Discussion

Freerksen: We shall now start discussion of the special parts as arranged in the program. Is there anyone who has asked for opportunity to speak on *pathologic problems?*

Klingmüller: I would like to add a remark on the paper by Dr. Convit. *M. leprae* lives in the cell, as do the agents of leishmaniasis. With respect to syphilis we have to put the question why the Wassermann reaction remains positive. Ortinikow, whose data are published in the WHO Bulletin, infected rabbits with *Treponema pallidum*. After eight months he observed lesions, in the plasma cells of which he could find treponemata which appeared highly virulent according to electron-microscope optical findings. We too noted this fact. After penicillin treatment he came upon virulent treponemata, and from this fact deduced that the Wassermann reaction remains positive because the treponemata are present in the cells. Penicillin is ineffective in syphilis treatment. It is criminal to speak of a "sero-stigma," and thus intimate, in other words: once syphilitic with a positive Wassermann reaction, forever syphilitic. Thus with regard to leprosy, we encounter the same problem in leishmaniasis and syphilis.

Freerksen: Neither from microscopic nor from electron-microscopic findings can one make a decision as to whether mycobacteria seen are virulent or not. *M. leprae* can be present intracellularly as well as extracellularly.

As there are no further questions concerning pathology, even though many unsolved problems remain, we now come to the section *"Bacteriology."*

Waters: I have one very brief comment. In his paper Dr. Rees commented on the stability of *M. leprae* infection in the footpad of the mouse. Back in 1959, at the suggestion of Dr. Rees, we started some experiments in Malaysia in the hamster. I have one strain which I inoculated in October 1959 and which I have kept going ever since. It is now in its tenth passage; throughout this time and through all these passages it has remained stable. It has not changed in its characteristics. We used the hamster ear nearly all of this time, an organ which, of course, does show a number of tissues not present in the footpad. We found *M. leprae* in the striated muscle, in Schwann cells, and in macrophages. We also found leprosy bacilli in the perichondrium and in melanocytes. This is in accord with the interesting remarks of Dr. Klingmüller on the possible role of the melanocyte in leprosy.

Freerksen: Please let me ask another question which partially concerns a bacteriologic problem. Is the infection transmitted only between men by direct contact, or are there other reservoirs, or is it produced by both the factors?

Convit: Our experience in epidemiology and control agrees with publications which show that the risk of acquiring the infection is several times higher for people living in the same house with a lepromatous leprosy patient than for the general population of the area. The possibility of insect transmission has been considered by some authors, but, for the moment, it is not based on strong evidence. Nevertheless, we should keep our eyes open regarding this possibility.

Browne: I think I may shed a little light on one of these problems. In most countries it is possible to trace infectious foci of leprosy patients, and, whenever the prevalence rate in a closed community is over one per thousand, then every person must be considered as a potential contact of somebody who has leprosy. There is a great difference between being in potential contact and actually receiving an infective dose of leprosy bacilli. Here I think we have not sufficiently stressed the possible importance of fomites. One sneeze from the nose may contain tens of thousands of viable leprosy bacilli. Leprosy bacilli are rarely shed through the intact, non-sweating skin. We have no knowledge of the viability of leprosy bacilli when shed from the nasal mucosa, but I think we must not minimize this possibility. With regard to infection of persons where there is no apparent contact, I would cite some experi-

ences in East Africa where from time to time children living in an isolated homestead, with no apparent contact through hurrying visitors, visits to markets, or travelling on public transport, will develop leprosy. Unless there are inapparent infections not suspected or undiagnosed, it is difficult to suggest the means whereby these small children have become infected, except for the possibility of fomites borne for miles on the persons of visitors who themselves do not have leprosy.

Leiker: From our intensive study in New Guinea in a highly endemic area we can gather that leprosy infections are transmitted between men by direct contact, because the disease is focalized to special houses marked by a close relationship. Leprosy is also spread by intermarriage, though not evenly. If, for instance, insects play an important role, one would expect, provided an insect with a very wide radius of prevalence is concerned, a more even distribution in our endemic area. We do not exclude the possibility that, incidentally, the stinging of insects may carry a few bacilli and contaminate someone, but this fact plays no important role. There may be, for instance, other sources of contamination, e.g., soil. Let me give an example from our New Guinea studies: We have an area with a row of villages along the coast, with one leprosy center in the middle. All people from the south commonly go barefooted every week to a market place in the north, and because there is a shortcut through the leprosy area they take a road leading directly through it. If contamination by soil played an important role, one would expect a more even distribution of leprosy in the southern area.

