of mitotic activity, all changes observed—drop of body weight, total protein level and albumin, rise in globulin fractions, especially of beta-globulin—were present not only in hepatectomized but also in sham-operated rats with the former showing more pronounced changes than the latter. This makes it likely that these changes may, at least in part, be associated not only with liver regeneration but also with recovery from trauma and growth processes, such as those initiated by laparotomy incision.

Summary. Changes in serum proteins and mitotic activity in the liver of Lewis rats were studied after partial hepatectomy or sham operation, at intervals of 6 hours to 15 days. A rise of beta-globulin fraction roughly paralleled the rise in mitotic activity. Serum protein changes in sham-operated animals showed a similar trend but were less pronounced.

1. Friedrich-Freska, H., Zaki, F. G., *Z. Naturforsch.*, 1954, v9B, 394.

2. Glinos, A. D., Gey, G. O., PROC. SOC. EXP. BIOL. AND MED., 1952, v80, 421.

3. Stich, H. F., Florian, M. L., *Canad. J. Biochem. and Physiol.*, 1958, v36, 855.

4. Christensen, B. G., Jacobsen, E., *Acta med. scand.*, 1949, v234, 103.

5. Bucher, N. L. R., Scott, J. F., Aub, J. C., *Cancer Res.*, 1950, v10, 207; *ibid.*, 1951, v11, 457.

6. Wennecker, A. S., Sussman, N., PROC. SOC. EXP. BIOL. AND MED., 1951, v76, 683.

7. Chanutin, A., Hortenstine, J. C., Cole, W. S., Ludewig, S., *J. Biol. Chem.*, 1938, v123, 247.

8. Roberts, S., White, A., *ibid.*, 1949, v180, 505.

9. de Lamirande, G., Cantero, A., *Cancer Res.*, 1952, v12, 330.

10. Emmrich, R., Petzold, H., *Z. ges. exp. Med.*, 1953, v122, 264.

11. Garaffa, G., Rovati, V., *Boll. Soc. Med. Chir. Pisa*, 1955, v23, 124.

12. Johnson, M. J., *J. Biol. Chem.*, 1941, v137, 575.

13. Chalkley, H. W., *J. Nat. Cancer Inst.*, 1943-44, v24, 47.

14. Higgins, G. M., Anderson, R. M., *Arch. Path.*, 1931, v12, 186.

15. Jaffe, J. J., *Anat. Rec.*, 1954, v120, 935.

Received October 13, 1959. P.S.E.B.M., 1960, v103.

Effects of Reserpine on Adrenal Responses to Nicotine.* (25560)

E. E. BAGWELL, E. F. WOODS AND J. A. RICHARDSON
Dept. of Pharmacology, Medical College of South Carolina, Charleston, S. C.

Small doses of nicotine injected into the thoracic aorta stimulate the adrenal medulla resulting in marked increases in levels of circulating catechol amines along with corresponding increases in heart contractile force (1,2). Our experiments were designed to study effects of previous reserpine treatment on (a) responsiveness of the adrenal medulla to chemical stimulation and (b) reactivity of the cardiovascular system to endogenously released catechol amines.

Methods. All experiments were performed on open-chest bilaterally vagotomized dogs. A total of 10 control and 25 reserpinized dogs were injected intra-aortically with test doses of 10 and 20 μg/kg of nicotine (administered as .01% solution of the alkaloid). Control dogs were anesthetized with 30 mg/kg pentobarbital sodium intravenously while reserpinized dogs, more sensitive to the anesthesia, were given only 15 to 20 mg/kg. Both groups were given supplemental doses as needed to maintain surgical state of anesthesia. Reserpine† was given intramuscularly and daily dosages varied from .05 to 1 mg/kg of body weight for 1 to 7 days. Plasma levels of epinephrine and norepinephrine were determined by modification(3) of the fluorimetric method of Weil-Malherbe and Bone(4). Blood samples were taken from indwelling polyethylene catheter placed in right femoral artery. The chest was opened by mid-line incision, and heart contractile force measured by suturing a strain gauge arch(5,6) directly to the surface

* This investigation was supported by grants from Nat. Heart Inst. and South Carolina Heart Assn.

