CONTINUING MEDICAL EDUCATION

IMMUNOTHERAPY IN LEPROSY

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Leprosy, a mildly contagious disease, has a very slow and insidious progress. Prior to the fifties, we hardly had any drug and the disease was thus considered to be incurable. With the introduction of diaminodiphenyl sulphone (DDS), a cheap and effective drug against leprosy, the era of gloom that prevailed prior to 1948 ended. But soon it was realized that this drug needed to be administered for a long time. Further, it was found that in those patients who were irregular and also among those who had been taking DDS religiously, bacillary positivity continued for years. Several of these cases apparently worsened despite treatment. In 1964, Pettit and Rees[1] showed that the organisms from these patients were viable as tested in the mouse foot pad and showed resistance to DDS. Since then, DDS resistance has been encountered in all parts of the world, where it has been looked for.[2] In short, it was rather too much to expect that DDS and for that matter any other drug given alone could render all *M. leprae* non-viable in highly bacillated lepromatous or near lepromatous cases.

Since 1965 and 1970, newer drugs like clofazimine and rifampicin respectively have been added for the treatment, and for last 6-7 years it is being strongly advocated that the drugs should be used in combination so that the problem of drug resistance could be reduced.[2] But soon it was found that despite the use of drugs in combinations, viable bacilli could persist in the tissues for long periods even in the presence of DDS and rifampicin to which the organisms remain quite susceptible. On an analogy with *M. tuberculosis*, the continued survival of these persisters has been attributed to a state of bacterial hibernation. During hibernation or dormancy, the metabolism of the organism is at such a low pace that conventional drugs (antibiotics) are not able to have an effect.

Such a phenomenon is not unique to leprosy. In tuberculosis, typhoid and many other infections also; drug sensitive viable organisms have been detected despite effective treatment. What is unique in leprosy is that unlike other diseases where host defences are partially or fully intact to deal with these smaller number of organisms, in leprosy the specific immunity is deficient and it does not return even with treatment as is evidenced by continued lepromin negativity. Therefore, the lepromatous cases are unable to deal with these persistor bacteria. Thus, there is a real possibility that when the drugs are withdrawn, in a proportion of cases, these drug sensitive organisms may start multiplying and result in a relapse. Such relapses have in fact been seen in 2.5 to 10% of the cases on withdrawl of the drugs. Further, because of lack of return of specific CMI, long treated cases theoretically, stand a greater risk of reinfection.

It thus stands to reason that these highly bacillated cases need some sort of assistance

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in getting rid of their *M. leprae*—whether these are resistant bacilli or persistor organisms. Multi-drug therapy appears to be the answer to the prevention and treatment of resistance and possibly also the persistors. Because of the limitations of therapy, and the prolonged course of treatment, it is desirable if some way could be found which would augment the host defences to a point that it is able to effectively deal with not only these small numbers of resistors and persistors but also reduce the time taken in reaching smear negativity and evolve in these individuals a reasonable specific cellular immunity.

Indeterminate leprosy, where the bacilli are not many, is yet another situation where the host CMI response has yet to fully evolve. In those indeterminate cases, who continue to be persistantly lepromin negative and thereby have a higher chance of going in for the bacillated types of leprosy, the need for inducing CMI is all the more. Immunotherapeutic procedures appear to be the answer to some of these problems.

Studies carried out by Dharmendra and Chatterjee[3] in Bankura (West Bengal) have shown that lepromin negative individuals in the community had 8 times greater risk of developing leprosy than their counter-parts who were lepromin positive. Further, the former group was at a greater risk of getting serious forms of the disease. This suggested that lepromin reactivity (Mitsuda type) is a strong indication of the outcome of infection, if it occurs. This thus implies, that if control measures are to succeed, the specific immunity to *M. leprae* in this group has to be cared for. As we all know that contacts of lepromatous cases run almost 8 times higher risk of getting the disease, Mitsuda negative lepromatous leprosy contacts thus need special attention in respect of the immunological measures. It could be argued that boosting specific CMI in these contacts is really vaccination. However, it can also be contended that several of these contacts may already be infected and incubating the disease, thus even vaccination in this group is a therapeutic measure. Lastly, a successful immunotherapeutic measure, in leprosy atleast, is an important step towards development of an effective leprosy vaccine.

