INTERNATIONAL JOURNAL OF LEPROSY

Volume 50, Number 1
Printed in the U.S.A.

Neuritis in Pregnancy and Lactation[1]

M. Elizabeth Duncan and John M. H. Pearson[2]

Mycobacterium leprae, the causative organism of leprosy, has the unusual property of entering peripheral nerves and multiplying within their Schwann cells. The intraneural inflammation which is elicited by this process accounts for the development of nerve damage in leprosy. In tuberculoid leprosy an inflammatory response can be elicited by low concentrations of mycobacterial antigen; but in lepromatous leprosy considerable numbers of bacilli can be seen within otherwise rather normal looking nerves. However, because of the slow multiplication rate of *M. leprae*, nerve damage progresses rather slowly in all types of untreated leprosy if the immune response is stable, and some recovery of nerve function can be expected under normal chemotherapy.

When the course of leprosy (whether untreated or under chemotherapy) is characterized by an unstable host parasite relationship, sudden episodes of increased inflammation, known as reactions, occur. These reactions can be caused by disturbances of cell-mediated immunity (reversal reaction [RR], Type 1 reaction) or of humoral immunity (erythema nodosum leprosum [ENL], Type 2 reaction); the neuritis associated with reactions is caused by intraneural reaction. Nerves can be damaged both acutely and extensively during reactions, and steroid treatment is often required to prevent irreversible damage.

Thus leprosy is a disease in which most of the clinical manifestations are brought about by the immunological response of the host. The "immunological instability" of pregnancy might therefore be expected to be associated with reactions and neuritis in leprosy patients. Such association has been reported by a number of authors ([3, 6, 7, 8, 9, 10, 13, 14, 15, 16]). However, all the information available at present has come from retrospective studies and reviews of case histories. No prospective studies have apparently been undertaken, and therefore the risk of neuritis which leprosy patients undergo by becoming pregnant has not been appreciated. This paper describes the association of neuritis with pregnancy as observed in a prospective study of Ethiopian leprosy patients.

PATIENTS AND METHODS

The patients were all Ethiopian women from the low socioeconomic class, of whom 96% lived in the villages surrounding the leprosy hospital. They were being treated for leprosy at the hospital outpatient clinics and were first seen for this study when they presented at the hospital antenatal clinic. Selection of patients was based on their willingness to participate in the study, to deliver their babies in the hospital rather than at home, and to be seen with their babies for regular assessment for a period of up to 2 years during lactation. Intake of patients was staggered over 12 months.

Classification and treatment of mothers. One hundred and forty-six women were studied during and after 153 pregnancies. There were 115 women with leprosy (119 pregnancies) and 31 healthy women with 34 pregnancies. The 115 women with leprosy were classified as follows using the scale of Ridley and Jopling ([12]):

Tuberculoid and borderline-tuberculoid leprosy (TT/BT) ... 39 (40 pregnancies)
Borderline lepromatous leprosy (BL) ... 44 (45 pregnancies)
Lepromatous leprosy (LL) ... 32 (34 pregnancies)

Patients studied twice, because of having

[1] Received for publication on 4 March 1981; accepted for publication on 1 October 1981.

[2] M. E. Duncan, M.B., Ch.B., F.R.C.S.E., F.R.C.O.G., Research Obstetrician, Medical Research Council Leprosy Project, Addis Ababa Leprosy Hospital, Ethiopia. Present address: National Institute for Medical Research, London, NW7 1AA, England; J. M. H. Pearson, D.M., M.R.C.P., Physician, Medical Research Council Leprosy Project. Present address: Dhoolpet Leprosy Research Centre, Hyderabad 500006, A.P., India.

a second pregnancy during the study period, are considered as two patients.

Eighty-seven patients were receiving treatment with dapsone monotherapy (50–100 mg daily). Twenty-six patients, 1 BL, the rest BT or TT, were believed to have been cured, had stopped treatment, and had been "released from control" (RFC). Three of these BT/RFC patients who relapsed with active BL leprosy during the third trimester of pregnancy ([4]) were reclassified as BL and are included in the BL group. Six patients (2 BL, 4 LL) had developed dapsone resistant leprosy and were receiving clofazimine (4 patients, all LL, 5 pregnancies) or rifampin plus thiambutosine (2 patients, both BL).

