SOME EXPERIMENTS WITH INJECTED SULPHETRONE.

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The treatment of leprosy by means of injectable sulphones has lately been receiving much attention. At the Cuba Conference it was resolved to continue experiments on this method of treatment as, should it be successful, smaller quantities of these expensive drugs could be used and the reduction in the cost of treatment would make them available to a larger number of patients. The problem is one of maintaining a stable and effective concentration of the drug in the blood without letting it accumulate to toxic levels. Stability of level is stressed because until we know to the contrary it seems possible that resistant strains of m. lepræ would develop if the concentration were allowed to fluctuate.

Tests were made with sulphetrone to see whether appropriate levels could be maintained by means of injection.

Thirteen patients (nine males and four females) were given subcutaneous injections of 20% aqueous solution of sulphetrone (1 part sulphetrone: four parts normal saline). At first, 7 cc were administered, but the dose was later increased to 10 cc. The injections were given in the arm or thigh. The level of sulphetrone in the blood and urine was tested four times after each injection—after 4, 24, 48 and 72 hours. In urine the level depended of course on the concentration of the specimen, but a rough estimate could be made on the rate of elimination. The average results obtained are shown in the following table. Patients 1-4 were females, 5-13

TABLE 1.

Blood and Urine levels of sulphetrone after subcutaneous injection of 7 cc of 20% solution.

Patient	After 4 hours mg%		After 24 hours mg%		After 48 hours mg%		After 72 hours mg%	
	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine
1	3	100	2	10	trace	10	trace	4
2	4	50	2	7	trace	6	trace	3
3	4	50	2	6	trace	10	trace	2
4	7	90	3	25	trace	18	trace	4
5	5	100	3	12	trace	8	trace	4
6	5	160	3	90	trace	9	trace	3
7	6	80	3	20	trace	6	trace	3
8	7	180	3	25	trace	4	trace	3
9	5	70	3	15	trace	12	trace	trace
10	5	70	3	15	trace	14	trace	8
11	7	120	3	15	trace	10	trace	3
12	6	140	4	30	trace	30	trace	3
13	8	100	4	25	trace	30	trace	3

males. All of them were adults. Their weights were: No. 1—117 lbs., No. 2—135 lbs., No. 3—140 lbs., No. 4—104 lbs., No. 5—156 lbs., No. 6—113 lbs., No. 7—110 lbs., No. 8—122 lbs., No. 9—173 lbs., No. 10—155 lbs., No. 11—151 lbs., No. 12—127 lbs., No. 13—100 lbs.

TABLE 2.

Blood and Urine levels of sulphetrone after subcutaneous injection of 10 cc of 20% solution.

Patient	After 4 hours		After 24 hours		After 48 hours		After 72 hours	
	mg%		mg%		mg%		mg%	
	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine
1	5	180	3	25	trace	5	trace	2
2	6	90	4	40	trace	5	trace	2
3	4	100	3	30	trace	6	trace	4
4	8	200	3	40	2	30	trace	7
5	5	120	3	30	trace	8	trace	8
6	5	120	2	45	trace	6	trace	2
7	6	100	3	45	trace	7	trace	4
8	7	120	3	30	trace	5	trace	trace
9	5	60	4	45	trace	3	trace	4
10	8	160	4	45	trace	16	trace	4
11	7	50	3	25	trace	7	trace	1
12	6	180	3	30	trace	1	trace	3
13	8	120	4	20	trace	7	trace	3

From these tables it will be seen that four hours after the injection of 7 cc of the solution the average level of sulphetrone is 5.5mg% which seems to be rather low for effective treatment. With an injection of 10 cc there is no significant rise in the level either after four hours or on the following day. In both cases after seventy two hours nearly all sulphetrone has been eliminated from the circulation. This suggested that the rate of absorption of the drug might be proportional to the strength of the solution, so in further tests 5 cc of a 33% solution (1 part sulphetrone : 2 parts normal saline) was used. The average results of this treatment are given in the following table.

The rate of absorption is thus seen to be in fact directly proportional to the strength of solution used. Although no toxic effects were seen with this higher concentration, from the experience obtained with sulphetrone given by mouth it would appear that the levels reached were as high as could be used with safety. On the second day the concentration has fallen to an average of 3.5 mg%, a level probably too low to be effective, and on the third day to about 2 mg%. It would seem that elimination is more or less constant and that by increasing the strength of the solution the drug is maintained longer in the circulation.