† Serpasil generously supplied by CIBA Pharmaceutical Products, Summit, N. J.

TABLE I. Adrenal Medullary Stimulation Produced by Nicotine in Control and Reserpinized Dogs.

	Nicotine dosage, μg/kg	Heart force, % increase	Epinephrine, μg/l of plasma	Norepinephrine, μg/l of plasma
Control	10 (10)*	86.6	15.6	3.5
	20 (6)	137.5	46.6	8.8
Reserpinized	10 (18)	99.6	4.7†	2.5
	20 (16)	153.0	14.8†	4.7

* No. of dogs in parentheses. † Significantly different from control response ($P < .01$).

of right ventricle. Blood pressure was measured from the right carotid artery through a Statham transducer and recorded by strain analyzer and direct writing oscillograph from the Grass Instrument Co. Nicotine injections were made through polyethylene catheter passed up the left femoral artery into the thoracic aorta to a point just above origin of adrenal arteries. This enabled high concentrations of nicotine to pass into the adrenal glands and minimized the amount introduced into the general circulation. Doses of nicotine in these experiments (10 and 20 μg kg) have been shown earlier to produce little or no effect when injected intravenously in intact animals or intra-aortically in adrenalectomized animals(2).

Results. Table I summarizes maximum mean percentage increases in heart contractile force and concentrations of epinephrine and norepinephrine during adrenal stimulation with nicotine. Ten μg/kg produced mean percent increase in heart force of 86.6% (S.E. ± 14.39) in normal dogs and 99.6% (S. E. ± 12.07) in reserpinized dogs. These differences were not statistically significant ($P > .1$). Blood pressure responses followed a similar pattern. However, on measuring plasma concentrations of epinephrine and norepinephrine from blood drawn at peak of response, the mean level of epinephrine was 15.6 (± 4.5) μg/liter of plasma in normal dogs while mean level in reserpinized animals was only 4.7 (± 1.4) μg/liter. This difference was highly significant ($P < .01$). Norepinephrine levels were not significantly altered ($P > .1$).

A similar pattern of response followed injections of larger doses of nicotine. Table I shows that increments in heart force produced by 20 μg/kg were not substantially altered by pretreatment with reserpine, while a marked differentiation may be noted in amounts of epinephrine present in plasma ($P < .01$). Again, norepinephrine concentrations were not significantly elevated.

Discussion. It is now generally known that reserpine depletes or reduces stores of catechol amines in such tissues as brain, arterial wall, heart, sympathetic nerve and adrenal medulla. Adrenals of the rabbit(7,8) and rat(9,10) are almost completely depleted of their amines, while the cat is more resistant and suffers only partial depletion with dosages of reserpine to 2.5 mg/kg(11). Maling *et al.* have more recently shown that the amine content of dog adrenals is also markedly reduced(12).

A question which has not been adequately studied is whether secretion of adrenal catechols, at rest and in response to stimulation, is diminished in proportion to reduction in tissue concentrations of these amines. Kroneberg and Schumann found that in rabbits the resting concentration of epinephrine in adrenal vein blood remained at 50% of normal when the adrenals were nearly completely exhausted by reserpinization(7).

Our experiments show that reserpine significantly decreases responsiveness of the adrenal medulla to chemical stimulation as indicated by smaller increments of plasma epinephrine in reserpinized dogs after nicotine injection (Table I). Since cardiovascular responses normally are proportional to levels of amines, it would be expected that changes in parameters such as heart force and blood pressure would also be less marked in reserpinized dogs. However, in our experiments, it appears possible that the cardiovascular system may be able to compensate for this diminution in adrenal responsiveness since heart force and blood pressure responses are not significantly different from those obtained in control dogs receiving the same doses of nicotine.

