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EDITORIALS

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Leprosy in Young Children—Past, Present and Future

The recent development of sRIA techniques to demonstrate and quantitate the presence of antimycobacterial antibodies in cord sera of children of mothers with leprosy has opened up new frontiers in clinical and experimental leprosy.[1]

There are now new exciting possibilities for defining a population at risk and for following the progression of the prodromal stage of leprosy as it develops into clinical leprosy, as for example in the children of mothers with leprosy, and for observing specific responses to infection measuring the IgG, IgM and IgA anti-mycobacterial antibody levels. In turn, these may be correlated to the clinical features observing, for example, the appearance of indeterminate leprosy and its subsequent resolution or progression to tuberculoid leprosy in those with high cell-mediated immunity or, alternatively, the development of lepromatous leprosy in those with reduced or poor cell-mediated immunity (CMI).

The development of lepromatous leprosy in those with impaired CMI probably depends on two factors: firstly, the nutritional status of the child/host and, secondly, the size of the antigen load. One might postulate that if the antigen load were high and maintained at a high level due initially to transplacental transfer of *Mycobacterium leprae,* followed by possible transfer of *M. leprae* in breast milk from an untreated mother together with droplet infection later from household contacts, that a state of tolerance would develop. Furthermore, these children would be most likely to develop later the clinical lesions of lepromatous leprosy precipitated by stress, intercurrent infection, the hormonal surge of puberty, or further nutritional factors.

Hitherto leprosy in children under the age of five has been regarded as very rare and congenital infection never substantiated, although a number of cases of leprosy in very young children have been described and reviewed.[2] Despite these reports, standard teaching at the beginning of the 20th century—"leprosy is manifested very exceptionally as early as the third year, rarely before the fifth or sixth year, which would correspond to the classical period of incu-

[1] Melsom, R., Harboe, M. and Duncan, M. E. IgA, IgM and IgG anti-*M. leprae* antibodies in babies of leprosy mothers during the first 2 years of life. Clin. Exp. Immunol. **49** (1982) 532–542.

[2] Duncan, M. E. *A Prospective Clinico-Pathological Study of Pregnancy and Leprosy in Ethiopia,* M.D. thesis, Edinburgh University, 1982, pp. 14–33.

bation of the acquired disease."[3, 4]—has only undergone slight modification in 80 years; "leprosy can occur at any age but is rare in infants."[5] Clearly, the whole concept of leprosy in very young children and the incubation period of the disease has to be reviewed and critically reappraised. In the same spirit, it is fascinating to look back at historical reports and review them in the light of new laboratory techniques and increased understanding and knowledge of the bacteriology and immunology of leprosy.

Did leprosy in fact occur in very young children?

Two cases of congenital leprosy were described by Navarro (1890).[6] Three cases of congenital leprosy were described by Zambaco (1897), who also recorded the details of five more children developing leprosy at a very early age from "a few days" after birth to five months.[7] A three-month-old child with skin lesions confirmed on biopsy as showing leprosy bacilli was reported by Nakayo (1914).[8] A child born with a suspicious lesion on the heel, who was followed up to the age of 14 months and considered to be an authentic case of prenatal infection, was described by Crozier and Cochrane (1929).[9] Sporadic case reports have appeared in the literature since that time but since few had biopsies or bacteriological investigation, many modern leprologists have tended to discount these as being not due to leprosy. Clearly, there was a risk that children born to leprous parents could develop leprosy.

The observation that leprous parents could give birth to healthy babies, but such babies could not remain free from leprosy unless they were separated from their parents at the time of birth and brought up in a healthy environment with wholesome feeding, was made by Schilling (1778).[10] Nearly a hundred years later LeLoir repeated this observation,[11] but it is interesting to note that the Annamites (among whom leprosy was very prevalent) declared "leper parents always given birth to leper children, although, on the other hand, the malady does not declare itself before the tenth, eleventh or twentieth year."[12] Thus was developed the practice not only of segregating those who have leprosy from the healthy community, but of separating the sexes unless the leprosy had become quiescent or, in certain cases, voluntary sterilization had been carried out.

One would argue then that the paucity of cases of leprosy in early childhood was due to the small size of the population at risk. However, it should be noted that in the 19th century large numbers of abortions occurred in women with leprosy. These were attributed to septicemia with *M. leprae*, resulting in placental infection leading to fetal infection and abortion. In 1897 Zambaco considered that the reason for these abortions not being diagnosed as due to fetal leprosy was that in many cases of abortion both fetus and placenta were discarded without being properly examined,[7] an observation repeated 30 years later by Montero.[13] However, evidence for maternal bacteremia and transplacental infection of the fetus was given by Rabinowitsch (1913), who observed acid-fast bacilli in the fetal heart blood at autopsy of an untreated lepromatous woman at six months' gestation.[14]

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[3] Morrow, P. A. Leprosy. In: *Twentieth Century Practice of Medicine.* Stedman, T. L., ed. London: Sampson Low, Marston and Company, 1899, vol. 18, p. 428.

