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Acedapsone[1] in Leprosy Chemoprophylaxis: Field Trial in Three High-Prevalence Villages in Micronesia[2]

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This report describes the leprosy experience of the study population up to the beginning of the trial in 1967, the rationale and procedure of the chemoprophylaxis trial, and the leprosy experience of the population during the three subsequent years of DADDS (acedapsone) mass chemoprophylaxis. The clinical response of the 68 active cases of leprosy to DADDS treatment is described in the accompanying report, which also presents the history of leprosy in Micronesia ([8]).

In 1966 Dharmendra ([1]) published an interim report on a study in India in which DDS (dapsone), given orally for three years to household contacts of known lepromatous cases, showed partial efficacy in preventing the development of clinical leprosy as compared with a control group taking a placebo. Noordeen ([3]) presented the final report of that study, which confirmed the interim findings. Since 1963 a mass-chemoprophylaxis trial of DDS in villagers in India has been reported by Wardekar ([9]) as showing a prophylactic efficiency of 90% in villagers up to age 25 by the fourth year of the study. An untreated control group was included in his study.

Shepard has demonstrated that DADDS is effective in preventing the growth of *Mycobacterium leprae* in mouse foot pads ([6]). When DADDS was given intramuscularly every 77 days in leprosy cases, it has been equivalent to the usual oral DDS therapy in terms of clinical and bacteriologic response in the results available to date ([5, 7, 8]). DADDS would seem, therefore, a useful drug to obviate the severe problems of cooperation that beset every attempt to use oral medication over a long period of time. It is also inexpensive and nontoxic, and thus seemed well worth a trial in chemoprophylaxis.

In order to carry out such a trial it was necessary:

1. to find a population in which the expected incidence of new cases would be large enough to yield valid results in a few years, yet compact enough to be administratively manageable;
2. to identify all existing cases in that population in order to deduct them from those considered at risk of developing the disease;
3. to give chemoprophylaxis consistently to all the exposed non-cases in the population; and
4. to observe the subsequent incidence of new cases through frequent and complete examination of that population.

MATERIALS AND METHODS

By the autumn of 1967 the population of Pingelap atoll was 677, served by a resident health aide, two resident Peace Corps volunteers, and by regular visits by an itinerant doctor from the District Hospital on Ponape Island, some 180 miles to the northwest and the home of about 80% of the twenty thousand people in the Ponape District of Micronesia.

Beginning in about 1918, the population pressure of Pingelap atoll had been relieved by resettlement to a village on Sokes islet, immediately adjacent to the District Center in Kolonia on Ponape island. By 1967 this village of Pingelap people had grown to a population of about 450 people, plus another 100 who work in Kolonia but return frequently to the village in Sokes. Sokes is served medically from the District Hospital in Kolonia.

Beginning in 1957 the population pres-

1 4,4′-Diacetyldiaminodiphenylsulfone (HANSOLAR®) will be referred to in this paper as DADDS.

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sure on Pingelap atoll had again been relieved by a resettlement to Mant village in the southeast sector of Ponape island. By the autumn of 1967 this village had grown to about 250 Pingelapese people, who were served by a resident health aide and a Peace Corps volunteer for that sector of the island. Both in the Sokes-Kolonia area and in Mant, the Pingelap people tend to keep to themselves, being separated by dialect differences from other Ponapean people, and with visiting and marriages tending to be almost entirely among themselves. They totalled about 1500 people in October, 1967, including the 97 Pingelapese high school students in boarding school in Kolonia. A very small number of Pingelap people, probably fewer than 30, had emigrated from this district for schooling or employment in other districts or in Hawaii.

A general census of the Ponape District was done in March and April, 1967, with the assistance of Peace Corps volunteers. It served as a basis for planning this study. All the records of known leprosy cases were reviewed by two of us (NRS and BJ). With the excellent assistance of the Medical Department, the Peace Corps volunteers, and the people themselves, almost every one of the 1500 eligible people was carefully examined under natural light and almost fully disrobed. These examinations were completed during the autumn of 1967 by a single experienced leprologist (NRS), who did repeat examinations in the autumn of 1968 (1379 people), 1969 (1420 people), and 1970 (1411 people). There had not been a complete examination of the entire Pingelapese population in any leprosy survey prior to 1967.

