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SULFONE THERAPY IN LEPROSY; A THREE YEAR STUDY [1]

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Two years ago one of us (N.R.S.), in a preliminary report to the Hawaii Territorial Medical Association (4), wrote, "It seems safe to say that for the first time drugs of real value for the amelioration of leprosy are at hand." Time has confirmed and strengthened that opinion. That report was of promin only, which we had then used for about a year. Now, with three years' experience with promin, two with diasone, and more than one with promizole, we are ready to agree with others (1, 2, 3) that a new day has dawned in the history of leprosy.

BASIS OF REPORT

This report concerns 346 patients—the age grouping and sex distribution as shown in Table 1, the type classification as shown in Table 3—who were treated with one or more of these drugs at the Kalaupapa Settlement and the Kalihi Hospital, or as out-patients. The statistics here given are as of April 1, 1949. We do not include the more experimental trial of sulphetrone and promacetin, which have been used recently with two groups of 4 patients each. Promin was given intravenously, the other drugs

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by mouth. Promin was received by a total of 211 patients, diasone by 176, and promizole by 27. These figures do not balance, as 71 patients changed from one drug to another; most of these stopped promin because of poor veins.

TABLE 1.—*Distribution by age and sex of patients treated, 1945-1949.*

Age group (in years)	Male	Female	Total
0– 9	2	0	2
10–19	19	19	38
20–29	44	30	74
30–39	65	30	95
40–49	46	28	74
50–59	22	17	39
60–69	10	8	18
70 & over	4	2	6
Totals	212	134	346

The maximum daily doses which we employ are: promin, 5 gm., diasone, 1.2 gm., and promizole, 6 gm. Treatment is omitted on Sundays, and a week's rest is given after two weeks of treatment with promin and after three weeks of diasone or promizole. Many patients cannot tolerate the maximum doses, but do well on less. Since we do not watch each individual to be sure he takes his medication by mouth, our dosage figures in some cases may be too high.

SIDE EFFECTS

Anemia.—Hemolytic anemia is common and sometimes severe; 52 per cent of our patients showed red blood cell counts of less than 3,500,000 per cubic millimeter, hemoglobin less than 10 grams per 100 cubic centimers, or both, at some time. This defines the "anemia" of Table 2. Almost one-half of these patients (23% of the total) showed what we classed as "severe" anemia—below 3,000,000 red cells or 9 gm. of hemoglobin. To combat this condition we used iron, vitamins, liver extract injections, folic acid in a limited number of cases, and blood transfusions. Blood was supplied by the Honolulu blood bank, and a total of 328 transfusions were given to 107 patients.

TABLE 2.—*Treated patients developing anemia.*

Drug	Male		Female		Total	
	No.	%	No.	%	No.	%
Promin alone	37	37	33	70	70	47
Diasone alone	27	41	36	73	63	54
Promizole alone	------	------	4	50	4	33
Two or more	20	49	24	80	44	62
Totals	84	40	97	72	181	52

We found no significant differences in the incidence of anemia with the three drugs employed, but there was an interesting difference in sex incidence. Anemia as defined developed in 72 per cent of the female patients but in only 40 per cent of the males.

Reactional conditions.—Lepra reactions of the lepromatous or tuberculoid variety occurred in 99 patients during the treatment, and the same number of patients—they are not all the same ones, however—developed reactions of the erythema nodosum type. These are analyzed in Table 3.

It is our impression that lepra reactions are little, if any, more frequent in treated cases than in untreated ones, but erythema nodosum reactions have been much more common than before the sulfone era. In our series there were fewer reactions with diasone than with promin.

The erythema nodosum reactions may be distressing, but some workers feel that they are a favorable occurrence (6). That was not the case with two of our youngest patients.

Twelve patients (all receiving promin) developed other cutaneous eruptions, mostly erythematous and pruritic but in one case urticarial. Two patients (one receiving promin, one diasone) suffered from generalized pruritus, apparently connected with treatment but without cutaneous lesions.

Polyneuritis, often severe and crippling, occurred in 9 patients (promin 5, diasone 1, promin and diasone 3). In our opinion this is probably more than would have occurred without treatment.

Other side effects.—Nausea is common in patients under any of the sulfones, perhaps most frequent in those taking the larger doses of promizole. Vomiting may occur. Some patients receiving promin sneeze regularly after each injection.

