more rapidly than solan, TCAB was the dominant azo residue. Second ranking was the asymmetric TCMAB and lowest was DCDMAB. This was to be expected because, in view of the rapid rate of propanil degradation, an excess of DCA molecules competed for CMA molecules released from the more slowly decomposing solan. Consequently, probability of asymmetric azobenzene formation is high if the two herbicides are applied simultaneously or if solan treatment precedes propanil treatment. Asymmetric azobenzene formation is unlikely if propanil treatment precedes solan treatment.

In conclusion, I have established that degradation products of two or more pesticides may combine in soil to form unexpected hybrid products. Insofar as similar reactions may occur in the field, the complexity of pesticide residue problems is increased.

RICHARD BARTHA

Department of Biochemistry and Microbiology, Rutgers University, New Brunswick, New Jersey 08903

References and Notes

1. S. Matsunaka, *Science* **160**, 1360 (1968).
2. R. Bartha and D. Pramer, *ibid.* **156**, 1617 (1967).
3. R. Bartha, *J. Agr. Food Chem.* **16**, 602 (1968).
4. ———, *Weed Sci.*, in press.
5. Weed Society of America, *Herbicide Handbook* (Humphrey Press, Geneva, N.Y., 1967), pp. 60 and 117.
6. L. M. Bordeleau and R. Bartha, *Bacteriol. Proc.* **1969**, 4 (1969).
7. This paper of the Journal Series, New Jersey Agricultural Experiment Station, was supported in part by PHS research grant ES-16.

22 July 1969

Vascular Smooth Muscle Reactivity in Normotensive and Hypertensive Rats

Abstract. *Aortic strips from spontaneously hypertensive rats were less responsive than normal animals to the contractile effects of norepinephrine, serotonin, and potassium chloride but more reactive to the relaxant effects of the stimulant of beta receptors, isoproterenol. Thus, hypertension is not the result of an absence of beta receptor or a hypersensitivity of the vascular smooth muscle.*

Increased peripheral resistance of the vascular system is characteristic of hypertension in humans (*1*). We have compared the reactivity in vitro of thoracic aortas from normotensive rats with those from a strain of spontaneously hypertensive rats (SHR) (*2*). The thoracic aorta was used as an indicator of vascular reactivity because it can be readily prepared for the recording of pharmacologic responses, although the aorta exerts little, if any, effect on total peripheral response. The hypertension exhibited by SHR may be analogous to essential hypertension in humans because histopathological changes are absent, especially in the cardiovascular-renal system before the development of hypertension (*3*). Aortas from hypertensive rats are less reactive to norepinephrine, serotonin, and KCl than those from normotensive animals. In addition, thoracic aortas from both the hypertensive and normotensive rats have beta adrenergic as well as alpha adrenergic receptor sites.

The blood pressures of unanesthetized male Wistar rats of the spontaneously hypertensive strain and normotensive Wistar rats (Carworth Farms), 7 to 10 weeks old, were measured by the tail-plethysmographic method (*4*). The animals were killed by a blow on the head, and spirally cut thoracic aortic strips were prepared by the method of Furchgott and Bhadrakom (*5*). Each strip was suspended in an isolated-organ bath (10 ml) containing a modified Krebs bicarbonate solution of the following composition (in grams per liter): KCl, 0.35; $CaCl_2 \cdot H_2O$, 0.37; KH_2PO_4, 0.16; $MgSO_4 \cdot 7H_2O$, 0.29; NaCl, 6.9; $NaHCO_3$, 2.08; and glucose, 1.8. The temperature of the baths was maintained at 37.5°C, and the Krebs bicarbonate solution was oxygenated with a mixture of 95 percent oxygen and 5 percent carbon dioxide. The strips were subjected to an initial tension of 1 g and were kept in the organ baths for approximately 1 hour before drugs were tested. Responses of the strips to drugs were measured isometrically with a force-displacement transducer and recorded on a polygraph as changes in tension in grams. The following drugs were used: L-norepinephrine bitartrate (Calbiochem), serotonin creatinine sulfate (Sigma Chemical), L-isoproterenol-D-bitartrate (Sterling-Winthrop Labs), and KCl (Merck and Co., reagent grade). The concentrations of norepinephrine, serotonin, and isoproterenol are expressed in terms of the free base.

