

Acedapsonone in Leprosy Treatment: Trial in 68 Active Cases in Micronesia¹

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This report describes the response of 68 active cases of leprosy, treated with DADDS (4,4'-diacetyldiaminodiphenylsulfone, [HANSOLAR®], acedapsonone) over a period of three years. Of these, 22 were known cases who had been receiving treatment with DDS (4,4'-diaminodiphenylsulfone, dapsonone) for varying periods of time prior to the beginning of this study. Forty more were newly diagnosed in 1967. Six additional cases were diagnosed in 1968, five of whom had been receiving DADDS from the beginning of the study. DADDS was being given to almost the entire population of approximately 1400 people who did not have leprosy in 1967 in a study of chemoprophylaxis, which is described in an accompanying report (6).

The repository sulfone DADDS was reported by Shepard (4) to be effective in preventing the growth of *Mycobacterium leprae* in mouse foot pads, and Shepard, Tolentino and McRae (5) have shown, in a small clinical trial in the Philippines, that its use in previously untreated patients resulted in a clinical and bacteriologic response similar to that seen with the usual DDS regimen. More recently, Russel *et al* (3) have confirmed this observation with DADDS in an extensive field trial in New Guinea. They did not observe any problem of development of resistant strains of *M. leprae* . . . at the low, constant blood levels . . . found with this drug which averages 50 ng DDS/ml, after the second injection (2), when it is given at 77-day intervals (five injections per year).

DADDS is given intragluteally, in a dos-

age of 225 mg (1.5 ml of a suspension in castor oil and benzyl-benzoate) to persons over six years of age. This includes all of our treatment group. The dosage is reduced to 150 mg (1.0 ml) for children between six months and five years of age.

Leprosy in the Trust Territory (Micronesia). Leprosy is present in all districts of the Trust Territory of the Pacific Islands, but there is considerable variation in its prevalence. Accurate figures are not available, as complete population surveys have been done only in the Pingelapese group. It appears that Yap has numerous cases, but there are few in the Marshall Islands.

The origins of leprosy in the Territory are not known, but it probably was present on several islands prior to World War I, and was introduced into Pingelap atoll in the Ponape District in 1918 by an immigrant from Nauru, a well-known leprosy focus. During the Japanese occupation, small islands were set aside in the different districts as places of isolation—rather than treatment—and these remained until the close of World War II, when the United States Navy became the governing power of the Trust Territory and Guam.

In 1948, the Navy established a leprosarium on Tinian, in the Marianas Islands north of Guam, under Dr. Jack Millar. It alternated under Naval and civilian control until 1956, when it was closed.

In 1952, one of us (NRS) who was then engaged in leprosy surveys for the South Pacific Commission, was asked to assess the leprosy situation, prior to the Navy's return to Tinian. (Naval authorities wished to close the leprosarium, and asked advice on where the patients might be sent.) A visit to Tinian resulted in the discharge of 41 of about 90 patients. A visit was then made with Dr. John Valentine, who had been the physician on Tinian, to all the administrative centers of the Trust Territory (except Saipan): Truk, Ponape, Majuro (Marshall Islands), Koror and Babelthup (Palau

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District), and Yap. The leprosy focus in Pingelap was visited briefly.

Following the close of the leprosarium on Tinian patients were treated in their own districts as out-patients, receiving DDS; with hospital care when needed. In the Ponape District the leprosy program has been managed by one of us (BJ).

The Pingelap trial. Pingleap is an atoll, less than a square mile in land area, located in the Ponape District, about 180 miles east-southeast of the central island of Ponape. It is said that in about 1775 a typhoon inundated the island, after which only about 30 persons were left alive. The entire Pingelapese population, as known today, is descended from this small group, with, perhaps, a small admixture from neighboring Mokil⁽¹⁾. Population pressure has caused two groups of Pingelapese people to move to the island of Ponape. Beginning about 1918 one group settled on the islet of Sokes, adjacent to the District Center at Kolonia, and two miles away by road. The second group began, in 1957, to settle in the southeastern part of Ponape in the village of Mant in the Metalanim area, about two miles from the sea. Although surrounded by other Ponapean people, the Pingelapese have clung rather closely together in marriage and social contact. Consequently, all members of the group are no more distantly related than close cousins⁽¹⁾.

