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

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Summary One hundred and fourteen women with leprosy and 33 women without leprosy were studied during 118 and 36 pregnancies respectively. Two healthy controls developed leprosy during the study period: 12 of 25 women with 'cured' tuberculoid leprosy relapsed with new lesions or nerve damage; 46 of 93 women with active tuberculoid or lepromatous leprosy showed increased activity of their leprosy either as a transient phenomenon (21 patients) or due to probable dapsone resistance (28 patients). These occurred chiefly during the third trimestre and are thought to be due to decreased host resistance and increased immunological instability during pregnancy.

Introduction

Pregnancy has long been associated with the first appearance of leprosy or aggravation of the disease.^{1–3} One study shows 75% of women studied to have developed the first sign of leprosy in association with child bearing, of whom two-thirds had the first signs of leprosy during the puerperium (the first 6 weeks after delivery).⁴ Suggested reasons for this are hormonal,⁵ metabolic⁶ or some suppression of host resistance.^{4, 7} Suppression of cell-mediated

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immunity (CMI) during pregnancy may also be associated with downgrading and a shift toward the lepromatous end of the spectrum. Hence one might expect recovery of CMI following delivery to be associated with upgrading phenomena and reversal reaction. Some patients present with the onset of leprosy and in reaction during the puerperium or first few weeks of lactation.⁸ Many of the observations quoted have been based on retrospective studies. This paper presents the results of a prospective study on the effect of pregnancy on leprosy carried out at the Addis Ababa Leprosy Hospital between 1975 and 1978.

Patients and methods

One hundred and forty-seven Ethiopian women were studied during 154 pregnancies. There were 114 women with leprosy (118 pregnancies) and 33 women without leprosy (healthy contacts: HC, with 36 pregnancies). The women who were all from the low socio-economic class lived, for the most part, in the villages surrounding the Addis Leprosy Hospital. They were first seen, for this study, when they presented themselves at the Hospital ante-natal clinic which supplied ante-natal care for registered leprosy patients, wives of leprosy patients and members of staff. Initially the patients studied were those with active tuberculoid leprosy, active lepromatous leprosy with positive skin smears and healthy contacts; later the study group was broadened to include women with 'cured' tuberculoid leprosy who had stopped treatment and women with chronic, quiescent lepromatous leprosy with negative skin smears. Selection of the patients within the above general classification was based on their willingness to participate in the study, to deliver their babies in hospital rather than at home and to be seen with their babies for regular assessment, including blood tests, for a period of up to 2 years during lactation.

CLASSIFICATION AND TREATMENT OF MOTHERS

The 114 women with leprosy were classified initially as follows using the scale of Ridley & Jopling:⁹

Cured tuberculoid and borderline tuberculoid leprosy (released from control)	(TT and BT/RFC)	25 (25 pregnancies).
Active tuberculoid and borderline tuberculoid leprosy	(TT and BT)	17 (18 pregnancies).
Borderline lepromatous leprosy	(BL)	40 (41 pregnancies).
Lepromatous leprosy	(LL)	32 (34 pregnancies).

Eighty-two patients were receiving dapsone monotherapy (50–100 mg daily)

but 26 patients (1 BL, the rest BT or TT) were believed cured, had stopped treatment and had been 'released from control' (RFC, see below). Six patients (2 BL, 4 LL) had already developed dapsone-resistant leprosy, as defined¹⁰ and were receiving clofazimine (4 patients, all LL, 5 pregnancies) or rifampicin plus thiambutosine and dapsone (2 patients both BL). Treatment and supervision of these patients was carried out through the hospital outpatient clinics: 81 patients receiving dapsone monotherapy (18 TT and BT, 36 BL, 27 LL) were supplied with dapsone tablets on a weekly or fortnightly basis by paramedical leprosy workers at hospital or municipality clinics, were referred to hospital clinics for treatment of reactions or other complications of leprosy, and were assessed by a doctor at the hospital 'Review Clinic' every 6 months when routine slit-skin smears were examined, 4 patients (2 BL, 2LL) receiving dapsone monotherapy 100 mg daily in a chocolate-coated tablet for suspected dapsone resistance¹⁰ and 7 patients (2 BL, 5 LL) with proven dapsone resistance were seen every 6 months at a special clinic for the treatment of drug-resistant leprosy, routine slit-skin smears were done every 6 months and biopsies were taken annually.

