EXPERIENCE WITH ACEDAPSONE (DADDS) IN THE THERAPEUTIC TRIAL IN NEW GUINEA AND THE CHEMOPROPHYLACTIC TRIAL IN MICRONESIA

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The therapeutic trial of DADDS in the Karimui of New Guinea and chemoprophylactic trial of DADDS in the Pingelapese population of the Caroline Islands both started in November 1967. The 7-year assessments of both trials were completed this year and they form the basis of this report.

The results of the Karimui trial at 6 years appeared in the May 1975 issue of the American Journal of Tropical Medicine and Hygiene, so it will not be necessary to describe those results in detail. It will be recalled that 336 patients have been treated starting in November 1967 to January 1968.

The clinical progress is shown in Figure 1. BOT stands for burnt-out tubuculoid and PN for polyneuritic. P stands for progressing, S for stationary, I for improving, and H for healed. Since leprosy had been diagnosed in most of the patients before treatment was started, a base line of clinical progress without treatment was available for comparison. Most of the burnt-out tuberculoid and polyneuritic patients were classified as stationary before treatment was started because they had residua, chiefly neurological deficits, and their condition did not change much with treatment, at least in the first 5 years. Of the 269 patients in the other categories who were followed before treatment was started, 68, or 25%, had reached healed status and 52, or 19%, were healing and improving. After treatment was started, the number of patients with healed disease increased progressively until, in 1974, 95% were so classified. With indeterminant, TT, TT/BT, or BT patients, 20-30% were classified as healed before treatment was started, and by 6 years of treatment nearly all had reached the healed status. In contrast, with BB, BL, BL/LL, and LL patients none were classified as healed before treatment was started, and it was only after 6 years of treatment that more than 50% reached the healed status.

