Effect of Dapsone in Eliminating *M. leprae* from the Skin of Lepromatous Patients' A Study of 609 Cases

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The effect of dapsone in eliminating M. leprae from the skin of 609 lepromatous cases is analyzed and possible corelations between the bacteriologic status and other factors such as age and sex of patients, stage of the disease, reactions during therapy and regularity in treatment are studied.

MATERIALS AND METHODS

The study was based on 609 lepromatous patients registered at the Out-Patient Clinic of the Acworth Leprosy Hospital during the period, January, 1952 to December, 1962. The treatment period ranged from six months to eight years. The dapsone dosage for adults was 600 mg per week, and for children, below three years, between 4 and 10 years and between 11 and 15 years, the weekly doses respectively were 75 mg, 150 mg and 300 mg.

In these cases, the only sulphone used was dapsone in tablet form. During therapy, if reactions occurred, dapsone was withheld or its dose reduced and anti-reaction treatment, as described by Koticha (⁵), instituted. Subsequent induction of dapsone was much slower. In none of the cases were corticosteroids given. Antianemic or other appropriate treatment was given when indicated.

For bacteriology, the "snip or section method I" (³) was employed in preference to "slit and scrape method" (⁹), since the cases negative for bacilli by the later method were found to be positive by the former method. The snip or wedge-shaped sections of skin were taken from two sites, one of which was the lobule of the ear. These examinations were done at six month or yearly intervals. Complete absence of bacilli, fragmented or rods, was the objective looked for. The positive and negative patients were distributed according to age and sex, regularity in treatment, stage of the disease, and reactions during therapy. The possible impact of these factors on the ultimate bacteriological outcome was analyzed. End-point in a negative patient refers to the date on which his bacteriologic examination revealed negativity for the first time during the treatment. In a positive patient the end-point is the date of the last bacteriologic examination, which obviously revealed continued positivity.

The total span of treatment is the time, in months, from the date of registration at the clinic to the point of negativity in each case. This period denotes the number of months of treatment during which the patient should have been taking treatment. This is contrasted against the period of actual treatment, i.e. the number of months in which the patient actually took treatment at the clinic during the total span of attendance. It is clear that the nearer the two periods coincide, the more regular is the patient. When a patient is given tablets from the clinic, it is presumed that he has consumed the same.

RESULTS

Of the 609 cases, 235 (38.59%) patients became negative while 374 cases remained positive (Table 1). The reason for this small percentage of negatives is that only a very few cases (16) had treatment for over six years while the majority of the cases (429) had treatment for less than four years.

Sex of patients. The ratio of males to females among the negatives was 4.6:1, and

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in the positives 4.4:1. The χ^2 value $(\chi^2=0.03 \text{ with P}<0.9)$ is insignificant. Thus the sex of a patient has no relation to negativity.

Age of patients. The ratio of the total number of negatives to the positives (235 to 374) is approximately 2:3. Hence, assuming the proportion of negatives to positives in each group to be 2:3, the χ^2 values of each group and the pooled χ^2 value were found insignificant. The age of the patient has, therefore, no bearing on attainment of negativity.

Stage of the disease. Table 1 shows that the 43.09% of the negatives were in the L1 group and 31.33% of the negatives in the L2 group (χ^2 =8.39 with p<0.0005). Thus the number becoming negative in the L1 group are significantly more than in the L2 group, indicating the benefit of early institution of treatment. (The analysis of variance of Table 4 confirmed the observation that fewer negatives were found in the L2 group than in the L1 group having similar treatment duration.) Reactions in leprosy. Table 1 reveals that 66.67% of cases having a single reaction (SR), 39.78% having no reactions (NR), and 17.65% having recurrent reactions (RR) became negative.

The proportion of negatives to positives in each group was assumed to be 2:3.

The χ^2 value for the NR group (0.01) is not significant, that for the SR group (4.45)is significant at 5% level, and for the RR group (10.62) it is highly significant (at 1% level). The pooled χ^2 value (15.08) is significant. The conclusion is that recurrent episodes of reactions definitely delay the attainment of negativity. This is logical since dapsone in such cases cannot be utilized again till reaction subsides. It may also be that the cases with occasional reactions became negative earlier than those without any reactions, although the number of cases with SR is too small as compared to the other two groups to warrant any such statistically significant conclusion.