PATIENTS RELEASED FROM CONTROL (RFC)

At the start of the study the practice in the hospital for stopping treatment of leprosy was as follows: TT patients were RFC after 2–3 years of treatment with dapsone 50–100 mg daily; BT patients were RFC after 4 or more years of treatment with dapsone 50 mg daily (300 mg weekly) when there had been no clinical evidence of active leprosy for at least 2 years; BL patients were RFC when they had received treatment for 15–20 years and had been skin-smear (bacteriological index: BI) negative with no clinical evidence of active leprosy for 10 years; LL patients continued on treatment for life and hence were not RFC.

The 25 patients classified as TT and BT/RFC were originally classified as TT or BT at the hospital new case clinic. Diagnosis had been made on clinical grounds supported by negative BI but without histological confirmation. Seventeen patients had been diagnosed at the Addis Ababa Leprosy Hospital and 8 at rural clinics or hospitals where they received their initial treatment before being transferred to Addis Ababa. One patient seen first in Addis Ababa and 1 patient coming from a rural clinic had had doubts raised regarding classification of leprosy and had been recorded as being 'LI' and 'BB' respectively on one occasion; on subsequent assessment by a senior hospital leprologist both were recorded as 'BT' on clinical grounds. The duration of stopping treatment ranged from 3 months to 10 years (mean 2.6 years).

ENTRY OF WOMEN TO THE STUDY: TIMING AND ASSESSMENT

At the time of entry to the study (Table 1) in addition to full obstetrical assessment, a general physical examination was made and the patient's leprosy

Table 1. Time of entry to study

Histological classification of leprosy	Number of women entering the study			Total pregnancies
	1st trimestre	2nd trimestre	3rd trimestre	
HC	2	11	23 (7)*	36
TT and BT/RFC	—	13	12 (2)	25
TT and BT/Active	1	6	11 (3)	18
BL	4	19	18 (4)	41
LL	4	13	17 (4)	34

*The number () indicates the number of women entering the study at or after 36 weeks gestation.

HC = healthy contacts; RFC = released from control.

status assessed clinically; skin smears were taken from leprosy patients and a biopsy for histological classification, if it had not already been taken. Subsequent detailed leprosy assessments were made as indicated by the patient's symptoms and clinical state.

The first group of women admitted to the study were taken in during the third trimestre, several of them at or after 36 weeks gestation. After the first 3 months of the study it was apparent that leprosy deteriorated during pregnancy, thereafter whenever possible, patients were admitted to the study during the first or second trimestre with detailed leprosy assessment at the time of entry and during each following trimestre and at 6-month intervals during lactation, more frequently if indicated.

ROUTINE ASSESSMENT OF STUDY PATIENTS

Women in this study were seen for routine ante-natal care at monthly intervals until 28 weeks gestation, every 2 weeks until 34 weeks and weekly thereafter. In addition to receiving the routine ante-natal care their leprosy status was assessed clinically, complications were recorded, and additional investigations arranged as indicated. They were admitted to hospital for 24-hour collections of urine for oestriol analysis and also for medical, obstetrical or social reasons as necessary. LL patients in particular were admitted to hospital for several weeks prior to delivery to prevent foetal wastage by precipitate delivery at home. As inpatients they received routine ante-natal surveillance but stopped attending outpatient ante-natal clinics (ANC). This factor accounts largely for the reduced attendance at ANC by LL patients (Table 2).