In the 1953 survey, 902 people were examined on Pingelap. Seventeen previously unknown cases of leprosy were found. This, when added to the known cases, gave a prevalence of approximately 40/1000.

In 1966 and 1967 the islands of Ponape and Pingelap were mapped by Peace Corps volunteers. Their complete census by families was used as the basis of a survey by the senior author in the autumn of 1967, in which each Pingelapese person was examined for clinical evidence of leprosy. In this way 40 previously undiagnosed leprosy cases were identified in addition to the 22 known clinically active patients. Additionally, 37 inactive leprosy patients were in the population at that time. Use of DDS in known patients was discontinued, and all persons over six months of age, whether patients or not, were begun on DADDS,

with the exception of a few chronically ill or very old persons. Subsequent injections were given at two and a half month intervals by nurses and health aides of the Ponape Health Department. Because of logistic difficulties (Pingelap is reached from Ponape only by sea, and only at approximately monthly intervals) the injection schedule was not always exactly regular, but it was followed as closely as possible. The DADDS injections will be continued for all leprosy cases until they meet arbitrary criteria for discontinuance. They were discontinued for the rest of the population in the autumn of 1970, after three years of chemoprophylaxis⁽⁶⁾.

Annual follow-up examinations were performed by the same examiner. Six new cases were diagnosed in the autumn of 1968, but none thereafter. Most cases, and all suspects, were biopsied annually, and the biopsies were all sent to the Public Health Service Hospital, San Francisco, to be read by one of us (PF). Lepromatous cases or suspected cases had skin smears which were read in the field by the examiner (NRS) and sent to the Center for Disease Control, Atlanta, to be read by another of us (CCS).

Results after three years of DADDS. The clinical classification of the patients who were known at the beginning of the study in 1967, or were diagnosed in 1968, is shown in Table 1.

Except for the two cases described below, all showed clinical improvement during the three years of treatment. This

TABLE 1. *Leprosy type distribution of 105 Pingelapese patients, 1967-1968.*

Type	Active	Arrested	Total
Lepromatous	9	14	23
Tuberculoid	43	15	58
Indeterminate	16	5	21
Dimorphous	—	2	2
Not seen	—	1	1
Total	68 ^a	37	105

^a Six of these (one lepromatous and five tuberculoid) developed clinical disease after beginning DADDS in the autumn of 1967 and were first diagnosed as very early cases in the autumn of 1968.

judgement was substantiated histologically in every case which had repeat biopsies (the majority).

Case Notes. Of the cases already existing in 1967, one patient showed two small indeterminate macules, in which no clinical change has been noted during three years of observation, while the histological reports have shown a shift from the indeterminate to tuberculoid type.

One lepromatous patient, who had been receiving DDS in full dosage regularly for several years, had shown little improvement and was subject to lepra reactions (not *erythema nodosum leprosum*). He was having a reaction at the time his treatment was changed to DADDS. After two years on DADDS he was again in reaction. His Bacterial Index (BI) was then 4.0 and the Morphologic Index was 4, a distinctly elevated value, indicating strongly that viable bacilli were still present. Through the courtesy of Dr. Chapman Binford of the Leonard Wood Memorial, B663 (clofazimine) was made available, and the patient's treatment was changed to this drug. He has improved clinically and has had no further reactions.

All other patients showed clinical improvement, many with complete disappearance of lesions. The new lepromatous case in 1968 was a 15 year old girl who showed slight induration of the skin of her chin, which revealed acid-fast bacilli. She has shown steady improvement clinically, bacteriologically and by histologic examination.

A 15 year old boy, who had been previously diagnosed but was quiescent and unknown to us at the beginning of the study, developed acute bilateral ulnar neuropathy while on DADDS. This subsided under corticoid treatment and he continued on DADDS uninterruptedly.

One other man, who was not known to have leprosy and who denied any previous symptoms, shows moderate enlargement of both ulnar nerves above the elbow, and says that at times he feels numbness in his fifth finger. Skin sensation was found to be normal and nothing was found on biopsy of the skin adjoining the enlarged nerve. If this is leprosy, it is probably not recent. He

is not counted as a case in the series reported here.

No evidence even suggestive of drug toxicity was seen. With the one exception noted, no lepra reaction has been found in our patients. No ENL has been seen during the three year period of observation, but this is not surprising since our previously untreated lepromatous cases were few and very early in their disease course when DADDS therapy was begun.

