

0.005 g of sulfanilamide. Contrasting the minimum therapeutic effect of diamino-diphenyl-sulfone with that of sulfanilamide we may conclude that the sulfone is about 10 times as therapeutic as sulfanilamide.

In Table VI we present a summary of results obtained with all 4 compounds used in these studies. The difficulties are obvious in selecting a dose which is considered to be the minimum therapeutic. It requires a careful study of individual experiments and of the averages. With certain reservations we consider the minimum therapeutic doses given daily for 5 consecutive days, according to the type of experiments performed, to be: for sulfanilamide, 0.005 g, for 4,4'-diamino-diphenyl-sulfone, 0.0005 g, for diamino-diphenyl-sulfide, 0.003 g, for di(acetyl-amino)-diphenyl-sulfone, 0.001 g, and for di(acetyl-amino)-diphenyl-sulfide, 0.002 g.

*Conclusions.* 1. 4,4'-diamino-diphenyl-sulfone is about 3 times as toxic for the rabbit as is sulfanilamide; 4,4'-diamino-diphenyl-sulfide is 5 times as toxic. 2. The corresponding diacetyl derivatives of sulfone and sulfide are less toxic than sulfanilamide. 3. The minimum therapeutic doses given daily for 5 consecutive days are as follows: for sulfanilamide, 0.005 g, for 4,4'-diamino-diphenyl-sulfone, 0.0005 g, for diamino-diphenyl-sulfide, 0.003 g, for di(acetyl-amino)-diphenyl-sulfone, 0.001 g, and for di(acetyl-amino)-diphenyl-sulfide, 0.002 g. 4. In mice infected with beta-*Streptococcus hemolyticus*, 4,4'-diamino-diphenyl-sulfone is therapeutically active in a dose 10 times smaller than that required by sulfanilamide. This indicates a considerably higher therapeutic efficacy of the sulfone over sulfanilamide.

## 10198

### Occurrence of Positive Vaginal Smears in Spayed Mice.\*

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We<sup>1</sup> reported that spayed mice painted with 1:2:5:6 dibenzanthracene had positive vaginal smears sporadically. In preparing to

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<sup>1</sup> Perry, I. H., and Ginzton, L., *Am. J. Ca.*, 1937, **29**, 680.

TABLE I.  
Vaginal Smears in Spayed Mice.

Treatment wks	Age wks	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Cl
11	27	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
17		II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
18		II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
19		II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
20		II	II	II	II	II	II	II	II	II	II	II	II	II	II	II	II
22	16	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III
28	44	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI
28	44	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI	VI
5	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
6	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
8	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
9	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
11	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
12	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
14	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
24	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
25	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
26	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
27	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
28	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
29	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
30	VI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
32	48	IIA	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
32	48	IIA	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	IIA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15	IIA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Separately caged

\*Dead. †All have papillomas treatment stopped.

repeat this experiment we<sup>2</sup> found that effective amounts of estrone may be transmitted from animal to animal. The animals used in this experiment were kept segregated as a group throughout the experiment. They were spayed. No accessory ovaries were found at autopsy. Smears were made twice daily for 5 days before treatment was begun; and they were all negative. Smears were omitted until 11 weeks after treatment began, to avoid pseudo-estrus<sup>3</sup> effects from mechanical stimulation of the vagina. Smears were made twice a week throughout the rest of the experiment, which terminated 41 weeks after treatment with 1:2:5:6 dibenzanthracene was begun. If a positive or plus-minus smear was found all animals were smeared daily until there was a return to negative. Two untreated spayed controls were kept in the box with the treated mice. Later 4 old spayed females with uterine implants of dibenzanthracene were segregated and kept as additional controls. They were caged separately. Table I shows the positive vaginal smears. Periods when all were negative or plus-minus are omitted for brevity. Estrus was occasionally observed in the treated animals and in the controls.

Frank<sup>4</sup> has reported positive vaginal smears in human post-menopausal and castrate cases. Loeb<sup>5</sup> has reported hyperplasia of the epithelium of the cervix and vagina of old mice. These data suggest that occasional definitely positive vaginal smears develop in old or sexually involuted females. Whether the response is to local or general stimuli is unknown, as is its significance.

## 10199

### Estrogenic Activity of 3-4 Benzpyrene.\*

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Cook and Dodds<sup>1</sup> reported that 3 of the carcinogenic hydrocarbons were estrogenic. The carcinogenic and estrogenic effects were

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<sup>2</sup> Perry, I. H., *PROC. SOC. EXP. BIOL. AND MED.*, 1937, **36**, 122.

<sup>3</sup> Emery, F., and Schwabe, E. L., *Anat. Rec.*, 1936, **64**, 147.

<sup>4</sup> Salmon, U. J., and Frank, T., *PROC. SOC. EXP. BIOL. AND MED.*, 1936, **33**, 621.

<sup>5</sup> Burns, E. L., Suntzeff, V., Muskup, M., and Loeb, L., *Am. J. Ca.*, 1938, **32**, 534.

\* Aided by grants from the Christine Breon Fund for Medical Research and the International Cancer Research Foundation.

<sup>1</sup> Cook, J. W., and Dodds, E. C., *Nature*, 1933, **131**, 205.