At detailed leprosy assessment the patient's complaints, state of health and drug treatment were recorded. The patient was then examined in a well-lit room, with inspection and palpation of the skin, peripheral nerves and regional lymph nodes. Clinical drawings were made of the skin lesions, slit-skin smears were taken from 6 sites (both ears and 4 smears from active lesions, or from both ears, elbows and knees when no active lesions were seen; smears were

Table 2. Frequency and timing of assessment during pregnancy

Classification of leprosy	No. of women	No. of pregnancies	No. of attendances at ANC (Mean ± SEM)*	Frequency of leprosy assessments [†]						Frequency of laboratory investigations [‡]								No. of admissions for obstetrical/medical/social reasons	
				X1	X2	X3	X4	X5	X > 5	X1	X2	X3	X4	X5	X > 5	Puerperal ¹	Lactation ²		Not done
HC	33	36	5.9 ± 0.5	32 (31)	4 (5)	—	—	—	—	14 (14)	—	—	—	—	—	1 (1)	8 (8)	13 (13)	4
TT and BT/RFC	25	25	6.2 ± 0.5	19 (17)	5 (6)	1 (1)	—	—	—	11 (11)	5 (4)	—	—	—	—	3 (3)	6 (6)	—	3
TT and BT/Active	17	18	5.1 ± 0.6	15 (3)	3 (5)	— (8)	—	—	—	13 (12)	3 (3)	—	—	—	—	—	2 (1)	—	4
BL	40	41	5.9 ± 0.5	32 (7)	9 (16)	— (13)	—	—	—	19 (17)	15 (14)	2 (3)	—	—	—	3 (3)	—	2 (2)	4
LL	32	34	4.5 ± 0.6	16 (4)	18 (15)	— (9)	— (5)	— (1)	—	16 (13)	13 (12)	3 (3)	— (1)	— (1)	— (2)	1 (1)	1 (1)	—	9

*Assessment by doctor (MED).
†First number equals the number of patient-assessments during pregnancy for this special study only; number within () equals the number of patient-assessments for the special study together with the routine 'full clinical assessments' at hospital review clinics and clinics monitoring suspected dapsone resistance.
‡First number equals frequency of laboratory investigations (skin smear for BI and MI/biopsy for histology/biopsy for mouse foot pad tests), singly or in combination; number () equals frequency of laboratory investigations and additional tests (VMT with ST/EMG/skin test with A6), singly or in combination.
HC = healthy contacts (without leprosy); TT and BT/RFC = tuberculoid and borderline leprosy 'released from control', i.e. 'cured'; TT and BT/Active = tuberculoid and borderline tuberculoid leprosy, active; BL = borderline lepromatous leprosy; LL = lepromatous leprosy; ANC = ante-natal clinic.
BI = bacteriological index, MI = morphological index.
¹When it was not possible to perform skin smears for BI or biopsy during pregnancy some were done immediately after delivery, during the puerperium.
²When skin smears for BI or biopsy had not been done before, some were done for the first time in the study during lactation at follow-up assessments.

taken from the same sites on subsequent occasions unless new lesions had appeared, in which case smears were taken from them) for bacteriological and morphological index (BI and MI).

Biopsies were taken for diagnosis and classification from active lesions or when the disease was quiescent from the buttocks. The biopsies were divided in two and read by two independent leprologists. Patients who were deemed healthy contacts were assessed in the same way as leprosy patients with the exception of the skin biopsy, which was only done if there was a suspicious lesion or nerve enlargement. Clinical classification was undertaken by two independent observers. When a patient was suspected of having developed dapsone-resistant leprosy a biopsy of an active nodule with a positive morphological index was taken and tested in mouse foot pads for dapsone resistance.¹¹

Sensory skin testing (ST)¹² and voluntary muscle testing (VMT)¹³ was done by the physiotherapy department. Nerve conduction velocity (EMG) was estimated in a few patients where it was difficult to decide whether nerve damage was of recent onset.

Skin testing using a standardized purified protein of *Mycobacterium leprae* grown in armadillos (A6) was done during lactation instead of lepromin testing.

The patients' hospital records were reviewed periodically and additional data regarding the initial diagnosis and treatment of leprosy, routine leprosy assessments, complications of leprosy and special investigations not obtained at the study assessments was abstracted and used in the final analysis of results. The frequency of assessment and of laboratory tests and other investigations carried out during pregnancy and lactation is shown in Tables 2 and 3. The total number of special investigations is not shown as tests carried out at the same time, regardless of number, are recorded as one time of testing.

