Transmembrane potentials recorded from rabbit sinoatrial node before and after perfusion with histamine 10^{-6} g/ml[a]

	AR/min	AP (mV)	MDP (mV)	TP (mV)	MDP-TP (mV)	SPP (mV/sec)	DAP_{50} (sec)
Controls (137)	109 ± 1.3	56 ± 1.1	55 ± 0.8	47 ± 0.8	8 ± 0.3	24 ± 0.7	115 ± 2.1
Histamine (40)	154 ± 2.2	58 ± 1.7	52 ± 2.3	33 ± 1.7	20 ± 1.0	132 ± 6.4	112 ± 4.6

[a] Mean values ± S.E.; No. of observations in parentheses.

about 10 times and the following measurements were made of the projected image: AR = atrial rate; AP = amplitude of the action potential; MDP = maximum diastolic potential; TP = threshold potential; MDP-TP = amplitude of the pace-maker potential; SPP = slope of the pace-maker potential; DAP_{50} = duration of the action potential measured at 50% of its height.

Histamine 10^{-6} g/ml produces a positive chronotropic effect associated with a sharp increase in the spontaneous depolarization rate, as qualitatively shown in the Figure. The quantitative effects of histamine action have been evaluated by comparing the data obtained from several cells, before and after histamine treatment. Mean values of 40 pace-maker cell potentials recorded during histamine treatment in 13 experiments are shown in the Table, where they are compared with the values of 137 potentials recorded in the same experiments before administration of the drug. The AR, SPP and MDP-TP of the pace-maker potential are markedly enhanced, the TP is reduced, while the AP, DAP and MDP do not show appreciable variations. All these changes are statistically significant ($p < 0.001$).

Our findings show that histamine has an effect on heart sinoatrial node cells consisting of an increase in generator potential steepness. This action produces an increase in frequency discharge of both impaled pace-maker and atrial cells, as revealed by surface electrograms. Moreover, our results suggest a possible explanation for the positive chronotropic effect of histamine which is released during heart anaphylaxis in vitro[7-9].

Riassunto. È stato dimostrato che l'istamina ha un effetto sulle cellule del nodo seno-atriale del cuore di coniglio. Tale effetto consiste in un marcato aumento della velocità di depolarizzazione del potenziale «pace-maker», cui consegue un effetto cronotropo positivo.

R. Levi[10] and A. Giotti

IV Gruppo dell'Impresa di Elettrofisiologia del C.N.R. presso l'Istituto di Farmacologia dell'Università di Firenze (Italy), July 25, 1966.

[8] P. F. Mannaioni, R. Levi, and A. Giotti, Boll. Soc. ital. Biol. sper. *37*, 1134 (1961).
[9] A. Giotti, A. Guidotti, P. F. Mannaioni, and L. Zilletti, J. Physiol., Lond. *184*, 924 (1966).
[10] Present address: Cornell University Medical College, Department of Pharmacology, New York (N.Y. 10021, USA).

Bowel Serotonin Levels in the Fasted and Non-Fasted Sprague-Dawley Rat

The gastrointestinal tract of the rat contains approximately 60% of its total body serotonin[1]. The majority is present in the mucosa[2,3], where it arises from the argentaffin cells[4]. Levels of the amine have been reported frequently and in a variety of animals[5,6], however its functional significance is unknown. Unambiguous reports of the effects of feeding or fasting on bowel serotonin levels were not to be found in the literature, yet in evaluating the effects of drugs or in vitro studies the effects of antecedent feeding or fasting might be important. Certainly gastroduodenal histamine levels are significantly elevated after fasting in rats[7].

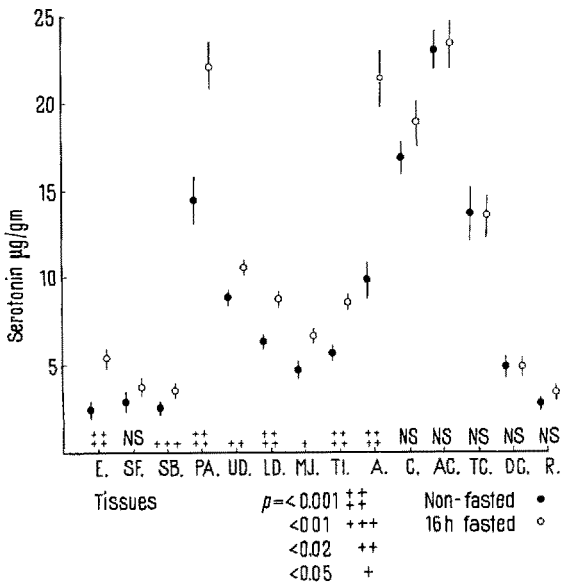
The results of our experiments with female Sprague-Dawley rats offer proof that a 16 h fast increases the bowel mucosal serotonin levels significantly in 8 of the 14 tissues studied. Details of our method of tissue preparation (and its efficacy) and spectrophotofluorometric analysis have been published elsewhere[2].