TABLE 3.—*Classification of patients treated, and incidence of various types of reactional conditions.*

Classification and reactions	Drug				Total
	Promin alone	Diasone alone	Promizole alone	Two or more	
Classification of the patients treated					
Lepromatous	118	71	8	56	253
Tuberculoid	23	35	3	12	73
Indeterminate	7	9	1	3	20
Totals	148	115	12	71	346
Reactional conditions observed					
Lepromatous:					
Mild and few	17	6	1	8	32
Many or severe	26	8	2	14	50
Totals	43	14	3	22	82
Tuberculoid:					
Mild and few	4	4	------	4	12
Many or severe	1	1	1	2	5
Totals	5	5	1	6	17
Erythema nodosum:					
Mild and few	30	18	1	4	53
Many or severe	19	10	2	15	46
Totals	49	28	3	19	99
Erythema nodosum and lepromatous	22	4	1	7	34
Erythema nodosum and tuberculoid	------	------	------	1	1

One asthmatic patient was unable to continue treatment because of aggravation of that condition. This was not important since her disease was already arrested, but she had requested treatment. One patient experienced febrile reactions to promin injections. In addition to 28 patients who died, 40 others stopped treatment. Of these, 15 had been "arrested" cases before starting

treatment and 21 stopped after the disease became arrested. Only 4 refused to continue treatment while still active.

RESULTS

The results of the treatment are striking. Ulcers heal, laryngeal stenosis is lessened, vision occasionally improves, nodules subside, and bacilli disintegrate and eventually disappear. Actual arrest (dare we say "cure"?) does occur; 50 patients have been granted "temporary release" since starting treatment, and in about 75 per cent of these we feel that the treatment was a major factor. Only 3 tracheotomies have been performed in the past two years, as compared with an average of 10 per year in the five years preceding; and 11 out of 39 patients with tracheal tubes have been able to remove them as a result of treatment. In several others the larynx is improved enough to permit removing the tubes, but the patients prefer to wait because of nasal obstruction (5).

As shown in Table 4, definite improvement ocurred in 83.5 per cent of all patients treated, while only 14.1 per cent failed to improve during the period under study. Most of the latter, however, had inadequate treatment or their disease was arrested before treatment began. Only 2 per cent—7 out of the 346 cases —regressed under treatment. Never before the sulfone period has any treatment of leprosy produced comparable results.

TABLE 4.—*Results of treatment, gross data.*

Drug	Cases	Improved	Unchanged	Worse
Promin alone	148	122 (83%)	21	5
Diasone alone	115	96 (83%)	17	2
Promizole alone	12	8 (67%)	4	----
Two or more	71	63 (89%)	8	----
Totals	346	289 (83.5%)	50 (14.5%)	7 (2.0%)

To ascertain the effect of varying amounts of the sulfones administered during the period of treatment, the cases are classed in four dosage groups, as shown in Table 5. Each group represents comparable total doses of the three drugs, singly or in combination. As seen in Table 6, the percentage of improvement rises with increasing dosage.

The figures given in Table 7 indicate that improvement occurs in most cases even after many years of illness. In many of

TABLE 5.—*Dosage groups, total grams of sulfones received.*

Group	Promin	Diasone	Promizole
I	Less than 500	Less than 100	Less than 600
II	500–1000	100–200	600–1200
III	1000–2000	200–400	1200–1800
IV	2000–3000	400–600	1800–2400

TABLE 6.—*Results of treatment by dosage groups.*

Group[1]	Cases	Improved	Unchanged	Worse
I	73	43 (59%)	28	2
II	62	50 (81%)	9	3
III	140	127 (91%)	11	2
IV	71	69 (97%)	2	------
Totals	346	289 (83.5%)	50	7

[1]—Groups as in Table 5.

the patients who did not improve the disease was actually arrested before treatment, but they had not applied for release. Hope for complete arrest of the disease, however, and for avoidance of deformity and blindness, is much the greater when treatment is begun early.

TABLE 7.—*Results of treatment, by period of commitment.*

Period	Cases	Improved	Unchanged	Worse	Released after treatment
Less than 1 year	75	64 (85%)	9	2	21
1 to 5 years	88	72 (82%)	13	3	7
6–10 years	71	62 (87%)	7	2	7
11–15 years	57	50 (87%)	7	------	7
16–20 years	26	20 (77%)	6	------	5
Over 20 years	29	21 (38%)	8	------	3
Totals	346	289 (83.5%)	50	7	50

As the data presented show, the percentages of improvement increase with the duration of treatment and with the total dose.

The matter of relation of type and advancement of the disease, dealt with in Table 8, will be considered later.

TABLE 8.—*Results of treatment by type and degree of advancement of the disease.*

Type and degree	Cases	Improved	Unchanged	Worse	Released after treatment
L3	77	69 (90%)	7	1	2
L2	135	115 (85%)	17	3	7
L1	41	34 (83%)	6	1	6
I3	4	1 (25%)	3	------	2
I2	2	1 (50%)	1	------	------
I1	14	10 (71%)	4	------	3
T3	3	2 (67%)	1	------	------
T2	29	25 (86%)	3	1	8
T1	41	32 (77%)	8	1	22
Totals	346	289 (83.5%)	50	7	50

What is perhaps most important is that in cases diagnosed and treated early, the patients in relatively good general condition, the disease does not progress. The advanced cachetic patient is now rarely seen in our wards. Today, we feel safe in assuring the patient who comes early for treatment that he has an excellent chance of recovery. This news is spreading, and more people are coming willingly for contact study and early diagnosis.