Treatment status. Positive patients. The average period of treatment of those who

Factors		Total Number of patients	Number of negatives	Number of positives	% of negatives
0	Male	498	193	305	38.76
Sex	Female	111	42	69	37.84
Stage	Ll	376	162	214	43.09
of the disease	L2	233	73	160	31.33
	None	543	216	327	39.78
Reactions	Single	15	10	5	66.67
	Recurrent	51	9	42	17.65
T	0-24	129	21	108	16.28
interval	25-48	300	108	192	36.00
months	49-72	164	98	66	59.76
	73-96	16	8	8	50.00
Total		609	235	374	38.59

TABLE 1. Results of treatment.

		Number of negatives		Nu			
Age group in years	Males	Females	Total	Males	Females	Total	Total
5-10	4	2	6	7	3	10	16
11-15	12	4	16	20	6	26	42
16 - 25	68	11	79	99	23	122	201
26-35	62	13	75	108	24	132	207
36-45	32	8	40	53	10	63	103
46-55	11	3	14	15	3	18	32
56-65	4	1	5	2	-	2	7
>65	-			1		1	1
Total	193	42	235	305	69	374	609

TABLE 2. Patient age related to treatment results.

remained positive till their end-point was 35.8 months. Median value is 34.1 with a standard deviation of 16.2. Thus, the maximum number of patients remaining positive were in the treatment group of 37 to 48 months.

was 45.7 months. Median value was 45.9 with a standard deviation of 15.3. Thus the maximum number of patients becoming negative were in the treatment group of 49 to 60 months.

Negative patients. The average period of treatment required for becoming negative

The percentage of the negatives was highest (59.76%) in the treatment interval 49 to 72 months and least (16.28%) in the treat-

Treatment in months	Total	Number of negatives	Number of positives	% of Negatives	X2
0-24	129	21	108	16.28	
25-36	136	42	94	30.88	2.83
37-48	164	66	98	40.24	(Not significant)
49-60	117	73	. 44	62.38	(significant)
61-72	47	25	22	53.19	
>73	16	8	8	50.00	
Total	609	235	374		

TABLE 3. Treatment results related to smaller time intervals.

ment interval 0 to 24 months, establishing the relationship between the length of treatment and the attainment of negativity. Further, the number of negatives progressively increased with the increasing period of treatment (the only exception being the treatment interval 73 to 96 months, which may perhaps be due to the very small number of cases in that group). It is therefore, concluded that, by and large, a lepromatous patient remains positive if he takes treatment for only 34 to 38 months, but becomes negative after 44 to 48 months of treatment.

The treatment intervals being broad, they are further broken down in Table 3. Here it is noted that 69.38% negatives (maximum) are in the treatment group 49 to 60 months. The χ^2 value between the intervals 25 to 36 months and 37 to 48 months is insignificant and this value between the intervals 37 to 48 months and 49 to 60 months is highly significant. Hence, it can be concluded that a treatment period of 49 to 60 months is the critical period when the maximum number of patients begins to become negative. Rodriguez (⁷) found this period to be seven years.

Regularity in treatment, i.e. actual treat-

ment versus total span of treatment. Coefficients of correlation of these two factors for negative and positive cases show that there is a definite correlation between these two factors. This was confirmed by statistical test values; 8.21 and 8.13 respectively in the negative and positive cases. It is concluded that not only is the absolute number of months of treatment with dapsone, say for instance 49 to 60, significant for attainment of bacterial negativity but the total span during which this absolute number of months of treatment is spread is also important. It stands to reason that the two periods should approximate as much as possible, i.e. the patient should take treatment without undesirable discontinuity.

Interactions. The interaction between the stage of the disease and treatment duration can be derived from Table 4.

The analysis of variance of Table 4 reveals that the duration of treatment and the stage of the disease are significant but not their interaction. Less number of negatives are found in the L2 groups than in the L1 group having similar treatment duration. Quagliato *et al* (6) found that not only the relationship between the stage of the disease and treatment status but also

			Months of treatment					
Stage of the disease		0-24	25-48	49-72	73-96			
L1	Total patients % Neg. Arc sin*	81 20.99 27.27	$173 \\ 39.88 \\ 39.16$	$113 \\ 62.83 \\ 52.44$	9 55.56 48.20	376 43.09 41.02		
L2	Total patients % Neg. Arc sin		$127 \\ 30.71 \\ 33.66$	$51 \\ 52.94 \\ 46.68$	$ \begin{array}{r} 7 \\ 42.86 \\ 40.90 \end{array} $	233 31.33 34.03		
Total	Total patients % Neg. Arc sin	129 16.28 23.73	300 36.00 36.87	$164 \\ 59.76 \\ 50.59$	$ \begin{array}{r} 16 \\ 50.00 \\ 45.00 \end{array} $	609 38.59 38.40		

TABLE 4. Interrelation of treatment duration and disease severity.

