after sufficiently large doses by a fall in positive intermediary potential. Since the enhancement correlates well with changes in blood pressure it is probably secondary to cardiovascular changes. The depression, however, would appear to be due to an action of the drug directly on the spinal cord since it was not correlated with alterations in blood pressure. Furthermore, it would not appear to be due to an action of the drug higher in the neuraxis since it was found in both decerebrate and decerebrate-spinal cats.

The inhibitory action of chlorpromazine on the positive intermediary potential described here probably does not account for the depression of spinal reflexes described previously(3,4,5,6). The reason for this conclusion is 2-fold. First, the dose of chlorpromazine necessary to inhibit the positive intermediary potential is much greater than that required to inhibit the spinal reflex. Second, whereas the reticular formation would appear to be necessary for the actions of chlorpromazine on spinal reflexes it would not appear to be necessary for the actions of chlorpromazine described here.

The observations reported here may explain those of DeMaar *et al.*(8) that chlorpromazine inhibits activation of the reticular formation by stimulation of the sciatic nerve. This correlation would be based on the relation between the positive intermediary potential and excitability of the spinal cord(1,10) and the fact that the dose of chlorpromazine required to depress the positive intermediary potential is approximately that required to inhibit activation of the reticular formation. Obviously, these data do not preclude the existence of chlorpromazine action higher in the neuraxis, or that such action may better explain DeMaar *et al.*'s observations. On the other hand, even if this is the case, the action of chlorpromazine on a spinal level may indicate the mechanism of its action higher in the neuraxis.

Summary. It was found that intravenous injection of chlorpromazine produces an initial brief period of enhancement of the positive intermediary potential of the cat's spinal cord. This is followed by a prolonged period of depression of the positive intermediary potential. The period of enhancement is probably associated with alterations in blood pressure. The period of depression would appear to be due to a direct action of chlorpromazine on the spinal cord.

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Mechanism of the Antidiuretic Action of Reserpine.* (27095)

N. KHAZAN, J. ADIR, Y. PFEIFER AND F. G. SULMAN
Department of Applied Pharmacology, Hebrew University-Hadassah Medical School and School of Pharmacy, Jerusalem, Israel

Antidiuresis has been reported to follow the administration of several agents which depress the central nervous system(1), such as reserpine(2,3) and chlorpromazine(4). The reports have suggested that, subsequent

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to administration of these agents, secretion of antidiuretic hormone (ADH) is stimulated, thus causing decreased urine flow. When reserpine is administered in small doses in treatment of hypertension and more massively in treatment of psychoses, fluid retention, with or without edema, sometimes develops(5-7).

Animals treated with reserpine excrete a large quantity of the serotonin metabolite, 5-hydroxy-indolyl acetic acid (5-HIAA). The brain and other body stores of such animals become depleted of their serotonin content. The serotonin-releasing activity is confined exclusively to rauwolfia alkaloids with tranquilizing action(8). This indicates that the release of serotonin might be responsible for the primary pharmacological properties of reserpine and rauwolfia alkaloids. Indeed, serotonin has a strong antidiuretic effect on hydrated dogs(9), and rats(10,11).

The purpose of the present study was to investigate which mechanism of action predominated in effecting reserpine-antidiuresis–ADH-release or serotonin depletion. The experiments described were designed to compare the patterns of ureter renal flow, and of sodium, potassium, chlorides and 5-HIAA urinary excretion in anesthetized hydrated dogs after i.v. injection of reserpine, serotonin, antidiuretic hormone, and solvent.

Materials and methods. Twelve male dogs, weighing 6-10 kg, were divided into 4 equal groups. The animals were anesthetized with 30 mg/kg sodium pentobarbital injected intraperitoneally and hydrated with 10 ml/kg body weight of water through a stomach tube followed by tracheotomy and cannulation. Laparotomy was performed, and both ureters were catheterized with polyethylene tubes into graduated cylinders. After preparation of a femoral vein each group of 3 dogs received 0.5 mg/kg reserpine;† 2 mg/kg serotonin;‡ 2 u/kg antidiuretic hormone,§ or reserpine solvent‖. Immediately thereafter, a second water load of 20 ml water/kg body weight was given. Starting one hour after the injection, urine was collected for 5 hours in graduated cylinders, and at houly intervals measured, then analysed for Na^+, K^+, Cl^-, and 5-HIAA. A mixture of 25 ml glacial acetic acid, and 3 ml toluol was added to each urine sample (2.5/100 ml) and the urine preserved at +4°C for 18 hours when the analysis of 5-HIAA was carried out.