Assessment of patients. Assessment of the patients' leprosy was made during pregnancy and after delivery at 6-month intervals whenever possible. Details of the patients' complaints, state of health, and drug treatment were recorded. Examination included inspection and palpation of the skin, clinical drawings, palpation of nerves and regional lymph nodes, slit skin smears, and biopsies.

Voluntary muscle power tests (VMT) were performed by standard methods and the muscle power graded on a 0–5 scale ([5]). Sensory skin tests (SST) were performed on the palms of the hands (using a stiff nylon bristle) and the soles of the feet (using a ballpoint pen tip); sufficient pressure was applied to indent the skin slightly. Standard sites (at least five for the area of distribution of each nerve) were stimulated and the result of each recorded as "felt" or "not felt."

Motor nerve conduction velocity (NCV) was measured in a few patients to determine whether nerve damage was long standing or of recent onset.

The patients' hospital case records were examined and data abstracted regarding leprosy status (clinical relapse, slit skin smear results and biopsy reports), frequency and type of reaction and assessment of nerve damage (VMT, SST and NCV) prior to admission to the study. Particular attention was paid to the three month period immediately preceding pregnancy. This was expected to provide a baseline figure for complications in Ethiopian women.

Definitions of neuritis. Neuritis in leprosy is usually defined as "pain and/or tenderness of nerves" ([11]). In this paper we define "overt neuritis" as pain and/or tenderness of nerve. In addition to pain and/or tenderness of nerves, all our patients with overt neuritis, except 9, also showed evidence of simultaneous impairment of nerve function. We define "silent neuritis" as impairment of sensory and/or motor function without nerve pain or tenderness.

Motor function was recorded as impaired if there was loss of 2 or more points (on the 0–5 scale) in 2 separate muscles within the same nerve distribution. (In three episodes of neuritis nerve damage was recorded when the motor deficit, though only 1 point, included almost all the tested muscles.) In the presence of obvious clinical changes (such as facial paralysis or "tic" of the facial muscles; wasting of the intrinsic muscles of the hand; "curving" of the fourth and fifth fingers; claw hand or foot drop) formal VMTs were sometimes omitted. These are reported as "clinical assessments."

Impairment of sensory function was recorded if loss of sensation had occurred in at least two test sites within the distribution of a single nerve. In a few patients with extensive anesthesia with anhidrosis, formal SSTs were omitted; they are reported as "clinical assessments."

RESULTS

There was a total of 85 episodes of neuritis during pregnancy and lactation. In 11 episodes no nerve damage ensued. In the remaining 74 episodes, 29 showed pure motor loss, 12 pure sensory loss and 33 mixed loss. By contrast, only two women (1 BT, 1 BL) had neuritis during the 3 month period immediately preceding pregnancy. However, both episodes of neuritis followed a previous pregnancy.

The general severity of the nerve damage, taking all types of leprosy together, is shown in Tables 1 and 2. The majority of patients with sensory loss were severely affected, whereas the motor deficits were in most cases mild. The apparently greater vulnerability of sensory nerves may indicate that damage occurred at both dermal nerve and nerve trunk levels. The danger that insidious silent neuritis will cause severe sensory loss is well shown. Neuritis

TABLE 1. *Severity of motor damage incurred during each episode of neuritis.*

Type of neuritis		Degree of nerve damage[a]	
		Mild	Severe
Overt	1 nerve only	7	1
	many nerves	11	6
Silent	1 nerve only	4	1
	many nerves	17	15
Total		39	23

[a] Mild damage = loss of 1 or 2 VMT grades in 1 or more nerves, or NCV evidence only. Severe damage = loss of 3 or more VMT grades in 1 or more nerves, or clinical assessment only.

