UCLA FORUM IN MEDICAL SCIENCES
NUMBER 5

GASTRIN

Proceedings of a Conference held in September, 1964
Sponsored by the School of Medicine, University of California, Los Angeles

EDITOR
MORTON I. GROSSMAN

UNIVERSITY OF CALIFORNIA PRESS
BERKELEY AND LOS ANGELES
1966

CITATION FORM

Grossman, M. I. (Ed.), *Gastrin*. UCLA Forum Med. Sci. No. 5, University of California Press, Los Angeles, 1966.

University of California Press
Berkeley and Los Angeles, California

Library of Congress Catalog Card Number: 66-25614
Printed in the United States of America

CHARACTERIZATION OF A PURE GASTRIN

STUART D. TAUBER
University of Texas
Dallas

As described by Dr. Gregory, studies over the past fifty years have indicated that there is an antral hormone, gastrin, capable of stimulating hydrochloric acid secretion from the stomach. More recently, gastrin-like activity has been obtained from the antral mucosa of several species, and from human pancreatic islet cell tumors. Not only may gastrin play an important physiological role in the humoral control of gastric acid secretion, but it may also be causally linked to the symptom complex which characterizes the Zollinger-Ellison syndrome.

The studies I shall describe were performed to isolate and characterize this hormone, both physicochemically and physiologically. In addition, I shall relate experimental evidence suggesting a biochemical similarity between gastrin and the gastric stimulatory activity extractable from tumor tissue of patients with Zollinger-Ellison syndrome.

For the purpose of testing gastrin activity during the isolation procedure, bioassays were performed in unanesthetized trained female dogs with chronic gastric fistulae. The test animal was placed in a Pavlov stand, and gastric secretions were collected by gastric cannula at 15-minute intervals during a control period when isotonic saline was being infused at a rate of 1.0 ml/min. After several control collections, the sample to be assayed was infused at the same rate for 30 minutes. The 30-minute period beginning 15 minutes after the onset of increased hydrochloric acid secretion was used for quantitating the response of samples being assayed. The total amount of hydrochloric acid from collected samples was estimated by titration to a phenolphthalein endpoint with 0.1 N sodium hydroxide.

Maximum histamine responses were determined in all dogs for comparison with the activity of the gastrin extracts. In these studies the unit of gastrin activity (U) is defined as that amount of administered hormone which produces a secretory response equal to one-half the maximal histamine stimulation.

The starting material for the purification of the hormone was an ether extract of acetone-dried powder from porcine antral mucosa, obtained by

TABLE 2

PURIFICATION OF PORCINE GASTRIN
Starting Material: Acetone-Dried Powder, Specific Activity 45 mU/mg

Step	Chromatography	Elution with	Specific Activity
I	G-25 Sephadex	0.001 M phosphate buffer, pH 7.0	100 mU/mg
II	Calcium phosphate, brushite form	0.005 M phosphate buffer, pH 7.0	476 mU/mg
III	DEAE Sephadex	0.32 M NaCl	1460 mU/mg
IV	G-75 Sephadex	0.2 M ammonium acetate buffer, pH 4.7	4120 mU/mg