40 Charles River female Sprague-Dawley rats weighing between 220 and 290 g were fed Purina laboratory chow, with a tryptophan content of 0.22%. The rats were randomly allocated to 2 groups. To avoid any possible circadian influences – to date only reported for brain[8] – rats were always assayed between 08.30 and 10.00 h. The rats in group 1 were assayed after an overnight (16 h) fast, while rats in group 2 had ad libitum access to both food and water prior to assay. The tissues sampled were: esophagus, stomach fundus, stomach body and pyloric antrum, upper and lower duodenum, mid-jejunum, terminal ileum, appendix, cecum, ascending, transverse, and descending colon, and proximal rectum. Serotonin was

[1] V. Erspamer, Experientia *10*, 471 (1954).
[2] J. H. Thompson and L. B. Campbell, Ir. J. med. Sci., in press.
[3] W. Feldberg and C. C. Toh, J. Physiol., Lond. *119*, 352 (1953).
[4] E. P. Benditt and R. L. Wong, J. exp. Med. *105*, 509 (1957).
[5] V. Erspamer, Experientia *2*, 369 (1946).
[6] V. Erspamer, *Ciba Foundation Symposium on Hypertension* (Little Brown and Company, Boston 1954), p. 78.
[7] A. Kahlson, E. Rosengren, D. Svahn, and R. Thunberg, J. Physiol., Lond. *174*, 400 (1964).
[8] W. B. Quay, Life Sci. *4*, 379 (1965).

assayed by BOGDANSKI's method[9]. Results were calculated from a graph drawn daily from standard serotonin solutions (prepared in 0.1 *N* HCl) and a reagent blank (0.1 *N* HCl), both of which were carried through the extraction procedure. Values are expressed as μg/g mucosa (wet weight).

The 2 groups of rats are shown in the Figure. Each point represents the mean of 15–20 estimations. Differences between the mean values for each tissue in the fasted and non-fasted rats were determined using the Student *t* test. With the exception of the stomach fundus, all the tissues from the esophagus to the appendix in the fasted rats demonstrate an increase in mucosal serotonin compared to the non-fasted animals. The largest increase is seen in the pyloric antrum and appendix, while the amine levels from the cecum to the rectum are similar in both groups.



Mean values ± 1 S.E. for esophogeal (E), stomach fundus (SF), stomach body (SB), pyloric antrum (PA), upper and lower duodenum (UD, LD), mid-jejunum (MJ), terminal ileum (TI), appendix (A), cecum (C), ascending, transverse and descending colon (AC, TC, DC), and proximal rectum (R), serotonin in fasted and non-fasted rats. Each point is the mean of 15–20 estimations, and the *p* value (determined with the Student *t* test) for each pair is indicated.

The physiological function of bowel serotonin is unknown. However, the most likely role appears to be associated with peristalsis[10,11]. It is interesting therefore, that in the proximal gastrointestinal tract, which is relatively empty after a 16 h fast (the rodent colon being more resistant to depletion of food residues than the small bowel), higher levels of serotonin are evident. These higher mucosal serotonin levels may assume importance when evaluating the in vivo and in vitro effect of drugs[12].

Zusammenfassung. Der Serotoningehalt der Darmmucosa aus 14 Schnittpräparaten von Sprague-Dawley Rattenweibchen nach 16-stündigem Fasten und nach normaler Fütterung wurde bestimmt. Grössere Serotoningehalte wurden im oberen Teil des Verdauungstraktus (ausschliesslich den Magenblindsack) der Hungertiere gefunden.

J. H. THOMPSON and L. B. CAMPBELL

Department of Pharmacology, University of California School of Medicine, Los Angeles (California 90024, USA), June 17, 1966.

[9] D. F. BOGDANSKI, A. PLETSCHER, B. B. BRODIE, and S. UDENFRIEND, J. Pharmac. *117*, 82 (1956).
[10] E. BÜLBRING and A. CREMA, Br. J. Pharmac. *13*, 444 (1958).
[11] E. BÜLBRING and A. CREMA, J. Physiol., Lond. *146*, 18 (1959).
[12] This research was supported by Grant No. AM 07909 from the United States Public Health Service.

Effect of the Mast Cell Disruptor B.W. 48/80 on Dietary Atherosclerosis in the Male Rabbit

It has been claimed that there is a relationship between tissue mast cell population and the incidence of atherosclerosis[1]. Studies have been carried out in our laboratory[2] and in another laboratory[3] to determine the role of the mast cells on the development of atherosclerosis in the rat. The synthetic polymer compound 48/80 (Burroughs Welcome Inc.), a drug having mast cell depletion properties, was used[4]. Rats fed high cholesterol diet and injected with compound 48/80 for 3 months or longer failed to demonstrate atherosclerosis[2,3] and showed an increase in the lipoprotein lipase activity of the arterial wall (aorta)[5].

To test further the hypothesis that compound 48/80 protects against the development of atherosclerosis, experiments were carried out on rabbits – animals in which atheroma is easily produced by dietary means. 32 male rabbits of undetermined strain with an initial body weight of about 1600 g, were distributed in 6 groups: (A) Control animals, receiving common rabbit diet; injected daily with saline solution i.p. (B) Animals receiving 1 g cholesterol daily added to the diet; injected with saline solution i.p. (C) Rabbits receiving common diet; injected with compound 48/80 (1.5 mg/day/kg body weight) i.p. (D) Animals receiving 1 g cholesterol daily added to the diet; injected with compound 48/80 (1.5 mg/day/kg body weight) i.p. (The animals of these four groups were maintained for about 65 days under experimental conditions, then sacrificed by bleeding.) (E) Animals receiving common diet

[1] P. CONSTANTINIDES, Science *117*, 505 (1953).
[2] C. R. DOUGLAS, M. PERELMAN, C. OBERTI, E. ESCOBAR, and J. TALESNIK, Acta Phys. Lat. Am. *12*, 271 (1962).
[3] W. C. WATSON, Br. J. exp. Path. *39*, 540 (1958).
[4] J. F. RILEY and G. B. WEST, J. Path. Bact. *69*, 269 (1955).
[5] C. R. DOUGLAS, E. ESCOBAR, R. SUÁREZ, R. CISTERNAS, S. GUILOFF, P. ARROYO, and A. ROSENKRANZ, Acta Phys. Lat. Am. *12*, 159 (1962).