Before we go on to the methods available for immunotherapy, a word about the immune defect in leprosy which is sought to be corrected. The exact defect of CMI in leprosy is not known. Both T-lymphocyte and macrophage functional defects have been implicated. Others have reported lack of macrophage lymphocyte interaction. Some have suggested that T-lymphocytes have been turned off either by the presence of too much antigen or by the action of suppressor cells or the presence of circulatory humoral factors. Further, there is evidence to suggest that the immune defect in leprosy is specific; non-specific immune depression appears to be a secondary phenomenon. This non-specific CMI deficiency does not appear to contribute to the evolution and the progress of the disease.[4,5] The specific immune defect appears to exist from prior to the contact with *M. leprae* as even successful treatment of the disease is not accompanied by lepromin conversion.

Based on these observations, various approaches have been made to break the immune tolerance of lepromin negative patients to *M. leprae*. These include use of, (a) BCG, (b) killed *M. leprae* and BCG, (c) saprophytic mycobacteria *Myco. w*, (d) related organisms such as ICRC bacilli.

BCG

The influence that a tubercular infection, spontaneous or provoked, may exert on the evolution of leprosy has been the subject of numerous investigations in the past. On the basis of epidemiological data, suggestions have been made that tuberculosis and leprosy are

antagonistic and that where former prevails, the latter declines.[6] Thinking on these lines, several groups of workers have tried BCG for its prophylactic value against leprosy. Lepromin test has been the index of its efficacy. Even though the workers in the earlier years found a high to very high percentage of lepromin conversion with its use in contacts, its role in the prevention against leprosy continues to be debatable particularly in the light of well controlled trials carried out in Uganda, Burma, Karimui and India. Side by side, BCG has also been tried for its immunotherapeutic role in leprosy patients. Lowe and McNulty[7] gave 0.1 gm of BCG to 104 tuberculin and lepromin negative lepromatous patients. On retesting 2 months later, 84.6% were found to be tuberculin positive. Definite lepromin conversion was noticed in 12, whereas another 34 showed a mild early or late reaction.

Convit and associates[8] had earlier shown that of the 113 lepromatous patients who had been rendered smear negative by sulphone treatment, 46 became lepromin positive. The lepromin conversion was higher among those who originally had tuberculin positivity (53.2%) as against those who were negative (25.4%). In the same study, injection of BCG to indeterminate patients who were both lepromin and tuberculin negative, showed conversion in 87.5% cases. Thus the authors suggested that BCG vaccine should improve the prognosis of lepromatous or potentially lepromatous cases, particularly in those in whom sulphone treatment had arrested the disease.

In a similar way, Menzes[9] vaccinated 16 indeterminate patients with 400 to 1200 mg BCG. Seven of the cases showed sudden transformation to reactional tuberculoid leprosy. The authors attributed this to a sudden increase in the antigen, may be *M. leprae* itself (in view of frequently observed smear positivity at the beginning of the reaction), or BCG alone as had been given in this experiment or in association with leprosy or tuberculosis bacillus. The authors found no such change in the cases having other types of leprosy including tuberculoid and lepromatous.

In contrast to these, a conversion in only 4 to 5% of the cases has been reported by other workers. On the whole, it has been found that inoculation with BCG, results in Mitsuda conversion in only a small proportion of the cases and the lepromin positivity thus achieved is transitory. Further, this was not associated with any protective immunity. These immunotherapeutic studies thus show doubtful beneficial role of BCG in leprosy. The procedure has therefore been given up. Even its role as an immunoprophylactic agent has not been found significant.

(b) Killed *M. leprae* with BCG immunotherapy

In 1972, it was demonstrated that lepromatous patients lacked the capacity to clear injected killed *M. leprae*, while the same patients developed a competent tuberculoid granuloma when another mycobacterium BCG was injected. This was in marked contrast to the response of Mitsuda positive patients and contacts.[10] In 1974, the same group reported that when BCG was added to the injection of killed *M. leprae*, even lepromatous patients developed competent granuloma at the local site with clearance of both BCG and *M.leprae*.[11] This provided the basis for use of a mixture of two mycobacteria, one providing the necessary specific antigen and the other triggering the macrophage digestion. Such a combination of two mycobacteria had in fact been tried earlier in murine leprosy. Resistance to *M. lepraemurium* was found to be enhanced following inoculation with killed *M. lepraemurium* and BCG.[12]

