

TRIAL OF A LONG-ACTING SULFONAMIDE  
SULFAPHENAZOLE (ORISUL, CIBA), IN  
THE TREATMENT OF LEPROSY

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The widespread success of the sulfones in leprosy has overshadowed earlier trials reporting good results with certain sulfonamides (<sup>1, 8</sup>). The suspected tendency of sulfonamides administered for intercurrent diseases in lepromatous patients to precipitate lepra reactions (<sup>1, 2</sup>) has also been a factor in discouraging further trials with compounds of this class in the treatment of leprosy. The advent of several long-acting sulfonamides, however, has revived a certain interest in the possibility of their use in the therapy of the disease.

While there may be only slight differences in the *in vitro* antibacterial activity of the various new sulfonamide drugs now on the market (<sup>3</sup>), it is not impossible that a sulfonamide derivative may one day be synthesized which has a definite lethal action on *M. leprae* and which is free from undesirable side-effects.

Schneider *et al.* (<sup>8</sup>) have reported some considerable success in a preliminary trial with sulfamethoxy-pyrazine (also known as sulfamethoxy-pyridazine, Sultirène, Lederkyn, Medicef, or Kynex), in 6 patients with tuberculoid leprosy. They note reduction in clinical activity, with repigmentation of the lesions and improvement in neuritic symptoms, associated with diminution of the enlargement and tenderness of the nerve trunks. In 4 lepromatous patients the clinical improvement is said to have been definite, although no precise bacteriologic data are given.

The present paper reports a small pilot trial conducted at the Uzuakoli Leprosy Settlement with sulfaphenazole (Orisul, Ciba). Adequate preliminary pharmacologic and toxicologic investigations of this compound were made by Neipp *et al.* (<sup>5</sup>), Rentchnick (<sup>7</sup>), and Nusslé (<sup>6</sup>) before the drug was marketed, and many reports on its clinical value in various bacterial infections have since appeared in the literature. It has a sustained but relatively low blood concentration, and is very active in experimental streptococcal infections and in such clinical conditions as pyuria and chronic bronchitis. The highest blood concentration is attained in 3-4 hours; no drug remains after 24 hours; the "half-life" is 9-10 hours.

MATERIAL AND METHOD

*Selection of patients.*—All untreated patients newly admitted to the Uzuakoli Settlement over a certain period were invited to participate in the trial. The total of 14 was

made up as follows: 2 lepromatous, 6 borderline (4 of them bacteriologically positive), and 4 tuberculoid, together with 2 lepromatous patients who had received treatment with a variety of drugs over prolonged periods (49 and 100 months respectively) but whose smears were still positive for bacilli.

*Dosage.*—A loading dose of sulfaphenazole of 2 x 1.0 gm. was given daily for three days; this was followed by 2 x 0.5 gm. daily for the rest of the trial. The 13 adults weighed on the average 116 lbs. (52.7 kgm.). The one child in the series received half the loading dose and half the maintenance dose.

Duration of the trial was 26 weeks, admittedly too short a period for conclusive results but sufficiently long to show if there had been any decisive bactericidal effect.

#### RESULTS

*Clinical findings.*—Lepromatous patients: There was no obvious change in 3 of these patients, and no arrest of the process of deterioration in the fourth (who was the patient who had been under treatment for 100 months).

Borderline patients: Slight improvement was noticed in 4 patients, with some flattening of the papular, centrally-raised lesions, reduction in erythema, and some repigmentation. In the remaining 2 patients, who were unstable immunologically, there was deterioration in the general condition and fresh lesions appeared in one of them.

Tuberculoid patients: There was marked improvement in 2, and less marked improvement in the other 2. The improvement consisted in reduction of the erythema and elevation of the lesions, and repigmentation and flattening of their central areas.

Eleven patients suffering from some degree of neuritis of the main peripheral nerve trunks in their superficial course, all reported improvement during therapy. In 3, the nerve trunks remained tender on palpation: no change was noted in the degree of hardness or enlargement. No ancillary treatment or physiotherapy had, purposely, been given to these patients.

*Bacteriologic findings.*—From all of the bacteriologically positive patients smears were made from eight sites at monthly intervals, and the numbers of *M. leprae* in each site were expressed according to Dharmendra's notation. The morphologic condition of the bacilli in typical fields was also recorded.