Skin biopsies were taken from all those either clinically diagnosed or suspected of leprosy, and smears were taken from all those diagnosed or suspected of lepromatous or borderline leprosy. All diagnoses since World War II have been based on biopsies read at the Public Health Service Hospital at Carville, Louisiana, usually by Dr. George Fite. All the biopsies taken during the surveys of 1967, 1968, 1969 and 1970 were read by one of us (PF). The smears done during these recent surveys were read in the field by the examiner and were sent for a second reading at the Center for Disease Control by another of us (CCS).

At the time of their first examination in this study, each person[4] was begun on a three-year course of DADDS injections at approximately 75-day intervals (five injections per year). The dose for those aged six years or older was 225 mg (1.5 ml of a benzyl benzoate-castor oil suspension) per injection. This dosage releases DDS at a steady rate, the acetyl groups having been slowly removed from either end of the molecule ([2]), averaging 2.4 mg DDS a day ([7]) and producing blood levels that average 50 ng DDS/ml after the second injection ([4]). The dose for those aged six months through five years was 150 mg (1.0 ml). Newborn infants were not begun on the injection schedule until they reached six months of age. No infant born after October, 1968, was given chemoprophylaxis, since they have not been exposed to untreated cases. All DADDS injections for those without leprosy were stopped in the autumn of 1970, after three years of chemoprophylaxis.

Lepromin, supplied by Dr. Claude Reich of the Leonard Wood Memorial, Cebu, was used for testing in Sokes village at the time of the 1967 survey. Three weeks later the tests were read and recorded in millimeters of induration by one of us (BJ) who was not aware at the time of the positive criterion to be used.

RESULTS

Estimation of the number of cases to be expected. Table 1 presents a summary of data derived from an examination of 902 Pingelap atoll residents in 1953 by one of us (NRS) under South Pacific Commission auspices, from a review of the district leprosy register since that time, and from the examination of the entire Pingelapese population in the autumn of 1967. Because many of the patients live without reference to a calendar, it was virtually impossible to assign cases accurately by year of onset.

[4] All 99 diagnosed leprosy patients were also included in the injection schedule, but excluded were 15 aged and infirm adults and 12 persons who had moved out of the District between the census and the beginning of the trial. A placebo group was considered, but was rejected for logistic and political reasons.

TABLE 1. *Distribution of Pingelapese leprosy cases by clinical classification in 1953 (incomplete survey) and 1967.*

Type	1953	1967 Arrested cases	1967 Active cases
Lepromatous	6 (13%)	14 (38%)	8 (13%)
Tuberculoid	21 (47%)	15 (41%)	38 (61%)
Indeterminate		5 (14%)	16 (26%)
Dimorphous		2 (5%)	0
Not classified	18 (40%)	1 (3%)	0
Total prevalence cases	45 (100%)	37 (100%)	62 (100%)

The records for the most recent four years, however, are sufficiently complete to permit the estimate that an average of about 11 or 12 new cases of leprosy were developing per year, giving an annual incidence rate of about 7/1000.

The median age of the 45 cases in the 1953 survey was 33 years. The median age of the cases entering the register during 1954-1963 was 27 years, falling to 15 years in the cases diagnosed during 1964-1967. This is clear evidence of an increasing case-finding effort, which would also explain the apparent shift to a higher proportion of tuberculoid cases, since many of those with minor transitory lesions would be overlooked with infrequent examinations.

The total of 99 active and inactive cases in 1967 corresponds to a total prevalence rate of 66/1000, but if only the 62 active cases are considered, the active prevalence rate is 41/1000. These cases were distributed among the three villages roughly in proportion to their population, except for a moderate excess in Mant. The number of cases is too small to calculate reliable rates for each of the three villages separately.

Lepromin testing in Sokes village. Table 2 shows the age-specific lepromin-positive rates in Sokes, the only village in which lepromin testing was done, using the $\geqq$ 3 mm criterion recommended for this lot of lepromin by Dr. Claude Reich.

These data show that the percent who are lepromin positive increases with age, an observation that relates well with the general epidemiologic observation that among exposed persons the risk of developing the disease diminishes with age.