In leprosy, BCG has been found to give equivocal results. Lepromatous patients have an enormous load of *M. leprae* (live and/or dead) and still do not seem to respond or are rather tolerant to the organisms. It thus stands to

reason that *M. leprae* or its antigen does not induce response against itself. Based on these observations Convit and his group [13-15] have used a vaccine comprising of heat killed armadillo derived *M. leprae* (6×10^{1}) organisms with BCG. The dose of BCG was adjusted depending upon the individual's response to 2 units of PPD. Heat killed *M. leprae* have been used as it had been shown earlier that immunogenicity of *M. leprae* is not detectably altered by autoclaving.[16]

The authors have used this vaccine as immunotherapy in 577 patients and contacts. These included 351 active BL/LL cases, 155 inactive (smear negative) BL/LL patients who had received long periods of treatment, 46 persistantly Mitsuda negative indeterminate cases and 25 lepromin negative contacts of lepromatous cases. In addition to the clinical and histopathological response, the authors studied reaction to the specific protein antigen (SPA). All the 25 contacts showed a positive reaction to SPA and all those who were tested showed Mitsuda positivity following single vaccination. In the later observation period, none of the contacts developed TT/BT leprosy even though some of them may have been harbouring infection. Of the 46 Mitsuda negative indeterminate patients, 94% showed SPA and 80% Mitsuda positivity after 2-3 vaccinations. Clinically, repigmentation was seen after 2-3 years. Of the 155 inactive BL/LL cases, 91 (59%) became positive to SPA after 3 or more vaccinations. In contrast, only 32% patients among the 351 active LL/BL group showed positive reaction to SPA. Higher positivity was obtained with repeated (more than 6) doses of the vaccine. 62% patients of the last group, showed some manifestation clinical and/or histopathological, of reversal reaction. Nodules and plaques with sharp borders appeared over the chronic lesions. Histopathologically, there was appearance of small macrophages, lymphocytes and epithelioid cells. A decrease in the bacillary content was also recorded. In several of these thus, there was a strong indication of having upgraded from LL to BL/BB and even BT. However, it must be mentioned here that none of the BL/LL active or inactive patients showed a positive Mitsuda reaction.

In this study, the authors came across 4 cases who developed severe neuritis and another 19 who had moderate neuritis which was reversed with timely administration of corticosteroids. The authors emphasize that there was complete absence of reaction in the nerve trunk. Additional side effects seen were, transitory jaundice in 2 BL cases and peripheral oedema of hands and feet in 5 cases.

(c) Immunotherapy with *Myco. w*—a cultivable saprophytic organism

Lepromatous patients are tolerant to *M. leprae* antigens which they contain in abundance. A school of workers believe that in order to break this tolerance, an organism which shares some antigens with *M. leprae*, but has others that are different from *M. leprae* would be more suitable. Further, as the requirement of organisms for production of vaccine is going to be very huge, a cultivable organism would meet the demand better. Talwar and his associates[17] have shown that a saprophytic organism *Myco. w* meets these requirements. The authors have given autoclaved *Myco. w* in a single intradermal dose of 5×10^{7} bacilli in 0.1 ml to 32 smear negative lepromatous patients,[18,19] who had received long periods of sulphone therapy and were persisantly lepromin negative. on testing with lepromin 4 to 8 weeks after the vaccination, 20 cases were found to be Dharmendra and Mitsuda positive. Histopathology of Mitsuda reaction showed a massive mononuclear infiltration in all the cases, granuloma formation was seen in 12, and definite giant cells in two cases. Retest studies done 7 to 11 months later, confirmed persistant positivity in 2/3 cases while

in the other L.M.I. tests were positive and so was the Fernandez response to Lepromin-A. One of the patients, who had concomitant pulmonary tuberculosis, showed severe local ulceration at the site of vaccination. In the other patients, no apparent local or systemic side effects were seen. With the use of this organism, the authors found conversion of Mitsuda lepromin of the order of 62.5% in long-treated, smear negative and persistantly lepromin negative lepromatous leprosy patients.

(d) ICRC VACCINE

Working on the same lines, another group of workers from Bombay have used killed (8— irradiation) ICRC bacillus as the vaccine.[20-22] This organism which has been cultivated from the human leprosy tissues, has a growth pattern similar to *M. leprae*. The bacillus shares several antigens with *M. leprae*, and a skin test antigen prepared from it gives a response similar to lepromin.[23,24] Before testing it as a vaccine, the authors have used it as an immunotherapeutic agent. Seventy one LL and 11 BB/BL, active, smear positive patients were inoculated intradermally with 0.1 ml of the vaccine containing 27 to 67 μg protein (50 μg equivalent to 1×10^9 bacilli). There were 19 LL and 10 BB/BL patients who had been given saline injections only and acted as controls. All the patients were Mitsuda lepromin negative before vaccination.