There were no appreciable changes in the bacteriologic indices or in the proportions of degenerate forms between the first examination and the last one, six months later. In one case there was a rise in the index during the fourth month of treatment, and an increase in the proportion of bacilli of normal morphology. In another case, normal bacilli reappeared in the smears during the third month of therapy, after being absent for nine months. In a third case, notwithstanding the final satisfactory index, an intermediate examination was the worst for twelve months.

The four borderline patients who were bacteriologically positive all showed improvement during the period of treatment.

*Toxic effects.*—In all cases monthly examinations of blood and urine

were made. No changes of note were seen in the blood.

In the urine, traces of albumin were found on three occasions in 2 patients: in 1, epithelial cells from the secretory epithelium were found. The albuminuria cleared rapidly and spontaneously, without treatment. No macroscopic hematuria was reported; crystalluria (triple phosphate, oxalate) was noted twice. In one female patient, a slight microscopic hematuria was associated with a *Trichomonas vaginalis* infection.

General toxic effects: One patient complained of nausea, vomiting and headache; albuminuria was present. Medication was temporarily stopped, and cautiously resumed, without untoward results. No case of dermatitis or psychosis was seen.

No case of generalized lepra reaction developed among the lepromatous patients. A mild and transient attack of erythema nodosum leprosum occurred once. Suppression of Orisul and symptomatic treatment coincided with the disappearance of the lesions, and resumption of the treatment did not occasion their reappearance.

#### CONCLUSIONS

While the number of patients in this pilot trial was too small, and the duration of the trial was too short, to permit the drawing of definite conclusions, the following tentative inferences may be submitted:

Sulfaphenazole may effect improvement in the bacteriologic condition in borderline leprosy, but within the limits imposed had no action on massive lepromatous infections.

Sulfaphenazole probably has a moderate effect on the resorption of the bacteriologically negative infiltrate in tuberculoid and borderline leprosy, causing partial repigmentation of the hypopigmented lesions. The drug had no effect on lepromatous infiltration, localized or diffuse.

The clinical improvement noted in the tuberculoid lesions is in conformity with the more striking observations—supported by photographic evidence—of Schneider *et al.* (<sup>8</sup>), but the mechanism of the repigmentation is obscure in the absence of noteworthy bacteriologic amelioration of the lepromatous patients.

#### CONCLUSIONES

Aunque el número de enfermos en este ensayo explorador fué demasiado pequeño y la duración del ensayo demasiado breve, para poder sacar conclusiones bien definidas, pueden ofrecerse las siguientes inferencias tentativas:

El sulfafenazol pudo lograr mejoría del estado bacteriológico en la lepra limítrofe, pero dentro de los límites impuestos, no ejerció efecto sobre las lesiones lepromatosas masivas.

El sulfafenazol ejerce probablemente efecto sobre la reabsorción del infiltrado bacteriológicamente negativo en la lepra tuberculoidea y limítrofe, produciendo repigmentación parcial de las lesiones hipopigmentadas. La droga no mostró efecto alguno sobre la infiltración lepromatosa, ya localizada o difusa.

La mejoría clínica notada en las lesiones tuberculoideas se conforma a las observaciones más notables—apoyadas por prueba fotográfica—de Scheider *et al.* (<sup>8</sup>), pero el

mecanismo de la repigmentación permanece oscuro a falta de importante mejoría bacteriológica en los enfermos lepromatosos.

#### CONCLUSIONS

Encore que cet essai clinique préliminaire ait comporté un nombre trop peu élevé de malades, et qu'il ait été trop court, que pour permettre d'émettre des conclusions sans appel, les appréciations provisoires qui suivent peuvent être rapportées :

Le sulfaphénazole peut agir d'une façon favorable sur la bactériologie dans la lépre border-line, mais—dans les limites imposées—n'a pas action sur les infections lepromateuses massives.

Dans la lépre tuberculoïde et border-line, le sulfaphénazole a probablement une action modérée sur la résorption des infiltrats bactériologiquement négatifs, entraînant une repigmentation partielle des lésions hypopigmentées. Le médicament n'a pas d'action sur l'infiltration lepromateuse, que celle-ci soit localisée ou diffuse.

L'amélioration clinique constatée dans les lésions tuberculoïdes concorde avec les observations plus frappantes rapportées, photographies à l'appoint, par Schneider et al. (8), mais le mécanisme de la repigmentation reste obscur en l'absence d'une amélioration bactériologique notable des malades lepromateux.

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