AN EVALUATION OF NEW TREATMENTS AND OTHER FACTORS IN LEPROSY

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To estimate the value of treatment in leprosy when that treatment is applied for a matter of months and not years is like estimating the rate of change of water in a tidal estuary. The whole picture is confused by the repeated ebb and flow, the constant remission and recrudescence characteristic of the disease.

An estimate based on the number of cases improved versus the number of cases not improved is fallacious to the extent that it merely indicates the different condition of the patients at two points of time without in any way measuring the true progress of the disease under the treatment or indicating how far any progress is likely to be maintained. It is common practice to find in a periodic review of one's patients that in whatever way we evaluate their progress most cases will show from time to time a worse picture than in the previous review.

If, therefore, we are to estimate the value of a treatment applied over a short period of time we can so influence the result as to make its significance worthless by disregarding the natural periodicity of the disease in selecting a time for survey, albeit unintentionally, when an unusual proportion of our patients are in remission or recrudescence.

Early estimates of the value of new treatments must however be made and the value of our first observations then allowed to await the proof of time.

In this paper an attempt has been made to evaluate five different treatments carried out for one year, and other factors of importance in leprosy. To minimise the influence of periodicity the individual has been disregarded and an estimate of the general progress of the disease in the group or series has been aimed at. Progress has been reduced to a numerical index and relapse or negative progress in an individual is a deduction from the positive score of progress in his group or series.

The analysis is concerned only with the various categories of lepromatous leprosy; where individuals with both lepromatous and neural lesions are involved, progress, positive and negative, does not in any way refer to the latter.

The clinical picture and the smear count were the criteria indicative of progress. Marks one to three were awarded for each,

thus: slight or moderate improvement—one mark; marked improvement—two marks; all lesions completely gone—three marks. The smears were taken from nose, ear lobes, supraorbitals and other skin lesions and the patient marked +, + +, + + + according to the highest smear count obtained. It was therefore necessary for a patient showing + + + in smears from various sites to show improvement at all sites before being classified as + +, and thereby gaining a mark. A change from + + + to + +, and + + to +, gained one mark; and + + + to +, and + to —ve, gained two marks; + + + to —ve and + + to —ve gained three marks.

The marking was reversible in that deterioration in clinical picture or smear counts obtained corresponding minus marks.

A similar system was employed for R.B.C. counts and Haemoglobin estimation.

Marks 1 to 3 were also given for severity of toxic manifestations and lepra reactions. There were of course no minus markings in these categories.

Marks then, for the clinical picture and smear count indicated progress under treatment. In these two items the total possible for any one individual to gain was six. In actual practice the highest score was five marks. Plus and minus were totalled for the group and that total divided by the number in the group, thus giving the index of progress in the group or the average gain per individual.

The treatments under review are:—

1. Sulphetrone intramuscularly 4 c.c. of a 50% solution, twice weekly. The full dose normally reached in four weeks from commencing treatment.
2. Sulphetrone by mouth 3 g. daily. Full dose reached in three months.
3. D.A.D.P.S. 200 mg. daily. Full dose reached in two months.
4. Neustab (Thiacetazone) A Series.
   1st month 25 mg. daily.
   2nd-7th month 50 mg. daily.
   8th-12th month increasing to 200 mg. daily reached during 12th month.
5. Neustab (Thiacetazone) B Series.
   Commenced with 25 mg. daily and reaching full dose of 200 mg. daily in three months.

In treatments 2, 3 and 5, one day's rest given every week and one week's rest after every two months.

An indication of the efficacy of these treatments is given in col. 6 of Table I. Intramuscular Sulphetrone and D.A.D.P.S. are

almost equally effective with indices of 2.16 and 2.18 respectively. Col. 2 of Table II, however, indicates that the D.A.D.P.S. is more toxic than the intramuscular sulphetrone with an index of .24 compared with the latter's .14.

The Oral Sulphetrone showed a comparatively poor result with an index of only 1.65. This does not necessarily indicate that the drug is relatively ineffectve. It may be that the dose of 3 g. daily is not adequate. Table II supports this interpretation as it shows no evidence of toxicity from this treatment, whereas there were varying degrees of toxicity in all other treatments.

Neustab Series A was an early use of this drug and the dosage is evidence of exaggerated caution. The result, a .35 index, shows clearly the need for adequate dosage when compared with Series B. So disappointing were the results in Series A that treatment in that series was switched to sulphetrone at the end of 13 months' treatment. The majority then showed rapid improvement.

Neustab B Series is unfortunately rather small and can only be taken as an indication of what might be expected from adequate dosage of this drug. The resulting index of 2.87 is by far the highest of the treatments reviewed. As regards adequate dosage it is of interest to record that the indices for Neustab Series B and the D.A.D.P.S. Series at the end of six months' treatment were respectively .87 and .91. The Neustab did not overtake and pass the performance of the D.A.D.P.S. until the second six months of treatment. This may partly be due to full dosage of D.A.D.P.S. being reached 4 weeks before that of Neustab.

