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EDITORIALS

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Strategy for Leprosy Control

The ability to control leprosy and to maintain this control long term represents the ultimate goal of all those working in the fight against this disease[1]. This apparently unattainable goal, with its numerous well-known scientific, technological and logistical limitations, may now be one step nearer, thanks to the accumulated efforts in, and the results of, fundamental and applied leprosy research. This has greatly benefitted from the very active support of the Special Program for Research and Training in Tropical Diseases (TDR) supported by the UNDP/World Bank and WHO. Published results and those reported at the XII International Leprosy Congress now enable us to take stock of the situation and to envisage a more coherent and integrated strategy for the control of this disease.

Three complementary aspects must be considered: is control theoretically possible, is it practically attainable, and how could such efforts be applied in the field?

Is leprosy control theoretically possible?

As for any transmissible infectious disease, the answer to this question depends on our knowledge of its transmission and of the reservoirs of the pathogenic agent. Leprosy was described as being a strictly human disease, and classically considered as being transmissible experimentally in its lepromatous form in healthy animals with only the greatest difficulty[2]. However, several recent reports mention firstly, the capture in Louisiana, Mississippi and Texas of wild armadillos carrying mycobacteria which could not be cultured and with characteristics making them indistinguishable from *Mycobacterium leprae*[3]; and secondly, the spontaneous appearance and transmission of *M. leprae* in a chimpanzee[4] and a mangabey monkey[5].

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Could these elements lead to a questioning of the theory of the absence of *M. leprae* reservoirs other than in man?

A certain number of epidemiological arguments indicate that this contamination may in fact have been caused by previous contact between human carriers and these animals which are highly sensitive to any mycobacterial infection[3], rather than the *a priori* existence of animals which spontaneously carry and transmit the bacilli[6]. However, our epidemiological knowledge of this situation is still only partial and, further, more detailed and particularly sero-epidemiological studies should be conducted in both populations concerned. It is nonetheless logical to think that man is the principal reservoir[7]; it is much more likely for a healthy individual, at high risk, to have the unfortunate experience of contact with *M. leprae* in a given human population containing an individual excreting infective bacilli than to be in chance contact with these potentially transmitting animals. However, certain exceptional situations should be kept in mind, such as that recently reported by Lumpkin, *et al.*[8], showing direct human transmission from infected armadillos.

As has already been achieved for smallpox, another infectious transmissible disease with a solely human reservoir, is there a chance that leprosy might be controlled? The history of the disease shows us that it is possible[9]. Observation of its disappearance and then non-reappearance in an endemic and/or epidemic form in certain regions where it was previously present endemically (Norway, France, Germany, United Kingdom) shows us the reality of this disappearance and also should indicate the path to follow, by analysis of the factors contributing to this situation. Unfortunately, analysis of the different factors involved in this natural success was until now based on incomplete epidemiological data, and we were thus reduced to speculation and hypothesis. Because of the socio-geographical predominance of the disease, certain classic hypotheses brought into play different climatic or nutritional factors which have in fact been easily refuted[1, 9]. Variations in living standards or hygiene which enabled a certain limitation of transmission do not in fact seem to have intervened at the time of the disease's disappearance. The role attributed to the drastic, obligatory isolation of leprosy patients also now seems to have been limited, as several documented studies have shown[9]. On the other hand, as emphasized by Chaussinand[10], the occurrence of mortal epidemics (plague, cholera, etc.) may have led to the sudden disappearance of transmitting individuals because of their confinement to colonies. The importance of this differential effect with regard to the non-affected population should thus have been associated with the efficacy of segregation of the transmitters in a given population. In the knowledge of the theoretical and practical imperfections of such measures, this action of selective mortal epidemics should be considered as cofactorial to the same degree as the previous factors. To explain both the disappearance and non-reappearance of the disease, the hypothesis of the natural selection of individuals resistant to leprosy, as emphasized by Chaussinand[11] and others[12], is attractive.