Rees: Regarding reservoirs of *M. leprae*, other than man, there could be no directive until it was proved that other animal species could be infected with human leprosy bacilli. Now we know that rodents, and in particular mice and rats, can support the multiplication of *M leprae*, these animals could act as nonhuman reservoirs. However, I believe that these rodents within their lifespan would be unlikely to generate sufficient *M. leprae* to be a danger to man. On the other hand, I believe that the successful transmission of *M. leprae* to rodents, and particularly mice, provides ideal experimental models for studying the problems surrounding transmission of leprosy to man. For example, the reproducibility and specificity of the infection in mice provides an unimpeachable test for the identification of *M. leprae*. Therefore any vector, such as an insect, which might transmit *M. leprae* from man to man could be examined for the presence of acid-fast bacilli and if these were recovered they could be identified by inoculation into mice. More importantly, the mouse can be used to study various routes of infection which might be relevant to the transmission of leprosy from man to man. We have made a start on this type of work by attempting to infect mice with *M. leprae* given as nasal droplets, by aerosols, by feeding through a stomach tube, and by applying to the surface of skin after minimal scarification. Small groups of mice inoculated by each of these routes were then killed 12 months or more later. To date we have found a few mice with histologic evidence of lesions consistent with *M. leprae* and the presence of a few acid-fast bacilli. These microscopic lesions were found in the ear or footpad skin, but only from the groups of animals that had been infected by aerosol or by nasal drops. No lesions were found in the lungs. We have suggestive evidence, therefore, that *M. leprae* in the mouse can enter the body by these routes of inoculation and may have done so by passing across the mucosa of the upper respiratory tract or by inhalation into the lung, where presumably they are picked up by alveolar macrophages and subsequently get dispersed systemically.

Vaidya: With regard to vector transmission of leprosy, I might note a project entitled "The Role of Anthropods in the Transmission of Leprosy," now being carried out in South India. Mosquitoes and many insects from the various leprosy centers and houses of leprosy patients in endemic areas were collected. In some of these insects acid-fast bacilli were found. These bacilli did not grow in artificial media. They were inoculated into the mouse footpad. The results are not yet known.

Browne: The potential infectivity of the

patient with nonlepromatous leprosy has always intrigued me. Epidemiologic studies suggest that such patients are from a third to a tenth as infectious as those patients whose nasal mucosa is heavily bacillated and who are distributing millions of viable *M. leprae* per day. This I consider a subject that should be investigated with much greater intensity and persistence. When one examines, for instance, a single sneeze, the number of viable bacilli may extend into hundreds or even thousands. In contrast, one may have to examine from 20 to 50 serial sections in the case of tuberculoid leprosy before coming across a single clump of nonviable acid-fast bacilli. Yet the potential infectivity of such a patient is not one millionth of that of a patient with lepromatous leprosy, but a third to a tenth. This to me is an inexplicable enigma.

Delville: Dr. Rees and Dr. Shepard: what do you think about the generation time of *M. leprae* in man? If one can explain what we observe in the clinic in leprosy patients, with relation to the duration of generation time, leprosy reactions seem to be associated with a very rich and rapid multiplication. But this fact is very difficult to interpret with respect to a generation time of 12 days. In tissue cultures, at least in macrophages, which I studied, the generation time appears to be remarkably shorter. For this reason I think that macrophages will furnish a medium closer to man than will mice, which are really not natural hosts to *M. leprae.*

Shepard: The most rapid growth that we have observed in mice, has corresponded to a generation time of 12-13 days in the logarithmic phase. At this rate enough organisms could be produced in two years to account for all the organisms in the lepromatous patient. Yet we all know that the incubation period in lepromatous patients is usually on the order of eight to ten years; in tuberculoid patients the incubation period is on the order of three to five years, but the number of organisms in the body is much smaller. This means that the organism is not multiplying at full logarithmic rates in the lepromatous or the tuberculoid patient much of the time. Our laboratory routine requires us to gather data for a large number of bacillary growth curves in mouse footpads, but we have never observed multiplication that has a generation time faster than 12-13 days.

Browne: Regular six-monthly whole-population surveys in a very highly endemic area, including multiple skin smears, suggest that the latent periods of all kinds of leprosy are approximately the same. Early lepromatous leprosy is frequently ignored by the victim and is not presented to the physician. Early tuberculoid lesions are usually obvious and diagnosable. When fortnightly smears are taken from the same early lepromatous leprosy, a sudden appearance of numerous organisms is frequently noted—suggesting a non-stainable phase, or a more rapid multiplication than is admitted.

Leiker: A short comment on diagnosing lepromatous leprosy when there is only one lesion. Lepromatous leprosy is usually diagnosed when the disease is generalized. At most, I would say one can diagnose borderline lepromatous leprosy when there is one indeterminate patch developing to what appears to be lepromatous, and in these cases I believe the incubation period is not much longer than in tuberculoid leprosy. It is just a matter of diagnosis. The early diagnosis of diffuse lepromatous leprosy always comes late, because there is so little tissue defense; there is practically no hypopigmentation, which helps to diagnose the case early.

Delville: A generation time of 12 days can be enough to explain the incubation period; but the transformation from one leprosy type to another, as well as the phenomenon of leprosy reaction, seems to represent an explosion of multiplication of *M. leprae.* This is, nevertheless, difficult to associate with a generation period of 12 days, which is relatively long. Or do we have, during this time, a latent phase? While these phenomena of evolution are occuring there will be a certain amount of bacillary destruction, which cannot be taken into consideration as a factor for the calculation of the generation time.