TABLE 2. *Severity of sensory damage incurred during each episode of neuritis.*

Type of neuritis		Degree of nerve damage[a]	
		Mild	Severe
Overt	1 nerve only	1	2
	many nerves	3	6
Silent	1 nerve only	4	2
	many nerves	6	21
Total		14	31

[a] Mild damage = loss of 1 or 2 sensory test areas in 1 or more nerves. Severe damage = loss of 3 or more sensory test areas in 1 or more nerves, or clinical assessment only.

affecting multiple nerves was usually more damaging than when only one nerve was affected.

Some indication of the severity of the neuritis may also be derived from the treatment that was employed. A total of 52 patients developed neuritis. However, in 14 cases the diagnosis (silent neuritis) was made only at the time of final assessment. Of the remaining 38 patients, 26 required treatment with corticosteroids during the study period.

The number of patients studied, and the proportion developing neuritis during the study period, are shown in Table 3. There was considerable risk of neuritis in all types of leprosy. The timing of the episodes of neuritis is shown in Figure 1. BL cases were almost free of neuritis during pregnancy but were greatly at risk in the first 6–9 months after delivery. In BT and TT cases, neuritis was less common and showed little relationship to the events of pregnancy.

Overt neuritis was usually associated with skin reaction, deterioration of the leprosy condition (due to relapse or dapsone resistance), or both. Early clinical deterioration not infrequently presented as apparent ENL (Type 2) reaction (Fig. 2c), and clinically puzzling mixtures of Type 1 and Type 2 reactions were occasionally encountered (Fig. 2b).

In general, overt neuritis was chiefly encountered just before delivery and during the 9–12 months postpartum. Silent neuritis, on the other hand, occurred at all stages (Fig. 2a), but became the predominant problem from about 6–9 months postpartum.

Healthy contacts (HC). One healthy contact got overt neuritis. She complained of "rheumatism" and was found to have enlarged nerves at 10 weeks postpartum. At 6 months postpartum she had tender nerves with loss of motor and sensory function. Biopsy showed active BL leprosy. She is included in the BL group.

Tuberculoid leprosy (TT and BT). Of 25 patients initially classified as TT and BT/RFC (including the three who relapsed as BL during the study period), eight patients had 12 episodes of neuritis in association with relapse.

TABLE 3. *Occurrence of neuritis among leprosy patients during pregnancy and lactation.*

Classification of leprosy	No. of patients studied	No. with neuritis	No. of episodes of neuritis	No. of episodes per patient
TT and BT	40	16 (40%)	24	0.6
TT and BT/RFC	22	6 (27%)	9	0.4
TT and BT/Active	18	10 (56%)	15	0.8
BL[a]	45	21 (47%)	35	0.8
LL	34	15 (44%)	26	0.8
Total	119	52 (44%)	85	0.7

[a] This group includes 3 patients (7 episodes of neuritis) originally classified as BT/RFC who relapsed with active BL leprosy during the study period.

