pounds are due to such factors as the half-lives of the compounds and their distribution in the animal, or there may be fundamental differences in the nature of the reactions with nucleic acids, proteins, or other cell constituents, or, of course, alkylation may not be the relevant reaction for biological activity. As compounds of this type are used in cancer chemotherapy, as well as in the study of carcinogenesis and mutagenesis, individual differences in the biological activities of different alkylating agents merit further investigation[12,13].

Résumé. La nitrosoguanidine administrée à des rats par sonde stomacale provoque la formation de très nombreux kystes biliaires dans le foie et, dans chaque cas, de tumeurs d'estomac squameuses.

V. M. Craddock

Toxicology Unit, Medical Research Council Laboratories, Carshalton (Surrey, England), 22 May 1968.

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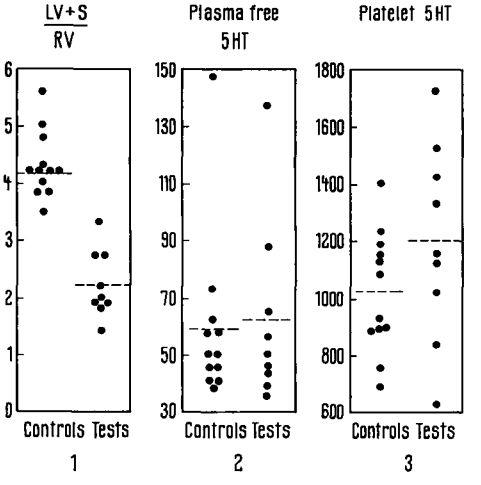
Blood 5-Hydroxytryptamine in Rats with Pulmonary Hypertension Produced by Ingestion of *Crotalaria spectabilis* Seeds

The prolonged oral administration of *Crotalaria spectabilis* seeds to rats induces pulmonary hypertension[1]. This is associated with cardiac enlargement due to right ventricular hypertrophy[2,3], thickening of the pulmonary trunk[4] and medial hypertrophy and arteritis in the muscular pulmonary arteries[3,5]. The active principle of *C. spectabilis* seeds is the pyrrolizidine alkaloid monocrotaline[6] and administration of the pure alkaloid induces pathological changes which are identical to those caused by the seeds[7].

The mechanism by which monocrotaline induces pulmonary hypertension is unknown. However, in this connection Takeoka, Angevine and Lalich[8] reported that proliferation of mast cells occurred in the lungs of rats fed on *C. spectabilis* seeds. Rat mast cells are rich in 5-hydroxytryptamine (5HT)[9] which is known to be a pulmonary vasoconstrictor in many animal species[10] and its release from mast cells may play a part in the normal regulation of vascular tone[11]. It was considered possible that the pulmonary hypertension induced by monocrotaline might be associated with abnormal 5HT release. Accordingly, experiments were conducted in which the plasma-free and platelet-bound 5HT levels were measured in rats fed on *C. spectabilis* seeds and the results compared with those obtained in rats given a normal diet.

Methods. Twenty-one female Wistar albino rats (initial weight 68–87 g) were divided into 2 groups consisting of 9 test animals and 12 controls. The test rats were given a diet of powdered Thomson rat cubes to which finely ground *C. spectabilis* seeds had been added to give a concentration of 1 g/kg diet. The control rats received a diet of unadulterated powdered rat cubes. On the thirty-third day of the experiment the rats were anaesthetized with ether and blood was withdrawn by cardiac puncture for 5HT assay. Determinations of plasma-free and platelet-bound 5HT were made using a spectrophotofluorimetric method[12,13]. After withdrawal of blood the animals were killed and their thoracic organs immersed in formalin. When fixation was complete the hearts were dissected free and their chambers were weighed separately using a method described previously[3]. The right ventricular weight was expressed as a ratio of the weight of the left ventricle and interventricular septum for assessment of right ventricular hypertrophy, the presence of which was accepted as evidence of pre-existing pulmonary hypertension.

Results. In the 12 control rats the ratio obtained by dividing the right ventricular weight (RV) into the weight of the left ventricle (LV) and interventricular septum (S) ranged from 3.5–5.6 with a mean of 4.2. The range in the 9 test rats was from 1.4–3.3 with a mean value of 2.2. The difference between these 2 means is highly significant ($P < 0.001$), indicating that all the test rats had right ventricular hypertrophy when compared with the controls (Figure 1).