Freerksen: With respect to the general principles of classic *experimental therapy,* we are dependent on (1) possession of the

germs available *in vitro* in any number, (2) their virulence for at least one laboratory animal, and (3) their capacity to induce a disease similar to that in man. These conditions have not been realized until now, so that we must continue to try to make *M. leprae* cultivable. Dr. Shepard developed the footpad method as a transit-model. We set up an analog-model with *M. marinum* (see M. Rosenfeld in this colloquium: "New results in the chemotherapy of mycobacterioses"). In any event the most important criterion in assessing the effectivity of a chemotherapeutic compound is the rate of inhibition, or still better, the rate of killing the bacteria so that they can be eliminated from the body. The other problems the organism will solve themselves. Are there any substances of bacteriostatic or bactericidal type against *M. leprae*? This question cannot be resolved in man. That we have DDS is somewhat fortuitous. This is why we need to seek new drugs by means of strictly defined methods. Dr. Shepard, may I ask you to express your opinion concerning this subject?

Shepard: In general, efficient chemotherapeutic drugs are active by themselves, and the host's immunity doesn't contribute very much to the rate of killing. There are a few exceptions, but the general rule with effective chemotherapeutic agents is that the rate of kill is determined primarily by the concentration of drug in the environment of the microorganism and the physiologic condition of the microorganism itself. With the available mouse footpad technique we cannot screen thousands of compounds, but we can test a few dozen compounds a year. So new compounds first have to be screened against other bacteria. It is especially useful next to test active compounds against cultivable mycobacteria. With these results available, we can then concentrate our testing against *M. leprae* in animals primarily on compounds with activity against another mycobacterium.

What we seek among the compounds we test in mice is one that has bactericidal activity in the so called "kinetic" technique. There are many compounds with bacteriostatic activity; their number now is perhaps 40 to 45. Some of them may be valuable. But among the few in the bactericidal group we have the three most important drugs in leprosy today, DDS, B.663 and rifampin. After learning something of the properties of a drug against *M. leprae* in the mouse it is essential to proceed with a clinical trial. This gets us into another area, i.e., how such a trial should be carried out. Many of the clinical trials in the past have not been as decisive as they might have been. Many drugs have been reported to show some activity against leprosy in man, but it is very hard to determine from reading the reports which drugs are really useful. Generally, it has been necessary to continue clinical tests for three or four years to see whether many of the patients will eventually deteriorate. Several drugs have produced an initial favorable response, only to be followed by deterioration later on. The usual bacteriologic techniques, measurement of bacterial index and morphologic index, are not suitable to detect the presence of a few viable bacteria. Mouse inoculation is a much more precise way of detecting small numbers of viable bacilli, and in recent clinical trials we have employed this technique with serially removed skin-punch biopsy specimens.

Freerksen: I would like to preclude a misunderstanding. When I said that chemotherapy as therapy of infectious diseases is antimycobacterial therapy, and that the drug has no effects on the disease, but only on the bacteria, I wanted to express my opinion that without such drugs the bacteria would not be affected unfavorably and that therefore recovery would not occur. Naturally, in the light of these aspects it is wrong to use animals in which the microorganisms introduced neither cause disease, nor have a chance to survive.

Today it is possible to find new drugs against leprosy even if we cannot induce this disease in animals. This is a point upon which we can agree with Dr. Shepard. We agree also that decrease in the number of germs is decisive. Man and animal modify the effectivity of such substances by their special properties, but that fact does not alter the principle.

With respect to experimental immunolo-

gy I like to say that the term "immunology" as used today no longer implies immunity only in the sense of protection. It is applicable to nearly all reactions that are observable in some way when an organism reacts to foreign materials. In connection with leprosy we must above all think of sensitization and vaccination.

The immuno-suppressive substances, e.g., thalidomide and its derivatives or cortisone, are concerned with sensitization in its therapeutic aspects (influence on the reaction). Are there any experimental tests which prove to be of diagnostic value? What about testing with sensitin from "atypical" mycobacteria? In cattle, but also occasionally in man, the so-called simultantest has been in use, i.e., a test with different, and sometimes many different, bacterial strains. Theoretically it would be possible to make sensitins from "atypical" mycobacteria that are akin to *M. leprae,* and to use them for differential diagnosis.

Bechelli: With regard to tuberculin or other antigens from mycobacteria, I don't think that up to now we have the possibility of diagnosing leprosy with any of them. The tuberculin test may be highly positive or positive in a very high proportion of lepromatous cases, as well as in tuberculoid cases. The lepromin test, as we have known quite well ever since the initial report of Mitsuda and the contributions of other authors, is not useful as a diagnostic procedure, but only as a prognostic one. Dr. Fernández from Argentina once proposed, in some doubtful cases with tuberculoid lesions, to differentiate these cases from tuberculosis by inoculating 1.5 ml. of lepromin. This method was not generally used. The early lepromin reaction does not help in the diagnosis of leprosy in the preclinical phase. In my experience—I have carried out these tests not only in Brazil but also in the United States, in New York and Cleveland—it should not be used for such purpose. The proportion of positive reactions is small, though higher in people with tuberculosis, but, even so, low in my experience. None of these tests could be used up to now as a diagnostic procedure in leprosy. One very important step that we have long awaited would be the diagnosis of leprosy infection, as in tuberculosis. This would be a most important contribution to leprosy research, especially to epidemiology. From this point of view we consider our colleagues working in tuberculosis as the rich cousins in the mycobacterial group. They have cultivated tubercle bacilli and purified tuberculin. They have methods for transmission of the disease, a lot of good drugs to use in tuberculosis, and BCG vaccine. In leprosy we are co-ordinating efforts in several directions; and one of them, debated here, is connected with the inoculation in footpads. Considering again the lepromin, it gave to the leprologists the possibility of carrying out interesting and important epidemiologic studies, besides its usefulness in the classification and prognosis of leprosy cases.

