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Serotonin and Histamine in Mast Cells

Previous investigations have demonstrated the presence of heparin (*1*) and histamine (*2*) in mast cells of various animal species. Asboe-Hansen (*3*) has presented evidence that these cells also produce hyaluronic acid. Recently, Benditt *et al.* (*4*) identified serotonin (5-hydroxytryptamine) in mast cell suspensions prepared from peritoneal washings of rats and found serotonin in rat skin in proportion to its mast cell content. Similar studies by Parratt and West (*5*) suggested that much of the serotonin, as well as histamine, in rat skin is held in the mast cells. The studies of Rowley and Benditt (*6*) in rats indicate that the edema-producing action of agents which damage mast cells may be mediated by "release" of both of these potent amines.

This is primarily a study of serotonin and histamine in mast cells of three animal species: mouse, dog, and man. Mice of the inbred strain DBA/2 and (BALB/c by DBA/2)F_1 hybrids bearing transplantable mast cell neoplasm P185 in subcutaneous solid tumor and ascitic forms (*7*) were made available for study during the 26th to 30th transfer generations. Several other reticular neoplasms in mice were obtained for assay. A first- and second-generation transplantable subcutaneous mast cell tumor of the dog was also used (*8*). Urine specimens were obtained from two patients with urticaria pigmentosa, a condition characterized histologically by dense accumulations of mast cells in the skin. In addition, a skin biopsy was obtained from one of these patients (*9*). Portions of skin from other patients were also studied.

The mouse tumor was composed chiefly of closely packed mast cells, whereas the dog tumor contained a considerable amount of fibrous tissue and a few eosinophils. Details of the discovery, technique of transplantation, and morphology of the mouse tumor have been presented by Dunn and Potter (*7*). One of the patients with urticaria pigmentosa also had skeletal involvement. A report of this case has been made by Zak, Covey, and Snodgrass (*10*). Chemical methods for the measurement of histamine, serotonin, and the serotonin metabolite, 5-hydroxyindoleacetic acid (5HIAA), were those developed previously in this laboratory (*11*).

The serotonin and histamine levels of various tissues are shown in Table 1. The solid mast cell tumors in mice contained large amounts of both serotonin and histamine, while in the dog tumor only the histamine concentration was elevated. Catechol amines could not be detected in the mouse tumor, and paper chromatographic studies showed serotonin to be the only 5-hydroxyindole present. Skin from the patient with urticaria pigmentosa contained a high level of histamine but insignificant amounts of serotonin. Measurements of urinary 5-hydroxyindoleacetic acid in the two patients with urticaria pigmentosa gave values of 5.1 to 7.2 mg/day (normal—2.0 to 9.0), confirming the finding that human mast cells do not contain serotonin.

It is known that carcinoid tumors, derived from the chromaffin cells of the intestinal tract, contain large amounts of serotonin and that patients with metastatic carcinoid excrete excessive amounts of 5-hydroxyindoleacetic acid in the urine (*12*). Recently, Waldenström *et al.* (*13*) reported an elevated urinary excretion of histamine in some of these patients and suggested the possibilities that some tumors might produce both serotonin and histamine or that the serotonin produced might liberate histamine from other tissues. Three carcinoid tumors were found to contain the usual large amount of serotonin but only a small amount of histamine (Table 1). If this is characteristic of all carcinoid tumors, then the increased histamine excretion by carcinoid patients must be a secondary phenomenon.

Table 1. Serotonin and histamine content of various tissues.

Material	Serotonin (μg/g)	Histamine (μg/g)
Tumors		
Mouse mast cell*	80–180	470–560
Dog mast cell	< 0.2	315, 160
3 human carcinoids	360, 570, 800	3.4, 2.0, 0.8
Other mouse tumors†	< 0.2	< 1
Human skin		
Urticaria pigmentosa	< 0.25	44
3 normals	< 0.7	4.7, 5.4, 5.0

* Several assays were done on pooled solid tumor specimens from a total of 20 DBA/2 mice.
† Several transplantable tumors (transfer generation indicated in parenthesis) were analyzed. In strain DBA/2: one type-A reticulum cell sarcoma, P228 (39) and one type-B, P195 (19), two lymphocytic, P228 (90) and P388 (63), and one granulocytic, P1081 (3); in strain C57BL: one lymphocytic, P1162 (5); in strain C3H: one well-differentiated plasma cell neoplasm, X5563 (8). A somewhat elevated amount of serotonin (22 μg/g) was found in a pooled sample of four poorly differentiated plasma cell neoplasms, 70429 (36) in strain C3H.

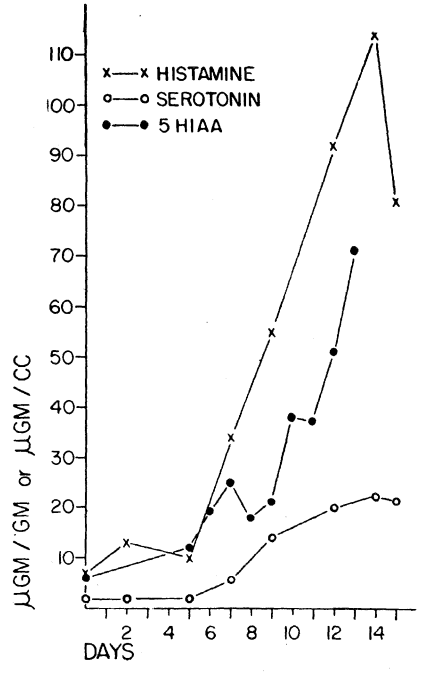

Fig. 1. Effect of mast cell tumor transplantation (ascitic form) on serotonin and histamine contents of whole mice (μg/g) and urinary excretion of 5-hydroxyindoleacetic acid (μg/ml). The animals usually died suddenly at 14 to 16 days.