[4] Manson, P. Leprosy. In: *Tropical Diseases.* 5th ed. London: Cassell and Company, Ltd., 1914, p. 626.

[5] Bryceson, A. and Pfaltzgraff, R. E. *Leprosy.* 2nd ed. Edinburgh: Churchill Livingstone, 1979, p. 130.

[6] Navarro, R. Congenital leprosy. Rev. Med. Bogota, Nov. 1st. Abstract in Br. Med. J. **2** (1890) 766.

[7] Zambaco, D. A. Progéniture des Lépreux. Mittheilungen und Verhandlungen der internationalen Wissenschaftlichen Lepra-Conferenz zu Berlin im October 1897, pp. 591–595.

[8] Nakayo. Primary leprosy in the newborn. Japanische Zeischrift für Dermatologie und Urologie **14** (1914) 1026. Abstract in J. Cutan. Dis. **33** (1915) 551.

[9] Crozier, G. G. and Cochrane, R. G. Leprosy in an infant. Br. Med. J. **1** (1929) 501–502.

[10] Schillingii, G. G. De Lepra Commentationes, 1778, p. 34. Batavorum, Lugduni.

[11] LeLoir, H. *Traité Pratique et Théorique de la Lèpre.* Paris: A. Delahaye et E. Lecrosnier, 1886, p. 286.

[12] Cantlie, J. Report on the conditions under which leprosy occurs in China, Indo-China, Malaya, the Archipelago and Oceania: In: *Prize Essays on Leprosy. [Second Series].* London: New Sydenham Society, 1897, p. 325.

[13] Montero, A. ¿La lepra, además de ser contagiosa, es una enfermedad hereditaria? Arb. ü. Tropenkrankh. (Festschr. B. Nocht.) **26** (1927) 357–360.

[14] Rabinowitsch, M. Lepra bacilli in the circulating blood of patients and in heart-blood of a lepra-foetus. Berliner klinische Wochenschrift **50** (1913) 252–253. Abstract in Trop. Dis. Bull. **1** (1913) 565–566.

It is worth observing that while congenital tuberculosis is not common, it is well documented.[15] Unfortunately, in the cases recorded there was little correlation of placental pathology with the degree and type of infection in the infant since most placentae were discarded soon after being recorded as macroscopically normal. Histological findings were recorded in only two cases where the placenta had "no gross pathological change"[16] or "the placenta was normal microscopically, but a direct smear of the placental material revealed the presence of acid-fast bacilli."[17] The normality of the placenta in terms of bacteriology and histopathology in women receiving treatment for leprosy has been reported recently.[18]

Relatively little has been recorded of the general state of health of children with mothers with leprosy, although Zambaco recorded that many children born to mothers with lepromatous leprosy were small "like an abortion at term" and that they died within a few months of birth of athrepsie.[7] In another context he wrote, and the translation is mine, "the children of mothers with leprosy, born like little old men, do not develop but succumb to athrepsie without showing any sign on their body of leprosy. This fetal cachexia which leads to death *in utero,* or shortly after birth, without diagnostic lesions is certainly due to leprosy and may be described under the name of paraleprosy."[19]

More recently, Gomez, Basa and Nicolas (1922) noted that whereas minor ailments were similar to those in children in the healthy community, among the children of leprosy patients skin diseases were very common and the infant mortality was very high, with 42% of the children dying of infections, debility, marasmus, and athrepsie.[20] A similar observation was made by Jeanselme (1933), "the children are of feeble vitality and often succumb shortly after birth."[21] He illustrated this by observing the high infant mortality reported from different leprosy colonies. In 1944 Wallace recorded that all children of leprosy parentage "are very delicate and seem to have a predisposition to respiratory and gastric diseases which take a big toll of them."[22]

These observations have been repeated recently in a prospective study[23] which showed that the children of mothers with lepromatous leprosy were particularly at risk.[24] Since it has also been shown that 30% of the children born to mothers with lepromatous leprosy have antibodies in their cord serum indicating exposure to *M. leprae in utero,*[1] one might postulate that, in the past, those children who should have developed leprosy at an early age following infection *in utero* had died out before the disease could be made manifest. This would then explain the lack of case reports in the early literature.[25–29]

It is also noteworthy that of the children of leprous parentage who emigrated from

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[15] Corner, B. D. and Brown, N. J. Congenital tuberculosis. Report of a case with necropsy findings in mother and child. Thorax **10** (1955) 99–103.