The mechanism by which this compensation

occurs is not known. Consideration should be given to the fact that increased sensitivity of such parameters as heart rate and blood pressure to injected amines after reserpinization has been shown by several investigators (13,14,15,16). One may also speculate that the cardiovascular system becomes more sensitive to amines released by adrenal stimulation after reserpinization. However, a more detailed study needs to be made on sensitivity changes before conclusions can be drawn on this point.

Summary. Increments in plasma levels of epinephrine resulting from nicotine stimulation of the adrenal medulla are markedly reduced by reserpine. However, increments in heart contractile force and arterial blood pressure produced by adrenal stimulation, normally proportional to catechol amine levels, are not significantly altered following reserpine.

1. Woods, E. F., Richardson, J. A., Richardson, A. K., Bozeman, R. F., Jr., *J. Pharmacol. Exp. Therap.*, 1956, v116, 351.

2. Woods, E. F., Richardson, J. A., *ibid.*, 1955, v114, 445.

3. Richardson, J. A., Richardson, A. K., Brodie, O. J., *J. Lab. Clin. Med.*, 1956, v47, 832.

4. Weil-Malherbe, H., Bone, A. D., *J. Biochem.*, 1952, v52, 311.

5. Boniface, K. J., Brodie, O. J., Walton, R. P., PROC. SOC. EXP. BIOL. AND MED., 1953, v84, 263.

6. Cotten, M.deV., Maling, H. M., *Am. J. Physiol.*, 1957, v189, 580.

7. Kroneberg, G., Schumann, H. J., *Arch. Exp. Path. Pharmacol.*, 1958, v234, 133.

8. Burn, J. H., Rand, M. J., *Brit. Med. J.*, 1958(1), 903.

9. Callingham, B. A., Mann, M., *Nature*, 1958, v181, 423.

10. Coupland, R. E., *J. Endocrinology*, 1958, v17, 191.

11. Muscholl, E., Vogt, M., *J. Physiol.*, 1958, v141, 132.

12. Maling, H. M., Cohn, V. H., Jr., Highman, B., *J. Pharmacol. Exp. Therap.*, 1959, v127, 229.

13. Bejrablaya, D., Burn, J. H., Walker, J. M., *Brit. J. Pharmacol.*, 1958, v13, 461.

14. Bein, H. J., *Experientia*, 1953, v9, 107.

15. Bein, H. J., Gross, F., Tripod, J., Meier, R., *Schweiz. Med. Wochenschr.*, 1953, v83(2), 1007.

16. Trapold, J. H., Plummer, A. J., Yonkman, F. F., *J. Pharmacol. Exp. Therap.*, 1954, v110, 205.

Received October 29, 1959. P.S.E.B.M., 1960, v103.

Inhibition of Hexamminecobaltic Chloride, DNA Interaction by Sera of Patients with Disseminated Lupus Erythematosus.* (25561)

GERALD WEISSMANN† (Introduced by Lewis Thomas)

Dept. of Medicine and Study Group for Rheumatic Diseases, N. Y. Univ. College of Med., and Third (N.Y.U.) Medical Division, Bellevue Hospital, N. Y. City.

Evidence obtained by immunologic technics suggested that serum of patients with disseminated lupus erythematosus (DLE) contains several factors reacting with various nuclear materials. Holman and Kunkel(1) and Friou(2) indicated that gamma globulin of such sera is bound to both nuclei and nucleoprotein, while Miescher's studies(3) showed that nuclei of several sources can absorb from DLE sera the factor responsible for L. E. phenomenon, and also remove from such sera measurable amounts of gamma globulin. Classical precipitin curves have been obtained between protein-free desoxyribonucleic acid (DNA) and DLE serum(4) while latex particles(5) and red cells(6) coated with such material have been agglutinated by DLE serum. The reaction between highly polymerized DNA and the polyvalent cobalt salt hexamminecobaltic chloride ($Co(NH_3)_6Cl_3$) results in production of a clot of insoluble DNA. While studying this reaction, it was observed that DNA which had been treated with serum from patients with DLE, failed to clot, while normal serum had no such effect. The present paper deals with a simple method for demon-

* Aided by grant from N.I.H.

† Fellow of Arthritis and Rheumatism Fn., 1958-59.