Freerksen: I agree with you entirely, Dr. Bechelli; without doubt it would be an important success if we found a test for early diagnosis of the sensitization of a macroorganism by *M. leprae* before the appearance of clinical symptoms. This should be possible, and at some time in the future we shall manage it. Thus these serious cases of leprosy need not occur, because one could start very early prophylactic therapy.

Klingmüller: I would like to revert to your question. The same is true, I think, for the primary sore, which we cannot see in leprosy, obviously. In syphilis this sore occurs after 21 days, according to the generation time of the causative germ. In tuberculosis it develops in about five weeks. In leprosy the antigenic action is so slow that there is no primary sore. This is why we can never diagnose leprosy in this phase by any test.

Freerksen: We have to judge this fact from another point of view. Mycobacteria don't sensitize by primary sores or primary infiltrates, but by their antigens. We really know nothing about the antigenicity of *M. leprae.* We do know, however, that minimal numbers of germs of nonvirulent mycobacteria, e.g., BCG, will very well sensitize for a long time. In tuberculosis only 1 per cent of the infected, i.e., those who receive mycobacteria, become truly ill. The number of infected is therefore high, while the

number of actual tuberculous cases is small. Thus the tuberculin reaction is one of the most important means to find the persons mycobacterially infected. This principle would be applicable in leprosy, if a tuberculin-like product specific for leprosy could be made from *M. leprae* or other mycobacteria akin to it. We can only emphasize what Dr. Bechelli said: Most important is the earliest possible diagnosis of those who are potentially ill from intake of the germ. Probably in leprosy the number of infected will also be remarkably higher than that of those who indeed become ill at some time.

Protection against leprosy is another question. Experiments in patients are impossible, but in this case also analog-experiments could be carried out in animals. For a long time we have known that mycobacterial vaccines will protect against mycobacterial infections—not remarkably well, but, nevertheless, demonstrably. Such vaccines are obviously the more effective the more akin they are to the strain causing the infection. This is why we can protect relatively well against *M. tuberculosis* infections with the BCG vaccine, but not at all against "atypical" infections. This gives us reason for expecting to find experimentally produced vaccines against leprosy more effective than BCG.

Shepard: Some years ago, when first studying vaccination against *M. leprae* in mice, we screened a number of mycobacteria that represented the various serologic groups among common mycobacteria. Included among these were human type tubercle bacilli and BCG; these were the most effective against the experimental infection, and there was no evidence that there was anything better than BCG or the human type tubercle bacillus. One of the things we still do not have for comparison is a satisfactory positive control vaccine containing leprosy bacilli. I think this is a matter of getting the thymectomized irradiated mouse infection to working on a more practical level. Your present question has to do with sensitins. This approach hasn't been taken with many different soluble products from mycobacteria, but there have been several studies of suspensions of different mycobacteria, comparing them with lepromin in lepromatous and tuberculoid patients, and the result has been that no other mycobacterium gives results similar to lepromin. One needs to remember that the tuberculoid patient has no more sensitivity to lepromin than the normal person has. This is a situation that is altogether different from that in tuberculosis.

Freerksen: Did you carry out experiments introducing *M. leprae* intradermally and then into footpads to compare the process in mice which had not had this pretreatment?

Shepard: The answer to the question is no, but we have experience related to that. The leprosy bacilli that we injected as vaccine were not given intradermally. We gave them intraperitoneally, when comparing them with other mycobacteria, and found them to be not particularly better than BCG. Another possible answer to your question comes in experiments in which the mouse was infected first in one foot and later reinfected in the other foot. The second infection developed at about the same rate as the first infection.

Freerksen: And what time difference did you have?

Shepard: We harvested the *M. leprae* when they grew up in the right foot (this was about six months after inoculation) and used them to challenge other mice in the group by inoculating the left foot.

Freerksen: Theoretically the conviction can be reached that *M. leprae* is a badly immunizing strain and other "atypical" ones are better for the purpose.

Browne: Although not experimental immunology, strictly speaking, there is an aspect of the subject that deserves consideration. The lepromin test is not the whole story in the matter of resistance or susceptibility to leprosy. In a population in Central Africa where I was working from 1936 onward, everybody contracted leprosy sooner or later. At any one time half the people in the villages would need treatment for leprosy. But the susceptibility to leprosy or its eventual overthrow by the organism did not always depend directly upon the development of lepromin resistance. Most of the children recovered spontaneously from their leprosy, but the lep-

romin reaction might remain negative; they had not yet developed "resistance" as shown by the lepromin test. This is an aspect of the matter closely related to experimental immunology, which hasn't yet been sufficiently explained.