[16] Hertzog, A. J., Chapman, S. and Herring, J. Congenital pulmonary aspiration tuberculosis. Am. J. Clin. Pathol. **19** (1949) 1139–1142.

[17] Harris, W. C. and Trenchard, H. J. Congenital tuberculosis. Tubercle **33** (1952) 273–276.

[18] Duncan, M. E., Fox, H., Harkness, R. A. and Rees, R. J. W. The placenta in leprosy. Placenta **5** (1984) 189–198.

[19] Zambaco, D. A. *Les Lépreux Ambulants de Constantinople.* Paris: Masson et Cie, 1897, p. 317.

[20] Gomez, L., Basa, J. A. and Nicolas, C. Early lesions and the development and incidence of leprosy in the children of lepers. Philippine J. Sci. **21** (1922) 233–256.

[21] Jeanselme, E. *La Lèpre.* Paris: G. Doin et Cie, 1933, p. 272.

[22] Wallace, C. A. Leprosy infection in children. East Afr. Med. J. **21** (1944) 73–75.

[23] Duncan, M. E. *A Prospective Clinico-Pathological Study of Pregnancy and Leprosy in Ethiopia,* M.D. thesis, Edinburgh University, 1982, pp. 140–148, 216–225.

[24] Duncan, M. E. Babies of mothers with leprosy have small placentae, low birth weights and grow slowly. Br. J. Obstet. Gynaecol. **87** (1980) 471–479.

[25] *Report on Leprosy by the Royal College of Physicians.* London: Her Majesty's Stationery Office, 1867, p. 28.

[26] *Report on Leprosy by the Royal College of Physicians.* London: Her Majesty's Stationery Office, 1867, p. 21–22.

[27] Cantlie, J. Report on the conditions under which leprosy occurs in China, Indo-China, Malaya, The Archipelago and Oceania. In: *Prize Essays on Leprosy. [Second Series].* London: New Sydenham Society, 1897, pp. 260, 366, 410.

[28] Choksy, N. H. Report on leprosy and the homeless leper asylum, Matunga Bombay. Indian Lancet (1902) 365–368.

[29] Rodrigues, J. N. Studies on early leprosy in children of lepers. Philippine J. Sci. **31** (1926) 115–145.

Norway to the United States of America, not one developed clinical leprosy. It might, of course, have been that leprosy was not diagnosed and that the failure in reporting leprosy was underdiagnosis. On the other hand, leprosy might have been present in the child without the parents being aware that anything was wrong,[30] or the lesions might have been so small and transient that they were missed unless special efforts had been made to find them.[31] Furthermore, leprosy in young children is often self-healing[32, 33] and therefore overlooked. In addition, nerve involvement causing sensory or motor loss, so often an early symptom in adult leprosy, frequently does not occur in children.[34] Finally, leprosy may masquerade as other skin disorders and vice versa.[35]

Specific chemotherapy for the mother's leprosy may affect the clinical features and timing of onset of leprosy in her child. With the advent and use of sulfones as specific chemotherapeutic agents for leprosy, the picture of leprosy in young children changed.[36] The overall prevalence of leprosy in children of leprous parents, which was 20.9% in the pre-sulfone era and 19.9% in the sulfone era, did not alter significantly. This was thought to be due to failure of compliance by the parents for fear that their leprosy might be healed and they would then be requested to leave the relative sanctuary of the Culion Leprosy Hospital. However, certain changes were apparent.

Prior to the advent of sulfones, of children developing leprosy by age five, 95% had developed it within the first three years of life. Following the advent of sulfones, only 57% of those developing leprosy by age five had developed it by the age of three years. The average age at onset of leprosy had increased from 20.7 months to 33.5 months in the sulfone era. The histological picture showed a decrease in the typically tuberculoid lesions and an apparant increase in the lepromatous lesions following the advent of sulfones. One might postulate that the dose of sulfone transmitted transplacentally or through the mother's milk was sufficient to cure the indeterminate or tuberculoid forms of childhood leprosy, but insufficient to deal with the lepromatous forms.