Apart from ulceration at the local site, the vaccine was well tolerated. In the following 3 to 4 weeks, ENL was observed in 42% patients. Mitsuda lepromin test done 4 to 10 months later showed a conversion of 57.7% of LL and 91% of BB/BL patients. During the same period only (10%) of the control patients in BB/BL group and none in the lepromatous unvaccinated group showed lepromin conversion. None of the converted patients developed any fresh nerve lesion. Lepromin conversion was stable even up to 3 years when retesting was done again.

In those who showed lepromin conversion, there were significant histopathological changes in the lesions. There was loosening of the granuloma with reduction in the number of macrophages, appearance of lymphocytes and reduction in the tissue bacillary load. Reversal reaction, clinical and histopathological, was observed in cases.[25]

It is thus seen that all the three groups of workers have shown and claimed efficacy of their vaccine. However, there are certain important things to be noted. These are :

1. In all these studies lepromin conversion has been taken to mean increased protective immunity. This may not be really so. To our mind, the best parameter is the follow up of the patients over the next 5 to 10 years. In the absence of this, Mitsuda reaction appears to be the next best thing. In the studies of Convit, SPA has been used in addition to Mitsuda. These authors have found no conversion of the latter in both inactive and active lepromatous (BL/LL) patients, whereas 62% of active BL/LL cases showed histopathological changes of improvement, thus suggesting that even though lepromin negativity might continue, there could still be improvement.

2. Further, in all these studies, even lepromin conversion has not been 100%. In Convit's study, there were 41% of cases who did not show conversion to SPA), corresponding figures for ICRC vaccine and *Myco. w.* are 40 and 38.5% respectively. It is therefore considered that there is a subgroup within LL that would not respond to the vaccine. This may be on account of genetic mechanisms whereby there is an inherent defect in the immune response against *M. leprae*, may it be through Ir gene. If there is indeed such a group, one wonders if vaccine will confer protection to all the persistently lepromin negative contacts.

3. Since the source of *M. leprae* for vaccination, is armadillo, any armadillo protein getting into the human system is likely to be hazardous. It is worth pointing out that the method used for purification of *M. leprae*, gives a reasonably pure suspension.[26]

4. Occurrence of the reversal reaction has been observed with all the three candidate vaccines, though percentage has varied. Reversal reactions on the one hand indicate good prognosis, but on the other there are dangers of these being associated with structural and functional damage to some organs, specially the nerves, eyes, joints etc. Often peripheral oedema may be associated. Damage to the nerves can be rather serious. With the use of *M. leprae* and BCG, nerve pain was observed in 23 cases, though because of the timely institution of corticosteroids, permanent damage was prevented. Though no such thing has been reported with the other two vaccines, the possibility must be kept in mind. Nerve problems were encountered only in the smear positive LL/BL cases and not in the smear negative cases. It is therefore suggested that to prevent occurrence of nerve damage, only smear negative cases should be given immunotherapy.

5. With ICRC vaccine, 42% of lepromatous cases developed ENL. Though no mention of such a thing has been made with the use of other vaccines, this is an expected event. Though most often it is not associated with irreversible damage, but its frequent occurrence can result in severe morbidity associated with immune-complex nephritis, neuritis, eye and joint problems.

6. Mycobacteria are known to act as adjuvants. In animals adjuvant arthritis has often been encountered with the use of mycobacteria. Possibility of occurrence of such a thing in patients can, thus, not be ruled out.

7. Clinical worsening of other concomittant mycobacterial disease, particularly tuberculosis is also likely to occur.

8. Since BCG has been very extensively used, several side effects associated with it have come to light. Their mechanism of occurrence is not known. These include fever, chills, anorexia and myalgias, occurring within 4 to 6 hours of vaccination. Hepatic dysfunction associated with granulomatous hepatitis has also been seen. Two cases of jaundice have occurred in Convit's series. Disseminated BCG infection has been reported among individuals with primary immunodeficiency.