TABLE 2. *Age-specific lepromin-positive rates, Sokes, 1967.*

	Age Groups				
	0–4	5–9	10–14	15–19	20+
% positive ($\geqq$ 3 mm)	29%	61%	86%	100%	93%

It should be noted that BCG vaccine was first used in the Ponape District in 1957, and that only the Pingelapese people residing in Sokes (whose lepromin results are given in Table 2) were given BCG at that time. It was given to those who were over three months of age in 1957 and who displayed a tuberculin reaction of less than 6 mm to 5 TU of PPD. BCG was again used in 1962-63, this time including the entire Pingelapese population in all villages who were over three months of age and who were tuberculin negative. Judging from a limited amount of follow-up with repeated tuberculin testing among those who received BCG in 1957, the BCG given then was very likely viable. The evidence is very clear, however, that the BCG given in 1962-63 was not viable. No BCG has been used in this population since 1963.

New cases appearing after the beginning of chemoprophylaxis. At the time of the reexamination of the population in the autumn of 1968, six new cases of leprosy were confirmed, all with early lesions appearing during the previous 12 months. One of these cases was a young man who appar-

ently had *not* received any DADDS injections during that time, but the other five cases (one lepromatous, four tuberculoid) had all received DADDS injections regularly. These six cases were distributed among the three villages roughly according to population (three in Pingelap, two in Sokes, one in Mant), and they have all responded promptly to continued DADDS therapy. *The repeated examinations of this population in the autumn of 1969 and 1970 have revealed no further new cases.* Thus, we have observed six new cases (actually five in the test population) during the three years, while we expected 11+ new cases per year, or about 35 in the three years (Chi-square= 20.8, 1 d.f., $p<0.001$).

Even if the estimate of 11+ expected new cases per year were grossly high, and the real expected figure were as low as five new cases per year, the results would still be significant at the 5% level of confidence. Although such statistical reassurance is important in itself, the biological significance of the clustering of all six of the observed new cases into the first year, with none thereafter, has profound implications as discussed below.

Another aspect of efficacy is the question of the emergence of DDS-resistant strains of *M. leprae* in patients treated with what amounts to a very low but constant dosage of DDS. There is reassuring evidence both from this study ([8]) and from the one in New Guinea ([5]) that resistant strains are not appearing with DADDS treatment.

Safety, acceptability, and cost. No chemoprophylactic agent can be assessed solely on the basis of efficacy. It must also be judged on the basis of safety, acceptability, and economy. As for safety, we examined mortality figures and some aspects of morbidity in this population.

Table 3 shows the distribution of deaths by age at death of all of the 42 Pingelapese people who died during the three years of the DADDS chemoprophylaxis study. This gives an average crude mortality rate of about 9.3/1000/year. This respectable figure would be even lower if it were not for the infant mortality ratio of about 60/1000 births, which is not an unexpected figure for this population in view of the small number of infant deaths available to make the calculation and the fact that infant mortality in this district was estimated in the neighborhood of 40/1000 in the general census of 1967 ([10]). Of the eight infants who died, only two had received any DADDS. One of them died of lobar pneumonia at eleven months of age after his third DADDS injection. The other died with febrile convulsions at about one year of age after his third DADDS injection. This infant had congenital heart disease of an unknown type—the only case of congenital abnormality seen in about 180 births during the DADDS chemoprophylaxis of this population. The one year old child who died had received no DADDS. The two teenagers who died (of trauma) had both received no DADDS. Of the 31 adults who died, only 14 had received DADDS, and only six of these 14 had received it regularly. We feel that none of these deaths could reasonably be attributed to DADDS.

During the period of chemoprophylaxis there was no apparent change in the fertility of this population, nor any rise in the number of stillbirths or congenital abnormalities.

TABLE 3. *Distribution of 42[a] Pingelapese people who died between October, 1967, and September, 1970, by age at time of death. Ponape District.*

	Age in years at time of death								
	<1	1–9	10–19	20–29	30–39	40–49	50–59	60–69	70[b]
Number of deaths	8	1	2	0	1	2	5	3	20

[a] 17 deaths in first year, 14 in second year, and 11 in third year.
[b] Including four old people of unknown age.

