day may be correlated with fertilization and early pregnancy changes.

These results indicate that the Burr-Lane-Nims technique may prove valuable for the early diagnosis of pregnancy as well as for the detection of ovulation in the chimpanzee.

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Therapy of Experimental Staphylococcus Infections with Sulfonamide Compounds.

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Staphylococcus infections either in man or in experimental animals have not yielded to treatment with sulfanilamide. However, Hörlein* has apparently reported successful results against this organism with "Di-Septal," a dimethylated derivative of di-sulfanilamide. The latter compound appears to have been first synthesized by Rosenthal,[1] who reported on its use in pneumococcal infections in mice. This communication represents a preliminary attempt to compare the efficacy of these 2 compounds with sulfanilamide, in experimental staphylococcus infections in mice and in man.

In the following mouse experiments, all infections were established by giving 0.2 cc. of a 20-hour, undiluted broth culture of an hemolytic *Staphylococcus aureus* into the tail vein. This strain (our No. 451) was isolated in this laboratory from a human case, and was virulent for mice. All medication was given daily by the oral route and consisted of 20 mg. of the drug suspended in 0.25 cc. of 15% gum acacia solution. Medication was continued for 15 successive days in each series, and in the case of those receiving immediate therapy was started on the day that the infecting dose was given. In the delayed therapy groups 3 days elapsed between infection and the institution of medication.

* In a paper read before the British Association for Advancement of Science, August, 1937. The information available to us refers to its use against staphylococci and the Welch bacillus, as well as hemolytic streptococci. Staphylococcal osteomyelitis was mentioned in connection with its favorable action.

1 Rosenthal, S. M., Bauer, H., and Branham, S. F., *Pub. Health Rep.*, 1937, **52**, 662.

Series I. The objective of this series was an evaluation of the *protective* effect of the 3 compounds. It consisted of 84 mice divided into 4 groups of 21 each. All were infected; one group was kept as a control; one group received sulfanilamide; one group received di-sulfanilamide, and the remaining group received di-methyl-di-sulfanilamide (D 373 Winthrop†). Table I shows the percent dead in each group at 2-day intervals. Animals surviving 32 days were killed and counted as survivors. In all these groups treatment was started immediately and continued for 15 days.

TABLE I.

Compound	No. mice	% dead at, days														% Survivals
		2	4	6	8	10	12	14	16	18	20	22	24	26	28	
Controls	21	0	19	29	29	33	43	52	62	67	71	71	71	76	86	14
Sulfanilamide	21	5	19	33	43	48	48	52	52	57	57	57	62	62	62	38
Di-sulfanilamide	21	0	5	5	10	14	14	14	14	14	14	19	29	33	38	62
Di-methyl-di-sulfanilamide	21	5	10	19	24	29	33	33	38	38	43	52	57	62	71	29

The pathological picture was uniform throughout the group, being characterized chiefly by miliary abscesses of the kidneys with only an occasional lesion of the liver or spleen. The histological studies on these tissues had not as yet been completed.

The following facts are apparent on the basis of the foregoing series: 1. On the basis of survivors, the effectiveness of the compounds falls in the following order: di-sulfanilamide, sulfanilamide, di-methyl-di-sulfanilamide. 2. On the basis of early deaths, sulfanilamide gives poorer results than do the controls. This may be due to the higher toxicity of the compound. 3. The continuation of deaths after the cessation of therapy may indicate that treatment should be continued for a longer period.

Series II. The objective of this series was an evaluation of the *therapeutic* effect of the drugs. The foregoing experiment was repeated with 141 mice. In this series non-infected mice receiving the same medication were introduced as drug controls. Di-sulfanilamide and di-methyl-di-sulfanilamide only were employed. The virulence of the infecting strain was increased for this series by 2 mouse passages. The infected mice receiving each drug were divided into 2 groups in one of which therapy was instituted immediately and in the other delayed for 3 days after infection. This period of delay gave ample time for the establishment of gross lesions in the kidneys. The results are reported in Table II.

It is apparent from Table II that: 1. In the early period there is no

† Both this compound and the di-sulfanilamide were kindly furnished us by the Winthrop Chemical Company and the Alba Chemical Company.

TABLE II.

Therapy	No. mice	% dead at, days 2	4	6	8	10	12	14	16	18	20	22	24	26	28	% Survivals
Controls	33	0	15	36	48	61	64	67	76	79	79	79	85	88	88	12
Di-sulfanilamide (immediate)	22	0	0	14	23	23	27	36	36	36	41	41	45	59	64	36
Di-sulfanilamide (delayed)	22	0	14	18	23	32	32	32	32	41	41	41	50	59	59	41
Di-methyl-di-sulfanilamide (immediate)	22	0	9	18	59	59	59	59	59	59	64	64	86	91	91	9
Di-methyl-di-sulfanilamide (delayed)	22	0	9	14	68	68	68	77	86	100	—	—	—	—	—	0

really significant difference between the di-methyl-di-sulfanilamide and the controls. 2. The time at which therapy is instituted is not critical for either drug. 3. Di-sulfanilamide is definitely superior to di-methyl-di-sulfanilamide.

The pathological picture was essentially similar to that found in the first series, differing only in being more severe. The uninfected controls receiving the drugs gave no results of significance. There was slight indication, however, that the di-sulfanilamide might be the more toxic. Weight curves kept for each group showed that over the period of the first 7 days the drug controls lost 16%, the infected controls, 28%, the di-sulfanilamide treated, 20%, and the di-methyl-di-sulfanilamide treated, 24% in average weight.

Four cases of chronic staphylococcic osteomyelitis have been treated for a period of several weeks, first with "Di-Septal," and later with di-sulfanilamide. The most severely ill patient died, as was anticipated, showing no clinical response to the drug's action. The clinical course of the remaining 3 cases has not been noticeably altered by either drug. No signs of toxicity have appeared. A case of acute staphylococcic arthritis in a child was uninfluenced by di-sulfanilamide and after several days developed septicemia, followed by death.

Conclusions. Generally speaking, our experience with these drugs in staphylococcic infections is in marked contrast to the decisively favorable results of sulfanilamide in hemolytic streptococcal infections. Disulfanilamide, by virtue of its apparent therapeutic effect over a limited time period has a certain promise, which, however, failed of clinical confirmation in the small number of cases observed. A more diversified experimental trial is merited. Both experimentally and clinically the results with "Di-Septal" in this preliminary study were essentially negative.