Apart from epidemiological arguments[11], which are not without apparent contradictions and may indicate an antagonism between leprosy and tuberculosis, are there other, more convincing arguments in favor of this last hypothesis? Present published data enable us to put forward both direct experimental and indirect arguments in man in its favor.

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Experimental data have demonstrated the similitude between immune responses to the different mycobacteria tested in animals[13] and also the existence of a common genetic control which commands the natural resistance of animals against pathogenic mycobacteria[14]. Analysis of the immune responses during experimental infections provoked by different mycobacteria such as *M. tuberculosis, M. leprae, M. lepraemurium* or *M. avium-intracellulare* has highlighted the major role played by cell-mediated immunity (CMI), where phenomena of cooperation between thymus-dependent lymphocytes and macrophages intervene[15]. A parallel has been demonstrated between the production of a state of delayed hypersensitivity (DTH) and acquired post-infection protection[16]. A certain amount of experimental evidence has shown the existence of crossreactivity, not only in measurements of DTH[17, 18] but also, and above all, in the study of acquired protection[19]. It has thus been demonstrated that immunization with *M. tuberculosis* Ri Ra protected against *M. tuberculosis* R1 Rv, and also against the H37 Rv strain[20]. In the same way, the BCG strain of *M. bovis* protected against *M. tuberculosis* H37 Rv and R1 Rv[16, 21], *M. leprae*[22], *M. lepraemurium*[23, 24, 25], and *M. avium-intracellulare*[26].

The reverse was also demonstrated[27]. However, infection with *M. kansasii* was ineffective and did not modify the protective value of BCG against infection with *M. tuberculosis*[28], thus invalidating the modulatory hypothesis put forward by Rook, *et al.* concerning a negative interference of atypical mycobacteria on the action of BCG[29]. This acquired resistance was demonstrated in actively immunized animals and also after the passive cellular transfer of thymus-dependent lymphocytes[30, 31, 32]

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from actively immunized animals to naive syngenic recipients, thus excluding any participation of nonspecific residual macrophagic activation which could explain the crossreactivity. However, this did not exclude the presence in transferred cells of a mixture of different T-cell clones, recognizing the antigens of each mycobacterial variety. This possibility was recently tested by the use of T-cell clones produced *in vitro* against *M. leprae*[33, 34, 35]. It was demonstrated that these clones, in the presence of accessory cells and specific antigens, *in vitro,* were capable of producing interleukin-2 (IL-2), and gamma interferon (IFN γ), of activating macrophages[33], and of inhibiting the growth of *M. tuberculosis* in these macrophages[34]. Also, the *in vivo* subcutaneous injection of these cloned T cells with the antigen led to the activation of macrophages which had acquired a bactericidal activity[33]. These different parameters for the *in vivo* and *in vitro* measurement of CMI demonstrate the responsibility of homogeneous cloned T cells in the acquisition of an acquired resistance. However, it should be emphasized that these activations occurred both when using the inductor antigen (irradiated *M. leprae*) and when using another mycobacterium such as heat-inactivated BCG[33]. On the other hand, no activation occurred with another bacterium such as *Listeria monocytogenes.* Crossreactivity, tested with cloned T cells, indicates that these cells were selected for an antigen common to these two mycobacteria[36], and that this antigen is immunodominant since the frequency of proliferation of this clone predominates (Kaufmann, S., personal communication). This enables a definite conclusion regarding the capacity of mycobacteria to induce active protection against other mycobacteria: for example, BCG against tuberculosis and leprosy. We will consider below the apparent contradictions of these results with regard to observations made in man.