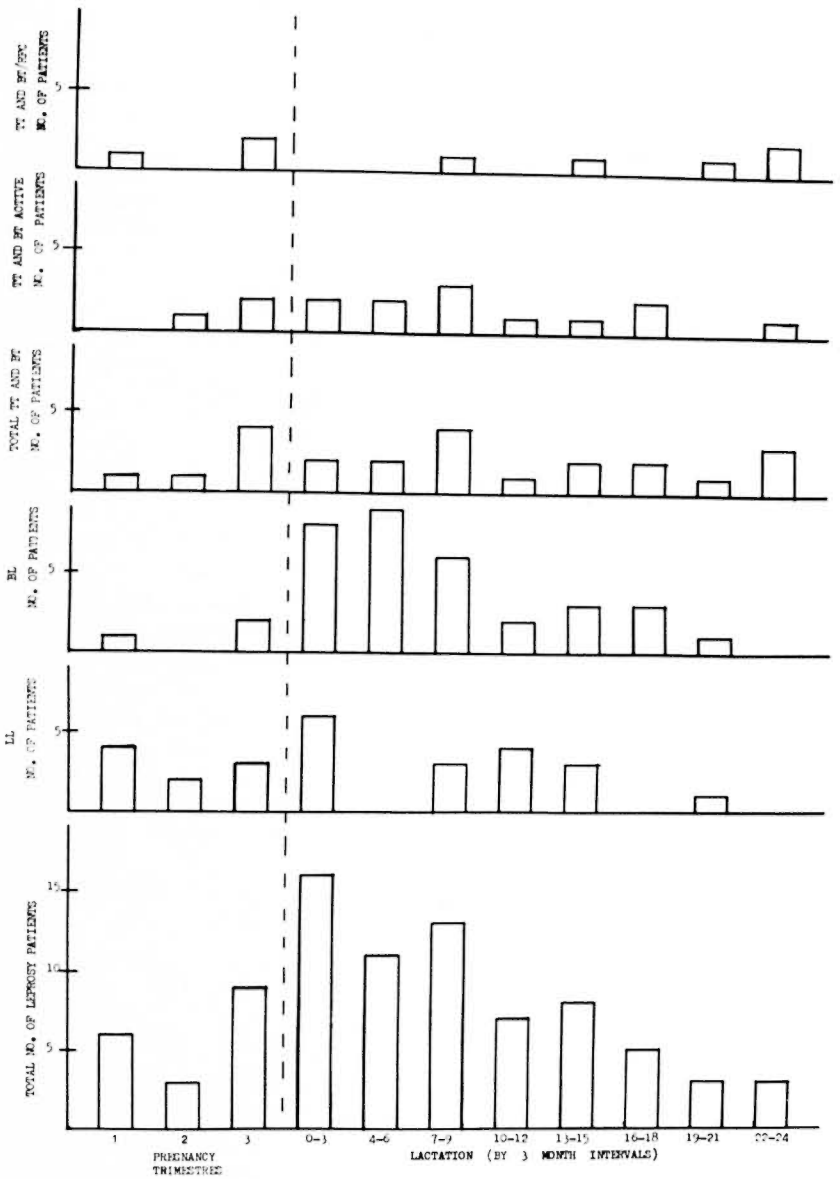

FIG. 1. Timing of episodes of neuritis during pregnancy and lactation according to the clinical classification of the patients at the outset of the study.

Sixteen out of 40 patients had 24 episodes of neuritis in association with pregnancy or lactation. Five patients had neuritis (six episodes) during pregnancy. These five patients, all of whom were either newly diagnosed or relapsed cases, had silent neuritis which was diagnosed early, by clinical or physiological testing, after Type 1 reaction was observed in the skin. Six of eight episodes of neuritis observed during pregnancy or the puerperium were in association with Type 1 reaction of the skin lesions. One patient only, a newly diagnosed case, developed "classical" overt neuritis at 6 weeks postpartum. The remaining cases of neuritis occurring during lactation were all silent, the majority being preceded by the complaint of "rheumatism" (generalized aches and pains) and new, non-tender, nerve enlargement.

Lepromatous leprosy (LL). Fifteen out of 33 patients had 26 episodes of neuritis. In