DEATHS

As said, 28 of the patients have died. In 4 cases—one of which died in acute lepra reaction—the cause of death was unknown and permission for necropsy was refused. A fifth patient died of cerebral edema, the cause of which was not definitely determined. It does not appear to have been caused by the sulfone treatment; possibly it was a reaction to sulfonamides which he received for an intercurrent infection. One died of agranulocytosis, possibly related to the treatment. If all six of these deaths were to be classed as connected with the treatment —and this is extremely doubtful—they constitute 21 per cent of the deaths, or 1.8 per cent of the cases treated.

Of the remainder, there were 2 deaths from bronchitis associated with an indwelling tracheal tube; one of these patients, who was mentally ill, removed his tube and put pieces of toothbrush down his trachea. One died of chronic nephritis, probably amyloid, of leprous origin. The others died of causes unrelated to leprosy or its treatment: tuberculosis (10 cases), carcinoma (3 cases), brain tumor, cryptococcus meningitis, cerebral hemorrhage with lobar pneumonia, and nephrolithiasis with pulmonary embolus (1 case each). It should be borne in mind that in some patients the leprosy improved as a result of sulfone treatment, but they died of other conditions.

QUESTIONS

1. Do the drugs affect tuberculoid as well as lepromatous leprosy? We feel that we are ready to say, "Yes." Evaluation is difficult, as tuberculoid cases frequently regress spontaneously although often with much scarring, but our results (see Table 8) seem significant. Of 61 presumably active tuberculoid cases —those which had not been granted "temporary release," prior to treatment—50, or 82 per cent, showed improvement, which figure is practically identical with that of the series as a whole. No less than 30 (49%) of these cases were granted "temporary release" after treatment.

2. Is early treatment desirable? Yes, definitely. It seems safe to say that almost no cases treated early become severe; and the earlier the treatment, the better the chance for arrest.

3. Have the sulfones cut the death rate? Yes, greatly. Other factors are involved, but deaths from bronchial obstruction, leprous cachexia, and renal amyloidosis have almost disappeared. The average death rate for the three fiscal years preceding sulfone treatment was 9.3 per cent; for the fiscal year 1949 it was 5.9 per cent.

4. Which is the best sulfone? We do not know. The statistical results with promin and diasone are almost identical, and we have used the other drugs on too few cases for their figures to be of value. Some patients appear to tolerate one drug best, some another. Often after a period of treatment with one drug a change will be of benefit. Naturally, we hope that better and less toxic drugs will soon appear.

5. Is outpatient treatment possible? Yes—for bacteriologically negative cases, if home conditions are satisfactory. In a highly endemic area such as Hawaii, we believe that all bacteriologically positive cases should receive institutional care. In our

series, 5 patients released from the institutions continued their treatment outside; and 9 "closed" cases (bacilli not demonstrated by ordinary methods) who are receiving home treatment have not been admitted. It is hoped that by early diagnosis the number of such cases may be increased.

6. Do pregnant patients stand the treatment well? Yes. Pregnancy cannot be considered a contraindication. We have no evidence of any effect on the child.

CONCLUSIONS

Experience over a period of three years with the sulfone drugs in the treatment of 346 patients has convinced us that they constitute the best treatment for leprosy now available. We believe that they are effective in tuberculoid as well as in lepromatous cases. They are certainly more effective in early cases than in later ones. Thus it is now more important than ever to diagnose cases of leprosy early and to give them prompt treatment.

REFERENCES

1. FAGET, G. H. and ERICKSON, P. T. Chemotherapy of leprosy. J. American Med. Assoc. **136** (1948) 451-456.
2. JOHANSEN, F. A. and ERICKSON, P. T. Studies on the therapy of leprosy. Proc. 4th Internat. Cong. Trop. Med. & Malaria, Washington, 1948, Vol. 1, pp. 365-373.
3. JOHANSEN, F. A. and GRAY, H. H. The modern treatment of leprosy. Med. Woman's J. **56** (1949) 9-24.
4. SLOAN, N. R. Promin and other sulfones in leprosy. Hawaii Med. J. **7** (1947) 19-22.
5. SLOAN, N. R. Effects of sulfone treatment on the larynx in leprosy. Internat. J. Leprosy **16** (1948) 329-333.
6. WOLCOTT, R. R. Erythema nodosum in leprosy. Internat. J. Leprosy **15** (1947) 380-388.