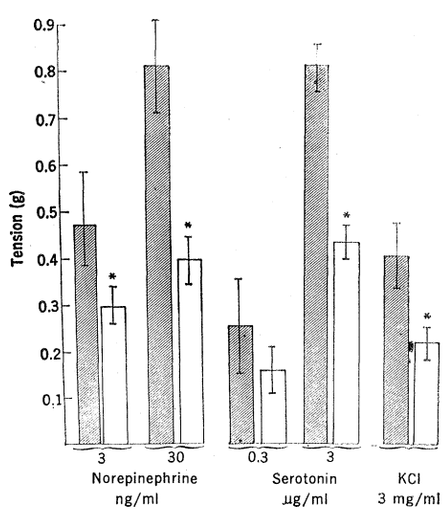

Fig. 1. A comparison of the contractile responses of thoracic aortic strips from five normotensive and nine spontaneously hypertensive rats to norepinephrine, serotonin, and KCl. Data given as means ± standard errors. The asterisks indicate statistically significant differences, $P < .05$. Shaded bars, normotensive animals; open bars, SHR.

The mean systolic blood pressure of nine SHR rats was 174 ± 6 mm-Hg, compared with 122 ± 6 mm-Hg in five normotensive rats. Contractile responses of aortic strips from the SHR to norepinephrine, serotonin, and KCl were less than corresponding responses of aortic strips from the normotensive rats (Fig. 1). The difference was observed not only at the concentrations shown, but over the entire dose-response range. In fact, the maximum contractions of the aortas from normotensive animals were about twice those of the aortas from the SHR (tension, 0.9 compared with 0.5 g).

Thoracic aortas of young rats and rabbits relax in response to stimulation of beta adrenergic receptors whereas aortas from old rats and rabbits lose this response (*6*). Since stimulation of beta adrenergic receptors is in part responsible for vasodilatation in certain vascular beds, we considered that loss of activity of beta adrenergic receptors might be a factor in the production of hypertension in SHR. We compared responses to stimulation of beta receptors of thoracic aortas from SHR and normotensive rats. These tissues were first made to contract with serotonin, and then the relaxation produced by isoproterenol, a beta adrenergic stimulant, was measured. Activity of beta receptors was present in the aortas from each group of rats (Fig. 2). In fact, the responses of aortas from the SHR were greater than those from the normotensive animals.

Vascular smooth muscle from a strain of genetically hypertensive rats is less reactive to specific (norepinephrine and serotonin) and nonspecific (KCl) smooth muscle contractile substances than is comparable tissue from normotensive animals. The mechanism responsible for this abnormality may be related to the intrinsic contractility of the muscle, since all of the agonists were affected to about the same degree. On the other hand, stimulation of beta adrenergic sites in aortas from both hypertensive and normotensive rats with isoproterenol produced the classical relaxation. Thus, hypertension in the SHR is not due to the absence of beta receptors in the vascular tree. Reduction of alpha receptor activity plus slight enhancement of beta activity may be a compensatory mechanism to reduce the elevated blood pressure. Other compensatory mechanisms may be operative in the SHR; for example, the biosynthesis and release of catecholamines are reduced (*7*). However, since the tissue response to a nonspecific stimulant, such as KCl, is depressed, it would seem that in the SHR the responsiveness of the muscle itself to contract is reduced rather than there being a specific modification of the alpha and beta receptors. Schild *et al.* (*8*) have shown an interaction between calcium and stimulating agents, such as epinephrine, and relaxing drugs, such as isoproterenol. The calcium content of vascular smooth muscle from SHR may perhaps be altered so that the effect of a stimulating drug is reduced while that of the relaxing agent is enhanced.

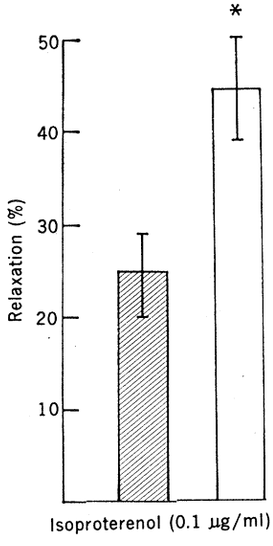

Fig. 2. A comparison of the relaxant beta responses of thoracic aortic strips from four normotensive and seven spontaneously hypertensive rats to isoproterenol. The aortic tissue was made to contract with 3 μg of serotonin per milliliter. Data given as means ± S.E. The asterisk indicates a statistically significant difference, $P < .05$. Shaded bar, normotensive animals; open bar, SHR.

