation period is derived from purposeful and accidental inoculations of man with the mycobacteria. In one intentional case the lesions are said to have been recognized one month later (Lagoudaky 1936). In another, an accidental one, a small anesthetic swelling was noted 6 months afterwards (de Langen 1933). Provoked by such concentrated doses of organisms the lesions probably develop faster than they would if they were the result of spontaneous inoculation.

Attempts to establish the incubation period dating from the injection of organisms into areas of the skin of lepers in parts of the body remote from all visible lesions, with resultant superinfection, are unsatisfactory, because the comparatively short periods of incubation noted may be attributed to depleted resistance.

Although the average period of incubation in natural infections may not be as long as is generally thought, it is nevertheless of sufficient length to give opportunity for adjustment between organism and host. The organism may change or it may cause the host to create a special fluid environment—whether extracellular or intracellular we do not know—which is more favorable to it. During this period of incubation no tissues have been studied microscopically, for we do not know from which area or even from what individual to take them. The change in organism or host or in both, results in a condition or conditions which favor or prevent multiplication of the organism. Obviously the organisms, when seen in sections or cultures, may differ much or little from the original invaders which we never see, and which we suppose come exclusively from other human beings. Those studied from intentional or accidental inoculations with material recently taken from established leprous lesions may be more virulent than the original invaders because they have already undergone the long process of adaptation mentioned.

2. IS HANSEN'S BACILLUS (Mycobacterium leprae) THE CAUSE OF LEPROSY? In our discussion we assume that it is, but are we sure? A very complete discussion of etiology has been contributed by McKinley. See also, Soule and McKinley. Long speaks of "our present lack of certain information on the bacterial cause of leprosy." Doubt is attributable to two facts.

Of little significance perhaps is the difficulty often experienced in finding any bacteria in the lesions of tuberculoid leprosy. I have been unable to detect acid-fast organisms in biopsy specimens of the cases kindly sent to me by Dr. James Knott of the Virgin Islands. If, however, more tissue had been examined or the cuts had been deeper, organisms might have been found. It cannot be said that they do not occur in some cases of tuberculoid leprosy in the face of their discovery by several well trained workers. Unfortunately, the fixation of the material I studied was not suited for the use of Giemsa's stain to the best advantage. The possibility of the occurrence of minute gram-negative organisms, like Rickettsia, was therefore not excluded.

More significant are failures to reproduce the disease in animals by inoculation with cultures of bacteria made from the leprous lesions. It must, however, be remembered that it is equally impossible to transmit the disease by the inoculation of emulsions of fresh tissue containing myriads of bacteria, for the reason that thus far no animal susceptible to human leprosy has been discovered. The difficulty is not in the culti-

vation of bacteria from leprous lesions, which has been done by numerous investigators. The cultures first made by McKinley and Soule in 1932 and carried on and greatly extended since then (McKinley and de Leon 1937) are the most promising. Injection of the cultures produces a temporary response, but not a continuing disease in animals capable of passage from animal to animal in series. Until some animal susceptible to human leprosy is discovered, little progress can be made. There is reason to think that resistance is lowered in rats deficient in both $B_1$ and $B_2$ vitamins (Badger 1936). No cases are on record of leprosy following accidental inoculation of humans with the cultured organisms. The fact that it has resulted from inoculation with fresh material containing the bacilli does not necessarily mean that the bacilli are the etiological agents, for a virus might also be present in the material. Apparently no leprologists believe firmly enough in the bacterial theory of causation to inject into themselves bacteria free filtrates of finely emulsified fresh leprous lesions. Negative results in sufficient number would strongly support the idea that the bacilli are the etiological agents. However, like the injection of children with rat organisms, the risk would be far too great.

3. IS LEPROSY CAUSED BY A VIRUS? This question keeps cropping up without, it seems to me, much justification. The difficulty mentioned of finding bacilli in tuberculoid leprosy is one reason. The now discredited idea of the existence of a filterable phase of the tubercle bacillus is another. Weak support is received from observations, which will be considered later, to the effect that granular forms of Hansen's bacillus grade down to the ultravisible. The fact that cultures fail to transmit the disease is explained by believers in virus etiology as due to nonpersistence of the virus in the presence of etiologically insignificant bacilli.

It is true that the search for an active virus has not been very thorough. The modern methods of injection (Markham and Hudson 1936) into fetuses *in utero* are among those which have not been used. Also, the materials injected have not been wisely selected. Instead of employing tissue emulsions of chronic lesions which have endured for years, a better way would be to employ as source of the hypothetical virus, very early lesions, particularly of the tuberculoid variety in the acute stage, and lesions during the lepra reaction.

Yet leprosy in its long incubation period, cellular reactions and chronic course has little in common with the virus diseases known to us.

4. IS LEPROSY CAUSED BY A BACILLUS PLUS A VIRUS? This possibility cannot be altogether dismissed because examples of diseases provoked