Sodium and potassium determination was carried out by flame photometry according to the internal standard method(12), chlorides according to the method of Scribner(13), and 5-HIAA according to that of Udenfriend *et al.*(14).

Results. The effect of reserpine, serotonin, antidiuretic hormone, and solvent on urine flow during water diuresis in dogs is shown in Table I. Data showing urinary electrolyte, chlorides and 5-HIAA excretion after injection of reserpine, serotonin, ADH and solvent respectively are presented in Table II. Reserpine gave a pattern similar to that of serotonin: lower Na^+ and Cl^-, and higher K^+ and 5-HIAA, but different from that of ADH: higher Na^+ and Cl^-, lower K^+ and 5-HIAA (Fig. 1).

Discussion. The mechanism of the endocrine side-effects of reserpine has been attributed to its interference with the functions of the anterior and posterior lobes of the pituitary. These side-effects are generally ascribed to its depressing action on the hypothalamus(15-17).

While the present experiments were performed in dogs under anesthesia with pentobarbital sodium, which has itself an antidiuretic effect, a parallel experiment was run in unanesthetized adult male rats. These experiments showed that the barbiturate does not interfere with the results obtained in regard to antidiuresis as well as to the patterns

† Reserpine as injectable solution and as alkaloid was generously supplied by Teva, Middle East Pharm. & Chem. Works, Jerusalem.

‡ Serotonin as serotonin creatinine sulphate was generously supplied by the Research Labs., Upjohn Co., Kalamazoo, Mich.

§ Antidiuretic hormone used was commercial Pitressin of Parke, Davis & Co., Detroit, Mich.

‖ Reserpine solvent: benzylalcohol 2 ml, anhydrous citric acid 250 mg, polysorbate '80' 10 ml, water for injection to 100 ml.

TABLE I. Effect of Intravenous Injections of Reserpine, Serotonin, Antidiuretic Hormone, and Solvent on Urine Flow in Anesthetized Hydrated Dogs (3 Animals in Each Group).

No. of hr after inj.	Avg urine volume excreted through ureters: Reserpine, .5 mg/kg	Serotonin, 2 mg/kg	ADH, 2 u/kg	Solvent
	ml			
1	0	0	0	0
2	3.2 ± .21	4.3 ± .20	4.3 ± .02	6.3 ± .02
3	6.5 ± 1.50	8.7 ± .20	8.5 ± 1.00	12.8 ± .10
4	10.0 ± 1.60	12.6 ± 1.10	14.0 ± 1.00	20.1 ± .24
5	14.1 ± 1.04	16.8 ± 2.04	21.2 ± .10	24.5 ± 1.10
6	16.9 ± 1.07	19.1 ± 2.01	22.8 ± .30	30.9 ± 2.10

TABLE II. Effect of Intravenous Injections of Reserpine, Serotonin, Antidiuretic Hormone, and Solvent on Urinary Electrolytes, Chlorides, and 5-HIAA Excretion in Anesthetized Hydrated Dogs (3 Animals in Each Group).

Assay	Avg values during 6 hr after inj. (9 assays each): Reserpine, .5 mg/kg	Serotonin, 2 mg/kg	ADH, 2 u/kg	Solvent
Na, meq/l	38 ± 2.7*	38 ± 2.1	206 ± 5.4	80 ± 2.9
K, meq/l	317 ± 5.9	335 ± 3.4	203 ± 4.1	223 ± 5.5
Cl, meq/l	24.5 ± 1.0	25.3 ± .26	94.2 ± 2.6	62.5 ± 2.4
5-HIAA, μg/ml	7.1 ± .12	10.1 ± 1.3	1.5 ± .01	1.6 ± .001

* Mean ± S.E.

of Na^+, K^+, Cl^- and 5-HIAA urinary excretion.