DIAGNOSIS OF DETERIORATION OF LEPROSY STATUS

- (i) New 'overt' cases of leprosy were diagnosed clinically and confirmed by skin smears and biopsy.
- (ii) Relapse in RFC patients was diagnosed clinically, by the appearance of new lesions and/or new nerve damage or by positive BI or biopsy showing active leprosy.
- (iii) Deterioration in leprosy status of patients receiving treatment was defined as the occurrence of one or more of the following: conversion from negative to positive or rise in the patient's BI or MI, appearance of new lesions, extension of existing lesions, erythema and oedema of margins or tuberculoid lesions (in the absence of reaction) or increased activity of the lesion as diagnosed by histology.

Table 3. Frequency of leprosy assessments and investigations during lactation

Classification of leprosy	No. of women	Frequency of leprosy assessments*							Not seen	Frequency of investigations†						
		X1	X2	X3	X4	X5	X > 5	Seen with baby, asymptomatic, no leprosy assessment		X1	X2	X3	X4	X5	X > 5	Not done
HC	36	11 (11)	3 (3)	—	2 (1)	— (1)	—	7 (7)	13 (13)	12 (11)	2 (4)	—	—	1 —	— (1)	21 (20)
TT and BT/RFC	25	9 (5)	5 (11)	3 (2)	—	—	— (1)	2 (1)	6 (5)	9 (6)	8 (8)	1 (3)	— (1)	—	—	7 (7)
TT and BT/Active	18	9 (4)	3 (5)	1 (1)	1 (2)	— (1)	— (3)	—	4 (2)	8 (3)	3 (5)	2 (2)	— (3)	—	— (1)	5 (4)
BL	41	8 (7)	6 (3)	6 (7)	6 (3)	2 (5)	1 (11)	6 (1)	6 (4)	10 (9)	14 (8)	4 (4)	1 (5)	2 (4)	2 (3)	8 (8)
LL	34	10 (3)	9 (7)	5 (10)	2 (5)	1 (3)	1 (5)	4 (1)	2 —	11 (7)	15 (12)	2 (6)	2 (2)	1 (1)	— (3)	3 (3)

*First number equals the number of patient-assessments during lactation for this special study only; number within () equals the number of patient-assessments for this special study together with the routine 'full clinical assessments' at hospital review clinics and special clinics monitoring suspected dapsone resistance.

†First number equals frequency of laboratory investigations (skin smears for BI and MI/biopsy for histology/biopsy for mouse foot pad test) singly or in combination; number within () equals frequency of laboratory investigations and additional tests (VMT with ST/EMG/skin test with 'A6') singly or in combination.

Results

HEALTHY CONTROLS (HC)

Of 33 women observed during and after 36 pregnancies, 2 developed leprosy. One asymptomatic woman developed a hypopigmented macule during the third trimestre of pregnancy which on biopsy showed indeterminate leprosy. Postpartum the lesion grew in size but the woman had no complications of leprosy. The second woman complained of severe 'rheumatism' at 10 weeks postpartum when she was found to have enlarged nerves which on biopsy showed active BL leprosy. Hypopigmented skin lesions and skin infiltration were apparent by 6 months postpartum.

'CURED' TUBERCULOID AND BORDERLINE TUBERCULOID LEPROSY (TT AND BT/RFC)

Of these 25 patients, 9 relapsed with active leprosy (6 BT, 3 BL) within periods of from 3 months to 3 years after stopping treatment. Eight of the 9 relapses were diagnosed on clinical grounds, 7 were confirmed on biopsy; 3 were BI positive. Five out of the 9 relapses occurred during the third trimestre of pregnancy.

In addition 3 patients were considered to have incipient relapse on the evidence of new nerve enlargement or neuritis though skin biopsies and BI were negative.

Ten out of 12 patients relapsed in association with the first pregnancy and 2 during the second pregnancy after RFC. Details of clinical features and investigations are shown in Table 4.

ACTIVE TUBERCULOID LEPROSY (TT AND BT)

Of 18 patients all on dapsone monotherapy, 8 had a transient increase in activity of the skin lesions, usually in the third trimestre, without any histological evidence of reaction. In 3 cases the lesions appeared more active with raised erythematous margins, in 4 cases there was conversion from BI negative to positive. In 2 cases there was increase in size and number of the skin lesions during lactation.

