ferrets not only inhibited strain "Long," but also strain "CH 18537" to about the same titer (1:32 to 1:256). In contrast, we never achieved an increase of the low titer (1:8 to 1:12) to the heterologous virus strain, even after 3 reimmunization cycles.

The antigenic behavior of the RS viruses is in some respects similar to those of the parainfluenza viruses(4). Both parainfluenza type 1, Sendai and HA-2 viruses were substantially neutralized in tissue cultures only by homologous antiserum. Heterologous strains were only slightly neutralized, or not at all. In complement-fixation test, however, Sendai proved to have a broader spectrum than HA-2.

An explanation for this variance has been proposed. Cook *et al*(4) believe that each member of the group possesses a complex of antigens sharing similar chemical configuration, but yet differing in each in a way imparting antigenic specificity. They develop the hypothesis that antigenic fractions shared between virus strains are not equally distributed quantitatively. We can only propose that from time to time a slight change in chemical configuration occurs among RS viruses contributing to different antigenic responses. Further evidence is required to substantiate this proposition.

Summary. Evidence is presented of antigenic heterogeneity between prototype "Long" and "87" strains of RS virus. In cross neutralization tests with animal antisera only the homologous virus strain was inhibited to high titer, while the SDE for the heterologous remained very low, even after 3 or 4 immunization cycles. Human sera failed to reveal disparity. Both strains shared a common CF antigen.

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Received October 14, 1963. P.S.E.B.M., 1964, v115.

Comparative Resistance of Vagotomized Monkeys to Intravenous vs. Intragastric Staphylococcal Enterotoxin Challenges.* (28881)

H. SUGIYAMA AND T. HAYAMA†

Food Research Institute and Department of Microbiology, University of Chicago, Chicago, Ill.

Vomiting induced in monkeys and cats is the pharmacological response employed in detection of staphylococcal enterotoxin. Parenteral administration of enterotoxin is required with the cat since vomiting is not provoked by feeding of relatively large amounts of enterotoxin. Monkeys, however, are sensitive to intragastrically (i.g.) administered enterotoxin(1).

Studies on the emetic receptor sites for staphylococcal enterotoxin have utilized both animal species. The incidence of vomiting was greatly reduced in the acute, bilaterally vagotomized cats injected intraperitoneally with heated, crude, enterotoxic filtrates, suggesting the existence of receptors in the viscera innervated by the vagus(2). Transthoracic vagotomy of cats did not confer complete protection against intravenous (i.v.) challenge of a highly purified enterotoxic preparation but resulted in a significant elevation of the threshold dose for emesis(3). The data presented suggest that the ED_{50} (50% emetic dose) may have been increased about 5 times.

* Supported by grant from U.S. Public Health Service.

† Permanent address: Laboratory of Pharmacology and Toxicology, Inst. of Food Microbiology, Chiba Univ., Japan.

Considerably higher tolerance than in cats was observed in monkeys subjected to vagotomy at the level of the diaphragm (abdominal approach) and challenged with enterotoxin by the i.g. route. Some of the vagotomized monkeys did not respond to 100 times the dose to which the animal should have responded without surgery; other animals vomited after administration of 30-40 times the pre-operative threshold dose(4).

The present study is concerned with the possibility that the greater degree of refractoriness to enterotoxin-induced emesis obtained in vagotomized monkeys than in cats is due to the route of administration of the challenging dose. Vagotomy was accomplished at the supradiaphragmatic level; complete vagotomy is more easily accomplished by this procedure than by the abdominal approach.

Materials and methods. *Macaca mulatta* of about 2 kg body weight were subjected to bilateral vagotomy below the heart in the thoracic cavity under nembutal anesthesia and artificial respiration. Emetic challenges were made after 3-4 weeks post-surgical rest. After completion of tests given at 1-2 week intervals, the monkeys were sacrificed and completeness of vagotomy verified by gross examination.

Two immunologically different enterotoxin types were used. I.v. injections were performed with Enterotoxin B sample of 95% purity possessing ED_{50} for normal animals of 20 μg/animal, i.g., and 0.8 μg/kg, i.v. The *per os* challenges with Enterotoxin B were with this sample or with another preparation of approximately 70% purity and i.g. ED_{50} of 50 μg/animal. Feeding tests alone were made with Enterotoxin A since only a 20% purity preparation with ED_{50} of 50 μg/animal was available.