Despite past indications that reserpine interferes with normal endocrine activity, our results clearly seem to contradict the hypothesis of stimulated ADH secretion(2,3). In our view antidiuresis results from the action of serotonin depleted from body stores after reserpine administration.

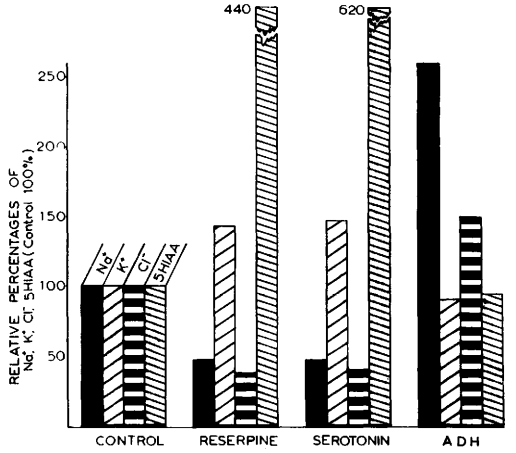

FIG. 1. Diagram of excretion of urinary electrolytes, chlorides, and 5-hydroxy-indolyl acetic acid (5-HIAA) after intrav. inj. of reserpine, serotonin, ADH, and solvent to anesthetized dogs. (Control = 100%.)

Summary. The urinary excretion of electrolytes, chlorides and 5-HIAA after administration of either reserpine or serotonin in dogs was found to be closely similar in pattern: lower Na^+ and Cl^-, and higher K^+ and 5-hydroxy-indolyl acetic acid. ADH administration, on the other hand, resulted in a different pattern: higher Na^+ and Cl^-, and lower K^+ and 5-HIAA. This suggests that the antidiuretic action of reserpine is due to release of serotonin, depleted from body stores, and not to release of ADH.

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Responses of the Snell Dwarf Mouse to Pituitary Tissue from a Bovine Dwarf Mutant.* (27096)

F. D. CARROLL AND P. W. GREGORY
University of California, Davis

Numerous distinct dwarf mutants of cattle and mice have been reported. The comparative genetic and biological nature of the mutants in the 2 species are of considerable interest and biological importance, including the problem of genetic homology. This report concerns an attempt to establish possible relationship, or lack of relationship, between a dwarf mutant from each of the 2 species. The study concerns pituitary extract made from a specific type of achondroplastic bovine dwarf mutant injected into a specific type of thyroid-pituitary deficient mouse mutant. The response may also reveal specific information on the physiological nature of both the donor and recipient mutants.

The general morphological characteristics of the bovine mutant that provided the pituitaries have been described(1,2); it is subnormal in size and belongs to an achondroplastic complex. In this laboratory it is called the brachysephalic dwarf(3,4). All components of the complex exhibit lesions of achondroplasia in the axial and/or the appendicular skeleton(5,6). In the brachycephalic dwarf the pituitary-thyroid axis is reported to be normal(7); growth, gonadotropic, and ACTH hormone activity in the pituitary tissue are reported to be normal or nearly normal(8,26); sensitivity to insulin is greater than in normal catle(27); but there is disagreement about whether the pituitary tissue is deficient in thyrotropic hormone activity (7,8,10). Limited work indicates body weight increases(9), but not skeletal growth, in response to hormone therapy such as stilbestrol, testosterone, thyroprotein, and combinations of these. The mouse mutant used is a recessive dwarf(11,12) and suffers from a thyroid-pituitary deficiency(13,14,15,16,17, 18,19,20,21). In being quite sensitive to insulin(28), it is similar to the bovine dwarf (27). Although the pituitary has high concentrations of gonadotropic hormones, its growth hormone activity is difficult to detect (14,15).

Materials and methods. Pituitary glands from normal and dwarf cattle, predominantly of the Hereford breed, were collected within 15 to 20 minutes of slaughter and placed in vacuum bottles containing dry ice. Glands from the 2 stocks were kept separate, and 2 extracts were prepared, one from the dwarfs and one from normal cattle. Before the pituitaries were macerated, the capsules were removed and the glands weighed. They were then sliced into several pieces, placed in a

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