Several recent reviews have analyzed the influence of genetic factors in susceptibility to pathogenic mycobacteria without any definite conclusions being reached[1, 13, 15, 37]. However, the existence of an autosomal and dominant gene has recently been demonstrated which is localized in chromosome 1 of the mouse and expressed in two allelic forms, enabling segregation of mouse strains with respect to their sensitivity (NS) or their natural resistance (NR) to infection by *M. bovis* (BCG)[14]. This gene, called the BCG gene, is phenotypically expressed in mononuclear phagocytic cells[38] and is associated with the metabolism of oxygen derivatives, and particularly the spontaneous and specific production of hydrogen peroxide (H_2O_2)[39]. It intervenes initially in the natural resistance of mice in the absence of T cells[40] by permitting or not permitting the growth of mycobacteria in macrophages. It also seems to be associated, probably indirectly, with the induction of an acquired cellular response[41, 42]. After immunization with BCG, the types of delayed hypersensitivity to tuberculin, classified according to their kinetic of expression, with either a

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maximum at 18 hours (DTH 18) or at 42 hours (DTH 42), seem in fact to be directly related to the expression of nonspecific natural resistance: NR strains present a DTH 18, while the majority of NS strains have a DTH 42 response (Hurtrel, B., *et al.*, manuscript in preparation). At the same time, NS strains presenting a DTH 42 after active immunization possess acquired resistance, while NR strains with DTH 18 do not[41]. From this we can suppose the determining influence of the BCG gene in natural resistance and also its relative influence in CMI. It has been demonstrated elsewhere that other genes (in particular those linked with H2) may intervene in the intensity of DTH expression in the mouse[43] and in man[44] after BCG vaccination, without this being directly associated with the intensity of secondary acquired resistance.

The influence of the BCG gene in resistance to *M. lepraemurium*[45, 46] has been demonstrated independently. This phenotypic expression characterizing the differences between strains in their reaction to these mycobacteria, particularly when the C57BL/6 (NS) and C3H (NR) mouse strains are considered, was found in the study of mortality produced by experimental infection with *M. tuberculosis*[47]. It was also seen in the analysis of the efficacy of antituberculosis chemotherapy (Lecoeur, *et al.*, manuscript in preparation), the C57BL/6 strain presenting a level of post-therapy relapses which was significantly lower than that seen in C3H (these relapse levels were evaluated from the number of mice carrying mycobacteria and the number of mycobacteria per mouse). Finally, the efficacy of irradiated *M. leprae* as a vaccine, studied in NS and NR strains, showed an identical variation, the former acquiring resistance and DTH 42, the latter a DTH 18 without the acquisition of transferable protection[48].

All of this experimental evidence enables the confirmation of a strong similarity; firstly, in the type of immune responses induced and secondly, in the genetic control of these responses[49]. Thus, phenotypic expression, linked to the BCG gene, directly and indirectly controls later cellular responses, which themselves can be modulated according to other regulatory mechanisms which are controlled genetically by H2. Early experimental evidence indicates the possibility of mouse strain classification according to an immunological spectrum, depending on linked genetic factors and those which depend on mycobacterial infection (dose, virulence, inoculation route)[15, 50]. Individuals could also be classified by their acquired responses to mycobacteria: at the extremes of the spectrum we find the stable dominant "responders" and "non-responders" and in the middle, those weak responders who, according to the mode and intensity of the infection and also additional regulatory factors, may vary within the spectrum with a preference for the non-responder pole. These latter would be "variable non-responders" but mimicking in the overall expression of the disease the form of "stable non-responders." This approach also enables a better understanding of imperfections in the observations made in the study of genetic control of human leprosy, among twins[51],

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and in the analysis of associations with HLA markers[37], the global definition of lepromatous leprosy (LL) individuals being incomplete.