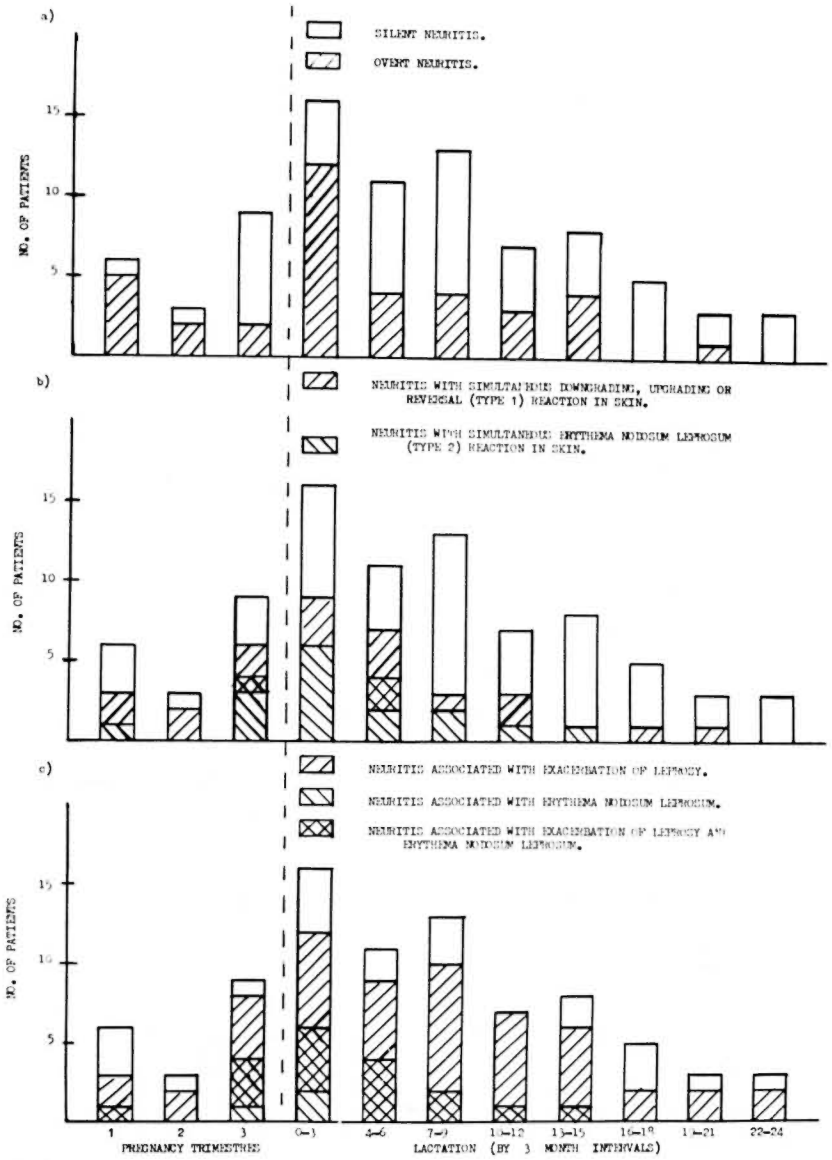

FIG. 2. Clinical aspects of neuritis in association with pregnancy and lactation. a) Timing of silent and overt neuritis; b) Timing of neuritis in association with simultaneous Type 1 and Type 2 lepra reactions; c) Association of neuritis with exacerbation of leprosy and Type 2 reaction.

11 cases there were also mixed ENL and clinical deterioration; two patients showed deterioration without reaction and two had ENL only. In most cases, ENL preceded the appearance of neuritis.

Fifteen episodes of neuritis were observed during pregnancy and the first 3 months of lactation; 12 were overt, 3 silent. Eleven episodes of neuritis occurred later in lactation, six of which were silent and usually preceded by the complaint of "rheumatism" and the finding of newly enlarged non-tender nerves. Nerve conduction velocity was measured in two cases (at 12 months postpartum) and indicated active nerve damage rather than slow residual fibrosis.

Borderline lepromatous leprosy (BL). Twenty-one out of 45 patients had 35 episodes of neuritis; only three episodes oc-

curred during pregnancy. The neuritis was almost always associated with deterioration of the leprosy (15 cases) or reaction (ENL, 8 cases; reversal reaction, 7 cases), and many patients showed both reaction and deterioration.

Overt neuritis (13 patients) was associated with reaction (9 cases) and/or clinical deterioration (8 cases); 14 of 19 episodes occurred during the first 12 months after delivery. Silent neuritis, on the other hand, was associated with reaction in only four cases and with clinical deterioration in 12 cases. It sometimes continued until 2 years after delivery and was in 11 cases still present at the patient's final assessment. As in LL cases, silent neuritis was usually preceded by the complaint of "rheumatism" and the finding of nerve enlargement. Nerve conduction velocity studies performed on three patients 12–15 months after delivery showed evidence of active demyelination.