SYDNEY SPECTOR
Roche Institute of Molecular Biology, Nutley, New Jersey 07110
JEROME H. FLEISCH
HARRIET M. MALING
BERNARD B. BRODIE
Laboratory of Chemical Pharmacology, National Heart Institute, Bethesda, Maryland 20014

References and Notes

1. A. N. Brest and J. H. Moyer, *Hypertension—Recent Advances* (Lea and Febiger, Philadelphia, 1961).
2. K. Okamoto and K. Aoki, *Jap. Circ. J.* **27**, 282 (1963).
3. ———, S. Nosaka, M. Fukushima, *ibid.* **28**, 943 (1964).
4. J. R. Williams, T. R. Harrison, A. Grollman, *J. Clin. Invest.* **18**, 373 (1939).
5. R. F. Furchgott and S. Bhadrakom, *J. Pharmacol. Exp. Ther.* **108**, 129 (1953).
6. J. H. Fleisch and H. M. Maling, *Fed. Proc.* **28**, 285 (1969); ———, B. B. Brodie, *Pharmacologist* **11**, 231 (1969).
7. W. J. Louis, S. Spector, R. Tabei, A. Sjoerdsma, *Lancet* **1968–I**, 1013 (1968); *Circ. Res.* **24**, 85 (1969).
8. K. A. P. Edman and H. O. Schild, *J. Physiol. (London)* **169**, 404 (1963); H. O. Schild, *Brit. J. Pharmacol. Chemother.* **31**, 576 (1967).

22 July 1969

Histamine and Spermidine Content in Brain during Development

Abstract. *Histamine concentration in fetal rat brain is high at 17 days gestation but decreases sharply just before birth. Values subsequently increase to a maximum postnatal concentration 5 to 10 days after birth, and then steadily decline to low adult values by time of weaning. Spermidine follows a pattern similar to that of histamine but with a 24- to 48-hour lag. The developmental pattern for histamine in the central nervous system is different from that for other neural amines. It appears that the marked fetal and neonatal changes in brain histamine correlate best with periods of rapid cell proliferation and growth during brain maturation.*

Although histamine occurs in the brain of various species, its function in the central nervous system is unclear. In the brain, histamine is concentrated mainly in the gray matter, and has a regional and subcellular localization analogous to other neural amines having probable transmitter function (*1*). Data obtained from peripheral systems show that increased capacity to form histamine is correlated with periods of greatest mitotic activity in rapidly growing tissues (*2*). The possibility exists that histamine may be involved in growth processes in the central nervous system as well as in neurotransmission. We determined the histamine levels (total histamine, expressed per brain and per gram of brain) in developing rat brain and compared them to levels of other amines and to phases of cell growth and differentiation. Spermidine, which similarly increases in peripheral tissues during rapid growth (*3*), was also measured in developing rat brain.

Sprague-Dawley rats (*4*) obtained at 10 days gestation were kept in individual cages where they gave birth and remained with their litters until the time of weaning. The rats were given free access to water and Purina laboratory chow. All animals were killed by decapitation. To provide a relatively constant sample weight, a varying number of brains were pooled depending on their size. The samples were immediately homogenized in cold 0.4*N* perchloric acid; the homogenate was centrifuged and the supernatant adjusted to *p*H 7.5 with tris(hydroxymethyl)aminomethane. Histamine and spermidine were adsorbed to Amberlite CG-50 (*5*). Columns were then washed with distilled water and eluted with 1*N* HCl. Spermidine was determined by reaction with *o*-phthalaldehyde (*6*). Histamine was extracted from the eluate and assayed by a modification of the method of Anton and Sayre (*7*). The modification entailed the substitution of a potassium phosphate-perchloric acid wash (solution identical to initial extraction media) for the chloroform wash. All samples were read in an Aminco-Bow-

Table 1. Regional changes in histamine during brain development. Each determination represents pooled brain parts from three to five animals of the same litter. Values are expressed as nanograms of histamine per gram of brain.

Brain section	Conceptual age (days)			
	28	32	40	70
Cortex	239	129	47	42
	304		49	44
	286			
Brainstem	172	127	113	94
	188		128	98
	138			
Cerebellum	160	119	56	30
	248		35	32
	195			