This reinforces the epidemiological approach of a possible interference between tuberculosis and leprosy, and the existence of non-responding subjects, with natural resistance to mycobacteria, who are not responsive to *M. tuberculosis* and probably to *M. leprae* as well. In tuberculosis, non-responsiveness leads to dominant selection by early death[52, 53]; while in the case of leprosy, no selective action can be observed because of a long incubation period and the lack of likely mortality. The apparently higher frequency of mortality caused by tuberculosis in LL subjects as opposed to subjects presenting another form of leprosy, reported by different authors[12], is insufficiently documented to constitute a formal argument. Further, mortality in tuberculosis can be caused in several different ways[54], thus no definitive conclusion can presently be put forward. However, this may be linked to the higher frequency of mycobacterial infection other than *M. leprae* in the armadillo[3]. Further, the modes and frequency of mycobacterial transmission may be different in each patient[55]. It is possible that the frequency of transmission in leprosy is caused more by multibacilliary LL subjects (non-responders) than by paucibacilliary TT responders[1]. This is certainly not the case in tuberculosis, where the intensity of the cellular immune response is associated in particular with pulmonary cellular destruction[56] which allows local bacterial multiplication and increased transmission. This would also partially explain the increase in tuberculosis morbidity among populations previously selected for their resistance to mortality[57].

Finally, another apparent contradiction concerns variable efficacy in the appreciation of BCG activity in the fight against leprosy[58, 59]. Reported results refer to protection varying from 20–80%, and have meant that BCG has been rejected as a potential vaccine against leprosy. The latest results obtained in the Chingleput trial in India also tend toward the same conclusion[60]. However, two major observations made during this trial should be emphasized. The first concerned the very weak efficacy apparent in tuberculosis prevention in a group of children previously non-sensitized by atypical mycobacteria[61]. Secondly, there was greater efficacy in the protection of reactogenic forms (BT and TT) when compared with other nonreactive forms (BL and LL), although the figures were too low to be statistically significant[60].

Thus, from results in man, how can these apparent contradictions by analyzed? Stanford, *et al.* have suggested that the impact of atypical mycobacteria leads to a previous sensitization which raises the level of resistance of subjects, and makes it no longer possible to judge the protective effect of BCG[62] which in any case is inhibited. For several years we have suggested[63] that another cause be considered for this apparent failure of BCG in the fight against tuberculosis and leprosy, that being a

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non-response to pathogenic or atypical mycobacteria linked to genetic control, as has clearly been shown in experimental models[43]. Thus, because of their genetic polymorphism, individuals do not present a uniform immune response to mycobacteria. As shown experimentally by G. Biozzi, *et al.*[64], independent genetic selection affecting the metabolic activity of macrophages has enabled a clear separation of individuals into responders and non-responders with regard to their immune responses. It is also possible that the combined pressure of independent (major endemia) and specific (tuberculosis) selection has led in certain regions to the control of leprosy, leaving alive only the large proportion of subjects able to produce a protective cellular immune response, after the exclusion of those incapable of producing this response but who were privileged carriers. With a decrease in transmission, and subjects acquiring a specific antituberculosis and thus antileprosy resistance (compare number of Mitsuda-positive individuals among PPD-positive subjects)[65], leprosy has died out in these regions.

Why however does this not seem to have occurred in all regions where at present tuberculosis and leprosy exist side by side? A striking example can be given concerning the Chingleput region, where the levels of incidence of these two diseases are both high[61]. In our view, two main arguments provide the answer to this problem. Firstly, the mycobacteria responsible for tuberculosis in this region is a Madras variant of *M. tuberculosis* which has been shown to be non-virulent in the guinea pig[66], and which is responsible for the uncharacteristically long period (8–10 years) between primary infection and the appearance of the tuberculosis disease[61]. Secondly, an epidemiological argument clearly shows the absence of post-primary infection acquired protection in this population, where the incidence of bacteriologically active tuberculosis disease is correlated in a linear way with the age of sick individuals. In contrast, in neighboring populations, with acquired resistance, incidence is slowed up between 15 and 55 years, as demonstrated by a characteristic plateau[43].