* Are sin transformation:—If a variable consists of the portion of individuals affected, the distribution tends to be binomial in form. To minimize statistical inaccuracy inherent in analysis of variance in such cases, a transformation is done that will place data on a scale on which the error variance is nearly constant. In this case the transformation is to the angle whose sine is the square root of the proportion or percentage, i.e., angle = are sin $\sqrt{}$ percentage. A ready table for this transformation is available and it weighs more heavily the small percentage which have small variance.

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Reactions		0-24	25-48	49-72	73-96	Total
None	Total patients % neg. Arc sin	$117 \\ 16.24 \\ 23.76$	$265 \\ 38.12 \\ 38.13$.	$147 \\ 60.54 \\ 51.08$	$14 \\ 50.00 \\ 45.00$	543 39.73 39.10
Single	Total patients % neg. Arc sin	$\begin{array}{c} 4\\50.00\\45.00\end{array}$		3 100.00 90.00	0 0.00 0.00	$ \begin{array}{r} 15 \\ 66.67 \\ 54.73 \end{array} $
Recurrent	Total patients % neg. Arc sin	8 0.00 0.00	27 7.41 15.80	$14 \\ 42.86 \\ 40.90$	$2 \\ 50.00 \\ 45.00$	$51 \\ 17.65 \\ 24.84$
Total	Total patients % neg. Arc sin	$129 \\ 16.28 \\ 23.73$	300 36.00 36.87	$164 \\ 59.76 \\ 50.59$	$ \begin{array}{r} 16 \\ 50.00 \\ 45.00 \end{array} $	$\begin{array}{c} 609 \\ 38.59 \\ 38.40 \end{array}$

TABLE 5. Lepra reaction and treatment duration.

the one between the regularity in treatment and stage of the disease has effect on attainment of bacterial negativity.

Interaction between the lepra reaction and treatment duration can be derived from Table 5.

Table 6 reveals that F values for the factors reactions, treatment interval and the χ interaction between these two factors are 5.20, 14.04 and 2.14 respectively, and these are highly significant. Hence, there is a close relationship between reactions and negativity, between treatment duration and negativity, and also between negativity and the interaction of reactions and treatment duration. The nature of relationship between these two factors is described above.

Interaction between the stage of the disease and the reactions can be derived from Table 7.

Table 8 shows that the F values for the stage of the disease is 5.47 and is significant and that for the factor of reactions is 5.20 and is also significant. Thus bacteriologic negativity is individually related to the stage of the disease and to reactions. Since, however, the F value for the interaction between these two factors is 0.82, i.e., not significant, negativity is not related to the interaction between the two factors. This, in other words, also demonstrates that the stage of the disease has no relation to the occurrence of reactions, and this is common knowledge.

Table 10 shows that the stage of the disease, treatment status and reactions individually affect the percentage of the negatives. Furthermore, the interaction between reactions and treatment has a signifi-

Source of variation	DF	SS	MSS	$\mathbf{F}^{\mathbf{a}}$
Reaction	2	8535.6891	4267.8446	5.20
Treatment interval	3	34586.6825	11528.8941	14.04
Interaction	6	10543.3877	1757.2312	2.14
Total	11	53665.7593		

TABLE 6. Analysis of variance of Table 5.

DF = degrees of freedom; SS = sum square; MSS = mean square; F = ratio = variance ratio.

a = significant at 1% level.

			Reactions		
Stage of the disease		None	Single	Recurrent	Total
L1	Total patients % neg. Arc sin	$343 \\ 44.61 \\ 41.90$	10 70.00 56.79	$23 \\ 8.69 \\ 17.15$	$376 \\ 43.09 \\ 41.02$
L2	Total patients % neg. Arc sin	$200 \\ 31.50 \\ 34.14$	5 60.00 50.77	28 25.00 30.00	233 31.33 34.03
Total	Total patients % neg. Arc sin	$543 \\ 39.78 \\ 39.10$	$15 \\ 66.67 \\ 54.73$	$51 \\ 17.65 \\ 24.84$	$609 \\ 38.59 \\ 38.40$

TABLE 7. Interaction between disease severity and lepra reaction.

cant effect on the percentage of negatives.