9. By procedures of this sort, there is a possibility of inducing an alteration in the homeostatic control mechanism of cellular immunity. There is a likelihood that this may result in generation of the suppressor cells which in turn may dampen CMI responses.

To sum up, even though the exact immune defect in leprosy, is still not clear, several approaches have been and are being made to actively boost the cellular immune functions. On the whole, results are fairly encouraging but need confirmation by other workers in a large number of patients with double blind controls. Tomorrow, such modes of therapy might prove extremely useful, but as of today the practical utility seems to be limited as great caution is needed because unexpected problems may crop-up.

Other modes of immunotherapy

It is believed that T lymphocytes are either deficient and/or non-functional in lepromatous patients. Some of the workers have therefore resorted to procedures which result in replenishment of these immunocompetent cells/factors. This has been done by use of drugs, blood components, lymphocyte factors, lymphoid cells and thymus extracts or implants. Some of the procedures are :

(a) Levamisole

Some of the anthelminthic compounds in current use, have been shown to have immune modulating effect. In this regard levamisole has a special place. The drug has been shown to increase the percentage of T cell rosette formation in normal and cancer patients, thus improving the T cell function.[27] It has also been shown

to improve the function of phagocytes.[28] B cell function does not seem to be much affected by this drug. The drug is being extensively evaluated for the treatment of cancer. In leprosy, though several groups of workers have used this drug, the over all effect has not been significant. Most of the authors have studied its effect on lepromin response. Meyers and co-workers[29] did not come across any lepromin positivity following its use in leprosy patients, whereas others have shown lepromin conversion with its use, [30,31] though this conversion was short-lived. In a study by Ramu and Sengupta[31] bacillary clearance too was found to be speeded up. Caravalho and his colleagues[32] reported a rapid clinical improvement and reduction in the intensity of lepra reaction with its use. Nelson et al[33] reported increased response to *C. albicans* and DNCB, but not to PPD in smear positive cases. In an experimental work using levamisole, Bullock[34] reported no significant reduction in either the bacillary load or mortality among rats infected with *M. lepraemurium*.

In short, as mentioned above levamisole does not seem to have any significant immunotherapeutic role for the treatment of leprosy.

Lymphocyte (Leucocyte) transfusion

Based on the idea that there is a functional deficiency of lymphocytes, attempts have been made in the past to reconstitute lymphocytes by transfusion. Paradisi et al,[35] Bullock et al[36] and Mendez et al[37] each gave one dose of cells from lepromin positive individuals to LL cases and observed a weak reaction in a proportion of recepients. Some of the cases showed a lymphocyte influx in histological sections. However, Antia and Khanolkar[38] did not find any worthwhile response following infusion of lymphnode cells. Lim et al,[39] Saha et al[40] and Izumi et al[41] gave repeated intravenous infusions of peripheral blood leucocytes from normal donors. Though claims have been made about the reduction and disappearance of AFB, appearance of lymphocytes and cessation of ENL, these have still to be confirmed.

Two modes of action are possible, (1) the infused lymphocytes survived long enough to mount an immune response before being killed by the host, (2) if the infused cells were promptly killed, transfer factor and/or lymphokines thus liberated were able to stimulate the host immune system.

Such a mode of therapy is not without hazards, some of the important side effects could be, (a) transfusion reactions on account of mismatching of minor blood groups, (b) a severe graft versus host reaction with a clinical picture showing skin rashes, hepatic dysfunction or intestinal affection with diarrhoea. Occasionally, there may be a further depression of the host's already limited immune response. Death is the likely event or a state of chimerism may be achieved, (c) a real danger of introducing transmissible diseases, especially B hepatitis and other viral diseases like herpes simplex etc. (d) sudden precipitation of reversal reaction resulting in damage to the nerves, skin, eyes and or joints. None of the above authors make any mention of these except of non-occurrence of GvsH in patients reported by Lim et al.

