by a component of the lysosomes[3,4]. Part of the evidence cited in support of this mechanism was the significant inhibition of tissue reaction to the extract after treatment of rats with an antihistamine drug. This observation, however, was made in animals treated with a large dose of the antihistamine, and no consideration was given to non-specific effects of such a dose on vascular response to generalized inflammatory stimuli. Additional experiments with appropriate controls for non-specific effects of the antihistamine have now been performed. This communication reports results which confirm our earlier conclusion.

Rats were injected intravenously with 6 mg of chlorpheniramine maleate/100 g body weight as before[2], and intracutaneous injections of the lysosomal protein fraction were given 5 min later. Other animals received no pretreatment and served as controls. Additional skin sites were injected with histamine, compound 48/80 (a histamine liberator), serotonin (5-HT) and bradykinin (agents which act on vascular permeability independently of the release of histamine). Tissue reactions were scored as exudations of circulating Evan's blue dye. Table 1 shows that this dose of antihistamine caused complete or nearly complete inhibition of the response to histamine, 48/80 and the lysosome fraction, whereas the responses to serotonin and bradykinin were only partly inhibited. Other rats were injected intracutaneously with smaller doses of lysosomal extract and 48/80 (see Table 1). These animals were pretreated with a reduced dose (0·6 mg/100 g) of the antihistamine drug. Low doses of the antihistamine depressed the 48/80 response to one-third of its control value and that of the lysosome fraction to even lower levels. On the other hand, responses to serotonin and bradykinin were almost as large as the reactions obtained in untreated rats. It is thus reasonable to assume that the bulk of the inhibition of inflammatory response to the lysosomal fraction in our original experiment resulted from specific effects of the antihistamine. It seems clear that only a small part of the inhibition observed in rats treated with 0·6 mg of antihistamine/100 g body weight can have arisen from non-specific actions of the drug.

In an ancillary experiment, rats were injected intracutaneously with 0·5 μg of protein of the lysosome extract obtained from exudate PMN leucocytes (rabbit) and with the same dose of a protein fraction extracted in identical fashion from peripheral PMN leucocytes of this species. Unlike the preparation from exudate cells, the lysosome fraction derived from circulating leucocytes fails to disrupt mesenteric mast cells *in vitro*. Investigations now in progress (Janoff, A., and Seegers, W., to be published) show that the mastocytolytic component of the lysosome is present in circulating PMN leucocytes in an inactive form and becomes activated in cells which appear in exudate fluids. The lysosome fraction prepared from peripheral PMN leucocytes, as expected, was not inflammatory in rat skin.

Finally, cutaneous inflammatory responses to the lysosome fraction were compared in rats and rabbits. In the former species mast cells abound in the skin; however, in rabbit skin their numbers are considerably reduced. The lysosome fraction (5 μg of protein/skin site) and 48/80 (0·5 μg) produced nearly maximal exudation of circulating protein-bound dye within 10–15 min (4+ reaction), but neither agent gave any skin blueing in rabbits at the same doses and within the same time interval. Others have reported blueing reactions in rabbit skin treated with similar lysosome fractions, but the reaction is not immediate and requires about 2 h to reach its peak (refs. 5 and 6, and Cochrane, C. G., personal communication). This response may result from a different component of the lysosome, which acts on permeability of vessels by a mechanism independent of mast cells.

Table 1. EFFECT OF CHLORPHENIRAMINE MALEATE ON INFLAMMATORY REACTIONS IN RAT SKIN

Pretreatment	No. of rats	Average response/μg of agent injected: Histamine	LPP*	48/80	5-HT	Bradykinin
None	8	3+ to 4+/2·0	4+ to 5+/10·0	5+/1·0	4+ to 5+/1·0	3+/1·0
6 mg chlorpheniramine/100 g body weight	8	0/2·0	1+/10·0	1+ to 2+/1·0	3+/1·0	2+/1·0
None	5	2+/1·0	2+/0·5	3+/0·05	3+/0·5	2+/0·5
0·6 mg chlorpheniramine/100 g body weight	5	0/1·0	Trace/0·5	1+/0·05	2+ to 3+/0·5	1+ to 2+/0·5

5+, Intense blue weal (raised). 20 mm or more in diameter. Trace, Faint blue spot (flat), 3 mm or less in diameter.
* LPP, Leucocyte lysosome cationic-protein fraction (prepared as described in ref. 1).