Vischer: This is a question for Dr. Rees or Dr. Gaugas. You have shown, with your thymectomized mice, that if you give them a thymus graft later on, you can produce a reversal reaction. Can you also produce an ENL reaction in these mice and can you test them with drugs that can suppress ENL reactions, like thalidomide?

Rees: No, Dr. Vischer. At the moment we don't know how to trigger in our mice a histologic picture that resembles ENL. Therefore the answer to the question you raise is that, unfortunately, we don't have a suitable model. However, we have found some animals with quite a number of polymorphs in their lesions which Dr. Ridley considers look like ENL. But we don't know why the mice went into ENL, and so we have no standard method at the moment for setting up an experimental model for ENL. Because leprologists consider that ENL is more common since the introduction of chemotherapy, we have taken thymectomized irradiated mice heavily infected with *M. leprae* and treated them with dapsone. To date these mice have not developed ENL.

To Professor Freerksen's question on whether experimental studies are going to contribute to the discovery of a more efficacious vaccine than BCG against leprosy, I am not at all optimistic. All experimental studies have shown that the most efficacious vaccine against a particular mycobacterial infection is obtained by using a "live" and attenuated organism of the same species as that causing the infection itself. If the same situation holds for leprosy then such a vaccine must await first the successful growth of *M. leprae in vitro* and in bulk. When this is achieved there will still be the very difficult problem of producing from *M. leprae* a safe, attenuated form that can be given to man. Until such a time all we can do at the moment is to test empirically the effect of any live mycobacterial vaccine that comes along in mice against experimental infections with *M. leprae.* Such vaccines must be compared in mice with the effect of BCG. There is one vaccine that might well be tried, namely vole vaccine, which the British Medical Research Council has shown to be as efficacious as BCG against tuberculosis.

To the question of what skin test materials can be used in leprosy, the only ones available are either heat-killed *M. leprae* (lepromin) or soluble fractions obtained from live or heat-killed suspensions of *M. leprae* obtained either from man or experimental infections in mice. This latter fraction can only be obtained in small quantities because of the limited source of *M. leprae.* However, the work of Larsen and his colleagues with such material from other mycobacteria has shown that they do give reasonably high specificity when used as skin test materials in animals.

Freerksen: If we use vaccines of human and bovine mycobacterial strains against infections with *M. tuberculosis,* it is easy to demonstrate that BCG is the most effective one. If we infect with "atypical" mycobacterial strains, the homologous mycobacterial vaccine will give a better protection than BCG. In discussing the matter of whether BCG could be effective against leprosy, we had also to make objection to other vaccines from "atypical" strains against leprosy as more effective than BCG. But this is only an idea—not more. A comparison with the lepromin reaction is difficult. If one is infected by *M. tuberculosis,* he reacts to tuberculin, whether he is infected only or already ill. With regard to lepromin, this is another situation.

Kimmig: Has there been experience regarding lepromin in the behavior of lymphocytes in the lymphocyte-transformation test?

Shepard: There have been a number of papers on lymphocyte transformation in leprosy. The general finding is an inhibited or depressed lymphocyte transformation in lepromatous leprosy and, usually, a slight depression even in tuberculoid leprosy. In other words, there is no increased transformation. Reports in the literature disagree only about the degree of the depression. The *in vitro* reaction to tuberculin and

lepromin, and to soluble preparations from leprosy bacilli, is decreased with lymphocytes of lepromatous patients, and this has now been reported several times.

Sagher: A comment on your question, Professor Freerksen, with respect to mycobacterial species used for skin tests. At the International Congress of Dermatology in Munich, we reported on our experiments with "cultured bacilli" from Olitzki, discussing the problem of their identity with *M. leprae*. For comparison we took an extract of Johne's bacilli, which he used to make the bacilli grow. With the Koch phenomenon in mind we injected patients with killed cultivated bacilli, living cultivated bacilli, and natural tuberculin, as well as extract of Johne's bacilli. In some cases the living bacilli caused remarkable ulcers, which closed very soon. Killed bacilli also did this, but significantly less intensely. All, however, caused reactions and did not behave like lepromin. Most interesting is the fact that Johne's bacilli will do the same.

Now a further point of discussion. I don't believe it is possible to find *M. tuberculosis* in man during the incubation period. In leprosy we are in quite another situation: already in contacts, while we observe no clinical or other symptoms, mycobacteria are found in monocytes. That is why we can find a man during the incubation period, and treat him, before outbreak of the disease.

Freerksen: The incubation period involves a very hard problem. Do you think it possible, as in tuberculosis, that one takes in leprosy bacilli, i.e., is "infected," without an outbreak of the disease? Obviously, one can be infected with *M. tuberculosis* and have a positive tuberculin reaction for decades, but never become ill. Nevertheless, one can become seriously ill some days after infection or after a very long time. In all cases the incubation period would be variable in length; it could take years or many decades. The diagnosis depends on the method available. By means of mass miniature radiography within short intervals we will find tuberculous cases which we could not discover otherwise, because they don't feel ill and go to the doctor. Only the fact that we have radiography makes this way of finding the disease possible. From clinical processes, and this may be true also in leprosy, we cannot easily decide on the duration of the incubation time. If you have the chance of finding mycobacteria in the monocytes, you can very early detect the infection. Others, who don't do so or can't do so, will not diagnose the infection at all, or only much later. On this point, I think, we agree; not every infection will cause disease. In this general behavior tuberculosis and leprosy are very similar. On the other hand, we don't know the prerequisite by which the infection results in disease, neither in tuberculosis nor in leprosy.