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The plasma free 5HT ranged from 38–148 ng/ml in the control rats compared with a range of 35–138 ng/ml in the test animals. There is no significant difference between the mean values of 59 and 62 ng/ml which were obtained with the control and test groups, respectively (Figure 2).

The platelet-bound 5HT levels ranged from 675–1393 ng/10^9 platelets in the control rats, with a mean value of 1007. The test rats showed a range of 606–1725 ng/10^9 platelets and a mean of 1183. There is no statistically significant difference between these 2 groups of figures (Figure 3).

Comment. All the test rats showed evidence of right ventricular hypertrophy which indicates that the diet of *C. spectabilis* seeds had induced pulmonary hypertension. This was not associated with an alteration in the concentration of 5HT in the plasma or platelets. The circulating free and bound 5HT levels are subjected to a number of counteracting equilibrating mechanisms viz. state of tissue 5HT liberation, rate of platelet uptake and release, and enzymatic degradation. The equilibrium maintained by the complex interplay of these factors makes it difficult to detect local changes in blood 5HT levels. The results of the present experiment therefore do not entirely exclude the possibility that 5HT may be concerned in some way with the development of the pulmonary hypertension.

It has recently been shown[14] that mast cells are not concerned in the genesis of the pulmonary hypertension produced in rats by ingestion of *C. spectabilis* seeds, but that their proliferation is a secondary phenomenon related to the exudative lesions which occur in the lungs coincident with the terminal onset of right ventricular failure.

In a further experiment the concentration of 5HT was measured in the lung tissue of 6 normal rats and 5 rats fed on *C. spectabilis* seeds for 34 days. The test rats showed evidence of pulmonary hypertension but the lung 5HT concentrations did not differ significantly from those observed in the controls.

Zusammenfassung. Der pulmonare Blutdruck in Ratten kann durch Abfütterung von *Crotalaria spectabilis* erhöht werden, ohne die Konzentration des plasmafreien und an die Thrombozyten gebundenen 5-Hydroxytryptamins zu verändern.

J. M. KAY, N. CRAWFORD and D. HEATH

Departments of Pathology and Physiological Chemistry, University of Birmingham (England), 5 July 1968.

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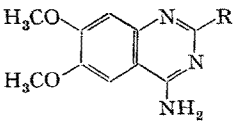
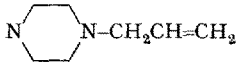
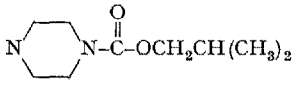
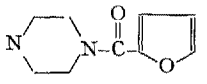
Pharmacological Studies with Some New Antihypertensive Aminoquinazolines

Following our investigation of the blood pressure-lowering properties of 2-amino-4(3H)-quinazolines[1], we extended our studies to a related family of 4-amino-quinazolines. This paper offers a preliminary account of the pharmacological activity of 4 members of the new series. Their chemical structures are presented in the Table.



Chemical name	R
I 2-dimethylamino-4-amino-6,7-dimethoxyquinazoline monohydrochloride.	$N(CH_3)_2$
II 2-(4-allyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline dihydrochloride.	
III 4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-carboxylic acid, isobutyl ester, monohydrochloride.	
IV 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine monohydrochloride.	

Blood pressure in the coccygeal artery was measured in conscious hypertensive[2] dogs with an electrosphygmograph and a pneumatic pulse transducer[3], and was recorded before, and at 2, 6 and 24 h after administration of a drug orally by capsule, or by gastric gavage. Each of the compounds was evaluated at 4–6 different doses in at least 10 dogs.

The dye dilution method of HAMILTON[4] was used to study the effect of drugs on cardiac output of normotensive dogs anesthetized with sodium pentobarbital, 30–35 mg/kg, i.v. Continuously recorded indocyanin-green dye curves were obtained with a Waters oximeter cuvette installed into the right femoral artery. Total peripheral vascular resistance was calculated according to the procedure of GREEN[5]. Blood flow in a femoral artery was recorded with a Shipley-Wilson flowmeter; drugs were injected intra-arterially in volumes not exceeding 0.1 ml.

The effects of drugs administered i.v. on contractions of the nictitating membrane induced by electrical stimulation of the sympathetic chain were investigated in cats anesthetized with chloralose, 75 mg/kg i.v. The cervical sympathetic chain was stimulated above and below the

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