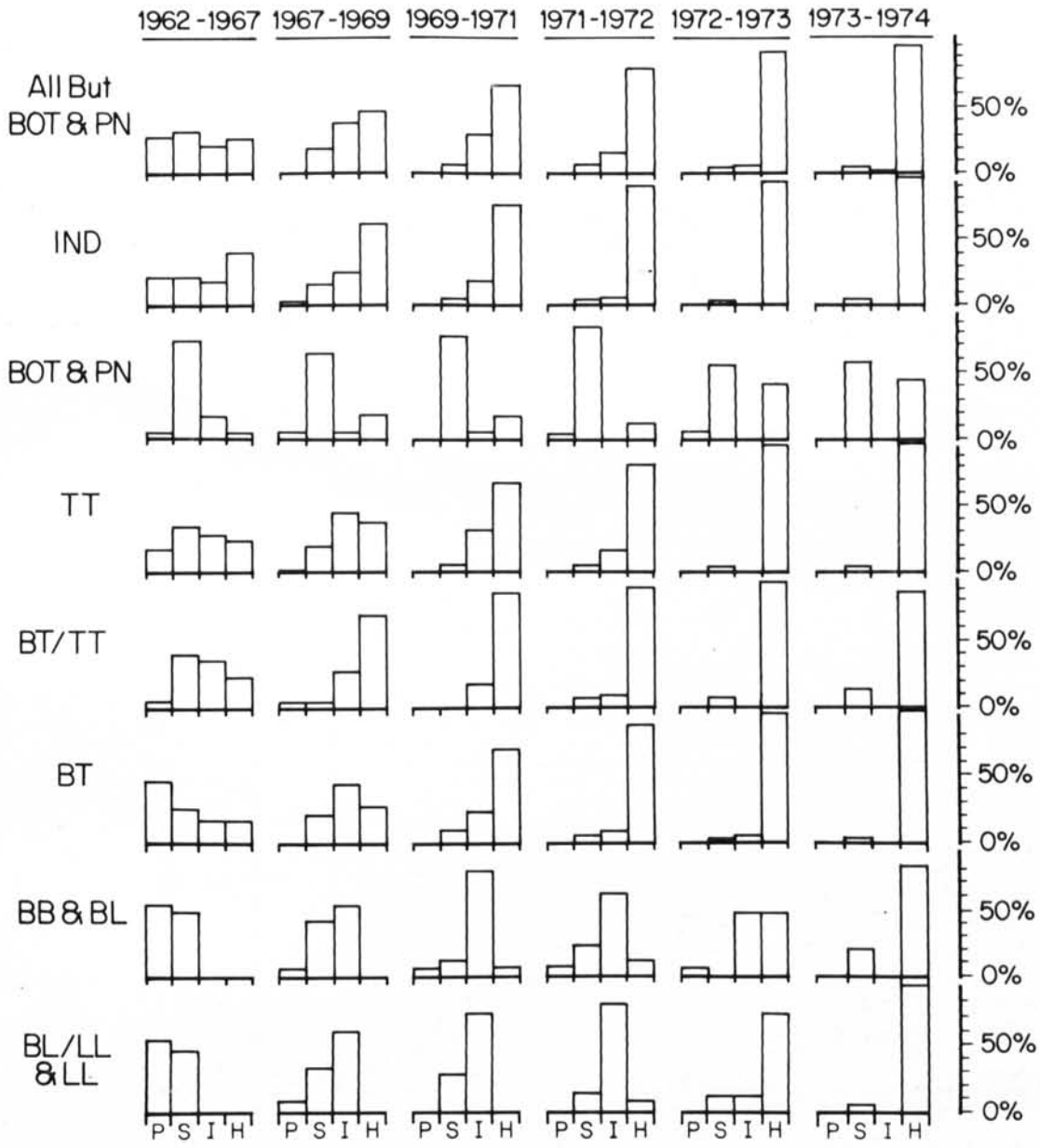

Figure 1. Clinical progress of Karimui patients before and after the start of DADDS therapy in 1967.