We shall now start the discussion on the very broad field of *clinic*. Under this keyword we have arranged in the program many a subject that needed greatly to be listed elsewhere, but deals particularly with the clinic. I would like to put the first question, a bit simply, but also somewhat provocatively. Which is the most effective therapy in leprosy today in the general consensus of leprosy experts? How would you treat a leprosy patient if you had any therapeutic possibilities whatever and unlimited funds at your disposal?

Browne: It all depends on what you mean by leprosy. I would express, somewhat as follows, the opinions of all those who worked with me in the early stages of the investigation of B. 663: "If we ever get lepromatous leprosy, Dr. Browne, will you give us this drug. We don't mind if we become redder or darker. We know that we shall get better from our leprosy." In the case of tuberculoid leprosy I would prefer dapsone, which is cheap, good, and reliable when given in small doses up to 200 mgm. per week regularly, attaining this maximum dose in three or four months. I would continue with this treatment for at least two years or at least one year after all clinical signs of activity had disappeared. I think that, in general, this is a simple way of dealing with those two types of leprosy. A type of leprosy that I should not wish to contract myself, would be one of the unpredictable serious, nerve-damaging, intermediate forms of leprosy. Patients with these types of leprosy get the worst of both

worlds. They are bacilliferous, and have early, unpredictably severe and widespread neurologic complications. I should be much more cautious in my attack on leprosy in these subjects. I certainly would not give 100 mgm. of dapsone daily in the initial stages, but I would attain a maximum dose of 200 mgm. per week in successive stages of cautiously given increments. I would continue this treatment for at least four years, or for at least two years after all clinical and bacteriologic signs of activity had ceased. In this connection, bacteriologic signs of activity would mean the presence of acid-fast material, suggesting the presence here and there of viable bacilli not usually sampled in our very gross technique of sampling. In the case of multibacillary disease, I would continue treatment at half the therapeutic dose in a cooperative educated patient for the rest of his life.

Freerksen: This recommendation is in agreement with that in tuberculosis. Also among tuberculosis doctors it has been the prevailing opinion that the therapy has to take a long time. Should it not be possible to find a therapy schedule in leprosy which brings about an effect, earlier and more effective? For this purpose we have only two procedures:

(1) to find substances more effective than DDS and perhaps also better tolerated. By means of the modern methods of assessing new compounds, including the footpad method, we can screen more and more drugs, which sometime will replace DDS. I believe today's therapy cannot be taken as a standard of effectivity, but it is the best possible way now.

(2) As in tuberculosis, can we combine highly effective substances, or do you think that in leprosy therapy we should use one compound alone? Dr. Browne, would you please be so kind as to express your opinion about this problem?

Browne: There is no evidence that in leprosy multiple schemes of treatment will hasten reduction in the morphologic index, facilitate bacteriologic clearance, or shorten the total time necessary for clinical and bacteriologic arrest of the disease. On theoretic grounds, the single medicament therapy must be criticized, but in practice it seems to be efficacious. If we had a drug more potent than dapsone we should immediately be faced with the possibility of severe reactional episodes consequent on the release of soluble mycobacterial antigens. It is not living *M. leprae* that cause most of the damage, but the cellular reaction to mycobacterial antigens, particularly in the peripheral nerves and the uveal tract of the eye. So it is not a question of killing *M. leprae* more rapidly, but rather of controlling the inevitable cellular reaction to dissolved mycobacterial antigens. So we are up against this difficulty: we want to render the leprosy patient bacteriologically negative, but we also want to cure him of his leprosy, which is the ensemble not only of a bacilliferous granuloma but also of a particular reaction in skin, nerves, upper respiratory mucosa and uveal tract to these antigens, and for the moment I can't say that any pursuit of the objective of a more potent bactericidal drug will help us. So far, we have not been able, in any way, to effect a reduction in the actual infection more rapidly by any combination of drugs than with a single drug. If we were to do it more rapidly we might find ourselves in a very difficult clinical position.

Meneghini[1]: In a current study 50 patients (32 male and 18 female), hospitalized for lepromatous leprosy, were examined. Forty are still undergoing treatment. Ten bacteriologically positive subjects who had never been treated before, and 40 subjects not tolerating previous routine therapies or tolerating them badly, were chosen. Account was taken of the bacterial and morphologic indices in evaluating Rifampicin. The daily dosage was 600 mgm. In 46 cases, 900 mgm. in three cases, and 450 mgm. in one case (a woman weighing 39 kgm.). The treatment period varied from two months to two years. Supportive therapy, vitamin, hepatoprotective and sedative, has been given in many cases. Laboratory investigations have been made before, during, and at the end of treatment, including blood examinations, blood

[1]In cooperation with Trimigliozzi, G., Lospalluti, M. and Angelini, G. Dept. of Dermatology, University of Bari, and Hansenian Hospital of Gioia del Colle, Bari, Italy.

counts, serum proteins, electrolytes, transaminases, immunoglobulin levels, bilirubinemia and urine tests.