The minimal emetic dose (MED) of enterotoxin for each animal was established from pre-operative feeding or injection as previously described(4,5). Enterotoxin dosages for the post-operative tests were calculated as the number of MED's by the selected route of challenge for the given animal at time of challenge, assuming no surgical intervention and compensating for the immunity resulting from prior administrations of enterotoxins.

TABLE I. Emetic Response of Vagotomized Monkeys to Intravenously and Intragastrically Administered Staphylococcal Enterotoxins.

	Enterotoxin challenges*		
	Intravenous	Intragastric	
Monkey #	B	A	B
1			Resist 40
2			" 50
3			" 70
4	Resist 2	Resist 50	
5	" 5	Not resist 70	
6	" 5	" " 70	Resist 30
7	" 7	Resist 70	" 20
8	Not resist 7	" 70	" 40
9	" " 10	" 70	" 20
10	Resist 5	Not resist 70	
11	Not resist 10	" " 60	

* Number of minimal emetic doses of respective serological type of enterotoxin to which given animal should have vomited without vagotomy.

The effect of vagotomy on the response of monkeys to 2 other emetics effective by i.g. administration was studied. Copper sulfate was used as an emetic which acts through receptors in the gastrointestinal tract(6,7) and Veriloid (veratrum alkaloid, Riker Laboratories) was tested as an emetic acting elsewhere than the gastrointestinal tract. In the cat the emetic triggering site of Veriloid is the nodose ganglion(8).

Results. The emetic responses of vagotomized monkeys to staphylococcal enterotoxin challenges are shown in Table I. The initial experiments (monkeys 1-3) confirmed the previously reported(4) high tolerance to feeding of enterotoxin after vagal interruption.

Monkeys 4-11 were first given i.v. challenges of the highly purified Enterotoxin B with subsequent oral administration of Enterotoxin A. Four of these animals were then tested against i.g. Enterotoxin B. Because of the unknown degree of immunity developed in animals treated in this manner further enterotoxin tests were not possible.

The data indicate that vagotomy of monkeys confers a degree of tolerance to i.v. challenge of enterotoxin which is significant but minor compared to the refractoriness developed against i.g. administered enterotoxin. The post-operative ED_{50}, i.v., is about 7

times the dose to which the animals should have vomited without vagotomy. By comparison, the post-operative, i.g., ED_{50} is about 70 times higher than the minimal doses estimated to be effective for animals without surgical intervention. Nevertheless, the tolerance developed in vagotomized monkeys against the i.g. challenge of enterotoxin is not complete. The degree of increase in the i.g. threshold dose for vomiting was more consistent in the present than in the previously reported series(4) but the general conclusion of high resistance is the same. Only Enterotoxin B was used for i.v. tests but there is no reason to assume that the results with Enterotoxin A would be different.

All of the animals were tested for the effect of vagal transection on the response to i.g. $CuSO_4 \cdot 5H_2O$. Only monkeys vomiting preoperatively within 45 minutes in response to 320 mg of this salt were vagotomized; after vagotomy they still vomited with the same dose but the latency was increased 2-5 times. Thus, vagotomy alone has only a minor influence on the sensitivity of monkeys to an emetic whose receptor sites reside in the gastrointestinal tract.

Vagotomy did not greatly affect the i.g. sensitivity of monkeys to an emetic which probably acts through receptors other than the gastrointestinal tract. Eight normal monkeys responded to 1.5 mg/kg, i.g., of Veriloid with an average latency of 65 minutes. All of the 6 vagotomized monkeys tested vomited with the same dose, the latency being reduced to 40 minutes. The results with $CuSO_4$ and Veriloid show that vagotomy does not significantly influence the motor portion of the vomiting reflex.

Discussion. The refractoriness to staphylococcal enterotoxin-induced emesis exhibited by vagotomized monkeys is significantly higher against intragastric than against intravenous challenges. The difference may arise from an effect of vagotomy which is unrelated to interference with the sensory pathway of the vomiting reflex. The sensitivity of normal cats to i.v. enterotoxin compared to the high resistance to i.g. administration suggests a gastrointestinal barrier, including digestive degradation of enterotoxin. The inactivation may be comparatively unimportant in the normal monkey, but atony and slower emptying time in the upper gastrointestinal tract following vagotomy(9) could increase the chances of this inactivation. Thus, a part of the increase in the threshold dose for vagotomized monkeys challenged with enterotoxin *per os* could be due to increased destruction of enterotoxin.