LEPROMATOUS LEPROSY (BL AND LL)

Sixty-eight women (36 BL, 32 LL) were studied through 71 pregnancies and followed up after delivery. (Four others were assessed only during pregnancy). Increased activity was found in 38 (54%) during pregnancy, puerperium or lactation (in 20 during the third trimestre or puerperium). At the time that

Table 4. TT and BT/RFC cases showing relapse in association with pregnancy

No.	Parity	Original diagnosis	Duration of treatment (years)	Years RFC before present pregnancy	Symptoms	Clinical features	Additional tests	Clinical diagnosis at relapse	Histological diagnosis	BI	Final diagnosis	Timing of relapse
A – relapse cases												
1	1 + 0	'T'	7	3/12	—	1 active new macule face; nerves normal		BT Active	Skin: BL early active AFB 3–4* in granuloma	2.3	BL	3rd TM during 1st pregnancy after RFC
2	2 + 0	BT	11	1½	Rheumatism	New nodules ++ on on legs; nerves normal		BL Active	Skin: solid AFB in nerves and deep dermis	3 +	BL	3rd TM during 1st pregnancy after RFC
3	5 + 0	BT	14	2½	—	Inactive skin; nerves normal		Quiescent BT	Not done	0.8 (4* at one site)	BL	3rd TM during 2nd pregnancy after RFC
4	1 + 0	BT	1	3	—	8 new macules (legs and arms); 6 enlarged nerves; new motor and sensory loss		BT Active	Skin: early BT. Nerve: early tuberculoid lepr.	0	BT	Lact. after 1st pregnancy after RFC
5	0 + 1	BT	4	1	'Burning' paraesthesiae	New macule, face skin reaction neuritis	EMG active demyelination	BT Active	Skin: normal. Nerve: BT Active	0	BT	1st TM during 1st pregnancy after RFC
6	3 + 0	'T'	9	1	—	New macule face; nerves normal		BT Active	Not done	0	BT	Lact. after 1st pregnancy after RFC
7	1 + 0	BT	8	1½	—	New nodules on face and ears; 3 enlarged nerves		BL Active	Skin: BT Active. Solid AFB in nerve	0	BT	2nd TM during 1st pregnancy after RFC
8	1 + 0	BT	8	2	Rheumatism	2 new macules face; nerves normal		BT Active	Skin: BT Active	0	BT	3rd TM during 2nd pregnancy after RFC
9	4 + 0	BT	5	2*	'Burning' paraesthesiae	Active erythematous edge of old macule, face; 3 enlarged nerves		BT Active	Skin: TT/BT Active	0	BT	3rd TM during 1st pregnancy after RFC
B – incipient relapse cases												
1	4 + 0	TT/BT	6	4/12	Rheumatism	Skin inactive; 2 enlarged nerves		Old BT	Skin: almost normal	0	BT	Lact. after 1st pregnancy after RFC
2	3 + 0	BT	7	1½	Rheumatism	Skin inactive; 3 enlarged nerves	VMT and ST motor and sensory loss	'Burnt out BT'	Skin: within normal limits	0	BT	Lact. after 1st pregnancy after RFC
3	2 + 0	BT	10	3*	Rheumatism	Skin inactive; 1 enlarged nerve	VMT motor loss	Inactive BT	Not done	0	BT	Lact. after 1st pregnancy after RFC

*RFC during previous pregnancy.

TM = Trimestre;

lact = lactation.

Figure 1. Timing of first evidence of deterioration of leprosy status (overt leprosy, relapse in 'cured' TT and BT patients, increased activity of disease in TT, BT, BL and LL patients receiving treatment for leprosy) in relation to pregnancy and lactation. (Note. The 4 patients relapsing between 19 and 24 months had not been assessed during the preceding 12 months: from the history and/or clinical findings, it is very likely that relapse occurred by 12 months postpartum.)

increased activity was first observed 17 out of the 38 patients had new nodules (a further 7 developed new skin lesions later); in 34 cases the increased activity was confirmed by a rise in BI, in 4 cases by biopsy only. In 16 cases the increased activity was a transient phenomenon, with fall in BI to less than the pre-pregnancy levels or reversion of the active biopsy to 'LL regressing' during early lactation. However, 6 patients then went on, within 11–15 months, to show a subsequent rise in BI and clinical evidence on relapse during late lactation or the next pregnancy. The phenomenon of transient increase in activity was shown by patients prescribed dapsone monotherapy, dual therapy with dapsone and rifampicin, and clofazimine monotherapy.