The increased production of serotonin and histamine in tumor-bearing mice was studied in two ways. First, a group of 16 mice, (BALB/c by DBA/2)F_1, were placed in a metabolism cage after intraperitoneal injection of tumor cells, and urine was collected for assay for 5-hydroxyindoleacetic acid. Control values were obtained on a group of eight nontumor mice of the same strain, which were studied for 2 weeks. Second, serotonin and histamine assays were done on homogenates of pairs of whole mice at various intervals after tumor transplantation. The results, shown in Fig. 1, indicate that there was a marked production of both substances in association with growth of tumor. A simple test for excretion of excessive amounts of urinary 5-hydroxyindoles, useful in the clinical diagnosis of carcinoid (*14*), also became positive in the tumor-bearing mice.

Assuming that the abnormal mast cells in the three species studied produce serotonin or histamine, or both, in a manner comparable to that of normal mast cells, a marked species variation is clearly

shown. It is well to bear this in mind when one attempts to relate results of animal experimentation to human physiology. It will be of interest to compare the cellular catalysts of serotonin- and nonserotonin-containing mast cells (*15*).

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Changes of Body Weight in Normal Men Who Stop Smoking Cigarettes

The role of overweight and obesity in the development of so-called degenerative diseases (*1*) and, consequently, the factors that affect body weight continue to be of interest.

We are all familiar with the occasional large gains in weight among men who stop smoking. Surprisingly enough, the phenomenon of weight change following a break in a lifelong pattern of smoking, which is not associated with intercurrent illness or a medically supervised dietary regimen designed to reduce or to increase body weight (*2*), has not been studied systematically. One reason for the absence of such information is the fact that longitudinal investigations on the "normal" adult man are difficult to carry out.

This study (*3*) was undertaken within the wider framework of researches on aging, focused on factors that are associated with the development of "degenerative" (noninfectious, noncongenital) heart disease and carried on in the Laboratory of Physiological Hygiene, University of Minnesota, since 1947. A group of approximately 300 business and professional men, examined at yearly intervals, serve as subjects. The laboratory staff refrains from giving advice to them, but findings indicative of the presence of disease are reported to their personal physicians. We wish to study the effects of the differences in the mode of life.

The "experimental" subjects are men who voluntarily stopped smoking cigarettes and on whom weight data are available for 2 years before and 2 years after the year in which they stopped smoking. A control group was obtained by selecting men who did not stop smoking and were matched in age, relative body weight (actual weight expressed as a percentage of "standard" weight for sex, age, and height), and actual body weight at the beginning of the first year of the 5-year period, without reference to weight trends during the rest of the period. The means and standard deviations and the t-tests of significance of the differences between means of the experimental and the control groups, respectively, were 49.8 ± 4.2 and 51.2 ± 3.5 years ($t = 1.20$, nonsignificant) for age; 97.5 ± 11.9 and 97.7 ± 11.2 ($t = 0.05$, nonsignificant) for relative body weight; and 75.8 ± 9.2 and 75.8 ± 9.2 kg for absolute body weight. Thus, at the outset, the two groups did not differ significantly in respect to any of the three criteria that were considered for matching. Both groups represent "normal," middle-aged men, with body weight close to their age standard. The intensity and total duration of smoking were similar.

Longitudinal observations on smoking and body weight are summarized in Table 1. Using the average weights for years 1 and 2, and for years 4 and 5, we obtained, in the control group, a small (1.1 lb), statistically nonsignificant decrement while, in the experimental group, there was a substantial (8.2 lb), statistically highly significant rise. The respective t-values refer to t-tests for paired varieties; with $(N\text{-}1)$, that is, 20 degrees of freedom, the reference value $t_{0.001} = 3.850$. On comparing the mean difference between the change in the experimental and matched group, we obtain a net difference of 4.23 kg (9.3 lb), which is also statistically highly significant; in this case the t-tests were calculated for unpaired variates, with $2(N\text{-}1)$, that is, 40 degrees of freedom. The corresponding $t_{0.001} = 3.551$.

Table 1. Mean weights, weight changes, and differences in weight change between the two groups.

Item	Experimental group		Control group
Weight (kg) for years 1 plus 2	76.05		76.36
Weight (kg) for years 4 plus 5	79.78		75.86
Weight change			
Mean	+ 3.73		− 0.50
Standard deviation	± 1.94		± 3.03
t within group	5.65*		1.18
Weight change difference (kg)		4.23	
Weight change difference, t between groups		5.39*	

* Statistically highly significant.

It should be emphasized that both our groups consisted of essentially "normal" men. We have not included several individuals who stopped smoking because of intercurrent coronary heart disease or in whom a rigorous dietary (reducing) regimen, together with termination of smoking on medical orders, was a part of therapy.

The present data provide information on interindividual variability in the weight gain, its average amount, and its statistical significance. The question of permanence of the gain beyond 2 years remains open. While the evidence concerning the effect on body weight of stopping cigarette smoking is convincing, no simple and definite interpretation of the phenomenon can be offered. Experimental observations on the inhibition of gastric hunger contractions by smoking (*4*) and the increase in tobacco consumption among individuals who are maintained on reduced calorie intake (*5*) suggest that smoking tends to depress the felt need for food.

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