Pupillary Reactions in Lepromatous Leprosy[1, 2]

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A unique "temperature-linked" neuropathy has been clearly demonstrated in lepromatous leprosy by Sabin ([10, 11]), in which nerves in cool regions of the body become affected while those in warm areas do not. In this process anhydrosis and vascular changes in the skin are present due to involvement of sympathetic nerve endings. This pattern of nerve involvement (Fig. 1) reflects the temperature dependence of *Mycobacterium leprae,* which in mouse foot pad has been shown to have a temperature optimum of 27-30°C ([14]). In lepromatous leprosy ocular damage also seems to be related to temperature. Conjunctiva, episclera, sclera, cornea, and iris are commonly involved while the vitreous humor and retina are almost invariably spared. Needle tip thermistor probes in rabbits have shown that the cornea and iris are quite cool and vary significantly with external temperature whereas the vitreous and retina are several degrees warmer ([12]).

Early corneal involvement consists of thickening of nerves with the formation of small pearly enlargements which represent lepromata ([3]). Resultant corneal insensitivity leads to ulceration and is an important cause of blindness in this disease.

Lepromatous involvement of the iris takes the form of military "pearls" or larger lepromata ([1]). In addition, acute and chronic iridocyclitis occur frequently either alone or as part of a systemic reaction leading to further visual impairment ([8]).

Because nerve involvement in the anterior part of the eye is such a constant feature of lepromatous leprosy it appeared likely that the iris would be denervated and thus demonstrate denervation hypersensitivity to topically instilled agents. This report describes the results of tests for sympathetic denervation hypersensitivity in the eyes of lepromatous patients. We postulate that

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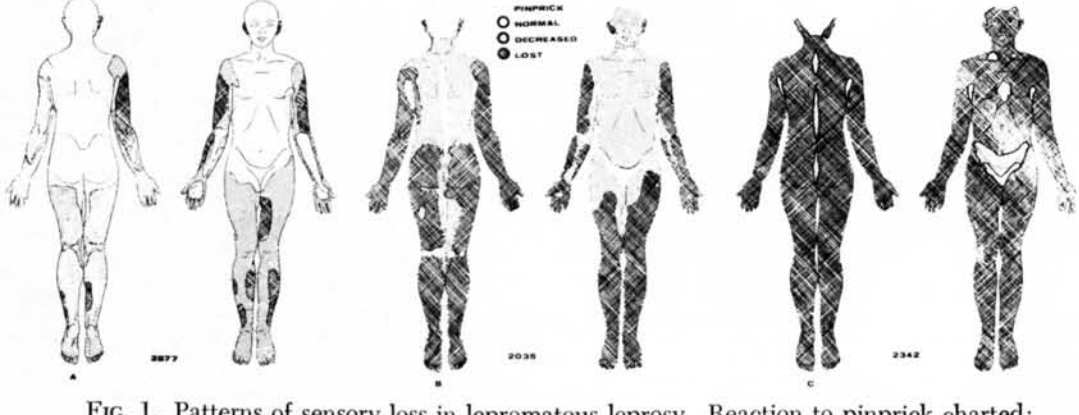

FIG. 1. Patterns of sensory loss in lepromatous leprosy. Reaction to pinprick charted: a) *Mild sensory loss.* Note involvement of cool body areas such as extensor portions of extremities and ears with sparing of warm areas such as scalp, axillae, groin, and flexor portion of forearms; b) *Moderate sensory loss.* The trunk is now involved but warm areas continue to be spared; c) *Severe sensory loss.* Note widespread analgesia with sparing of warm areas of scalp, axillae, groin, midline of back, and supraclivicular areas which overlie carotid and subclavian arteries.

the disease provides a model of peripheral postganglionic denervation.

MATERIALS AND METHODS

Twenty patients with biopsy-proven lepromatous leprosy and twenty normal subjects were chosen. None of the control subjects or patients were receiving drugs which might interfere with pupillary responses. We chose patients who had minimal ocular disease from our patient population. All had ocular tensions recorded; none had glaucoma. Two patients had had iritis. In one, both eyes were mildly affected; in the other, one eye was affected.