OTHER CLINICAL FEATURES ASSOCIATED WITH INCREASED ACTIVITY OF LEPROSY (BL AND LL)

The complaint of 'rheumatism' either preceded or accompanied the increased activity of the disease in more than half of the patients. Erythema nodosum

leprosum (ENL) preceded or accompanied the increased activity of the disease in one-half of the patients, occurring for the first time during pregnancy in most cases. In contrast reversal reaction was seen postpartum when recovery of CMI would be expected to occur. New nerve enlargement was observed in one-third of the patients, and neuritis (due to ENL or reversal reaction) was observed in more than half of the patients who had increased activity of the disease, including those who had only a transient rise in BI during pregnancy. Neuritis is discussed in detail elsewhere.¹⁴

Twenty-eight patients who were considered to have evidence of dapsone resistance are discussed elsewhere.¹⁵

RELAPSE IN ASSOCIATION WITH DOWNGRADING PHENOMENA (BL AND LL)

Six patients (all BL) downgraded from BL to LL, 5 during pregnancy and 1 during lactation. They were diagnosed on histology, but 3 also had clinical evidence of relapse due to dapsone resistance. In addition 3 relapse patients showed, for the first time, the histological features of polar lepromatous leprosy (LL_p)¹⁶ during the third trimestre or immediately after delivery. After delivery 3 of the patients who had downgraded to LL upgraded to BL or BT.

Discussion

Protection and survival of the foetus as an allograft is the result of adaptive maternal responses to pregnancy including transient suppression of CMI.¹⁷ Suggestive evidence for this is the increased survival time of adult skin homografts on pregnant hosts, especially during the third trimestre, compared with non-pregnant hosts;¹⁸ the depression of tuberculin sensitivity in the third trimestre of pregnancy;¹⁹ the increased severity of certain viral diseases during pregnancy²⁰⁻²² and amelioration of diseases such as rheumatoid arthritis,²³⁻²⁴ ulcerative colitis²⁵ and sarcoidosis²⁶ during pregnancy with deterioration postpartum. The pregnancy-associated alterations of these conditions pertain to cell-mediated immune reactions.²⁷

Host resistance to mycobacterial disease is dependent on CMI and can be measured *in vitro* by the lymphocyte transformation test (LTT). Results of such tests, using phytohaemagglutinin (PHA) and purified protein derivative of tubercle (PPD), indicate suppression of CMI during pregnancy which ceases at delivery or shortly afterwards.²⁸⁻³¹ It is possible that pregnancy-associated α -macroglobulin plays a part in this process.³² In pregnant leprosy patients it is likely that plasma contains suppressive factors in addition to those normally associated with pregnancy, as plasma from mothers with

leprosy had a greater inhibitory effect on their babies' LLT than plasma from healthy mothers.³³

Before the era of chemotherapy it was observed that there was a sex difference in the mortality from tuberculosis: according to the United States Census Bureau Statistics there was a consistently higher death rate in females aged 15–25 years of age from 1900 to 1942.³⁴ It was well recognized that pregnancy had an adverse effect on tuberculosis. In many cases the first sign of tuberculosis was observed soon after parturition and where tuberculosis was already established mortality was increased during later pregnancy and the puerperium,^{35–39} although with proper sanatorium care throughout pregnancy the danger was greatly diminished if not avoided.⁴⁰ A similar adverse effect of pregnancy on tuberculosis was observed in cattle⁴¹ and experimental animals.⁴²

In leprosy the overall prevalence in men is greater than in women. However, women appear to develop the disease at an earlier age than men. For instance, among leprosy patients in India 50% of the women had developed leprosy by the age of 20 years, compared with 30% of men.² In Ethiopia as many as 75% of female patients in the studies of the Medical Research Council Leprosy Project had developed leprosy by the age of 20 (M E Duncan & J M H Pearson, unpublished observations). It is tempting to link this early onset with an increased risk of infection and rate of evolution associated with increased endocrine activity during puberty and suppression of CMI in frequent pregnancies during the late teens.