Relapse. Of the 235 negatives, only three relapsed. Two of these three had virtually given up the maintenance treatment, but the cause of relapse is difficult to ascertain in the third case who was regular in treatment even after achieving negative status. Such a small number of cases of relapse may be due to the fact that those cases who became negative were basically regular and continued treatment even afterwards. The period of maintenance therapy is variable, and the one recommended at Acworth is of six years after the attainment of negativity (2). The principles determining the duration of maintenance therapy have been recently reemphasized by Skinsnes (8).

Of 113 cases who took treatment for less than 24 months, 20 (17.7%) became negative. It is significant that 18 of these 20 had no reaction while the remaining two had only one episode of reaction each. It is difficult to explain the attainment of negativity in these 20 cases.

Of 16 cases receiving treatment for more than 72 months, eight have remained positive. Four of these eight had taken treatment irregularly, one had recurrent attacks of reaction, but in the remaining three it is difficult to explain the continuation of positivity. It is possible that the urinary excretion of dapsone $(^4)$ in these cases may be high, and increasing their daily dose up to 150 mg may render them negative. This is under study.

SUMMARY

A study of the treatment results of 609 lepromatous patients treated with dapsone over a period of eleven years (1952 through 1962) presents a number of conclusions.

The age and sex of patients had no bearing on the attainment of negativity.

Source of variation	\mathbf{DF}	SS	MMS	F
Stage of the disease	1	4489.2801	4489.2801	5.47 ^a
Reaction	2	8535.6891	4267.8446	5.20
Interaction	2	1353.9638	676.9819	0.82 (n.s.)
Total	5	14378.9330		and a second sec

TABLE 8. Analysis of variance of Table 7.

a = significant at 1% level; n.s. = not significant.

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The stage of lepromatous leprosy had some significance, L1 cases became negative earlier than L2 cases.

Recurrent reactions were harmful and

retarded the attainment of negativity, but single episode seemed to be beneficial.

The majority of patients who remained positive took treatment for less than 36

Stage of the disease	Reaction	Months of treatment	Total	% Neg.	Arc sin
LI	None	0-24	73	20.55	26.95
	110110	25-48	156	42 31	40.57
		49-72	106	64 15	53 22
		73-96	8	50.00	45 00
		Total	343	44.61	41.90
	Single	0-24	4	50.00	45.00
		25-48	4	75.00	60.00
		49-72	2	100.00	90.00
		73-96	0	0.00	0.00
		Total	10	70.00	56.79
-	Recurrent	0-24	4	0.00	0.00
		25-48	13	0.00	0.00
		49-72	5	20.00	26.56
		73-96	1	100.00	90.00
		Total	23	8.69	17.15
	Total	0-24	81	20.99	27.27
		25 - 48	173	39.88	39.16
		49-72	113	62.83	52.44
		73-96	9	55.56	48.20
		Total	376	43.09	. 41.02
L2	None	0-24	44	9.09	17.55
		25 - 48	109	32.11	34.51
		49-72	41	51.22	45.70
		73-96	6	50.00	45.00
		Total	200	31.50	34.14
	Single	0-24	0	0.00	0.00
		25 - 48	4	50.00	45.00
		49-72	1	100.00	90.00
		73-96	0	0.00	0.00
		Total	5	60.00	50.77
	Recurrent	0-24	4	0.00	0.00
i		25-48	14	14.29	22.21
		49-72	9	55.56	48.19
		73-96	1	0.00	0.00
		Total	28	25.00	30.00
	Total	0-24	48	8.33	16.77
		25-48	127	30.71	33.66
		49-72	51	52.94	46.68
		73-96	7	42.86	40.90
		Total	253	91 99	24 02

TABLE 9. Disease severity, reactions and duration of treatment.

