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Content in Spreading Factor and Toxins in Organs and Poisonous Secretions of Snakes.

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While moderate amounts of the active spreading factor exist in practically all mammalian tissues[1] as well as those from other zoological groups* the most active products so far described have been associated with cell secretions. These may be noted as follows: (a) secretions endowed with a powerful physiological effect such as those from the testicle of mammals,[3] (b) secretions having anticoagulating powers as that from the leech,[4] (c) toxic secretions exemplified by the venom of certain snakes,[5] (d) soluble substances or secretions from toxic and invasive bacteria (Staphylococcus, Streptococcus, etc.).[6]

The idea suggested by these facts is that the living cells may be only a potential source of the factor, the activity of which does not become manifest until the secretion itself has undergone some change.† With this deduction in mind the secretions of certain poisonous snakes have been tested for their content of spreading and local toxic effect, in comparison with similar properties of extracts of the secreting glands.

Six different species of snakes were used, 4 poisonous and 2 non-

1 Duran-Reynals, F., *J. Exp. Med.*, 1929, **50**, 327; Claude, A., and Duran-Reynals, F., *J. Exp. Med.*, 1934, **60**, 457.

* Moderate amounts of spreading factor have been demonstrated in several species of birds, fish, lizards, newts, frogs, toads, snails, and harmless insects.[2, 5]

2 Duran-Reynals, F., unpublished observations.

3 Duran-Reynals, F., *C. R. Soc. Biol.*, 1928, **99**, 6; *J. Exp. Med.*, 1929, **50**, 327; Hoffman, D. C., and Duran-Reynals, F., *J. Exp. Med.*, 1931, **53**, 387; McClean, D., *J. Path. and Bact.*, 1931, **34**, 459.

4 Claude, A., *J. Exp. Med.*, 1937, **66**, 353.

5 Duran-Reynals, F., *Science*, 1936, **83**, 286; *J. Exp. Med.*, in press.

6 Duran-Reynals, F., *J. Exp. Med.*, 1933, **58**, 161; McClean, D., *J. Path. and Bact.*, 1936, **42**, 477.

† The supposition outlined above is supported by experiments that indicate that some tissues are potential sources of large amounts of spreading factor. This factor may be liberated under certain conditions such as autolysis (*in vitro*) of rabbit's brain,[2] experimental intestinal obstruction in the same animal,[2] and certain bacterial infections.[2] The malignant transformation of a tissue also results in a marked increase of spreading factor.[7, 8]

7 Duran-Reynals, F., and Stewart, F. W., *Am. J. Cancer*, 1931, **15**, 2790.

8 Boyland, E., and McClean, D., *J. Path. and Bact.*, 1935, **41**, 553.

poisonous. The potency of the spreading factor in venom, blood serum and tissue extracts of these snakes was determined. The tissues were ground and extracted with 1 or 10 volumes of saline and the resultant pulps were centrifuged. From the supernatant fluids as well as from the blood serum and the venom, progressive dilutions were made in saline. In 3 of the experiments dealing with poisonous snakes the venom gland was cut with scissors and thoroughly washed with saline in order to remove all traces of secreted venom.

Two parts of each dilution were mixed with one part of India ink diluted 1:2, and 0.75 cc of each of the mixtures were injected intradermally in one side of rabbits. In these injections the India ink served as an indicator of the area of spreading of the mixtures. The same injections were repeated in the other side of the same animal using saline solution in place of the India ink, in order to be able to judge the severity of the resultant lesions uncomplicated by the presence of the ink. A mixture of 0.50 cc of saline plus 0.25 cc of ink was always injected as a control. Results after 24 hours are recorded in Table I.

The results shown in Table I seem to warrant the conclusion that the spreading and toxic power of extracts of the poison gland are much lower than the spreading and toxic power of its secretion, the venom. This difference is still more marked when the gland has been cleansed of any secreted venom adherent to its tissue. The fact that washing removes much of the toxicity suggests that traces of venom still remaining in the excretory ducts are responsible for at least part of the toxicity still shown by gland extract. Extracts of the poison gland at 1:1 dilution have a toxic and spreading effect only slightly superior to that shown by dilutions of the venom at 1:1000. The content of spreading factor of the poison gland does not seem to be greater than that found in other tissues of the snake.

The results show that there is a close correlation between the strength of the spreading factor and the toxicity of the venom or extracts of the poison gland. This is in line with our previous observation[5] which was that both spreading and toxic power of the venom are neutralized by the specific antiserum. The present findings suggest that both spreading factor and toxicity are a product rather than a component of the gland cell.