No skin rashes or febrile reactions relating to DADDS injections were noted during the three years. There were only four cases of post-injection fainting, three in teenage girls, and in one man. All occurred after the first injection in 1967. The three girls quickly recovered, but the man complained for one day of a sensation of numbness radiating downward from the injection site into his thigh and leg. There were no post-injection abscesses or paralyses, and there were only minor complaints about local soreness at the injection site, which was always deep intragluteal.

Among the 231 adult males eligible for screening by annual microhematocrit, about 170 had them done regularly, and of these there were seven who had a drop of at least 10% in their microhematocrit at some time during the three years under DADDS chemoprophylaxis. This is a ratio of about one man in 25 being observed. Likewise, among the 35 adult men who did not take DADDS but did come in for regular examination, there was one who had a similar fall in microhematocrit. The number of men who had a hematocrit below 36% did not increase during the period of chemoprophylaxis (pre-DADDS = 11, 1968 = 5, 1970 = 11).

With regard to the urine examinations for albumin and blood, the proportion of the population with more than trace amounts of albumin in their urine remained constant during the four successive annual examinations (about 1%). Those showing blood in their urine dropped from a pre-chemoprophylaxis level of about 12% to below 1% for each of the next three years, probably reflecting a learning process of the technicians who were doing the examinations.

The best measure of acceptability is actual performance. Table 4 shows that 51% of the eligible population (excluding leprosy cases and deaths) received DADDS consistently for all three years, another 22% for at least two years, another 14% for one year, and the remaining 13% irregularly or not at all. The proportion of people who cooperated increased as the trial progressed.

The infrequency of the injections kept the administrative costs low. Only five Medical Department staff were used to give the injections to 1500 people, and they were used only intermittently on this project, since all had other regular duties. The 4 ml DADDS ampoule requires no refrigeration, which further simplifies storage and

TABLE 4. *Distribution of 1393[a] Pingelapese people who did not have leprosy in October, 1967, by age and by frequency of DADDS injections in 1967–1970.*

	Frequency of DADDS injections					
Age in 1967	Consistent[b] all 3 years	Consistent[b] for 2 years	Consistent[b] for 1 year	Irregular[c] 1–2 years	Very Irregular[d]	Total
0–9	271	99[e]	57[e]	9	43	479
10–19	162	69	27	19	3	280
20+	275	138	69	22	66[f]	570
Age not recorded	1	7	41	7	8	64
Total	709 (51%)	313 (22%)	194 (14%)	57 (4%)	120 (9%)	1393 (100%)

[a] Excluded are 42 people who died between October, 1967, and September, 1970, and 99 cases of leprosy known in October, 1967.
[b] 4–5 doses of DADDS per year.
[c] 2–3 doses of DADDS per year.
[d] 0–1 dose of DADDS per year.
[e] About 45 infants born between October, 1967, and September, 1968, who were started on DADDS at age six months, are in these two groups.
[f] This group includes 15 people not given DADDS due to senility and/or infirmity and 12 who moved out of the district between the census and the start of the trial.

distribution problems in the field. This drug will soon be commercially available through Parke, Davis (Sydney, Australia), and the drug cost per person per year will be very low.

DISCUSSION

Although a double-blind placebo trial would have been the best study design to test the chemoprophylaxis value of DADDS, the administrative difficulty and ethical problems of doing such a study in this particular population led us to settle for a less rigorous test. By using a temporal control rather than a concurrent placebo group we had to be prepared to face equivocal results. However, the fact that this prophylactic scheme has lowered the incidence of new cases to zero within one year and has kept it there has avoided the statistical problems we might otherwise have had.

The fundamental question that has now been raised is of great practical importance. Has the development of new cases merely been temporarily suppressed or is it permanent? Has the disease been prevented in just a few people who would have otherwise developed it, or has the transmission cycle of leprosy been permanently broken in this population? This entire population will be kept under intensive surveillance for new cases for at least ten more years in order to answer these questions. For the purpose of this continued surveillance the population can be conveniently considered in five groups:

1. Those born before October 1968 and who
   a. received DADDS regularly for two or three years (about 1020 people)
   b. received DADDS for one year or less (about 250 people).
   c. received no DADDS (about 120 people)
2. Those born between October 1968 and December 1970 who received no DADDS treatment intramuscularly, but who may have received some transplacentally or in their mother's milk (about 100);
3. Those born after December 1970 who have received no DADDS by any route and who are now running free in the population to be exposed to any source of leprosy.