(c) Transfer factor

Transfer factor, which is a dialyzable material obtained from lymphocytes, is effective in the transfer of delayed cutaneous sensitivity to tuberculin and streptococcal antigens. The important thing about this factor is that it does not induce antibody formation against itself in the recepient even after repeated injections. Several groups of workers have used transfer factor in lepromatous cases. Bullock et al,[36] Silva et al,[42] Saha et al[43] and Weiser[44] gave one injection of transfer factor. These authors observed a response similar to that of lymphocyte infusion. In fact Silva et al failed to transfer hypersensitivity to *M. leprae*, even though the transfer factor had been prepared from lepromin positive

donors. Most important work in this regard has been that of Hastings and his coworkers.[45,46] These workers gave alternate day injections of transfer factor for 12 weeks (36 doses) prepared from 7.4×10^9 lymphocytes obtained from healthy lepromin positive individuals, to 4 LL and 1 BL patients. During this treatment, all the four LL but not the BL patients developed reversal reaction which was also histopathologically documented. There was an enhanced rate of clearing of the organisms, only as long as transfer factor was being given, even though the reversal reaction continued to appear long after discontinuation of the transfer factor therapy. Inhibitory role of naturally occurring suppressive factors has been postulated to be the cause of lack of response in BL cases. As the reversal reaction that occurred in 4 cases was not accompanied by a parallel in vitro lymphocyte response to *M. leprae*, it has been considered that transfer factor had acted in a non specific way.

To sum up, the transfer factor results in flare reactions (which are really reversal reactions) with skin test conversion in nearly half the cases. Dramatic, but on the whole temporary improvement is seen with an enhanced rate of bacillary clearance. The problems associated with the use of transfer factor include, the possibility of nerve damage as part of the reversal reaction and occurrence of ENL. Fever, nasal congestion, arthralgia, lymphadenitis associated with abnormal lymphocyte have also been observed.[26] Two other important side effects which have been seen, particularly in primary immune deficiency disorders include, auto-immune haemolytic anaemia,[47] and uncontrolled proliferation of the antibody producing cells.[48] Whether these side effects are due to the transfer factor, or due to the primary disease process is as yet unsettled.

(d) Thymic hormones and human foetal thymus transplantation

In several primary immune deficiency states, administration of thymosin, a thymus hormone, has been found to maintain the T cell count in peripheral blood at a near normal level with correction of several, but not all immune defects.[49] Based on this, trials are underway in cancer and leprosy patients to see if their CMI could be augmented—a T cell defect having been implicated in lepromatous leprosy.[50] Further, its need is underscored by a recent report where thymosin has been shown to prevent dissemination of BCG infection in T cell depleted mice.[51] Earlier, Gaugeas et al[52] had reported occurrence of the reversal effect in lepromatoid leprosy in thymectomized irradiated mice following thymus implantation. As an extension of the same, Saha et al[53] have given 3 thymus implants to leprosy patients (4 BI, 2 LL and 1 I). Following implantation, all chemotherapy was witheld. The authors reported marked clinical improvement in 6 of the 7 cases along with a decrease in the severity of ENL in all cases. Authors reported even the return of sensations. Histopathological assessment, done 9-11 months after transplantation, showed reversal reaction in 5, decrease in bacterial load in 4 and a progressive fall in MI in 6. Though in 6 of the 7 patients, return of non-specific cellular immunity was found, none of the patients showed conversion of Mitsuda lepromin. After several months, the disease appeared to relapse with a great severity. No mention is made of any problem with this mode of immunotherapy.

(e) Role of Interleukin-2

This lymphokine has been shown to trigger clonal expansion of the antigen or mitogen activated T-cells. By doing so, it provides the requisite T cell help needed for generation of T effector cells from T cell deficient population. Recently, it has been shown that IL-2, like interferon can augment natural killer cell (NK/K cell) activity in the in vitro system. Recently, it has also been reported that the nude mice show cytotoxic T lymphocyte activity after in vivo treatment with IL-2 containing supernatant.

IL-2 has been tried in clinical situations like cancer and AIDS where preliminary results with its use do not seem to be encouraging. In leprosy, inhibition of IL-2 production has been shown in borderline and lepromatous cases[54] and this has been attributed to the presence of, (a) suppressive factors released from monocytes, (b) possibly phenolic glycolipids which are an important constituent of mycobacterial (*M. leprae*) cell wall.[55] It has so far not been tried in leprosy.

To sum up, several groups of workers have attempted to passively infuse factors that are known to be essential and probably are responsible for the immune deficiency in leprosy. So far, only case reports are available, and often with contradictory results. Assessment of the patients has not been adequate and proper. Further, some of these procedures need to be confirmed by other workers using a longer sample and double blind procedures. At the moment, it could be said that there is no passive immunotherapeutic procedure available which could be used in the field. Further more, if trials on any of these lines are to be undertaken, these should only be done in centres which are well equipped to meet all the foreseen and even the unexpected side effects.

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