Neustab both in the low and the high dosage series gives higher toxicity than any of the other drugs, Neustab B Series giving an index more than 2½ times that of intramuscular sulphetrone.

It will be seen from Table II that there is no correlation between toxicity and effect on R.B.C.s or haemoglobin. Indications of toxicity were, in the main, dermatitis and signs of hepatic damage.

Other factors investigated which may be thought to influence the result of treatment are shown in Table I. Cols. 1 and 2 are two different groupings of the cases according to lesions or type of leprosy.

In Col. 1 they have been divided into L or lepromatous group with no neural lesions, and LN, a group with both neural and lepromatous lesions.

In Col. 2 LL indicates the diffuse spreading non-resistant type of leprosy and diffuse nodular leprosy; T represents the tuberculoid or more resistant types with circumscribed lesions. The differentiation was made purely on the macroscopic appearance.

The bottom line of the table summarises the position for all

groups of treatment in the comparison of the various factors investigated. It will be seen that there is little significant difference in the results of treatment between the lepromatous and the mixed types but the tuberculoid improved more than the diffuse lepromatous type. The difference however is not statistically significant.

In Col. 3 the cases are divided into those that gave a +ve lepromin reaction at the beginning of treatment or developed it during treatment and those that gave —ve reactions or became —ve during treatment. Here the index for lepromin +ve of 2.05 and lepromin —ve of 1.74 gives some support to the theory that a +ve reaction is an indication of resistance. But again, the difference between the indices when tested statistically is not significant.

There is also in Col. 4 little difference between those showing lepra reactions and those that do not. This does not necessarily mean that an individual who has a lepra reaction may not eventually show an improvement from it. It merely means that in the group that has reactions there is no difference in the overall improvement to that in the group that does not have lepra reactions.

In Col. 5 cases have been divided into two groups depending on whether their haemoglobin was above 13 grammes or was 13 grammes or below per 100 ml. The standard was that shown at commencement of treatment or attained soon afterwards and maintained throughout the treatment.

The index of improvement in the high Hb. is 83% better than that in the low.

Some idea of the significance of these indices may be obtained as follows. They are derived from our computation that 80 cases of high Hb. obtained 174 progress marks and 41 cases of low Hb. cases obtained 49 marks. The maximum number of marks obtained by any patient was 5 and that number was a possibility for all patients; therefore, the 80 cases had a possible of 400 and 41 cases a possible of 205. The significance of our figures then lies in the testing of the proportions: 174/400 and 49/205. The difference between these proportions is five times its standard error. In other words, the difference between the progress indices for high and low haemoglobin cases is highly significant.

Tested in a similar manner the differences between the lepromin indices and between the indices of LL and T types are only equal to their standard errors and cannot therefore be considered significant.

Another point which is not without significance with regard to the good result shown by Neustab in the B Series emerges from a study of Table I. All the 8 cases in that series were of the more resistant to treatment LL type, but 7 of the 8 were in the high Hb.

group and the high marks for the series were obtained entirely from these 7, the remaining member of the series was low in Hb. and contributed no marks.

It is extremely difficult to arrive at the real implication of this significant difference in the response to treatment in low and high haemoglobin cases. But some attempt must be made to ascertain its real meaning so that we can apply that knowledge to a proper interpretation of the varying results from treatment.

The haemoglobin may be reduced by extrinsic or intrinsic factors.

Factors extrinsic to the disease are malnutrition and chronic disease other than leprosy. Intrinsic factors are the leprosy itself and the toxic effect of the drugs used in treatment.

All the cases reported on had treatment with iron and vitamins prior to specific treatment. Anti-anaemia treatment was maintained throughout the course. There is no malaria among the population and, apart from yaws, little or no chronic disease.

Extrinsic factors were therefore negligible. If the anaemia arose from the leprosy itself it may indicate that there is a type of leprosy that produces anaemia and is also resistant to treatment. Our other classifications of the disease including clinical picture, lepromin reaction and lepra reaction have, however, shown no other characteristic giving a division similar to that of anaemia. It is therefore somewhat unlikely that we are dealing with a special type of leprosy. In treatment also it is difficult to see why the lower dose of Neustab in A Series should cause anaemia rather than the bigger dose in B Series. Similarly, the Oral Sulphetrone is associated with a greater decrease of haemoglobin than the more toxic doses of Intramuscular Sulphetrone and the D.A.D.P.S. (Table II).

We are then faced with the alternative that the poor results in Sulphetrone Oral and Neustab A Series were due to a chance distribution of an unusually large number of low haemoglobin cases in these series or that the dosage of the drugs in these series was such as to produce low haemoglobin. The second alternative seems the more probable and gets some confirmation from Table III.

In Table III 12 cases were treated for 2 years with Oral Sulphetrone 3 g. daily. The index for haemoglobin decrease is again high and the greater proportion again fall in the low haemoglobin group. The index of the 7 cases in the low haemoglobin group treated for two years is lower than the index for the 7 cases in the high haemoglobin group treated for one year on the same treatment.