In testing for sympathetic denervation hypersensitivity two drops of a 0.1% or 1.0% solution of L-epinephrine were instilled into the conjunctival sac of the right eye one minute apart and reactions noted at 30 minutes. A response was considered positive if the treated pupil dilated 0.3 mm or more above control values. This was calculated according to the formula: change in right pupillary size after epinephrine= (size right pupil minus size left pupil after drug) subtracted from (size right pupil minus size left pupil before drug) or $\Delta R = (R_A - L_A) - (R_B - L_B)$. As can be seen, the untreated pupil is necessary to serve as a control both for initial anisocoria as well as for spontaneous variation in pupil size which occurs even under constant lighting conditions ([7]). We noted that during spontaneous fluctuations in size of normal pupils, both pupils took part in the change in size, and also that any initial difference in size between the two pupils would continue to be present regardless of the direction or magnitude of the change. The ciliospinal reflex also was elicited. This reflex comprises mydriasis following a painful stimulus on the neck. In man, the test is dependent on sympathetic reflex dilatation of the pupil ([2]). It was elicited by pinching the neck with a small hemostat.

Color photographs were taken of the eyes immediately prior to each test and at appropriate intervals thereafter. Illumination was carefully measured and was constant. A millimeter rule was held beneath the left eye of each subject. Pupillary size could be measured accurately to tenths of millimeters by projecting the transparencies onto a large screen and measuring the pupils with calipers, which were then read against the projected millimeter scale.

Body sensory loss was mapped using a pin and was graded as mild, moderate and severe. Representative examples of such sensory loss are shown in Figure 1.

Corneal sensory loss was measured in four quadrants with a standard Cochet and Bonnet aesthesiometer. Readings vary from 0 (no sensation) to 6 (normal sensation).

RESULTS

None of the patients or normal subjects had any reaction to 0.1% epinephrine. When 1.0% epinephrine was used, eleven of the twenty patients and one normal subject developed significant pupillary dilatation (Fig. 2). In many patients and in the one control responding, the pupillary response was quite bizarre, the pupil becoming elliptical with most of the dilatation occurring at about 5 or 6 o'clock. Ninety percent of final dilatation occurred by 20 minutes and

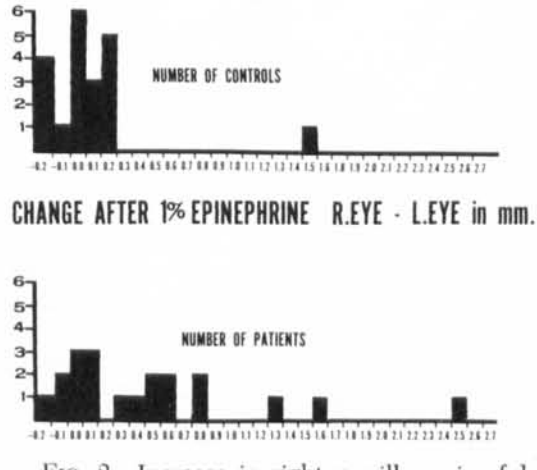

FIG. 2. Increase in right pupillary size following epinephrine 1%. This is calculated according to formula given in text. Note that one normal and eleven patients respond with 0.3 mm or greater change in right pupil. There is a significant difference between patient and normal control groups ($P = <.05$).