In leprosy where the host resistance is dependent chiefly on CMI, one would expect pregnancy to be associated with (i) the first appearance of leprosy; (ii) relapse in cured patients; and (iii) increased activity of the disease with a tendency to shift towards the lepromatous end of the spectrum and increase in bacillary load. These features were all seen in our study.

(i) NEW CASES

In Addis Ababa the new case rate for the city is 1 per 3,000 population; in the villages surrounding the Leprosy Hospital the rate is higher, 1 per 1,000 population (0.1%). It is therefore significant that of 33 women observed during 36 pregnancies, 2 (5.6%) showed the first sign of disease during the third trimester or early lactation. Our observation confirmed earlier reports.^{1–4, 6–7, 43} Women already infected with *Mycobacterium leprae* and incubating the disease show overt leprosy in late pregnancy or early lactation as a result of decreased host resistance of pregnancy.^{1, 7, 43}

(ii) RELAPSE OF 'CURED' PATIENTS

The relapse rate in patients with cured TT and BT leprosy in Ethiopia has been reported⁴⁴ as 5% per annum. A considerable number of patients relapsed because they had been misclassified as BT rather than BB or BL, and thus had

received inadequate treatment prior to stopping therapy. Our observation that 9 'cured' TT and BT patients relapsed with active leprosy (3 as BL and 6 as BT) confirms the above findings. While the original clinical diagnosis had not been in doubt in any of our cases and all were BI negative, none had had histological confirmation. In pregnant women the skin lesions may not be typical of either BT or BL leprosy, thus causing difficulties in clinical classification as happened with two of the patients who relapsed in our study (Table 4). Ideally (to ensure adequate treatment), histological confirmation and classification is recommended in all patients especially women presenting with overt leprosy in association with pregnancy or lactation. It is also possible that the initial 'BT' classification in our patients was correct but that 3 of these women who were all parous had downgraded to BL during a previous pregnancy.

Nerve damage was a feature of relapse in BT/RFC patients, 4 out of 8 had nerve damage early. This is the same as is found in early active tuberculoid leprosy (JMH Pearson, unpublished observation). The observation of Naafs (B Naafs, personal communication) that 'rheumatism' was a symptom of relapse in these patients was confirmed in this study although we found it was more consistently a symptom of 'late silent neuritis'.

It has been suggested that pregnancy be regarded as a test of cure of leprosy.⁴³ Seven of the 9 women who relapsed with active leprosy did so during the first pregnancy after stopping treatment and 2 relapsed in the second pregnancy after stopping treatment (Table 4). Thus one pregnancy cannot be regarded as a test of cure and we recommend that all women with 'cured leprosy' who have stopped therapy, be carefully assessed during and after all subsequent pregnancies if late nerve damage is to be avoided.

(iii) INCREASED ACTIVITY OF LEPROSY WITH A TENDENCY TO SHIFT TOWARDS THE LEPROMATOUS END OF THE SPECTRUM AND INCREASE IN BACILLARY LOAD

We observed increased activity of their leprosy in just under half of the patients with active TT or BT leprosy (8/18) and in rather more than half (38/71) of the BL and LL patients who were followed up. The very high rate of relapse or deterioration of leprosy status, half of which appeared to be a transient phenomenon, would undoubtedly have been overlooked had these patients not been assessed frequently with the use of routine skin smears and biopsies even in the absence of skin lesions. The importance of carrying out routine skin smears at regular intervals cannot be overemphasized, as it is only by so doing that relapse can be detected early.⁴⁵⁻⁴⁶

The increased activity of the patient's leprosy recorded in 17 of the 89 patients was diagnosed on the basis of a rise in BI and/or MI or on increased activity at the histological level in women who did not at any time during the study show new or active skin lesions. The timing and transient nature of this

phenomenon was of interest in that it was related to the third trimestre of pregnancy when CMI would be maximally suppressed. A similar observation was made by Browne who refers to a transient non-significant rise in BI which he attributes to hormonal disturbances of pregnancy.⁴⁷ However, by having the opportunity to follow up these Ethiopian patients we found that 6 out of 16 lepromatous women who had a transient rise in BI during pregnancy developed the clinical picture of dapsone resistance during the next 15 months (4 with new nerve damage) and 9 others developed new nerve damage during lactation. Thus we feel that a transient rise in BI during pregnancy can no longer be considered as significant.