The table also shows that the spreading factor exists in moderate amount in the extracts of most tissues from both poisonous and non-poisonous snakes. Testes, from snakes yield no more of the factor than the other tissues which is contrary to the findings in mammals.

TABLE I.

Content in Spreading Factor and Toxin in Salivary Secretion and Tissues of Poisonous and Nonpoisonous Snakes Tested by Intradermal Injections in the Rabbit.

	Areas of spread and lesions produced by injection of .50 cc tissue extr. of venom + .25 cc India ink or saline sol. Dilution injected				Area of spread of .50 cc of saline + .25 cc India ink
	1:1 cm²	1:10 cm²	1:100 cm²	1:1000 cm²	
Rattlesnake poison gland 1st Exp., not washed		52.8 mod. severe	41.1 mild	6.5 no lesion	6.7
Same washed, 2nd Exp.	35.5 mild	14.1 very mild	10.0 very mild	8.1 " "	6.9
Same washed 3rd Exp.	39.0 "	15.2 " "	11.6 " "	9.6 " "	7.8
Water moccasin poison gland, washed	20 mod. severe	7.1 mild	7.0 mild	8.2 very mild	5.8
Pine snake supralabial gland		12.9 no lesion	5.5 no lesion	5.1 no lesion	5.0
Chicken snake supralabial gland		30.0 " "	10.0 " "	6.0 " "	5.0
Pine snake ovary		6.1 " "	6.0 " "	6.0 " "	6.1
" " spleen		15.5 " "	8.6 " "	4.5 " "	4.5
" " musele		4.7 " "	4.5 " "	4.0 " "	4.2
Rattlesnake, chicken snake testicle (avg)		8.5 " "	6.0 " "	6.1 " "	6.1
Rattlesnake, chicken snake, and pine snake liver (avg)		18.5 " "	7.5 " "	6.1 " "	6.0
Rattlesnake, chicken snake, and pine snake pancreas (avg)		14.0 mild	8.8 " "	5.8 " "	5.8
Rattlesnake, chicken snake, and pine snake blood serum (avg)		10.5 "	6.8 " "	6.2 " "	5.8
Rattlesnake, chicken snake, and pine snake kidney (avg)		12.1 no lesion	9.7 " "	5.8 " "	5.8
Water moccasin venom		90.0 very severe	45.0 severe	15.1 mild	7.6
Rattlesnake venom (avg 6 tests)		150 ext. severe	95.0 very severe	30 mod. severe	6.3

On the other hand blood serum of snake shows some activity while that of mammals is practically inactive.

Summary. Spreading factor and venom are found only in negligible amounts in the secreting cells of the venom gland of snakes. As both the factors appear together in the secretion they either act together as a unit or are the same substance. The spreading factor in moderate amounts exists in most tissues from both poisonous and harmless snakes.

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Cerebral Mechanisms in Auditory Localization.*

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Bikov[1] has reported that following complete transection of the corpus callosum it was possible to condition a dog to salivate to the sound of a whistle placed at the level of, and some distance from, the left ear. He was unable to subsequently develop a discrimination so that the animal did not salivate to the same stimulus sounded from its right side. Pavlov[2] concluded from this study that "a differentiation of the direction of a sound required a united activity of both hemispheres."

Bikov's data and Pavlov's interpretation are consistent with the view that hearing is crossed. That is, impulses produced in the left cochlea end in the right hemisphere, while those impulses originating in the right cochlea terminate in the left hemisphere. Since both ears are essential for the correct localization of sounds in space (L-R habit), destruction of the corpus callosum would prevent the integration of the impulses produced in the peripheral mechanisms. From this logic, it would also follow that extirpation of the auditory cortex of one hemisphere (temporal lobe) would have the same effect as does the destruction of one cochlea.

Recent studies, however, indicate that this view is incorrect. Results procured in the dog[3] and the cat[4] support the contention that

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1 Bikov, K. M., and Speransky, A. D., *Col. Papers, Physiol. Labs. of I. P. Pavlov*, 1924, **1**, 150.

2 Pavlov, I. P., *Conditioned Reflexes*, Oxford University Press, 1927, p. 150.

3 Mettler, F. A., Finch, G., Girden, E., and Culler, E., *Brain*, 1934, **57**, 475.

4 Brogden, W. J., Girden, E., Mettler, F. A., and Culler, E. A., *Am. J. Physiol.*, 1936, **116**, 252.