Conclusions. In this series, in which DADDS has been used for three years in the treatment of patients with lepromatous, tuberculoid, and indeterminate leprosy, it has been shown to be an effective therapeutic agent of low toxicity. As yet no evidence of acquired drug resistance has been seen in previously untreated patients.

It is hoped that the drug will speedily be released for general use.

SUMMARY

The complete examination of about 1500 Pingelapese villagers in the Ponape District in Micronesia during a leprosy survey in 1967 identified 62 active and 37 inactive cases of leprosy, confirmed by current or previous biopsy (41/1000 active prevalence, 66/1000 total prevalence). All 99 patients were placed on a standard dose of the repository sulfone DADDS (acedapsone) 225 mg intramuscularly every 75 days. All were re-examined each autumn in 1968, 1969 and 1970. One lepromatous patient who had already been on oral DDS for several years without improvement continued to show no improvement during the two years on DADDS, but has been improving since his treatment was changed to B663 (clofazimine). All other active patients have shown clinical and/or histologic improvement, with the exception of one, who has had two small unchanging macules and whose biopsies have revealed a gradual shift from indeterminate to tuberculoid characteristics over the three year period of observation. Six new cases were discovered in 1968 (while in their first year of DADDS chemoprophylaxis), and all have responded promptly to continued treatment. No problems of toxicity have been seen.

RESUMEN

El examen completo de alrededor de 1500 habitantes de aldea Pingelapesos, en el Distrito Ponape en Micronesia durante un survey de lepra en 1967, identificó 62 casos activos y 37 casos inactivos de lepra, confirmados por biopsia actual o previa (prevalencia de 41/1000 de prevalencia activa, 66/1000 prevalencia total). Los 99 pacientes fueron tratados con una dosis standard de la sulfona de depósito DADDS (acedapsona) 225 mg intramusculares cada 75 días. Todos fueron re-examinados en 1968, 1969 y 1970, en el otoño. Un paciente lepromatoso que había estado en tratamiento con DDS oral durante varios años sin mejoría, continuó sin mostrar mejoría durante los dos años que estuvo en tratamiento con DADDS, pero ha estado mejorando desde que se cambió su tratamiento por B663 (clofazimina). Todos los otros pacientes activos han mejorado clínica y/o histológicamente, excepto uno, que ha tenido dos pequeñas máculas que no han sufrido ningún cambio y cuyas biopsias han mostrado un gradual cambio de indeterminado hacia tuberculoide durante el período de observación de tres años de duración. En 1968 se descubrieron seis casos nuevos (durante su primer año de quimioprofilaxis con DADDS), los cuales han respondido prontamente al tratamiento continuado. No se han observado problemas de toxicidad.

RÉSUMÉ

Environ 1500 personnes du village de Pingelap, dans le district de Ponape, en Micronésie, ont été entièrement examinés au cours d'une enquête de lèpre menée en 1967. Cette enquête a permis de reconnaître 62 cas de lèpre active, et 37 cas de lèpre inactive, confirmés par biopsie antérieure ou par biopsie prélevée au moment de l'examen. Ceci correspond à une prévalence de 41 pour mille pour les cas actifs, et à une prévalence totale de 66 pour mille. Les 99 malades ainsi dépistés ont été mis sous administration standard de la sulfone-retard DADDS (acedapsonne), à raison de 225 mg par voie intramusculaire tous les 75 jours. Tous ces malades ont été réexaminés à l'automne, en 1968, 1969 et 1970. Un des malades, un lépromateux qui avait déjà été soumis à un traitement à la DDS par voie buccale durant plusieurs années, sans amélioration, a persisté à ne témoigner d'aucune amélioration avec la DADDS; par contre, son état s'est amélioré depuis que le traitement a été changé et que l'on est passé

au B663 (clofazimine). Tous les autres malades atteints d'une affection active ont montré soit une amélioration clinique, soit une amélioration histologique, ou les deux à la fois, à l'exception toutefois d'un seul. Chez ce dernier, qui avait présenté deux petites macules persistant sans modification, les biopsies ont révélé un passage progressif des caractéristiques indéterminées aux caractéristiques tuberculoïdes au cours des trois années d'observation. Six nouveaux cas ont été découverts en 1968, alors qu'ils étaient dans leur première année de chimioprofilaxie. Tous ont rapidement répondu à la prolongation du traitement. Aucun problème de toxicité n'a été rencontré.

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