Even though mass-chemoprophylaxis has been successful in a high-prevalence, small village, highly cooperative environment such as we found among the Pingelapese, it is clear that mass-chemoprophylaxis would be inappropriate for the usual low-prevalence, large village situation in which leprosy is endemic in Asia, Africa and Latin America. It would seem that the logical next step would be a series of experiments in these more usual environments to test how far one must extend DADDS chemoprophylaxis into the web of household and neighborhood contacts before one runs into serious problems of non-cooperation and/or inefficient benefit.

SUMMARY

Approximately 1500 highly inbred people originating from the Pingelap atoll in the Ponape District in Micronesia are now living in three small villages in the district and have been known to have a high prevalence of leprosy for at least 20 years. A complete examination of that population by an experienced leprologist in the autumn of 1967 identified 62 active and 37 inactive cases of leprosy, confirmed by biopsy (41/1000 active prevalence, 66/1000 total prevalence). Judging by the previous four years of experience, it was expected that this population would produce about 11 new cases per year. The entire population (including all leprosy cases) was placed on the repository sulfone DADDS at 75-day intervals for three years. The entire population was re-examined each autumn in 1968, 1969, and 1970 by the same examiner. Six new cases appeared during 1968. None have appeared after that. The treatment of non-cases was stopped in the autumn of 1970, and the population will remain under surveillance for at least ten more years. No problems with toxicity were encountered during the three year period of mass-chemoprophylaxis.

RESUMEN

Aproximadamente 1500 personas de alta consanguineidad, nativas del atolón de Pingelap en el Distrito Ponape en Micronesia, viven ac-

tualmente en tres pequeñas aldeas en el distrito y durante por lo menos 20 años se ha sabido que tienen una alta prevalencia de lepra. Un examen completo de esta población, practicado por un leprólogo de experiencia en el otoño de 1967, identificó 62 casos activos y 37 casos inactivos de lepra, confirmados por biopsia (41/1000 de prevalencia activa, 66/1000 de prevalencia total). En base a la experiencia previa de los cuatro años anteriores, se esperaba que esta población produjera alrededor de 11 casos nuevos por año. Toda la población (incluyendo los casos con lepra) fué colocada bajo tratamiento con la sulfona de depósito DADDS a intervalos de 75 días, durante tres años. Toda la población fué re-examinada cada otoño, en 1968, 1969 y 1970, por el mismo examinador. Durante 1968 aparecieron seis casos nuevos. Desde entonces no ha aparecido ningún otro caso. El tratamiento de los nocasos fué interrumpido en el otoño de 1970 y la población seguirá bajo control durante por lo menos diez años más. No se encontraron problemas de toxicidad durante el período de tres años de quimioprofilaxis masiva.

RÉSUMÉ

Environ 1.500 individus à degré de consanguinité très élévé, originaires de l'atoll de Pingelap—dans le district de Ponape, en Micronésie—résident à présent dans trois petits villages de ce district. Cette population est connue pour avoir présenté une haute prévalence de lèpre au cours des vingt dernières années au moins. Au cours de l'automne 1967, un examen complet de cette population, par un léprologue expérimenté, a permis d'identifier 62 cas de lèpre active et 37 cas de lèpre inactive, confirmés par biopsie. Ceci correspond à une prévalence de 41 pour mille pour les cas actifs et à une prévalence totale de 66 pour mille. Si l'on en juge par les quatre années d'expérience déjà connues, on devrait s'attendre à se que cette population livre environ 11 nouveaux cas par an. La population entière, y compris tous les cas de lèpre, a été mise sous administration d'une sulfone-retard, la DADDS, administrée pendant trois ans à des intervalles de 75 jours. Toute la population a été réexaminée à chaque automne, en 1968, 1969 et en 1970. Six nouveaux cas sont apparus au cours de 1968. Aucun cas n'est apparu ensuite. L'administration du médicament à la population non atteinte de lèpre a été interrompue à l'automne 1970. La population restera sous surveillance pendant au moins dix années supplémentaires. Aucun problème de toxicité n'a été rencontrée durant la période de trois ans au cours de laquelle cette chimio-prophylaxie de masse a été appliquée.

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