More recently the presence of an unidentifiable, noncultivable, acid-fast bacillus (NCAFB) has been demonstrated in human skin of adults and also in the skin of 15 out of 82 fetuses of 2–3 months' gestation obtained at therapeutic abortion. None of the persons from whom a specimen or fetus was obtained had leprosy. This unidentifiable mycobacterium, which was also isolated from 1 out of 6 samples of amniotic fluid obtained at aspiration, was tested in parallel with lepromin and thought to be *M. leprae*.[37] The occurrence of NCAFB in the environment and its relation to *M. leprae* is currently under investigation.[38]

There are a number of puzzling cases reported by leprologists of repute of very young children born to healthy parents or, in some cases, a healthy mother while the father was noted to have lepromatous leprosy.

In attempting to explain these cases, a quotation from Browne[39] is apt:

> The observant and thoughtful technician embarking on a serious study of leprosy

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[30] Aredath, S. P. The occurrence of leprosy in an eight-member family—a case report. Lepr. Rev. **55** (1984) 47–50.

[31] Lara, C. B. and de Vera, B. Early leprosy in infants born of leprous patients with report of cases. J. Philippine Islands Med. Assoc. **15** (1935) 252–257.

[32] Cochrane, R. G. In Preventoria: A symposium on the care of children of leprous parents. Lepr. Rev. **16** (1945) 40–57.

[33] Lara, C. B. and Nolasco, J. O. Self-healing, or abortive and residual forms of childhood leprosy and their probable significance. Int. J. Lepr. **24** (1956) 245–263.

[34] Cochrane, R. G. and Rajagopalan, G. An investigation center for the study of childhood leprosy. Int. J. Lepr. **6** (1938) 325–330.

[35] Duncan, M. E., Melsom, R., Pearson, J. M. H., Menzel, S. and Barnetson, R. St.C. A clinical and immunological study of four babies of mothers with lepromatous leprosy, two of whom developed leprosy in infancy. Int. J. Lepr. **51** (1983) 7–17.

[36] Lara, C. B. and Ignacio, J. L. Observations on leprosy among children born in the Culion leper colony during the pre-sulphone and the sulphone periods. J. Philippine Med. Assoc. **32** (1956) 189–197.

[37] Mori, T., Kishi, Y., Innami, S. and Nishimura, S. Acid-fast organisms in the skin of man and the human fetus. Int. J. Lepr. **37** (1969) 173–182.

[38] Kazda, J. Occurrence of non-cultivable acid-fast bacilli in the environment and their relationship to *M. leprae*. Lepr. Rev. **52** Suppl. (1981) 85–91.

[39] Browne, S. G. Introduction. In: *Leprosy in Children*. Noussitou, F. M., Sansarricq, H. and Walter, J. Geneva: World Health Organization, 1976, pp. 7–9.

> in children . . . will be forced, willy nilly, to use all his professional wits in the search for 'index cases' and 'viable bacilli' and portals of 'exit.'

to which I would add "portals of 'entry'."

Is there perhaps some truth in the statement that leprosy may be transmitted as a venereal disease? It has been shown[40–42] that in women of low socioeconomic status who suffer from dietary deficiency, particularly that of zinc, nonpathogenic organisms can cross intact membranes and, as an ascending infection from the vagina to the uterus, cause an intrauterine infection and, in particular, intrauterine pneumonia.

It is well known that male patients with advanced lepromatous leprosy carry a considerable number of *M. leprae* on the skin of the genitalia and leprous urethritis has been reported.[43] It is not, therefore, unreasonable to suggest that *M. leprae* deposited in the female genital tract during coitus could ascend and cross intact membranes to affect the baby without the mother herself having leprosy. In cases where neither parent had leprosy, one wonders whether the mother had another sexual partner who had leprosy.

A second possible explanation for these very early cases might have been that the woman was already infected with leprosy and incubating the disease, but that it had not become overt. During pregnancy, with suppression of cell-mediated immunity, the bacilli would have had the opportunity to multiply in sufficient numbers to cause a bacteremia without skin lesions becoming manifest. With the recovery of cell-mediated immunity postpartum, many of the bacilli would have been destroyed by the mother's defense mechanisms and her leprosy might not have become overt during the period of observation.

It is tempting to ask what happens to the child born to a mother with lepromatous leprosy whose cord serum IgG, IgM and IgA show that *M. leprae* antigen has crossed the placenta,[1] whose increased lymphocyte responsiveness to PHA indicates intrauterine stimulation of T lymphocytes,[44] and who has a reduced thymic and splenic weight,[45] when this child is subsequently bombarded by *M. leprae* after birth, either from a family contact or from the mother relapsing with dapsone-resistant leprosy.[46]

Is this the child with the early, spontaneously resolving primary lesion of tuberculoid histology[47] of whom the question was asked, "Has the child sterilised his system of leprosy bacilli, or have the bacilli gone into hiding, e.g., in lymph nodes, nerve, testis or other body tissue to reappear later?"[48] Or is this the child who develops the indeterminate lesions with poorly defined edges which progress in middle childhood to lepromatous leprosy and indicate a massive infection with a poor immune response on the part of the child?[34, 49]

How much of this child's infection is due to immune tolerance and to what degree may there be partial tolerance to *M. tuberculosis,* either because of shared antigenic components or because antigen crossreactivity at the T-cell level is considerably broader than at the antibody level, resulting

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[40] Naeye, R. L. and Blanc, W. A. Relation of poverty and race to antenatal infection. N. Engl. J. Med. **283** (1970) 555–560.