Treatment of neuritis. Twenty-six patients were treated with corticosteroids. Not all had completed their courses of treatment during the study period, but at the time of their final assessments 9 of 26 (35%) showed improvement (using the reverse of the criteria for deterioration) both clinically and on VMT and SST. Twelve patients with neuritis did not receive corticosteroids; only two (17%) improved.

DISCUSSION

These findings are summarized simply. Nearly half of the Ethiopian women with leprosy who were studied suffered from deterioration of nerve function during a single pregnancy and/or during lactation. All patients, including those with tuberculoid leprosy treated for some years and apparently "cured" (RFC), were at risk. Insidious silent neuritis, leading to sensory and motor nerve damage during lactation, was a particularly dangerous and hitherto undescribed risk of pregnancy.

Overt neuritis is usually associated with reaction in leprosy and is a manifestation of the reactional process as it occurs within nerves. Thus in borderline and tuberculoid leprosy there is initial edema of the intraneural granuloma, and subsequently increased granuloma formation as the immune response to *M. leprae* progresses, so that Schwann cells are progressively replaced by the epithelioid granuloma. The patients most at risk were those classified as BL, although newly diagnosed or relapsing BT or TT cases could also be affected. The neuritis usually started after delivery, thus coinciding with recovery of cell-mediated immunity (CMI) after the immunosuppression of normal pregnancy. We have shown elsewhere that there is some increased bacillary multiplication during pregnancy, in some cases as a transient phenomenon ([4]) due to lowered host CMI and possibly also reluctance of women to take any medication, including antileprosy drugs, during pregnancy. Peripheral nerve is a partially immunologically privileged site ([17]), and the immunosuppression of normal pregnancy might therefore be particularly influential.

The description given by Rose and McDougall ([13]) of adverse reactions following pregnancy in untreated patients with "dimorphous" leprosy gives us the picture of evolution of leprosy during late pregnancy or early lactation as a result of suppressed CMI and occurrence of skin and nerve reactions during lactation due to the recovery of CMI after delivery.

In lepromatous leprosy overt neuritis probably represents intraneural ENL. This reaction requires the presence of *M. leprae* within the nerve and appears to be more common and severe when there is a high concentration of intraneural antigen. Thus bacillary multiplication unchecked by chemotherapy (as when a patient is developing dapsone resistant leprosy) or CMI (suppressed during pregnancy) is a likely precipitating factor that applies to many cases in this series. Neuritis in these patients was likely to occur at any stage of pregnancy or lactation.

While any form of neuritis is of concern to both the patient and the leprosy worker, overt neuritis is more readily diagnosed and therefore treated, and hence is the lesser evil for the lactating mother. Silent neuritis with its slow, insidious progress means that permanent nerve damage can occur before the patient, or leprosy worker, is aware that anything is wrong. The diagnosis of silent neuritis was made possible in this study by regular sensory and motor function tests; however, among our patients persistent

"rheumatic pains" were frequently associated with silent neuritis and indicated that something was wrong. This symptom and its significance will be described elsewhere.

The etiology of silent neuritis remains uncertain. One obvious possibility is that it is due to late fibrosis in nerves that have previously been damaged by intraneural granulomata. In our study, however, "new active demyelination" was reported in several patients with silent neuritis during lactation. Segmental demyelination at sites where bacilli were not present has been demonstrated in all types of leprosy ([1]). However, the apparent localization of nerve damage to sites where they are particularly vulnerable to physical changes in their environment makes autoimmune demyelination unlikely as a cause of silent neuritis.

Silent neuritis appears to cause more damage to sensory nerves than to motor nerves. This suggests that the process may cause damage at both dermal nerve and nerve trunk levels. The reversibility with corticosteroid treatment implies an immunological cause. This possibility is supported by the work of Bullock on trapping of sensitized lymphocytes ([2]), but since little is known of immunological or endocrine function in women who prolong lactation for 2 or more years, it is difficult to discuss possible immune mechanisms. Further studies, including nerve biopsies, will be required to elucidate the mechanisms of neuritis in lactating women.