From these experiments, as well as those reported earlier[2,4], it is concluded that the immediate increase in vascular permeability in rat tissues treated with lysosomal basic protein results from the disruption of mast cells and the release of vasoactive amines.

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Role of 3,4-Dimethoxyphenethylamine in Schizophrenia

IN 1962, Friedhoff and Van Winkle reported the detection of 3,4-dimethoxyphenethylamine (DMPEA) in the urine of schizophrenic patients but not in that of normal individuals[1]. Attempts to confirm these findings have led to conflicting results. Two independent groups have verified that DMPEA is indeed produced by a high percentage of mental patients[2,3], but another has also found it in the urine of control subjects as well[4]; yet others have been unable to detect it in either[5,6]. A recent report[7] has presented a convincing correlation between the appearance of the "pink spot" equated with urinary DMPEA, and the diagnosis of schizophrenia. The interest in this specific base stems both from its close structural kinship to mescaline, a well established psychotogen, and from its implication in the metabolic chemistry of the endogenous catecholamines. 3,4-Dihydroxyphenethylamine (dopamine) serves, in normal metabolism, as the precursor of noradrenaline and epinephrine, but it has been argued that an abnormal methylation might occur preferentially in psychotics. This specific conversion, yielding DMPEA, has been shown *in vivo*[2,8]. Alteration of dopamine metabolism has been observed in schizophrenic patients[9] and this has been associated with abnormal transmethylation[10]. An important question has not been answered; is DMPEA a psychotomimetic agent in normal human subjects?

This present communication reports a study conducted to ascertain the psychotropic efficacy of DMPEA in non-schizophrenic adult volunteers. Graded dosages of the amine hydrochloride were administered *per os*, at levels that ranged from 20 μg/kg to approximately 6·8 mg/kg body weight. Three experiments on three separate subjects were conducted at this highest level, and each received 500 mg of the amine salt. Yet another subject received a total of 900 mg distributed over a 7 day period. In no instance were any behavioural or psychotropic effects noted, nor were there any indications of autonomic disturbance. Analysis of the urine of one subject receiving 100 mg showed that, although 3,4-dimethoxyphenylacetic acid was the primary excretory product and accounted for more than half the administered dose, unchanged DMPEA could still be detected from the original ingestion.

If DMPEA is eventually established as a component characteristic of the urine of schizophrenics, its presence

must be interpreted as a result of a state of abnormal metabolism. The absence of any psychogenic properties speaks against its participation as a causal agent in the aetiology of the disease.

Note added in proof. After this communication was accepted, a report appeared that presented experimental data substantially in agreement with those presented here (Hollister, L. E., and Friedhoff, A. J., *Nature*, **210**, 1377; 1966).

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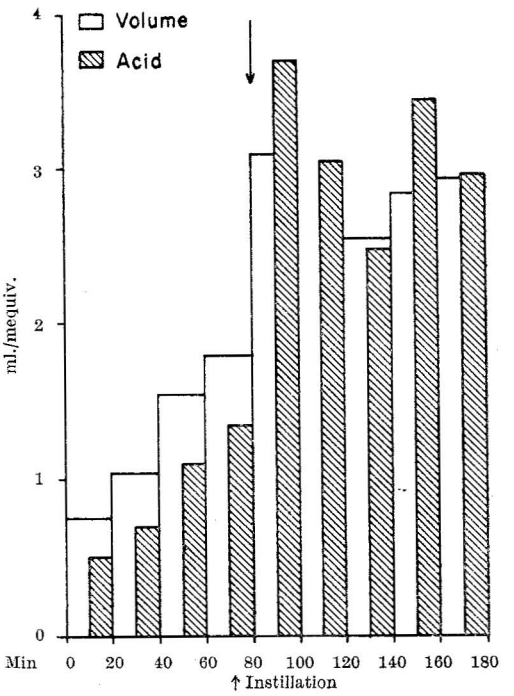

Fig. 2. Instillation of pancreatic juice into the duodenum 80 min after a test meal produced a very significant increase in pouch volume and acid secretion compared with pre-instillation levels ($P < 0{\cdot}1$ per cent). Diagram shows mean values of all experiments on six dogs.