Several limiting elements which do not allow a definitive conclusion should be considered in this increase. Firstly, our lack of exact knowledge of the different forms of tuberculosis expression and secondly, the type of immune response presented by these individuals. Is this a homogeneous population? An indication may be given by the analysis of cutaneous responses to tuberculin after BCG vaccination. In infants who were previously not sensitized by mycobacteria (PPDS and PPB negative), two clear categories were seen—one presenting classic persistant positive reactions and the other apparently paradoxical, whose positivity lasted only a short time, being present at the fourth month but absent after 2½ years, whatever the dose and the BCG strain used[61].

And, in the same way, is the leprosy population homogeneous in its non-responsive mechanisms? No data presently available enables a firm conclusion on a local level. However, this may be the case, as was clearly seen from the discussions at the XII International Leprosy Congress, based on two recent studies conducted by Convit, *et al.*[67] and Nogueira, *et al.*[68]. The first clearly demonstrated the existence of heterogeneity in the efficacy of immunotherapy achieved using multiple injections of BCG and *M. leprae*: "a core of patients (around 30%) exists who do not show clinical or immunological

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changes after a series of 8 to 10 injections during a period of two years; also preliminary data suggest that a similar irreductible core exists in the healthy contacts of patients with leprosy." The second study, carried out *in vitro* on Brazilian leprosy subjects, clearly showed the deficit in INF γ production among LL and BL subjects. For certain individuals (about two thirds), this deficit was corrected by the addition of purified IL-2 and antigen (*M. leprae*), the remaining third never being corrected. During the study it was thus possible to note the existence of heterogeneity with regard to local lesions as well as the non-response mechanisms of specific blood cells of LL-classified subjects. This test would thus enable the prediction among LL anergic forms of those who are primary nonreactive subjects and those who would become so secondarily through an acquired suppressive mechanism, which could at least be corrected *in vitro*. However, this test was not predictive in contact subjects who are non-responders and not previously infected[68]. It should also be noted that anergy and a deficit in IL-2 were recently found in murine leprosy[69] and in BCG parenteral infection, the latter being corrected by the injection of purified IL-2[70]. It thus seems there is a clear consensus, presently based on immunogenetic evidence, regarding the heterogeneity of LL forms in man and experimental models. These data should lead us to fundamentally modify our concept of vaccine potential (using *M. leprae* alone or associated with BCG) in prophylactic and immunotherapeutic methods for the control of leprosy based on the wholesale vaccination and chemotherapy of leprosy patients.

Is it possible to control leprosy? The answer will come from the clear-cut strategy to be adopted, which should have simple application methods enabling its use in all regions and under all sanitary conditions. With our knowledge of the heterogeneity of anergic forms, a clear strategy can be planned. In contrast with that successfully applied in the fight against smallpox, where an insurmountable immunological barrier was raised against smallpox virus transmission, the plan for leprosy must build a solid chemotherapeutic wall around true high-risk subjects, that is to say, primary nonreactive subjects and secondary carriers. The strategy must therefore have two main aims: firstly, to detect these primary nonreactive subjects and secondly, working from them, to detect active carriers so that they can be given effective and controlled chemotherapy. This strategy has the advantage of being directional and preventive and working from a previously clearly defined aim.

What means do we have at present to detect these individuals on a large scale? They have evolved from already known data and recent progress concerning both the recognition of the *M. leprae*-specific phenolic glycolipid I antigen[71] and the determination of the capacity to inhibit intracellular BCG macrophages[72]. The first enables the production of a highly specific immunoassay for the early detection of the humoral immune response of subclinical leprosy infection[73, 74, 75], and the detection of an antigen soluble both in the tissues and perhaps the urine of infected subjects. The second would confirm nonspecific natural resistance to mycobacteria before any contact.