The implications of this study are clear. Women with leprosy (even apparently cured) run a serious risk of deterioration of nerve function when they become pregnant. They may develop overt neuritis, or an insidious silent neuritis; in either case, regular tests of nerve function are required to demonstrate nerve damage and follow the response to treatment. With training this sort of management could be provided in the context of a "vertical" leprosy control program; it will be more difficult to ensure proper care in integrated primary health care programs. Health education to make women with leprosy aware that pregnancy can seriously damage their health must be undertaken, and may well be the correct long-term response to the problem of neuritis in pregnancy and lactation.

SUMMARY

One hundred and forty-six women were studied during and after 153 pregnancies (31 healthy contacts: 34 pregnancies; 115 leprosy patients: 119 pregnancies). One healthy contact and 51 leprosy patients developed neuritis during the study period. All leprosy patients, including those who were considered to be cured and had stopped treatment, were at risk. Neuritis was accompanied by Type 1 and Type 2 lepra skin reactions and/or deterioration of the patients' leprosy status; this was particularly the case when neuritis was associated with nerve pain or tenderness (overt neuritis). Neuritis without nerve pain or tenderness (silent neuritis), preceded by the complaint of "rheumatism" and the clinical finding of enlarged peripheral nerves, was seen more frequently than overt neuritis (48:37 episodes). Insidious silent neuritis with loss of sensory and motor function during lactation was a particularly dangerous and hitherto undescribed risk of pregnancy.

RESUMEN

Se estudiaron 146 mujeres durante y después de 153 embarazos (31 contactos sanos: 34 embarazos; 115 pacientes con lepra: 119 embarazos). Uno de los contactos sanos y 51 pacientes con lepra desarrollaron neuritis durante el periodo de estudio. Todas las pacientes con lepra, incluyendo a aquellas que se habían considerado curadas y que por ésto habían suspendido su tratamiento, estuvieron bajo el riesgo de desarrollar neuritis. La neuritis estuvo acompañada de reacciones dérmicas del tipo 1 e del tipo 2, con o sin deterioro del estado leproso de las pacientes; este fue particularmente el caso cuando la neuritis estuvo asociada con dolor de nervios o con gran sensibilidad de los mismos (neuritis abierta). La neuritis sin los síntomas anteriores (neuritis silenciosa), precedida por molestias de "reumatismo" y agrandamiento de nervios periféricos, fue observada con más frecuencia que la neuritis abierta (48:37 episodios). La neuritis silenciosa e insidiosa con pérdida de las funciones motora y sensorial durante la lactancia fue uno de los riesgos particularmente peligrosos (hasta ahora no descritos) del embarazo.

RÉSUMÉ

On a étudié cent quarante-six femmes, pendant et après 153 grossesses (31 contacts non malades, correspondant à 34 grossesses, 115 malades de la lèpre, représentant au total 119 grossesses). Au cours de la période d'étude, un contact sain et 51 malades de la lèpre ont développé une névrite. Tous les malades de la lèpre, y compris ceux qui étaient considérés comme guéris et avaient interrompu le traitement, étaient ex-

posés au risque. La névrite était accompagnée par des réactions lépreuses cutanées de type 1 et de type 2, ainsi que par une détérioration de l'état des malades en ce qui concerne leur maladie lépreuse; ces deux manifestations pouvaient coexister. Cette association était particulièrement notée dans les cas où la névrite était associée avec des douleurs nerveuses ou une sensibilité des nerfs (névrite ouverte). La névrite sans douleurs nerveuses ou sensibilité des nerfs (névrite silencieuse), précédée par des plaintes de "rhumatismes," et par l'observation clinique d'un épaississement des nerfs périphériques, a été constatée plus fréquemment que la névrite ouverte (48 épisodes sur 37). Une névrite silencieuse insidieuse, avec perte des fonctions motrices sensorielles, au cours de la lactation, s'est révélée particulièrement dangereuse; il s'agit là d'un risque de la grossesse qui n'avait pas été décrit jusqu'à présent.