The results may be summarized as follows:

(a) the bacterial index became negative in two cases in a period of six months; neither had been treated previously;

(b) in the forty cases still undergoing treatment a progressive improvement in clinical and bacteriologic conditions has been observed.

In thirty-four cases the intensely positive initial bacterial index (++++) has been greatly reduced (+), and the morphologic index took account of the granules. In the other six cases the result has been similar, though the initial bacterial index was less marked. The side effects for which treatment was not discontinued were: pruritus in three cases, brownish erythema in light-exposed areas in three cases, and headache in thirty cases (only for the first few days of treatment). Side effects for which the treatment was discontinued were: lepra reaction in two cases, severe gastric intolerance in three cases, and reversal reaction with increase of bacterial index after 5-11 months' treatment in three cases. These therapeutic observations are being continued in order to collect other and more precise data.

Freerksen: When the first effective tuberculostatics were introduced in the clinic, different side effects which could not be explained were observed. It was feared that the drugs would destroy the bacteria so quickly that the catabolic products released would cause other dangerous disease. In tuberculosis treatment we now possess effective compounds and don't see these threatening phenomena any longer. In leprosy the situation can naturally be quite different. If this is the case, as you suggest, would it not be reasonable to develop a therapy scheme which is antibacterial as well as immunosuppressive?

Browne: In leprosy the situation is not the same as in tuberculosis. On theoretical grounds we may say that it might happen, but in practice we know that it does happen and it will happen. Many of us here have given a dose of 10 mgm. of dapsone and within 24 to 48 hours have seen a patient in severe exacerbation, with a temperature of 39 to 40°, and severe pain in muscle masses, in joints (with effusion), and in all the peripheral nerve trunks, etc. It does happen, and this is no theoretic objection. I wish it were.

Schuppli: I think that when discussing the problem of the leprosy reaction we should remember the Herxheimer reaction. It may not be the same, whether you treat a tuberculosis patient and observe side effects, or whether you see the analogy on the one hand between syphilis treatment and the Herxheimer reaction, which starts where spirochetes settle, and the analogy on the other hand to leprosy, which also starts where bacteria settle. We have the same side effects in leprosy reaction and in the Herxheimer reaction. For this reason I believe it is not reasonable to administer high doses, e.g., of Rifampicin and cortisone, although in the *praxis aurea* penicillin and cortisone are given in order to avoid fever in the patient. The situation in leprosy is quite another thing. In this case, I fear, you cannot cease immunosuppressive therapy, because if leprosy reaction occurs, you can control it no longer. This is quite different in the Herxheimer reaction. I think that your idea is not wrong, but somehow it seems too dangerous to me. We should start with small doses, as in syphilis treatment, but in leprosy I think it is a bit more complicated.

Freerksen: I would not like to underestimate the complications in leprosy, and apply the conditions of the *praxis platinea* to the jungle. My question was aimed at a principal problem. The immunologic phenomena are considered as an essential part of leprosy, but, nevertheless, leprosy remains an infectious disease. I think we are allowed to carry out experiments in men in order to examine whether the combination of both the therapeutic principles (chemotherapy and immunosuppression) will have an effect.

Languillon: I would like to answer the question of Professor Freerksen. For twelve years I have used sulfonamides in leprosy therapy, and have treated more than 500 patients with different sulfonamides. I em-

ploy Sultirene, a special sulfonamide, Madribon, acetyl Kelfizine and sulforthomidine or Fanasil. My knowledge pertains only to African leprosy patients. It is very important to say that the sulfonamides usually administered will cause remarkably few reactions. Furthermore, the reactions are very mild, so that I never discontinue sulfonamide treatment, even if a reaction occurs. In cases of nephritis these drugs play an important role. We do not hesitate to say that, although it is stated that sulfonamides will produce renal damage, we have observed good efficacy in lepromatous nephritis. In the tuberculoid form of leprosy we have employed different sulfonamides, and all the patients recovered within two and a half years, i.e., 100 per cent. These results are of special importance, because 90 per cent of the cases in Africa are tuberculoid. Otherwise I think that the sulfonamides are very well tolerated. We have never observed skin reactions, in contrast with the experience of many other leprologists. Among the sulfonamides I prefer sulforthomidine, because of its weekly oral route of administration. In French-speaking Africa there are more than 750,000 leprosy patients, and the drugs are taken directly to them in the villages. Therefore drugs that need be given only once a week are especially useful.

Merklen: I would like to say that I can corroborate the effectivity of certain sulfonamides in the treatment of leprosy, but, nevertheless, I don't use Fanasil at present for economic reasons. I administer Sultirene for the most part, and can say that it is more efficacious than sulfone in neuritis. But I say it with some reservations: after administration of Sultirene I observed after two or three years a few partial failures and turned to sulfones; I had some reactions with Sultirene, but nevertheless I continued the treatment. Contrary to the practice of many physicians I give high doses of 100-150 mgm. daily for three weeks per month, because I think the chance of healing will be better. Sometimes I observed bacteriologically negative results after shorter delays than one or two years.

