groups received 0.1 mg of prostigmin daily.

Although the ovarian weights were unchanged in the seven day group and only slightly larger in those injected thirty days there was an increase in the percentage weight of the uteri in both Groups (4 and 5, Table I) which showed an analysis to have a "significant ratio" of 3 and 1.5 in Groups 4 and 5 respectively (Table I). Since uterine weights are more variable than those of the ovaries these "significant ratios" for the uteri are all the more interesting.

Pathology-histological examination§ showed no consistent change in the ovaries. The uteri of the castrated prostigmin rats (Group 3) show the most changes; there were more round cells, edema and inflammatory cells, both polynuclear leucocytes and lymphocytes, than in the controls. The changes were almost completely confined to the submucosa. In the castrated controls both polynuclear leucocytes and lymphocytes are present but not numerous. Some edema and inflammatory cells were found in the submucosa cell groups including the controls. No changes in epithelial or musculature structure were observed in the prostigmin injected rats. The difference between the prostigmin and control animals is minor and pathologically there is no marked alteration.

Discussion. The ovaries of prostigmin injected rats were apparently in good condition as seen histologically and by the estrous cycles. Twenty additional rats injected twice daily with 0.5 mg of prostigmin at each injection showed no significant change in estrous cycles as compared to saline injected controls. We were impressed by the fact that when the background was a mature uterus, induced by age as in Groups 4 and 5, or in hyperemic state brought about by estrogens Groups 1 and 3, prostigmin further increased the weight. This is also evident after corrections are made for differences in body weight and after desiccation. Thus in Group 3 the uteri in the prostigmin injected rats were 8.8, 9.9 and 9.2 percent heavier in the uncorrected, corrected for body weights and desiccated tissues respectively. This clearly shows that the increase in weight of the uterus after prostigmin was not due to edema.

Summary. Prostigmin was given to young rats in daily amounts of 0.04 to 0.1 mg. The ovaries were slightly increased in weight. The uteri if mature as the result of age or estrogens showed increase in weight following injections of prostigmin and these changes were present after desiccation. Estrous cycles showed no significant change from normal. Cellular elements of inflammatory cells were more abundant in the submucosa after prostigmin. On the whole, pathological changes were not marked; therefore, from the pathological viewpoint effects of prostigmin are minor as far as changes in the ovaries and uterus are concerned.

§ Histological and pathological studies were kindly made by Doctor A. Nettleship of the Pathology Department.

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Essential Hypertension. Therapeutic Trial of Veriloid, a New Extract of *Veratrum viride*.* (17415)

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Veriloid (Coe Chemical Company), a purified alkaloidal fraction of *Veratrum viride*,[1]

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1 Stutzman, J. W., Maison, G. L., and Kusserow, G. W., PROC. SOC. EXP. BIOL. AND MED., 1949, **71**, 725.

has been found to be an active hypotensive agent in hypertensive patients. Effective by mouth, it has produced fewer toxic side effects (nausea and vomiting), than any other active oral preparation presently available. This preliminary report summarizes our experience to date with this agent.

Methods and Results. The subjects were clinic and private cases of established essential hypertension. In 10 hospitalized patients the drug was given acutely after a control period of at least 48 hours of bed rest. Measurements of arterial pressure and pulse rate were made by 2 independent observers at least 3 times a day, and (when these had stabilized) every half hour for the 2 hours before and 4 hours after the acute administration of the drug. The average (to the nearest 5 mm Hg) of the 4 measurements immediately before, and of the 4 lowest consecutive measurements after the administration of the drug were used to characterize its action.‡ In the 10 patients the average arterial pressures were lowered as follows: 220/125 to 155/90, 220/130 to 135/95, 220/140 to 135/90, 180/100 to 150/90, 190/125 to 160/110, 190/125 to 180/115, 195/100 to 170/95, 230/140 to 200/115, 190/125 to 165/110, and 240/130 to 190/110 mm Hg. In only 3 patients was there nausea, and in only 1 of these vomiting.

In 25 ambulatory cases at least 3 measurements were made of arterial pressure and pulse rate under standard conditions (sitting and/or lying) during each visit. After suitable control observations the patient was instructed initially to take 1, or (in large persons) at most 2, mg of Veriloid 4 times a day at intervals of at least 4 hours (after each meal and at bedtime§), unless this caused nausea, in which case he was to reduce the next dose, or if still nauseated to omit it entirely. After 1 week he was to return for a check-up, at which time, unless satisfactory results had already been achieved, he was instructed gradually to increase the dosage by not more than 1 mg a day (provided this caused no symptoms), adding 0.5 to 1 mg first to the bedtime, then to the after-breakfast, the after-lunch, and the after-supper doses, in that order, and to return for weekly checkups.