The conversion to BI positive with increase in size and number of new lesions in BT patients, the tendency to downgrade from BL to LL during pregnancy with upgrading following delivery, and the onset of leprosy with reversal reaction during early lactation⁸ are evidence of the increased instability of women with leprosy during pregnancy, especially those classified as borderline.

While further investigation is required to elucidate the mechanisms of the adverse effect of pregnancy on leprosy, the practical implications which should be made widely known to all leprosy workers are:

1. The pregnant woman, because of physiological suppression of CMI most marked during the third trimestre, is especially at risk. If she is a known leprosy contact incubating leprosy, she is most likely to show overt disease either in late pregnancy or during lactation when it may well be complicated by reaction. 'Cured' BT patients run the risk of relapsing with active disease, and in patients receiving treatment for leprosy there is a 50% chance of the disease being aggravated with a shift towards the lepromatous end of the spectrum, increased bacillary load, subsequent risk of ENL and in the puerperium reversal reaction possibly with severe nerve damage.
2. In relapsing RFC patients and those who are developing dapsone-resistant leprosy, with multiplication of viable bacilli during pregnancy, there is a real risk that the foetus may be infected *in utero*⁴⁸⁻⁴⁹ and go on to clinical leprosy in early childhood; furthermore the woman herself will become a risk to her household and the community as she is likely to be infectious. We therefore recommend:
 - (I) *Health education.* Incorporation of this knowledge into health education of women in the reproductive age group. At the same time advice on family planning should be given so that as far as possible pregnancies can be postponed until after the leprosy is well under control.
 - (II) *Increased surveillance.*
 - (i) For women with active leprosy: increased surveillance during pregnancy, (a) to ensure a maximal patient compliance, if possible substituting parenteral for oral dapsone therapy during the first

trimestre if emesis gravidarum is troublesome; (b) routine assessments with skin smears and biopsies, as possible, during the second and third trimestre and at 3 and 6 months postpartum, by which time most relapses should have occurred.

- (ii) For women with cured leprosy (TT and BT/RFC): clinical assessment with particular attention to peripheral nerves during pregnancy and at 6, 12 and 18 months postpartum. Additional tests, namely skin biopsy, nerve biopsy (if possible), VMT, ST or EMG when relapse is suspected but clinical findings are not diagnostic.
- (iii) For healthy contacts, especially of infectious cases: assessment during the third trimestre of pregnancy and postpartum, ideally at 3 and 6 months.
- (iv) For the child born to a woman who has had an active relapse during pregnancy there is risk of clinical leprosy in early childhood. This is likely to be of the indeterminate type and self healing, particularly in the very young child, and probably occurs more frequently than realized hitherto. Regular inspection at child health care clinics when weighing and measuring the child, naked, provides diagnostic opportunities. A history of lactation should be obtained as anti-leprosy drugs are transmitted through the mother's milk. (This will be discussed more fully elsewhere.)⁵⁰

(III) *Additional anti-leprosy drugs.* The question of additional anti-leprosy drugs during pregnancy and lactation requires careful thought and is discussed elsewhere.¹⁵ To prevent relapse in TT and BT/RFC patients, we underline the recommendations made by Touw-Langendijk and Naafs⁴⁴ that very careful review of the patient's initial diagnosis, treatment, progress and date of leprosy 'inactivity' be made before the patient is RFC. We add to this a recommendation that no female patient be RFC either during pregnancy or within a year of delivery; all pregnancies and dates of delivery should be noted in the patient's records. These two recommendations would reduce the number of patients being RFC prematurely. For those already RFC and becoming pregnant, increased surveillance during and after pregnancy and an awareness of the risk of relapse to allow early diagnosis is probably preferable to blind treatment of RFC patients for an empirical period of time during and after pregnancy, which could mask clinical relapse.

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