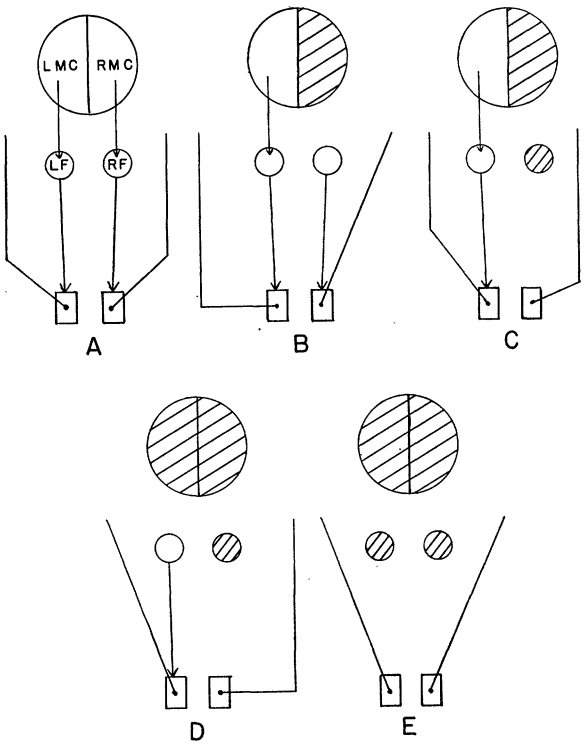

FIG. 1.

of tonus is present in the leg of the contralateral side. Subsequent removal of the fastigial nucleus (*RF*) on the side of previous cortical ablation gives an immediate and clear-cut reversal of the cortical picture (Fig. 1, *C*).

The effects following removal of the remaining cortex of the anterior lobe, and its fastigial nucleus are illustrated in *D* and *E*. The bilateral augmentation of extensor tone seen in *E* is identical with that following bilateral destruction of cortex only.

These effects are related only to median or vermian cortex of the anterior lobe and to the fastigial nuclei. The lateral or hemispheric anterior lobe cortex and its nuclei of projection, the so-called interpositus nuclei, are relatively inoperative on postural tone under these conditions. Their stimulation, however, gives ipsilateral, moderate extension and wrist supination, followed by a rebound of opposite direction. Stimulation of the medial area confirms the usual picture previously described, involving contralateral as well as ipsilateral forelegs in a reciprocal manner.

The general conclusions from this work are as follows:

1) Imposed upon a background of decerebrate rigidity, one half of the medial cortex of the anterior lobe, or its fastigial nucleus, always influences postural tone in the forelegs in a reciprocal manner. An increase in extensor tonus in one leg is accompanied by extensor decrease in the contralateral leg. Flexor tone, although less marked, follows in each leg reciprocally.

2) The effect of removal of this cortex is reversed by removal of its fastigial nucleus. This nuclear picture has hitherto been unrecognized, and makes necessary considerable alteration in the concept of cerebellar function.

3) These results, obtained in acute preparations, have been completely confirmed in chronic animals with unilateral cerebellar lesions produced 3 weeks previous to decerebration.

4) The picture following unilateral cortical removal is thus the same as that of extensor rebound following electrical stimulation of cortex or nucleus. The picture following subsequent unilateral nuclear removal is similar to that occurring during the stimulus of cortex or nucleus (i.e., extensor inhibition accompanied by flexion).

5) The release of this nuclear effect following cortical removal indicates an important afferent supply, other than from the anterior lobe cortex, which allows independent function of the fastigial nucleus.

6) Additional acute experiments indicate that the postural effects described above are intact following unilateral and bilateral destruction of the labyrinths, of the dorsal roots of the first three cervical nerves, after hemisection and transection of the thoracic spinal cord, and after previous removal of all parts of the cerebellum except the anterior lobe and the fastigial nuclei.

7) The distribution of tone in the forelegs is similar following bilateral destruction of cortex and nuclei to that following bilateral destruction of cortex alone. The opposite postural effects of cortex and fastigial nucleus are apparent after unilateral lesions only, and would appear to be a manifestation of an imbalance in the reciprocal distribution of tone, dependent upon the unilaterality of the lesions, and centered at a spinal level.

The Pharmacologic Analysis of Intestinal Stimulants[1]

Sydney Ellis

Department of Pharmacology,
Temple University School of Medicine,
Philadelphia, Pennsylvania

A recent report from this laboratory dealt with the inability of even high concentrations of atropine to interfere with the stimulating action of nicotine on the isolated intestine of the rabbit (*1*). Although this observation may be found in the literature (*2*), it is quite evident that the rabbit's intestine has been used for testing the ability of atropine to antagonize stimulating actions of drugs on this preparation without a knowledge of the above information. The widely accepted concept that the stimulating action of nicotine on the intestine is antagonized by atropine appears true in reference to other animals. This has been con-

[1] This work was supported in part by a grant from the Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Association.

firmed on intestinal strips obtained from guinea pigs, rats, dogs, and cats. On the basis of these observations a revaluation of certain data in the literature concerning the sites of action of several intestinal stimulants is needed.