Gastric Hypersecretion following Intraduodenal Injection of Pancreatic Juice or Non-absorbable Antacid

WE have carried out a series of experiments intended to explain the increase in gastric secretion found in the dog when the pancreatic ducts are ligated or when all pancreatic juice is diverted to the outside. This hypersecretion was first demonstrated by Greenlee[1], who transplanted a segment of duodenum containing the principal pancreatic duct into a subcutaneous position where it could drain to the outside, and then anastomosed the residual duodenum end-to-end to re-establish intestinal continuity. This gastric hypersecretion was also found by McIlrath[2] when the principal pancreatic ducts were ligated. Some authors feel that this phenomenon could be explained by gastrin released from the pancreas, but we think that obstruction to the duodenum with consequent release of duodenal and antral gastrin is responsible for the increased gastric secretion observed.

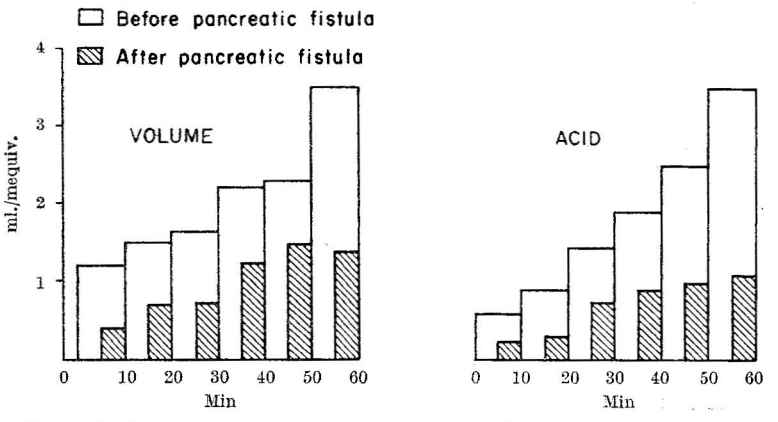

Fig. 1. The two histograms show the mean volume and acid responses of the denervated gastric pouches in the seven dogs to a standard test meal of commercial dog food. The differences in acid and fluid level were significant in each collection period ($P < 5$ per cent). The differences were even more significant in the last two collection periods ($P < 0{\cdot}1$ per cent).

To test our hypothesis we first prepared seven dogs with denervated gastric (Heidenhain) pouches. These dogs were fed test meals of standard proprietary dog food. The volume and total acid produced in response to the meals were measured every 10 min in each dog for two or more experiments. At a second operation a polyvinyl catheter was inserted into the main pancreatic duct of each dog, after the accessory pancreatic duct had been ligated[3]. Pancreatic secretion was thus effectively diverted to the exterior without duodenal obstruction. The dogs secreted 200–300 ml. of pancreatic juice daily, which was collected in balloons and fed back to the dogs. When the feeding experiments were repeated we found, much to our surprise, that the gastric secretory response to feeding was very significantly lower when the pancreatic juice was diverted to the outside than when it went directly into the duodenum. The differences in fluid volume and acid production before and after creation of the pancreatic fistula in the twenty-one paired experiments were significant for each collection period ($P < 5$ per cent). For the last two of the six collection periods the significance of the difference was even greater ($P < 0{\cdot}1$ per cent) (Fig. 1).

Since external diversion of pancreatic juice had reduced the secretion of the stomach in response to test meals, we wanted to know whether increasing the amount of pancreatic juice or alkali in the duodenum would stimulate gastric secretion. We took six more dogs with a denervated gastric pouch, this time with plastic duodenal cannulas. When we fed these dogs, collected gastric juice as before, then injected pancreatic juice into their duodena, a very significant rise in gastric secretion immediately became evident ($P < 0{\cdot}1$ per cent) (Fig. 2). This increase was also clearly seen after injecting a commercial antacid preparation ('Phosphalugel') into fed dogs, or pancreatic juice into the duodena of fasting dogs.

The fact that gastric secretion in response to a test meal was reduced when pancreatic