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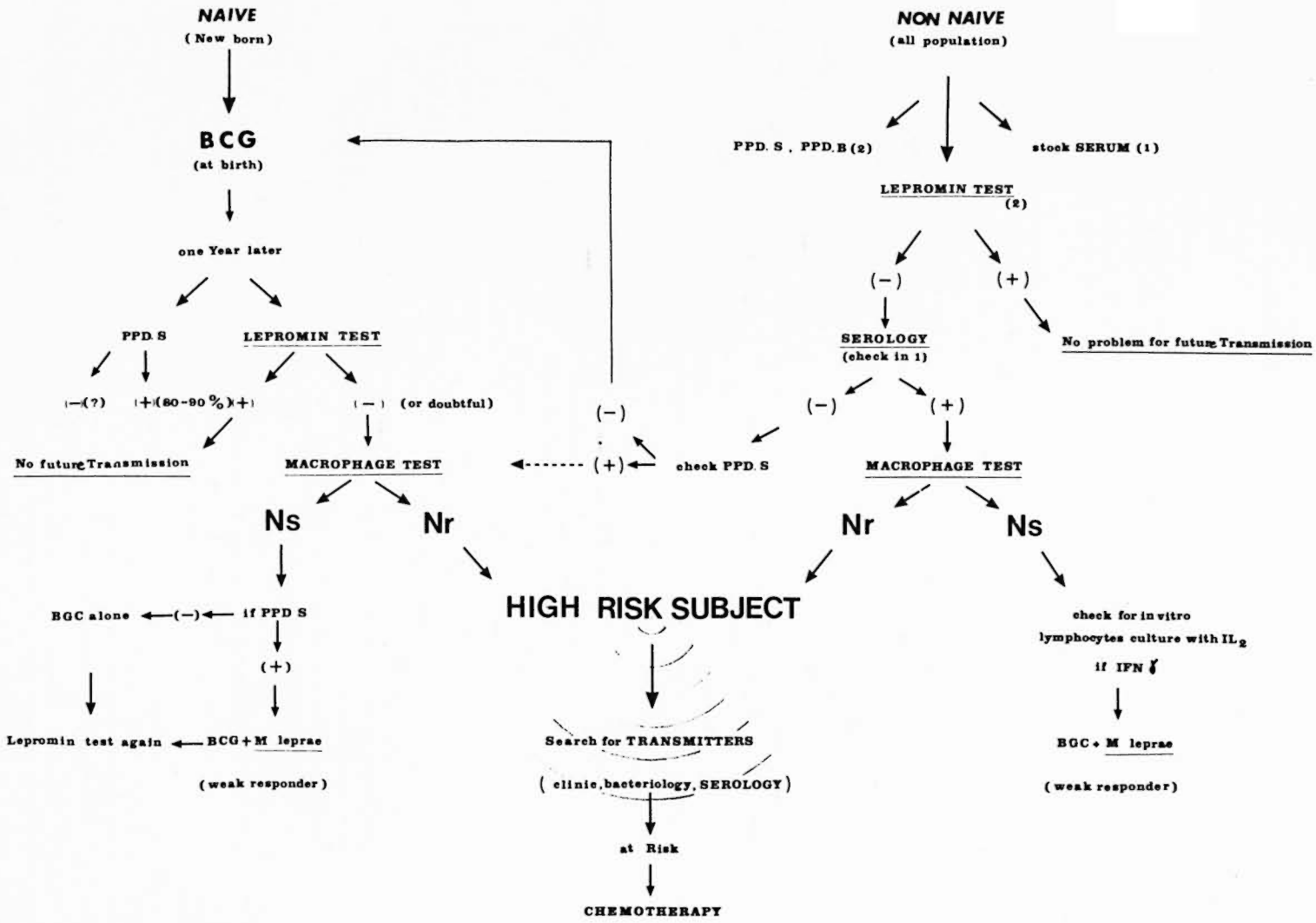

THE FIGURE. Schematic diagram for leprosy control, by detecting primary non-responders from total population in respect to their contact with mycobacteria.

Although many studies are required to confirm these results, the way is now open to a coherent strategy for implementation in endemic zones (The Figure).