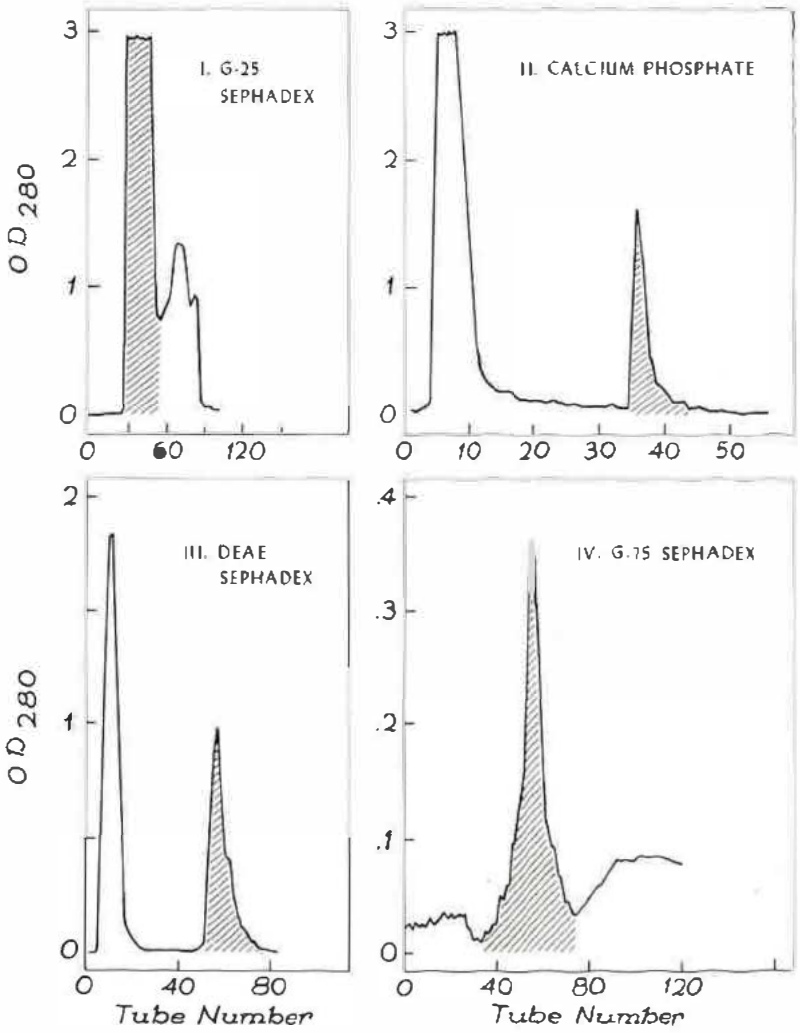

Figure 10. Chromatographic steps in the purification of gastrin extracted from porcine antral mucosa. Gastrin activity indicated by shaded areas. See text. (Modified from Tauber & Madison, 10.)

the method of Gregory & Tracy (2). The subsequent isolation procedure developed in our laboratory consisted of the following steps, as shown in Table 2. In Step I, the crude material, with a specific activity of 45 mU/mg, was chromatographed on G-25 Sephadex and eluted with 0.001 M phosphate buffer, pH 7; the specific activity was then 100 mU/mg. Further fractionation of this active peak was carried out in Step II on a column of calcium phosphate in the brushite form; the biologically active material eluted with 0.005 M phosphate buffer, pH 7, had a specific activity of 476 mU/mg. This product was then subjected to anion exchange chromatography on DEAE Sephadex (Step III); the gastrin, eluted by addition of 0.32 M sodium chloride, had a specific activity of 1460 mU/mg. The final chromatographic step (IV) was carried out on G-75 Sephadex; elution with 0.2 M ammonium acetate buffer resulted in recovery of a peak of gastrin activity which had a specific activity of 4120 mU/mg, representing a ninetyfold purification over the starting material. Figure 10 depicts the chromato-

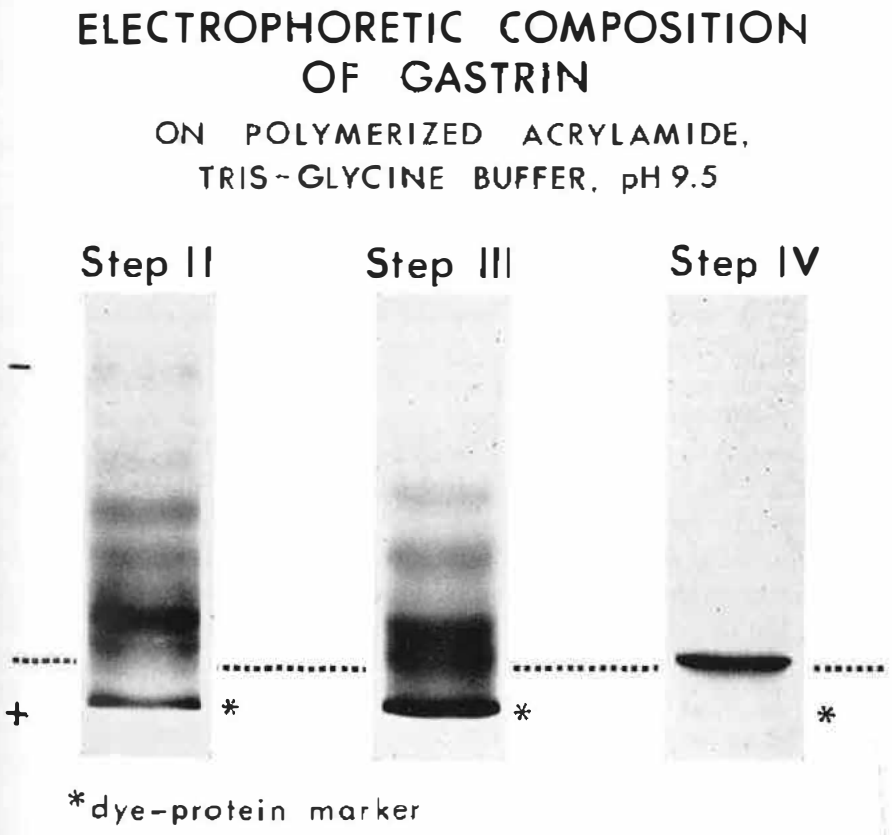

Figure 11. Disk gel electrophoresis of gastrin at various stages of purification. Step II, calcium phosphate chromatography; Step III, DEAE-Sephadex chromatography; Step IV, Sephadex G-75 chromatography. The dotted line locates the position of gastrin at Stages II and III with reference to the purified hormone at Stage IV. (From Tauber & Madison, 10.)

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