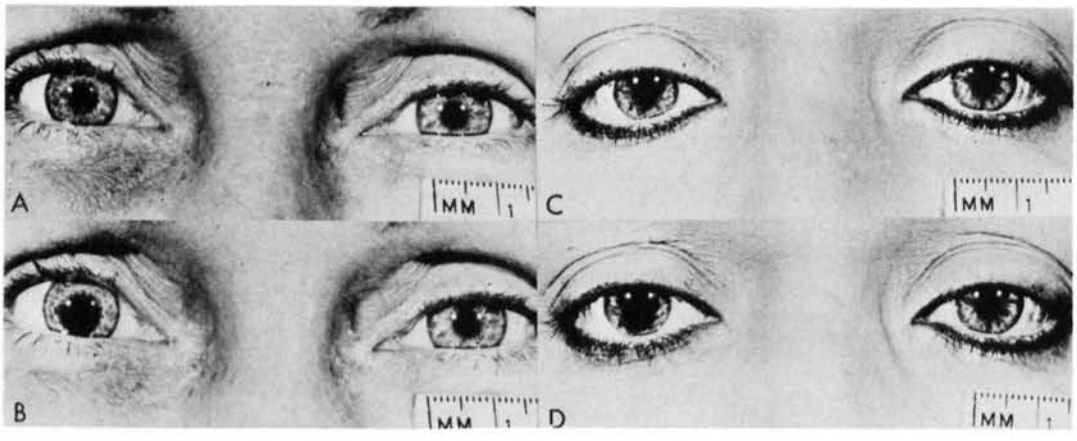

FIG. 3. Pupillary response to epinephrine 1.0% in right conjunctival sac; a) only normal subject to respond (possibly inapparent Horner's syndrome) before epinephrine, b) thirty minutes after epinephrine; c) patient with lepromatous leprosy before epinephrine, d) thirty minutes after epinephrine. Note in both instances the asymmetrical dilatation of the pupil.

it was complete at 30 minutes. Figure 3 shows the one normal subject before and 30 minutes after 1% epinephrine, and one of the patients who responded. Although the one normal subject who responded had no history of ocular disease, we suspect that she has bilateral partial sympathetic denervation. She has small pupils and mild ptosis with compensatory wrinkling of the frontalis.

Ciliospinal responses were present in all normal subjects, in all of the nine patients who did not respond to epinephrine and in nine of the eleven patients who responded. This is surprising in that many of the patients were unable to feel the pinch used to elicit the reflex because of body sensory loss. Pupillary responses to light and near vision were normal in all patients and controls.

An unexpected finding was the excellent ability of the unaided eye to spot pupillary inequality. We found that careful examination of the eyes allows one to say that pupils are unequal when pupillary differences of as little as 0.1 to 0.2 mm are present, as we proved on reviewing the projected transparencies. Epinephrine response did not appear to correlate with the degree of corneal sensitivity, degree of body sensory loss, history of *erythema nodosum leprosum*, presence of other ocular disease, concomitant drug therapy, or duration of disease (Table 1).

DISCUSSION

Active pupillary dilatation is controlled by the sympathetic nervous system. Sympathetic tone originates from neurons in the hypothalamus which synapse in the upper

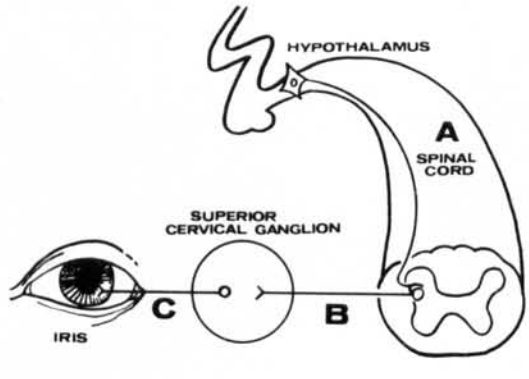

FIG. 4. Diagram of sympathetic pathway to dilator pupillae muscle; a) neurons originating in hypothalmus traverse brain stem to synapse on cells of the intermediolateral cell column of upper thoracic spinal cords, b) axons of preganglionic neurons reach superior cervical ganglion, c) axons of cells in superior cervical ganglion reach dilator pupillae muscle by way of long ciliary nerves.