Acknowledgments. We thank the staff and patients of the Addis Ababa Leprosy Hospital for their cooperation in this study; Miss Jean Watson, Mr. Wym Brandsma, and the staff of the physiotherapy department for carrying out the sensory skin testing and voluntary muscle testing; and Dr. B. Naafs for measuring NCV in selected patients. We are also grateful to Dr. D. S. Ridley, who provided independent histological classification of the patients in this study.

M. E. Duncan was supported for part of the study by a research grant from the British Leprosy Relief Association (Lepra).

REFERENCES

1. Antia, N. H., Shetty, V. P. and Mehta, L. N. Study of evolution of nerve damage in leprosy. IV. An assessment. Lepr. India **52** (1980) 48–52.
2. Bullock, W. E., Jr. Perturbation of lymphocyte circulation in experimental murine leprosy. II. Nature of the defect. J. Immunol. **117** (1976) 1171–1178.
3. Chowduri, S. K. and Ghosh, S. Clinical observations on "reaction" in tuberculoid leprosy: preliminary report. Bull. Calcutta Sch. Trop. Med. **13** (1965) 52–53.
4. Duncan, M. E., Melsom, R., Pearson, J. M. H. and Ridley, D. S. The association of pregnancy and leprosy. I. New cases, relapse of cured patients and deterioration in patients on treatment during pregnancy and lactation. Results of a prospective study of 154 pregnancies in 147 Ethiopian women. Lepr. Rev. **52** (1981) 245–262.
5. Goodwin, C. S. The use of the voluntary muscle test in leprosy neuritis. Lepr. Rev. **39** (1968) 209–216.
6. Jeanselme, E. *La Lèpre*. Paris: G. Doin and Cie, 1933, p. 382.
7. Jopling, W. H. Treatment of acute phases (reactional states) in lepromatous leprosy. In: *Leprosy in Theory and Practice*, 2nd ed. Cochrane, R. G. and Davey, T. F., eds. Bristol: Wright, 1964, p. 418.
8. Jopling, W. H. *Handbook of Leprosy*. 2nd ed. London: William Heinemann Medical Books Ltd., 1978, p. 93.
9. Lawson, J. B. and Stewart, D. B. *Obstetrics & Gynaecology in the Tropics & Developing Countries*. London: Edward Arnold, 1967, pp. 47–49.
10. Maurus, J. N. Hansen's disease in pregnancy. Obstet. Gynecol. **52** (1978) 22–25.
11. Pearson, J. M. H. and Ross, W. F. Nerve involvement in leprosy—pathology, differential diagnosis and principles of management. Lepr. Rev. **46** (1975) 199–212.
12. Ridley, D. S. and Jopling, W. H. Classification of leprosy according to immunity. A five-group system. Int. J. Lepr. **34** (1966) 255–273.
13. Rose, P. and McDougall, C. Adverse reactions following pregnancy in patients with borderline (dimorphous) leprosy. Lepr. Rev. **46** (1975) 109–113.
14. Symmers, W. St. C. Sudden appearance of a lepromatous eruption during prolonged administration of stilbestrol in a case of unsuspected leprosy. Int. J. Lepr. **19** (1951) 37–43.
15. Tajiri, I. Leprosy and childbirth. Int. J. Lepr. **4** (1936) 189–194.
16. Trần Diñh Dê, Hoang Ngoc Minh and Cao Minh Trung. Contribution à l'étude de l'association lèpre et gravido-puérperalité. À propos de 86 cas. Gynecol. Obstet. (Paris) **63** (1964) 649–654.
17. Weddell, A. G. M. and Pearson, J. M. H. Leprosy—histopathologic aspects of nerve involvement. In: *Topics on Tropical Neurology*. Hornabrook, R. W., ed. Philadelphia, Pennsylvania: Davis, 1975, pp. 17–28.