Emetic receptor sites for enterotoxin may be situated along the greater part of the gastrointestinal tract. Vagotomy would interrupt the sensory pathway for emesis for the upper portion, resulting in some increase in tolerance. The concomitant increased inactivation of enterotoxin due to the longer time required to reach the still innervated receptors in the lower part of the gastrointestinal tract, as postulated above, would augment further the threshold emetic dose for intragastric challenge. Enterotoxin injected i.v. presumably would be carried directly to the still innervated receptors without digestive breakdown and only a small increase over the preoperative threshold dose would be required for post-operative vomiting.

Vomiting responses of vagotomized monkeys to i.g. copper sulfate and Veriloid are in agreement with this explanation. The longer latency for vomiting with $CuSO_4$ in the vagotomized monkeys could represent the increased time required to reach the lower intestine. The responsiveness to i.g. Veriloid would not be greatly reduced since the receptors for emesis probably lie elsewhere than the gastrointestinal tract(8).

All the symptoms of staphylococcal food poisoning need not originate from action of enterotoxin on a single type of receptor. Activation of receptors other than the primary emetic receptors by small doses of i.g. enterotoxin may not exceed the threshold level sufficient to provoke emesis as a secondary effect, but under challenge with large amounts of enterotoxin or in special situations such as reticulo-endothelial system blockade(10) vomiting originating from other than the primary emetic receptors may occur. This may account for the comparatively high but incomplete resistance of vagotomized monkeys to i.g. enterotoxin. I.v. enterotoxin

could act more directly on these other receptors so that only a low degree of protection would result.

The results with vagotomized monkeys reported in this communication after i.v. challenge are in general agreement with the findings in vagotomized cats given enterotoxin by the same route(3).

Summary. Rhesus monkeys subjected to transthoracic vagotomy were challenged with staphylococcal enterotoxin and observed for vomiting. A significantly higher tolerance was shown against intragastric administration than against intravenous injection of enterotoxin. Complete protection was not obtained even against oral challenge. Responsiveness to enterotoxin-induced emesis in vagotomized monkeys and cats is similar if the challenge is by the intravenous route.

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Received October 14, 1963. P.S.E.B.M., 1964, v115.

Antibodies in Systemic Lupus Erythematosus and Myasthenia Gravis Which React with Thermally Denatured DNA-Coated Bentonite. (28882)

BENJAMIN C. STURGILL, ROBERT R. CARPENTER, ARTHUR J. L. STRAUSS AND HOWARD C. GOODMAN

Laboratories of Clinical Investigation and Immunology, National Institute of Allergy and Infectious Diseases, N.I.H., P.H.S., D.H.E.W., Bethesda, Md.

Antibodies to native deoxyribonucleic acid (DNA) have been demonstrated in the sera of some patients with systemic lupus erythematosus (SLE) by several techniques including precipitation, complement fixation, and aggregation of tanned red blood cells or of bentonite particles coated with native DNA(1,2,3,4). The diagnostic usefulness of these tests has been limited by the low incidence of anti-DNA antibodies detected.

Levine *et al*(5) first reported enhanced immunologic reactivity of DNA after thermal denaturation. Stollar *et al*(6) have shown by complement fixation that sera from patients with SLE react with thermally denatured DNA more frequently than they react with native DNA. Because of its technical simplicity, we have employed a modification of the bentonite particle technique described by Bozicevich *et al*(4) to compare the reactivity of native and thermally denatured DNA with sera from patients with SLE and certain other diseases.

The finding by White and Marshall(7) of an antinuclear antibody in some patients with myasthenia gravis led us to look for antibodies to thermally denatured DNA and certain other antibodies in the sera of patients with this disease.

Materials and methods. Serum. Most sera were kept frozen for various periods up to several months prior to testing. Some of the sera from the patients with myasthenia gravis had been kept at 4°C for several months.

Native DNA bentonite test. The method of Bozicevich *et al*(4) was used.

Thermally denatured DNA bentonite test.