Evidence that a substance stimulates the intestine of the rabbit and that this action is "atropine-fast" indicates only that the substance is not "muscarinic" and does not differentiate between "musculotropic" and "nicotinic" modes of action. On the other hand, a stimulating action on the guinea pig's intestine which is inhibited by atropine indicates musculotropic action but does not distinguish between actions which are either muscarinic or nicotinic.

For examples of different types of intestinal stimulants we have reinvestigated 3 compounds, whose sites of actions on the intestine do not appear sufficiently clear from the data available. Furfuryltrimethylammonium iodide (Furmethide) was reported (*3*) to have nicotinic action on the blood pressure of atropinized animals and to have a stimulant action on the rabbit's intestine which could be inhibited by atropine. Piperidine has been reported to stimulate the intestine (*4*). Von Euler considered the actions of piperidine similar to, but less potent than, those of nicotine. On the rabbit's intestine atropine did not inhibit the action of piperidine. Lockett (*5*) described the action of piperidine on the guinea pig intestine as muscarinic, based upon the ability of atropine to interfere with its stimulating action on this tissue. A recent abstract (*6*) indicated that a purified extract of Veratrum Viride (Veriloid®) increased the tone of the isolated rabbit's intestine. This action was not prevented by previous treatment with atropine.

The actions of Furmethide, piperidine, and veratridine[2] were compared with the actions of acetylcholine and nicotine on the isolated, atropinized intestines of rabbits and guinea pigs in order to determine the classification of these stimulants of the intestine. The data are summarized in Table 1.

TABLE 1

ACTION OF INTESTINAL STIMULANTS IN THE PRESENCE OF ATROPINE (1: 1,000,000)

Drug	Conc.	Intestine of	
		Rabbit	Guinea pig
Acetylcholine	$1:10^6$	No action	No action
Nicotine	$1:10^6$	Stimulates	"
Furmethide	$1:10^6$	No action	"
Piperidine	$2:10^5$	Stimulates	"
Veratridine	$1:10^6$	"	Stimulates

Since Furmethide is unable to stimulate the atropinized intestine of either the rabbit or the guinea pig, it is justifiable to call its effect muscarinic. Piperidine then appears as a nicotinic agent. Further evidence favoring a nicotinelike action for piperidine is that large amounts of nicotine prevent the stimulating action of piperidine (but not that stimulation due to acetylcholine nor to Furmethide).

Veratridine stimulates the intestine in a manner that can be classified as neither muscarinic nor nicotinic. Its stimulating action is not blocked by atropine on intestinal strips from either the rabbit or the guinea pig. Furthermore, high concentrations of nicotine which produce ganglionic blockade do not prevent the action of veratridine. Amounts of D-tubocurarine sufficient to prevent the action of stimulating amounts of nicotine, do not prevent the action of veratridine.

The mechanism of action of an agent which stimulates the isolated intestine can be analyzed quite simply as muscarinic, nicotinic, or musculotropic by the expedient of using atropinized intestines of both the rabbit and the guinea pig. Results obtained with the intestine of only one of these species are misleading.

[2] A pure sample of veratridine was obtained through the kindness of Otto Krayer, of the Harvard Medical School.

References

1. ELLIS, S., and RASMUSSEN, H. *Federation Proc.*, **10**, 292 (1951).
2. VON EULER, U. S. *Acta Physiol. Scand.*, **7**, 285 (1944).
3. FELLOWS, E. J., and LIVINGSTON, A. E. *J. Pharmacol. Exptl. Therap.*, **68**, 231 (1940).
4. VON EULER, U. S. *Acta Pharmacol. Toxicol.*, **1**, 29 (1945).
5. LOCKETT, M. F. *Brit. J. Pharmacol.*, **4**, 111 (1949).
6. COURZIE, J. T., and BAUER, R. O. *J. Pharmacol. Exptl. Therap.* (abst.), **101**, 14 (1951).

The Bacterial Oxidation of Tryptophan: A Study in Comparative Biochemistry[1]

R. Y. Stanier and O. Hayaishi[2]

Department of Bacteriology, University of California, Berkeley

As discovered independently by several workers (*1–3*), the analysis of adaptive patterns is of much value in the study of microbial metabolism. This technique (sometimes referred to as "simultaneous adaptation" or as "successive adaptation") is essentially an extension and refinement of the technique of kinetic analysis, and may be used to study the course of any microbial metabolic process that is under adaptive enzymatic control (*4*).

One of the specific problems that has been investigated primarily by the analysis of adaptive patterns is the pathway for the complete oxidation of tryptophan by bacteria belonging to the *Pseudomonas* group. Suda, Hayaishi, and Oda (*2*) found that an unidentified *Pseudomonas* sp.[3] adapted to oxidize tryptophan was also fully adapted to oxidize kynurenine, anthranilic acid, and catechol, but not to

[1] This work was supported by grants-in-aid from the Rockefeller Foundation, and from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council. We are indebted to R. E. Kallio, W. C. Evans, D. Bonner, T. Sakan, and the Research Division of Merck & Co., Inc., for gifts of chemicals, and to S. H. Hutner for the provision of biological material. In addition, we wish to express our thanks to Martha Tsuchida for help with many experiments.

[2] Present address: National Institutes of Health, Bethesda, Md.

[3] This organism has been subsequently identified by us as a typical member of the *P. fluorescens* species group.