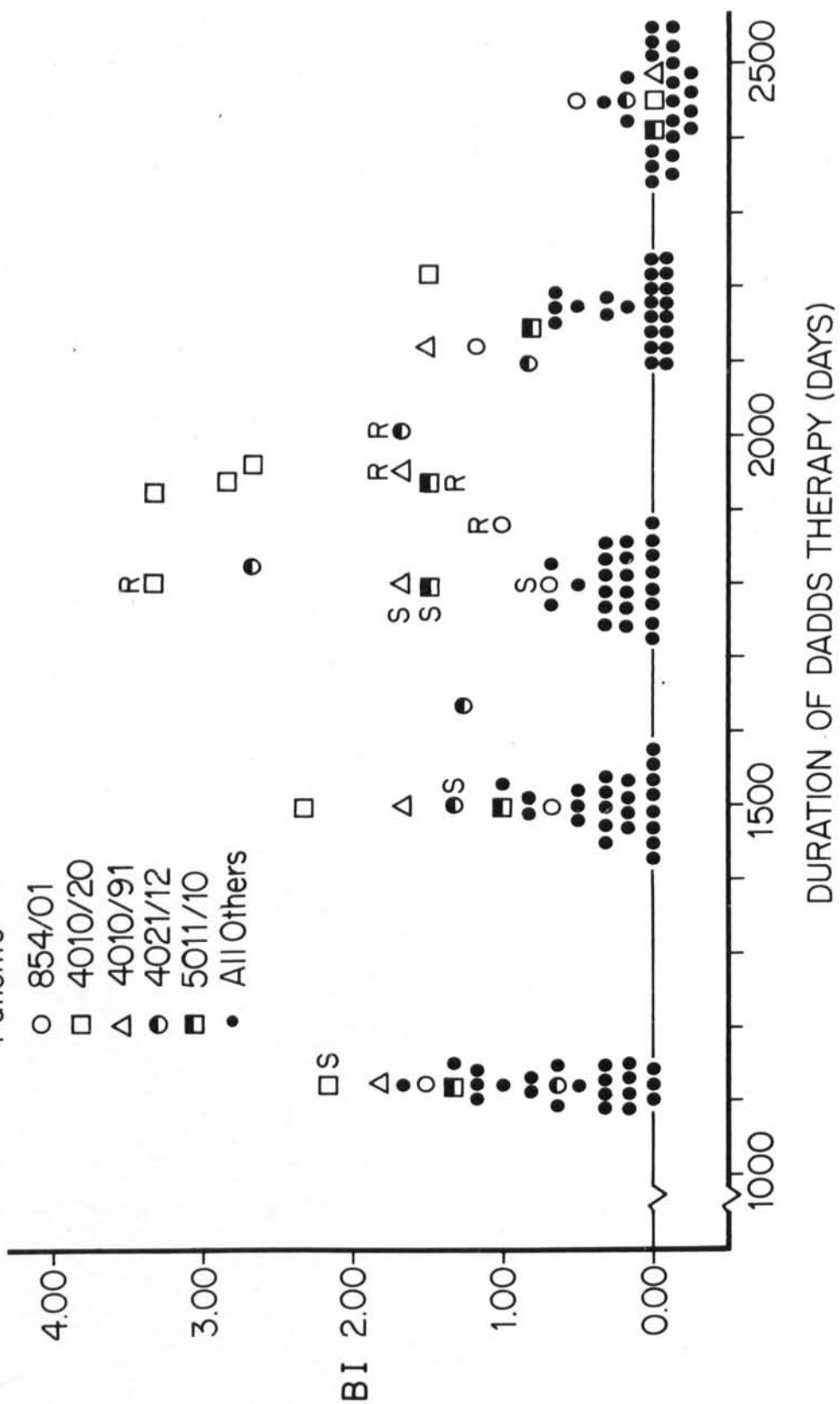

Figure 2. Bacterial indices in the 28 multibacillary Karimui patients in the period of therapy after 1000 days. S marks the appearance of solidly staining bacilli in the skin smears, and R marks the onset of the 90-day rifampin course.

The multibacillary patients were followed also with skin smears. Of these, 28 are included in the following analysis because they had enough bacilli for repeated assessment of the solid ratios, they were followed throughout the entire period, and they had received no previous therapy. The initial response of all the 28 patients was satisfactory, but after 3-5 years, five patients stopped improving because of the phenomenon we described in some detail in the recent publication, and which we believe to be long-term survival of living, DDS-sensitive M. leprae in the continuous presence of inhibitory concentrations of DDS. Strains of M. leprae were isolated from three of the five patients and shown to be normally sensitive to the minimal effective dosage of DDS. Plasma sulfones were shown to be at normal levels in the five patients and clearly in excess of the minimal inhibitory concentrations of these particular patient strains.

A 90-day course of rifampicin, 600 mg daily, was given to all the multibacillary patients, including these 28, in 1973. In Figure 2, we show the results after 1000 days. S marks the time the solid bacilli were first observed and R, the time the rifampin course was started. Solid bacilli have disappeared, and the BI's of all the patients are now zero, or nearly zero. We feel that this is an important observation because whatever the cause of the escape of the M. leprae from the action of DDS, whether it was bacterial latency or anatomical location or an unknown cause, the bacilli seemed to be normally susceptible to rifampin.

Sulfones were determined in the plasma of most of the patients by Dr. Peters and colleagues. We have reported elsewhere that patients with higher levels of sulfones did not respond any more rapidly to treatment than those with lower levels. These observations offer no encouragement to the notion that a repository that releases DDS, say, twice as rapidly, or to the notion that increasing the number of DADDS injections to, say, twice the frequency, will significantly better the therapeutic response in the first 7 years.

We conclude from the evidence available so far that (Table 1) DADDS is a convenient and effective antileprosy drug, but it should not be used except when it can be administered very regularly. If it were to be used irregularly and haphazardly, the risk of appearance of DDS resistance would be too high. The time saved by the convenience of the drug should be used in maintaining a regular treatment program. Second, multibacillary patients should receive a significant therapeutic addition of another drug whose mechanism of action is different from dapsone's.

Table 1. Conclusions from Karimui DADDS study (therapeutic)

DADDS is an effective antileprosy drug but it should only be used

1) when it can be administered very regularly, and

2) when multibacillary patients can also receive a 90-day course of rifampicin (600 mg/day), or an equivalent course of another drug whose mechanism of action is distinct from that of DDS.

For practical reasons we chose 90 days of rifampin; an equivalent course of another drug, such as ethionamide or B663, would need to last several years.

I turn now to the chemoprophylactic trial in the Pingelapese population. You will remember that DADDS injections were offered during 1967-1970 to the 1,600 people in three villages. They have been examined for new cases of leprosy each year since November 1967. All cases (except two who are sulfone-resistant) have been continued on DADDS therapy, with multibacillary cases receiving, in addition, a 90-day course of rifampin.

At the fourth annual post-treatment round of leprosy examinations in February 1975 there were 2,103 people eligible, consisting of 1,597 potential DADDS recipients born in 1967 or earlier and 506 born later and not offered DADDS. All but 116 were examined this year (a 94.6% examination rate). The unexamined people were almost all adults who were away from their villages. Another 71 of the original roster have died since 1968; none of them had developed leprosy by the time of death.