[41] Naeye, R. L., Dellinger, W. S. and Blanc, W. A. Fetal and maternal features of antenatal bacterial infections. J. Pediatr. **79** (1971) 733–739.

[42] Jeanselme, E. De l'urethrite lépreuse. Bull. Soc. Pathol. Exot. Filiales **7** (1914) 557–559.

[43] Bjune, G., Duncan, M. E., Barnetson, R. St.C. and Melsom, R. *In vitro* modulation of lymphocyte responses to phytohaemagglutinin by plasma in mother and baby at the time of birth. Clin. Exp. Immunol. **32** (1978) 517–522.

[44] Duncan, M. E. *A Prospective Clinico-Pathological Study of Pregnancy and Leprosy in Ethiopia,* M.D. thesis, Edinburgh University, 1982, pp. 200–202.

[45] Duncan, M. E., Pearson, J. M. H. and Rees, R. J. W. The association of pregnancy and leprosy. II. Pregnancy in dapsone-resistant leprosy. Lepr. Rev. **52** (1981) 263–270.

[46] Nolasco, J. O. and Lara, C. B. Histopathology of early lesions in fourteen children of lepers. I. Analysis of previous skin blemishes in relation to sites of biopsies and other positive and probable lesions. Philippine J. Sci. **71** (1940) 321–358.

[47] Nolasco, J. O. and Lara, C. B. Histology of clinically healed "primary" lesions of leprosy in children of lepers. II. Their clinical progression and final resolution into healed scars. Report of thirteen cases. Monthly Bull. Bureau of Health, Manila **24** (1948) 97–128.

[48] Lara, C. B. Leprosy in infancy and childhood. Monthly Bull. Bureau of Health, Manila **24** (1948) 61–89.

[49] Duncan, M. E. Perspectives in leprosy. Advances in International Maternal and Child Health. Vol. 5. Jelliffe, D. B. and Jelliffe, E. F. P., eds., 1985, pp. 122–143.

in impaired responsiveness to BCG vaccination?[49]

One might ask what role nonpathogenic mycobacteria might play in the development of leprosy in a very young child. Studies of perinatal infection and mortality in Ethiopia have demonstrated intrauterine infections due to organisms of low pathogenicity, namely, commensal bacteria of the lower genital tract. These infections have been attributed to dietary deficiencies, especially zinc, and associated with low household water utilization, particularly in women of low socioeconomic class.[50]

One might therefore postulate that in an environment where mycobacteria other than *M. leprae,* for example, *M. smegmatis* and others, abound, these organisms could gain access and be present from an early age in the skin of fetuses *in utero.* The mycobacteria, while not causing any evidence of infection, could impair the ability of certain babies to deal effectively with an infecting dose of *M. leprae* received late in pregnancy. These babies would then be the ones to exhibit clinical evidence of the disease during the first year or two of life.

Continued observation of the cohort of children under study and repeated tests for some years to come is likely to bring to light more information which may greatly increase our understanding of the pathogenesis of leprosy.[35] Meanwhile, in the endeavor to control infection in the neonate and young child, three steps may prove beneficial: firstly, improvement of nutrition of the child *in utero,* possibly with a zinc supplement being given to the pregnant woman; secondly, dual or triple therapy for pregnant women which would decrease the risk of relapse of leprosy, development of dapsone-resistant leprosy, and the risk of infecting the unborn baby[46]; and thirdly, the treatment of giardiasis in the infant which not only produces a vicious circle of suppression of CMI and reinfection but also causes a malabsorption syndrome which leads to impaired nutrition and further suppression of CMI.[23, 50] These recommendations may appear to be "pipe dreams" in the context of the current population explosion and economic crises in so many developing countries where leprosy is endemic, but their implementation in a few centers could be undertaken as a pilot study.

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[50] Naeye, R. L., Tafari, N., Judge, D., Gilmour, D. and Marboe, C. Amniotic fluid infections in an African city. J. Pediatr. **90** (1977) 965–970.