In this way, patients were gradually worked up to their nauseating dose, and then maintained at a slightly reduced dosage which averaged 2 mg of Veriloid 4 times a day at the end of 3 to 4 weeks. Patients were repeatedly cautioned, if nauseated or otherwise uncomfortable, to remain recumbent and to reduce slightly their subsequent doses. On this regimen, severe collapse reactions were rare after Veriloid. That definite toxic reactions could occur had been discovered during acute trial of the drug given in single doses of 4 to 6 mg. The antidote used for these reactions was the same as for those after other Veratrum preparations, namely, ephedrine sulphate intramuscularly (30 to 45 mg) and/or atropine (0.5 to 1 mg). Similar, but milder reactions occasionally occurred in patients on continued administration. Characteristically, these appeared only after several weeks of treatment and required a further small reduction of dosage. However, in only 3 patients was it necessary to discontinue the drug altogether.

Of 25 patients maintained to date on 6 to 11 (average 8) mg of Veriloid a day, 9 were followed for 12 to 20 weeks and had their average arterial pressures lowered as follows: 245/135 to 190/100, 250/150 to 210/110, 235/135 to 185/115, 235/150 to 230/135, 205/110 to 180/90, 180/120 to 140/85, 175/110 to 160/90, 180/115 to 150/95, and 190/110 to 155/90 mm Hg. Eleven patients took the drug for 6 to 12 weeks and had their average pressures changed from: 200/130 to 150/90, 160/100 to 130/80, 210/130 to 140/105, 250/140 to 170/80, 230/135 to 185/110, 210/140 to 150/90, 235/115 to 195/105, 185/110 to 170/95, 210/110 to 195/100, 195/110 to 180/110, and 185/90 to 175/80 mm Hg. Five patients were followed for 2 to 4 weeks and had pressures changed as

‡ The method of acute administration of the drug will be reported in detail later.[2]

[2] Wilkins, R. W., Stanton, J. R., and Freis, E. D., to be published.

§ In animals[1] as well as in man, *Veratrum viride* is less nauseating when food is already in the stomach and/or the subject is lying down. However, if food is taken within 3 hours after the drug, nausea is liable to occur.

follows: 260/150 to 190/110, 180/110 to 140/90, 200/115 to 180/110, 190/115 to 170/100, and 200/115 to 170/100 mm Hg.

Thus, on chronic as well as acute administration Veriloid was an active hypotensive agent, clinically similar to other Veratrum preparations previously tested.[3-5] Relative to its hypotensive effects, however, it appeared to produce somewhat less nausea and vomiting, the chief symptoms found in previous experience to interfere with the long-term usage of *Veratrum viride*. As with other preparations, meticulous adjustment of dosage to patient was the most important single point in the chronic use of Veriloid. Patients objected so strongly to the symptoms associated with overdosage that it was the practice in the present study to be satisfied with moderate lowerings of arterial pressure, rather than to attempt dramatic effects at the expense of even occasional unpleasant side reactions.

Summary. In hypertensive patients Veriloid is an active hypotensive agent when administered acutely, or chronically for periods as long as 5 months. Meticulous regulation of dosage is important in obtaining optimum results. After several weeks of continuous therapy it is frequently necessary to reduce the dosage in order to avoid nausea and vomiting. Nevertheless, relative to its hypotensive effects Veriloid seems to produce fewer toxic reactions than any other oral preparation of *Veratrum viride* presently available.

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[3] Freis, E. D., and Stanton, J. R., *Am. Heart J.*, 1948, **36**, 723.

[4] Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H., and Wilkins, R. W., *J. Clin. Invest.*, 1949, **28**, 353.

[5] Wilkins, R. W., Freis, E. D., and Stanton, J. R., *J.A.M.A.*, 1949, **140**, 261.

Oral Toxicity of a New Miticide, Di-(p-chlorophenyl)methylcarbinol.* (17416)

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Di-(p-chlorophenyl)methylcarbinol(DMC) synthesized by Bergmann and Bondi,[1] and later by Grummitt *et al.*,[2] has been shown to possess marked miticidal properties.[3] A preliminary study of its acute and subacute toxicity for rats and mice, following oral administration, is the subject of this report.

Acute Toxicity. Young albino rats (80-100 g) and adult albino mice (18-22 g), of the female sex, were given single doses of DMC by stomach tube. Solutions in corn oil and suspensions in aqueous mucilage of tragacanth (2%) were used. Mice were observed for 10 days, and rats for 21 days, following intubation. The results of these experiments are shown in Table I.

With the oil solution of DMC the largest single dose tolerated by all 5 rats in a dosage group was 250 mg/kg. With the aqueous suspension one animal died following a dose of 375 mg/kg, although no fatalities resulted from dosage with 500 mg/kg. Fatalities from larger doses usually occurred 48 to 96 hours after administration. Urinary incontinence, tremors, ataxia, and impairment of righting reflexes were present for approximately 24 hours before death. Such abnormalities were not seen in animals which survived. Autopsies performed immediately after death revealed no gross pathological changes beyond

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[1] Bergmann, E., and Bondi, A., *Berichte*, 1931, 64B, 1455.

[2] Grummitt, O. J., Buck, A., and Becker, E., *J. Am. Chem. Soc.*, 1945, **67**, 2265.

[3] Witman, E. D., and Waters, H. A., unpublished observations.