Stage of the disease	Reaction	Months of treatment	Total	% Neg.	Arc sin
Total	None	0-24	117	16.24	23.76
		25 - 48	265	38.12	38.13
List.		49-72	147	60.54	51.08
		73-96	14	50.00	45.00
		Total	543	39.78	39.10
	Single	0-24	4	50.00	45.00
		25-48	8	62.50	52.24
		49-72	3	100.00	90.00
		73-96	0	0.00	0.00
		Total	15	66.67	54.73
	Recurrent	0-24	8	0.00	0.00
		25-48	27	7.41	15.80
		49-72	14	42.86	40.90
		73-96	2	50.00	45.00
		Total	51	17.65	24.84
	Total	0-24	129	16.28	23.73
		25-48	300	36.00	36.87
		49-72	164	59.76	50.59
		73-96	16	· 50.00	45.00
		Total	609	38.59	38.40

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months. The majority of patients who became negative took treatment for more than 49 months. Even the actual number of treatments, when spread out over a long period, did not help in rendering the patients negative. Achievement of bacterial negativity was related to the interaction between reactions and treatment status. There was no relationship between the stage of the disease and reactions. A few patients (17.7%) did become negative within a short period of 24 months. A small number of patients remained positive in spite of regular treatment uninterrupted by reactions.

TABLE 10. Analysis of variance of Table 9.

Source of variation	DF	SS	MSS	F
Main Factors				
Stage of the disease(S)	1	4489.2801	4489.2801	5.47ª
Reaction (R)	2	4267.6891	4267.8446	5.20^{b}
Treatment Interval (T.I.)	3	34586.6825	11528.8941	14.04
Interactions				
$S \times R$	2	1353.9638	676.9819	0.82(n.s.)
$S \times T. I.$	3	332.7007	110.9002	0.14 (n.s.)
$R \times T. I.$	6	10543.3877	1757.2312	2.14^{b}
$S \times R \times T$. I.	6	3842.9746	640.4957	0.78 (n.s.)
Total	23	63684.6785		

^a = significant at 5% level; ^b = significant at 1% level; n.s. = not significant.

RESUMEN

Se hace un estudio de los resultados obtenidos en 609 pacientes lepromatosos tratados con dapsona durante un período de once años (1952 hasta 1962) y se presentan algunas conclusiones.

La edad y el sexo de los pacientes no tenían relación con el alcance de la negatividad.

La etapa de la lepra lepromatosa tenía alguna significación: los casos L_1 se hicieron negativos antes que los casos L_2 .

Las reacciones recurrentes eran perjudiciales y retardaban el alcance de la negatividad, pero un episodo único párecía ser beneficioso.

La mayoría de los pacientes que permanecieron positivos siguieron tratamiento durante menos de 36 meses. La mayoría de los pacientes que se hicieron negativos siguieron tratamiento durante más de 49 meses. Aún un número (alto) de tratamientos, cuando se realizaban durante períodos alejados, no servían para volver inactivos a los pacientes. El alcance de la negatividad bacteriológica estaba relacionado con la interacción entre los estados reaccionales y la etapa del tratamiento. No había relación entre la etapa de la enfermedad y las reacciones. Unos pocos pacientes (17,7%) se hicieron negativos durante un período corto, de 24 meses. Un pequeño número de pacientes permaneció positivo, a pesar de tratamiento regular no interrumpido por reacciones.

RÉSUMÉ

Un certain nombre de conslusions sont présentées à la suite de l'étude des résultats du traitement de 609 malades lépromateux traités par la dapsone pour une période s'étendant sur 11 ans, soit de 1952 à 1962.

L'âe et le sexe des malades n'ont pas eu d'influence en ce qui concerne l'obtention de résultats bactérioscopiques négatifs.

Le stade de l'affection lépromateuse présentait une certaine signification; les cas L1 sont devenus négatifs plus rapidement que les cas L2.

Les réactions récidivantes étaient préjudiciables et retardaient le moment où les malades devenaient négatifs. Par contre, des épisodes uniques de réaction paraissaient avoir un effet bénéfique.

La plupart des malades qui sont restés postifs

avaient été soumis au traitement pour moins de 36 mois. La majorité des malades devenus négatifs avaient été traités pendant plus de 49 mois. Même le nombre voulu de seances de traitement, lorsqu'il est dispersé sun une longue période, ne permet pas de rendre les malades négatifs. L'obtention d'une négativité bactériologique est liée à l'intéraction entre les réactions lépreuses et la thérapeutique. On n'a pas noté de relation entre le stade de la maladie et les réactions. Quelques malades seulement (17,7%) sont devenus négatifs endéans une période de 24 mois. Un petit nombre de malades sont restés positifs, malgré l'administration d'un traitement régulier noninterrompu par des réactions.

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