thoracic spinal cord on cells of the intermediolateral cell column. From here, preganglionic sympathetic efferents pass to the superior cervical ganglion where ganglionic neurons send their axons to the *dilator pupillae* muscle (Fig. 4). Lesions of any of these three segments (at A, B, or C) will produce varying degrees of miosis, apparent enophthalmos, ptosis, and hypohydrosis. After a lesion of the postganglionic neuron (at C), supersensitivity to both systemic and topically applied epinephrine occurs ([6]). Although very weak concentrations of epinephrine (0.05 to 0.1%) have classically been used to demonstrate supersensitivity ([4]), higher concentrations (0.5 to 1.0%) may be necessary to demonstrate inapparent or "latent" Horner's syndrome ([5, 15]). The reason higher concentrations must be used are thought to be the incompleteness of the nerve lesion, although a decrease in epinephrine sensitivity with time, such as occurs in glaucoma, may also play a role ([13]). Eleven of twenty patients in this study developed significant pupillary dilatation to epinephrine 1.0%, indicating denervation. The presence of intact ciliospinal reflexes in the majority of those responding suggests that the denervation is not complete. That the involvement of sympathetic fibers must be peripheral within the iris and ciliary body and not further posteriorly in long ciliary nerves, carotid plexus, or superior cervical ganglion is suggested by the frequent finding of lepromatous infiltrates within the iris and the absence of nerve lesions in areas of higher temperature.

These findings may be related to the pathogenesis of iritis in leprosy. In one study the iris was attacked in 180 of 826 cases of lepromatous leprosy, or 24.5% ([9]). Of these, 139 were acute or subacute diffuse iritis, 69 were the miliary nodular form, and 33 were old and healed iritis. In our group abnormal iris responses occurred in eleven of twenty patients, an incidence of 55.6%. If the hypothesis is correct that these pupillary responses are indicative of early nerve involvement, then the incidence of iris disease in lepromatous leprosy must be much higher. In three of our responding patients, hypersensitivity was present at a time when corneal sensitivity was normal (patients 1, 6, 8). Further studies will be carried out to see if this method is a sensitive one for identifying those patients with inapparent iris involvement, and to see whether patients showing hypersensitivity responses are destined to develop overt iritis at a later date. We suggest a potential usefulness of this simple and inexpensive test in field programs, especially in underdeveloped countries, to identify the iritis-prone. Those lepromatous patients showing responses to 1% epinephrine should be followed closely for the appearance of iritis so that early treatment might be instituted and blindness prevented.

SUMMARY

Pupillary responses to dilute epinephrine solution and ciliospinal responses were studied in 20 patients with lepromatous leprosy and in 20 normal subjects. Eleven of the twenty patients demonstrated mydriasis in response to 1.0% epinephrine as opposed to only one of the controls. All but two patients had intact ciliospinal responses. These findings are consistent with postganglionic sympathetic nerve involvement within the iris. The incidence of iris involvement in lepromatous leprosy as detected by this method is 50% or more, which is much higher than the incidence as determined by direct examination.

RESUMEN

Se estudiaron las respuestas pupilares a una solución diluída de epinefrina y las respuestas cilioespinales en 20 pacientes con lepra lepromatosa y en 20 sujetos normales. Once de los veinte pacientes mostraron midriasis en respuesta a epinefrine al 1,0% en comparación con sólo uno de los controles. Todos menos dos de los pacientes conservaban sus respuestas cilioespinales intactas. Estos hallazgos son compatibles con un compromiso del nervio simpático postganglionar dentro del iris. La incidencia de compromiso del iris en lepra lepromatosa que se detecta con este método es de 50% o más, lo cual es mucho mayor que la incidencia que se determina por medio del examen directo.