Injections of 33% solution gave therefore a satisfactory level

of sulphetrone in the circulation on the day of injection. It would, however, be almost unbearable to the patient to have daily injections of 5 cc of fluid over a period of several months or years, but a stability level of sulphetrone will not be maintained otherwise. So it would seem that when on economic grounds it is necessary to administer the drug by this means, the injection should be given at least on alternate days in order that the concentration should never fall below an appreciable level.

Finally it remained to be tested whether the drug would not accumulate to toxic levels in the blood. Table 4 shows that the level in the blood of sulphetrone given by injection on alternate days has not risen after fifteen days.

It seems probable that if injected in a less readily absorbed form the sulphetrone level could be maintained more constant in the blood. Cochrane has experimented on injections of emulsion of sulphetrone in oil and he found that about 25% of cases showed areas of lack of absorption which continued for several months. He concluded that until this problem is overcome any sulphone in an oily medium which gives lack of absorption cannot be recommended.

SUMMARY.

1. Subcutaneous injections of 7 and 10 cc of 20%, and 5 cc of 33% aqueous solutions of sulphetrone were administered to 13 patients with the object of finding if stable levels in the blood could be maintained by this means.

2. With 20% solution the level reached was even on the first day too low to be effective.

3. With 33% (1 part sulphetrone : 2 parts saline) a satisfactory level was obtained on the first day but the concentration had diminished rapidly by the second day.

4. As the discomfort of daily injections of 5 cc of fluid would be unbearable to patients where for financial reasons sulphetrone cannot be given orally, injections on alternate days of 5 c.c. of 33% of aqueous solution of the drug are suggested.

BIBLIOGRAPHY.

R. G. Cochrane, K. Ramanujam, H. Paul, D. Russell: Two and a half years experimental work on the sulphone group of drugs. *Leprosy Review* XX (1949) 4.

TABLE 3.

Blood and Urine levels of sulphetrone after subcutaneous injection of 5 cc. 33% solution.

Patient	After 1 hr. mg%	After 2 hrs. mg%	After 4 hrs. mg%		After 24 hrs. mg%		After 48 hrs. mg%		After 72 hrs. mg%	
	Blood	Blood	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine
1	12	14	12	240	4	50	1	15	trace	10
2	12	8	12	240	5	60	2	15	trace	40
3	8	8	9	120	5	35	1	15	trace	35
4	10	6	12	60	3	15	1	10	trace	10
5	10	10	10	100	4	45	3	25	trace	45
6	10	12	10	220	4	60	2	35	trace	50
7	12	10	12	240	3	90	2	40	trace	10
8	10	10	10	200	3	10	2	10	trace	15
9	9	9	12	100	3	15	3	15	trace	10
10	8	8	12	200	3	60	3	35	trace	20
11	8	8	10	180	3	40	2	10	trace	10
12	8	8	12	240	3	50	1	10	trace	15
13	10	10	8	40	3	20	1	15	trace	10

NOTE.—Spacing for blood and urine should be everywhere equal.

TABLE 4.

Blood and Urine levels of sulphetrone after subcutaneous injection of 5 cc. of 33% solution on alternate days.

Patient	First Injection				Second Injection				Third Injection				Fourth Injection				Eighth Injection	
	After 4 hrs. mg%		After 24 hrs. mg%		After 4 hrs. mg%		After 24 hrs. mg%		After 4 hrs. mg%		After 24 hrs. mg%		After 4 hrs. mg%		After 24 hrs. mg%		After 4 hrs. mg%	
	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine	Blood	Urine
1	14	90	3	50	12	240	4	90	14	120	4	80	14	320	3	100	12	360
2	10	90	3	25	12	240	3	45	8	160	3	50	10	120	3	30	9	180
3	9	80	3	15	6	50	2	40	10	80	5	20	6	180	4	30	10	160
4	8	220	3	50	10	80	3	40	8	240	5	40	10	180	3	80	10	340
5	7	180	4	45	10	120	4	90	8	120	5	45	7	200	4	30	7	160
6	8	220	3	45	12	180	4	100	10	180	6	120	7	210	3	50	9	200
7	10	180	3	45	12	240	4	100	10	200	5	80	12	360	4	50	10	240
8	8	220	3	90	10	300	3	50	10	200	4	20	8	180	4	120	9	200
9	9	120	3	15	12	120	5	20	8	90	6	15	7	180	3	60	8	90
10	8	180	4	30	8	60	3	25	8	160	3	80	9	200	3	40	10	160
11	8	80	3	15	10	120	3	45	9	120	3	35	9	90	3	30	10	160
12	8	140	3	15	9	160	4	60	7	160	13	50	10	240	4	80	10	360
13	14	160	3	25	12	240	4	45	12	200	7	50	8	180	4	20	12	200

NOTE.—Spacing for blood and urine should be everywhere equal.