As can be seen in Table 2, a different pattern has developed in the Pingelapese on Ponape Island as compared with that in their relatives on Pingelap, a remote atoll which was the source of all the patients in this trial. In this table is shown the number of people receiving different numbers of shots and, in parenthesis, the number of new cases of leprosy. In the two villages on Ponape the epidemic of leprosy appears to be coming to a halt. The two cases marked with a "t" are tuberculoid and not likely to cause new infection; they are both children of an old DDS-resistant lepromatous patient who was active in 1968 but is now under control, after treatment with B663, in the village of Mant. These two children are the only new cases in that village in the past 6-1/2 years. There are two old, potentially troublesome cases in Sokes, so a few more years of favorable observations would be needed before one could state with confidence that transmission has ceased there.

The picture on Pingelap is quite different. Five new cases have appeared in 1974. Three of them were in children born after the beginning of the mass DADDS, thereby proving that leprosy transmission on Pingelap continued after mass DADDS was started.

Table 3 shows the chronological evolution of the cases. The period of mass DADDS is enclosed in the square. The six cases in 1968 had their onsets in the first 6 months of 1968. After that time, no new cases were seen until mass DADDS stopped. At that time a few new cases began to appear. They were of two origins at first: (a) two cases developed in the children of the DDS-resistant case in Mant. (b) Several cases developed in persons who had received only a fraction of the 15 shots they should have had; most of these cases were multibacillary and they may represent incompletely treated infections that were in the

Table 2. Distribution of 2,103 Pingelapese people by place of residence, age, DADDS preventive treatment status, and incidence of leprosy during 1971-1974, Ponape District, Micronesia

		Number DADDS shots received in 1967-70			
	Age	0-3	4-13	14-15	Total
On Ponape (Mant, Sokes)	>6	193(1)*	228(1)t	455(0)	876
	0-6	286(0)	13(1)t	4(0)	303
On Pingelap	>6	113(1)a	163(5)	445(1a,1b)	721
	0-6	201(3)a	2(0)	0	203
					2,103**

*: ( ) = new cases which have appeared in this group since 1970.
**: 71 other people have died since 1968, none with leprosy.
t: Two children (onset 1971, 1973) of an old sulfone-resistant case.
a: Five new cases during 1974.
b: One new sulfone-resistant

Table 3. Distribution of 125* Pingelapese leprosy cases by place of residence, year of onset, and type of leprosy, Ponape District, 1950-1974

	Year of onset of leprosy										
	63	64-66	67	68	69	70	71	72	73	74	Total
On Ponape (Mant, Sokes)											
No. multibacillary	7	5	1	0	0	0	0	1 R	0	0	14
No. paucibacillary	22	11	13	3	0	0	1t	0	1t	0	51
On Pingelap											
No. multibacillary	8	3	1	1	0	0	2	1a R	1 R	0	17
No. paucibacillary	11	6	17	2	0	0	0	0	2	5	43
				DADDS campaign							125*

*: including three cases who have died since 1967.
R: Three old cases who have reactivated as multibacillary (at the time indicated).
t: Two children of an old sulfone-resistant multibacillary case.
a: One new sulfone-resistant multibacillary case.

incubation period when mass DADDS was started. In 1974 on Pingelap, however, five new cases appeared, apparently as a result of new transmission. Indeed three of them were in children born after 1967.

Our conclusions (Table 4) are that 3 years (15 injections) of DADDS will reduce the risk of acquiring leprosy in a heavily exposed and susceptible population to zero, except during the first 6 months after beginning DADDS and except for those who are infected with DDS-resistant strains of M. leprae. Eradication of leprosy in a population with the use of prophylactic DADDS, however, cannot be achieved without the simultaneous and continuing therapeutic control of all multibacillary cases in the population. By the end of another 2 years of surveillance of the two villages on Ponape, if the results are favorable, we should have considerable confidence in having accomplished eradication there, particularly in Mant where there have been only two new cases since 1968, both explainable as spread from a sulfone-resistant case, now under control. It is clear that these conditions were not met on Pingelap, which is remote from the district center and difficult to provide with adequate therapeutic control. Household contacts of multibacillary patients on Pingelap are now being offered 3 years of prophylactic DADDS and it is hoped that this will stop the appearance of new cases there.

Table 4. Conclusions from Pingelap DADDS study (prophylactic)

1) DADDS given for 3 years (15 injections) will reduce the risk of acquiring leprosy to zero in a heavily exposed and susceptible population except

   a) during the first 6 months, and except

   b) for those infected with DDS-resistant strains.

2) Eradication of leprosy cannot be achieved with prophylactic DADDS without simultaneous and continuing therapeutic control of all multibacillary cases in the population.

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