Two complementary approaches could also be pursued: a) that concerning subjects who are totally naive with regard to mycobacteria (pathogenic or not), e.g., neonates and babies, and b) that concerning individuals who, after birth, might have been in contact with mycobacteria.

The first approach would envisage the use of BCG vaccination at birth, both as a direct prophylactic method and as a means for characterizing the immune response, the vaccine strains being strictly controlled. After a year, vaccine efficacy and immunological analyses would be evaluated by the study of cutaneous reactions to both tuberculin and lepromin (Mitsuda reaction: no other test available at present has been shown to be equivalent to this reaction for its prognostic value). Analysis of the latter would make it possible to classify subjects into responders and non-responders. Responders have a high probability of being unaffected in the future by lepromatous infection; while, in contrast, non-responders might constitute a part of the primary nonreactive population. How can the size of this population be judged? In our view, only one test presently available would be suitable, that being the measurement of the ability of their macrophages-monocytes to inhibit or not the *in vitro* growth of BCG as has recently been demonstrated. LL subjects having a natural capacity to significantly inhibit this growth are then classed NR, while TT subjects only weakly inhibiting growth are classified as NS[72]. Two types of response may be observed among these non-responders after BCG vaccination. With this test, subjects might be classified as NS individuals (the first BCG vaccination being ineffective), in which case they are given a second vaccination of BCG alone or BCG + *M. leprae,* according to their reaction to tuberculin. Their conversion then would classify them as NS weak responders but with a favorable prognosis. On the other hand, using this test, certain individuals will be classified as NR and, in our view, they constitute the true, primary nonreactive subjects. It is from these subjects that the second part of the antileprosy strategy must be evolved, that of a systematic and constant detection, working from them in an excentric circle toward active and potential carriers. These would be tracked down by clinical, bacteriological and, above all, immunological screening (anti-phenolic glycolipid serology). Each active or potential carrier would then, according to the probability of potential transmission, be isolated and effectively treated by polychemotherapy until the disappearance of the risk. According to the degree of risk for these primary nonreactive subjects, chemoprophylaxis using rifampin could be envisaged for these individuals after a systematic check of their specific antibody titers. Any abnormal increases in antibody titers over the period would lead to a suitably adapted therapy.

The second approach concerns those subjects in endemic zones who are not naive with regard to mycobacteria. If, because of age, BCG vaccination has or has not been undertaken, the key examination remains that of the Mitsuda skin test, associated with reactivity to PPDS. Here again, these two tests will permit a prognostic differentiation of responders and non-responders. Among non-responders, the first analysis would then be a serological study to evaluate the level of *M. leprae* infection, rather than a test for BCG growth in macrophages. Those with a negative serology, probably belonging to a population without previous contact with *M. leprae,* should then be vaccinated or revaccinated with BCG and rechecked a year later using the same cutaneous and serological tests, and we would then return to the previous analysis of subjects who are naive against mycobacteria. Those with a positive serology, whose levels should be determined by a broad range of sero-epidemiological studies, would then be examined using the test for BCG growth in their macrophages so as to classify them as NS or NR individuals. NS subjects would then be systematically examined for their *in vitro* lymphocyte responses by IFN γ production in the presence of *M. leprae* and IL-2. Pre- or post-chemotherapy correction would be undertaken according to their bacteriological levels, using BCG and *M. leprae.* NR subjects would correspond to primary nonreactive subjects, and their levels of bacteriological infection evaluated (antibodies, soluble antigen) in order to pursue a suitably

adapted therapy. And, once again, using these subjects, active carriers could be detected and then treated.

Thus, by using effective chemotherapeutic weapons, high performance immunological assays, and a clearly defined strategy, we might hope to achieve the long-awaited control of leprosy. But two major obstacles must still be overcome. Firstly, the feasibility of such a plan, which is logistically so complicated, and secondly, its true reliability. However, these points could be evaluated immediately under suitable field conditions, particularly in certain endemic regions where the necessary scientific and sanitary infrastructures are already operational.

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