The over-all impression obtained is therefore that where leprosy is treated with a toxic drug in doses that are sub-optimal there exists

a summation of the toxic effect of both the disease and the drug causing a decrease in the haemoglobin which is detrimental to the beneficial effect of the treatment.

As the geographical distribution of leprosy coincides with that of secondary anaemia from malnutrition, malaria and other chronic diseases, it may not be irrelevant to suggest that the importance of haemoglobin in treatment may also apply in prevention. Increased haemoglobin levels in populations at risk may lead to a reduced incidence of leprosy.

SUMMARY AND CONCLUSIONS :

121 cases of leprosy were divided into five series and given different treatments for one year.

A further series of 12 cases had treatment for two years.

The results are analysed numerically and would appear to indicate the following conclusions:—

1. A short series on Neustab 200 mg. daily gave the best result.
2. Intramuscular Sulphetrone and D.A.D.P.S. in much larger series gave equal results, not quite so good as the Neustab.
3. Intramuscular Sulphetrone was the least toxic and Neustab the most toxic.
4. Sulphetrone by the oral route 3 g. daily gave comparatively poor results due largely to a fall in the haemoglobin of the patients.
5. Neustab in doses (as stated) less than 200 mg. daily was ineffective and also was associated with low haemoglobin.
6. Haemoglobin above 13 g. is necessary to obtain the best result from treatment.
7. Under dosage or sub-optimal dosage is associated with a fall in haemoglobin far more than occurs with full dosage.
8. It is suggested that low haemoglobin may predispose to the development of the disease in populations at risk.
9. With regard to improvement of the disease under treatment, no significant advantage was shown between the various types of leprosy or between lepromin + ve and lepromin —ve cases or between those with lepra reactions and those without.

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TABLE I.
(One year treatment)

		1. L.	1. LN.	2. T.	2. LL.	3. Lepromin Reac. +ve	3. Lepromin Reac. —ve	4. Lepra Reaction +	4. Lepra Reaction Nil	5. Haemoglobin High	5. Haemoglobin Low	6. TOTALS
Sulphetrone Intramuscular ...	No. Cases	21	22	5	38	14	29	3	40	30	13	43
	Marks	52	41	11	82	24	69	4	89	72	21	93
	Index	2.48	1.86	2.2	2.16	1.71	2.38	1.33	2.22	2.4	1.62	2.16
Sulphetrone Oral	No. Cases	7	10	4	13	7	10	6	11	7	10	17
	Marks	8	20	7	21	13	15	6	22	18	10	28
	Index	1.14	2	1.75	1.61	1.86	1.5	1.0	2.0	2.57	1	1.65
D.A.D.P.S.	No. Cases	18	15	8	25	10	23	12	21	24	9	33
	Marks	34	38	25	47	30	42	27	45	50	22	72
	Index	1.89	2.53	3.12	1.88	3.0	1.83	2.25	2.14	2.08	2.44	2.18
Neustab A Series	No. Cases	4	16	7	13	7	13	2	18	12	8	20
	Marks	1	6	6	1	4	3	2	5	11	—4	7
	Index	.25	.38	.86	.07	.57	.23	1	.28	.92	—0.5	.35
Neustab B Series	No. Cases	3	5	—	8	3	5	3	5	7	1	8
	Marks	7	16	—	23	13	10	10	13	23	0	23
	Index	2.33	3.2	—	2.87	4.33	2	3.33	2.6	3.29	0	2.87
Neustab A & B Series combined	No. Cases	7	22	7	21							29
	Marks	8	22	6	24							30
	Index	1.14	1.0	.86	1.14							1.04
All Treatments	No. Cases	53	68	24	97	41	80	26	95	80	41	121
	Marks	102	121	49	174	84	139	49	174	174	49	223
	Index	1.92	1.78	2.04	1.79	2.05	1.74	1.88	1.83	2.18	1.19	1.84

LL. : Lepromatous and nodular leprosy.
T. : Tuberculoid leprosy.

TABLE II

(One year treatment)

	1. Number of Cases	2. Toxicity		3. Lepra Reactions		4. Decrease in HG.		5. Decrease in RBC	
		Points	Index	Points	Index	Points	Index	Points	Index
Sulphetrone Intramuscular	43	6	.14	7	.16	14	.33	19	.44
Sulphetrone Oral ...	17	0	0	10	.59	26	1.53	16	.94
D.A.D.P.S.	33	8	.24	15	.45	15	.46	20	.61
Neustab A Series ...	20	6	.3	4	.2	15	.75	13	.65
Neustab B Series ...	8	3	.37	4	.5	0	0	4	5
Total all treatments ...	121	23	.19	40	.33	70	.58	72	.59

TABLE III

TWO YEAR'S TREATMENT WITH ORAL SULPHETRONE.

	High Hb.	Low Hb.	Total	Haemoglobin Decrease
No. of Cases	5	7	12	12
Marks	15	16	31	9
Index	3.0	2.28	2.58	.75