Azulay: Another comment on the problem of vaccination. I would like to answer your question about the possibility of discovering a new mycobacterium more closely related antigenically to *M. leprae*. Up to now, BCG is the mycobacterium that is more related antigenically to *M. leprae*. In my experience in newborns I found almost 95 per cent lepromin positivity; if we are sure that the lepromin reactivity is an antigen reaction, then we are in a position to say that BCG is most similar to *M. leprae* antigenically. It may not be true, but it is what we have up to now.

Scheiber: Do you think it reasonable to isolate patients suffering from lepra lepromatosa or borderline leprosy, and to separate newborns from their mothers with such types of leprosy?

Bechelli: In a WHO Pan-American Seminar in 1958, it was recommended that the isolation of infectious cases be gradually replaced by outpatient care. This is more acceptable to the patient and considerably more economical. I think that all the leprologists here agree on this point. I can understand that in your first contacts with leprosy patients you thought of isolating all the infectious patients. This was the dominant idea in the past. In early 1924 when leprosy control started in the State of São Paulo, Brazil—let me speak of my own country—the authorities wanted to send all the leprosy cases to sanatoria. In 1933 the impression of the proponents of such a technical policy was that after some fifteen years the leprosy problem would be solved. But in practice the results were quite different. When an advanced lepromatous case was detected and isolated, he had already transmitted leprosy to some individuals. In this phase he was already naturally isolated by his neighbours, who knew that he had leprosy and avoided contact with him. Therefore it was too late to take action. The real moment you could take some action would be in a patient with indeterminate leprosy or moving toward the lepromatous type, or in any patient starting to be infectious. You cannot determine these cases in a population unless you have a close surveillance of contacts or survey of the population, or unless it is a highly educated one. To do this you should not

send patients to sanatoria, for it would complicate in a remarkable way the development of leprosy control. Patients would hide from public health authorities, and the situation would be much worse, without considering the increasing of prejudice, and, not less important, personal aspects, the disruption of families, and related conditions. When considering the economic aspects, I might mention the example of India. The number of patients in India is estimated as 2.5 millions. If you take into consideration that 20 per cent are lepromatous, there are 500,000 such cases. How could the country afford to isolate them, even if isolation were a good method? These are some of the arguments which may be used with regard to the isolation of lepromatous and borderline patients. Indiscriminate isolation of these patients is really over, in the history of leprosy. I am not criticizing the authorities who in the past tried to take very severe measures of isolation against leprosy patients, for the knowledge of leprosy was deficient, and the drugs to treat it were very poor.

Rees: Very important trials are going on in Burma, New Guinea and Uganda on the value of BCG against leprosy and you are all aware that there is a very big difference between results in Uganda and Burma. The results given by Dr. Bechelli today are rather more extensive than those published to date by WHO, and in particular his new figures suggest that there may now be some slight protection in the children given BCG. Since the timing of intake into the Uganda trial was a single intake at the beginning, whereas in the Burma trial children were taken in year by year, I wonder whether Dr. Bechelli has had an opportunity to analyse his results in relation to the length of time since BCG vaccination. In other words has he any evidence that BCG protection is showing up in the children vaccinated earlier compared with those vaccinated more recently?

Bechelli: In fact the trial in Uganda and the trial in Burma have followed different lines. In Uganda Dr. Kinnear Brown and his group tried to examine all the child population, allocating them to BCG and to control groups, and the follow-ups were started only later. In this type of study, when the re-examination is made, the interval between the first examination and the second or third is not similar for all children. In view of this Dr. Brown and Dr. Sutherland were obliged to take an average period; let's say, in the first follow-up, the average interval between intake and follow-up was about two years and a half. In the Burma trial there is a yearly intake of children, and therefore these children are reexamined at exactly yearly intervals. The question that Dr. Rees puts is a very interesting one. We have been trying to study it for two years. The material is now in the computer, so that, unfortunately, I cannot give you the full answer. So far there seems to be no substantial difference in each cohort of children. The first group or cohort of children included in the trial does not seem to show results that are substantially different from the results in the other cohorts.

Lechat: May I say just one word on the isolation of children by demonstrating some epidemiologic data. The probability of infection in children living with their lepromatous parents in a leprosarium is about 20 per cent, as has been observed in the Philippines. The probability that these children will be spontaneously cured from illness is three-quarters; that means for 25 per cent the risk of going on with the leprosy they have acquired. The probability not to be cured, for children staying in leprosaria and observed by a physician when their cases were detected at the beginning, is one-tenth after one year according to observations made in Africa. Therefore, the chance to develop severe leprosy is about five per 1000, nothing to compare with the mortality of these children when they are removed from their parents, as observed in many so-called preventoria in the world.

Freerksen: As no one has asked for permission to speak about surgery or orthopedics and rehabilitation, we shall see a film which Dr. Selvapandian produced in cooperation with the DAHW.

After the showing of this film the colloquium came to an end at the castle of Tremsbüttel near Borstel. The participants then assembled for a banquet in the great banquet-room.