LETTERS TO THE EDITOR

Inhibition of Peptic Activity, Protection against Histamine Ulceration in the Guinea Pig, and Combination with Gastric Mucin by an Algal Polyanion

SIR,—Levey and Sheinfeld in 1954[1] reported that chondroitin sulphate, sodium polyanhydromannuronic acid sulphate and heparin inhibited the proteolytic action of pepsin acting on casein, noting that heparin was the most active of the substances tried. They also reported that oral administration of chondroitin sulphate to the Shay rat markedly reduced the number of gastric ulcers, the chondroitin sulphate inhibiting pepsin *in vitro* and *in vivo*.

We have found that carrageenin in its usual form and a carrageenin degraded to give solutions of low viscosity and without gelling properties (but retaining about 30 per cent combined sulphate) will inhibit peptic activity *in vitro* and *in vivo*, the degree of inhibition observed varying with the type and concentration of substrate used (viz. haemoglobin, casein, plasma protein) for a given amount of degraded carrageenin.

Simulated gastric juice and juice from patients with peptic ulcer have been investigated. In guinea pigs we have demonstrated inhibition of peptic activity and also that it will completely prevent histamine-induced duodenal ulceration in appropriate oral dosage.[2]

Carrageenin (viscous, gelling solution) is not more active than degraded carrageenin (non-gelling solution of low viscosity) provided the combined sulphate content remains unchanged. Degraded carrageenin is considerably more active than chondroitin sulphate and only slightly less so than purified heparin. Over a range of substrate concentrations the ratio of the inhibitory activity of purified heparin to degraded carrageenin varies from 1 to 1·5.

The interference with peptic activity is due not only to reaction with the enzyme but also to reaction with substrate, hence this variation in inhibitory power of a given weight of carrageenin, heparin or chondroitin sulphate. Reaction will occur between the negatively charged sulphate groups and positively charged (at the pH of the activity test — 1·6 to 2·1) groups in the protein molecules.

We have shown that this degraded carrageenin will adhere to the mucus lining the human stomach and its presence has been demonstrated with toluidine blue in the lining of extirpated stomach removed three hours after the oral administration of three grams. We suggest that a reaction similar to that occurring between protein substrates in the test for activity occurs with mucoprotein. We have also found degraded carrageenin will react with fractions of porcine mucoprotein with consequent increase in viscosity followed by precipitation.

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Tryptamines in Tomatoes

SIR,—Last year I reported the presence of two indole derivatives in extracts of tomatoes[1]. Estimations of the more active derivative, 5-hydroxytryptamine (5-HT), indicated that red ripe tomatoes contained over 3 μg./g. tissue whilst green unripe specimens showed only traces. In all extracts, however, there appeared to be much more tryptamine (T) than 5-HT. A study has now been made of the regional distribution of these substances.

Fresh tomatoes were skinned and the pips were separated from the pulp. Each part was then extracted with acetone (1 g./5 ml.). After reducing the extracts to a small volume, aliquots were either tested for 5-HT activity on the isolated rat uterus or subjected to paper chromatography using different solvent systems (Table I). The indoles were detected on the chromatograms

TABLE I

THE R_F VALUES OF SOME INDOLE DERIVATIVES IN THREE SOLVENTS

Solvent	Indole derivative				
	5-HT	5-HTP	T	TP	5-HIAA
Sodium chloride, 8 per cent	0·35	0·36	0·48	0·50	0·56
*iso*Propanol/ammonia/water, 20:1:2 ..	0·57	0·10	0·79	0·14	0·06
n-Butanol/acetic acid/water, 4:1:5	0·33	0·26	0·60	0·33	0·76

using Ehrlich's reagent as the spray reagent. Duplicate spots were eluted and the eluates tested biologically for 5-HT activity. In the ripe fruit, the highest concentration of 5-HT was present in the pulp, though the skin and pips contained significant amounts (Table II). When the unripe fruits were tested, the pulp was the only part possessing 5-HT activity.

TABLE II

ESTIMATES OF 5-HT AND T (μg./g.) IN PARTS OF UNRIPE AND RIPE TOMATOES

Indole derivative	Unripe pulp	Ripe tomatoes			
		Skin	Pulp	Pips	Pips (washed)
5-HT	0·2	1·5	3·4	1·0	0·8
T	1·0	1·8	4·0	4·8	7·6

Two-dimensional chromatography using the solvents listed in Table I results in good separation of 5-HT and T from their respective amino acids, 5-hydroxytryptophan (5-HTP) and tryptophan (TP), and from the chief end product of 5-HT metabolism in animals, namely, 5-hydroxyindole acetic acid (5-HIAA). However, in the present experiments with tomato extracts, 5-HTP, TP and 5-HIAA were not detected. The tryptamine activity was estimated by comparing the developed spots on the chromatograms with those of the synthetic material similarly treated. In the ripe fruit, the highest concentration of T was present in the pips which when washed free of pulp showed even greater T activity (Table II). Only the pulp of the green unripe fruit showed T activity, the concentration of which was five times that of 5-HT.

The high concentration of T in the pips of the ripe tomato suggests that it may play a role in metabolism, possibly regulating new growth. On the other hand, it may simply be the precursor of 5-HT though why this latter amine is concentrated in the pulp is not yet clear. It is of particular interest that

TP and 5-HTP were not detected, as these two amino acids are generally recognised as intermediates in the formation of 5-HT in animals. Further work on the relationship of indole derivatives to the tomato plant is in progress.

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BOOK REVIEW

THE CHEMISTRY OF DRUGS. By Norman Evers and Dennis Caldwell. Pp. 415 (including Index). Ernest Benn Limited, London, 1959, 84s.

Readers who are familar with earlier editions of The Chemistry of Drugs will find that, although in its new form it has been completely rewritten and greatly extended, it still conforms to the same general plan. There is undoubtedly a great deal to be said for the classification of synthetic drugs on a pharmacological basis, though difficulties arise where there is a multiplicity of useful actions in the one substance. It seems a pity, therefore, that the authors have felt it necessary to retain the division between the synthetic drugs in Part I and naturally occurring drugs in Part II. It is the opinion of the reviewer that the inclusion of the alkaloids from Part II within the ambit of the pharmacological classification of Part I would have given a uniformity which the book lacks in its present form, since classification on use is already adopted for the other naturally occurring substances such as vitamins, hormones and antibiotics. This apart, however, the new edition is to be welcomed as providing a most useful, extensive, and up to date survey of the chemistry of synthetic drugs and natural products of medicinal importance. It is natural that the treatment of synthetic drugs should emphasise synthetic methods, and in this the authors excel, but it is disappointing to note a general failure to place the same degree of emphasis on chemical properties of pharmaceutical importance. Much useful information of this character is in fact included, but so much more that is of value could have been added, perhaps at the expense of sections on the cryptopine, protopine, strychnine, aconitine and certain of the steroidal alkaloids. The chapter on antibiotics could also have been usefully extended, though deficiencies such as these are counterbalanced by the enlarged and up to date bibliography which is a feature of the new edition, and in this the authors are to be congratulated. The book, too, is easy to read, the subject matter being liberally interspersed with formulae and equations. There are remarkably few errors, but attention should be drawn to those in the formulae of pethidine, di*iso*propylidine-sorbose, and streptomycin, and also to the persistent use of pentavalent- for quaternary-nitrogen, a practice which is deplored. Nonetheless, the book contains a wealth of information which should prove invaluable to chemists, pharmacists and students alike.

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