Patient number	Cilio-spinal	Coreal sensitivity[a] OD	OS	Epinephrine response[b] (mm)	Iritis	Body sensory loss	*Erythema nodosum leprosum*	Duration disease (years)	Other ocular disease	Medications
1	+	6 6 6 6	6 6 6 6	+2.5	Both eyes mild iritis	None	Yes	8	OD-Iritis	Sulphetrone
2	0	2 3 3 4	2 2 2 2	+0.8	Left eye mild iritis	Severe	Yes	21	Corneal lepromas	Sulphetrone
3	+	3 3 3 3	3 3 3 3	+0.5	No	Severe	No	5	Central post. sub-capsular cataracts	Diaminodiphenyl sulfone (DDS)
4	+	3 3 3 4	3 3 5 3	+0.8	No	Severe	Yes (Neuritic)	6	Corneal leproma	DDS Prednisone
5	0	3 3 3 3	3 3 3 3	+0.5	No	Severe	No	21	None	DDS Valium
6	+	6 6 6 6	6 6 6 6	+0.6	No	Moderate	Yes	24	None	Sulphetrone Phenobarbital
7	+	5 6 4 3	6 5 5 5	+0.5	No	None	No	20	None	Diasone
8	+	6 6 6 6	6 6 6 6	+1.6	No	Mild	No	25	Old keratitis	Diasone
9	+	5 4 6 5	4 4 5 5	+0.6	No	Mild	Yes	6	None	Diasone Eskatrol
10	+	5 5 5 5	6 6 5 6	+1.3	No	Mild	Yes	9	Classical nerve beading	DDS Thorazine
11	+	5 6 6 6	5 5 6 5	+0.3	No	Moderate	No	9	None	Mellaril DDS

[a] Cochet and Bonnet Aesthesiometer (Readings 1 [no sensation] to 6 [normal sensation]). OD = right eye, OS = left eye.
[b] (Right $Pupil_{After}$-Left $Pupil_{After}$) — (Right $Pupil_{Before}$-Left $Pupil_{Before}$) = ΔRP

TABLE 2. *Patients not showing hypersensitivity.*

Patient number	Cilio-spinal	Corneal sensitivity[a] OD	OS	Epinephrine response[b] (mm)	Iritis	Body sensory loss	*Erythema nodosum leprosum*	Duration disease (years)	Other ocular disease	Medications
12	+	5 5 5 6	6 6 6 6	−0.2	No	None	Yes	2	Nerve changes	Thalidomide B-663
13	+	5 5 6 6	5 5 6 6	−0.1	No	Mild	Yes	3	Nerve changes	Sulphetrone Steroids
14	+	5 6 6 6	6 5 6 6	+0.1	No	None	No	16	Superficial episcleritis	DDS
15	+	5 6 5 6	6 6 6 6	+0.1	No	Severe	Yes	10	None	B-663
16	+	4 5 6 5	3 3 5 4	−0.1	No	Moderate	No	23	None	None
17	+	5 3 5 6	5 5 4 5	0.0	No	Moderate	Yes	11	Superficial keratitis	Orthonovum Phenobarbital
18	+	5 5 6 5	5 5 4 6	0.0	No	Moderate	Yes	8	Episcleritis	Diasone
19	+	4 3 5 2	3 4 4 4	0.0	No	Moderate	Yes	21	None	INH Valium
20	+	3 3 3 3	3 3 3 3	+0.1	No	Slight	Yes	2	Corneal nerve beading and low grade iritis	DDS

[a] Cochet and Bonnet Aesthesiometer (Readings 1 [no sensation] to 6 [normal sensation]). OD = right eye, OS = left eye.
[b] (Right $Pupil_{After}$-Left $Pupil_{After}$) — (Right $Pupil_{Before}$-Left $Pupil_{Before}$) = ΔRP

RÉSUMÉ

Chez 20 malades souffrant de lèpre lépromateuse et chez 20 individus normaux, on a étudié la réponse pupillaire à une solution d'épinéphrine, de même que les réponses ciliospinales. Onze des 20 malades étudiés ont présenté de la mydriase, á la suite de l'application d'épinéphrine á 1 pour cent, alors que seulement un des témoins réagissait de la sorte. Tous les malades, sauf deux, présentaient une réponse ciliospinale intacte. Ces observations sont compatibles avec une atteinte post-ganglionnaire des nerfs sympathiques dans l'iris. La fréquence déune atteints de l'iris au cours de la lèpre lépromateuse, telle qu'elle peut être détectée par cette méthode, est de 50 pour cent ou davantage, ce qui dépasse largement la fréquence de cette atteinte telle qu'elle est déterminée par l'examen direct.

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