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Abstract

1. Considering an imaginable important role of histamine in inflammations or allergic reactions, some clinical and experimental studies were made for the purpose of findings the relationship of the pathological changes of A. P. to local histamine. 2. Gingivae in the case of A. P. showed a remarkable quantitative increase of histamine, compared with those in the case of normal healthy controls. It could be noticed that this increase had an increasing tendency in proportion to the degree of inflammatory pathologic changes in the gingiva. 3. In the gingivae of A. P. an increase of mast cells and their morphologic changes, particularly disintegration, were seen and the grade of changes was almost parallel to an increase of histamine. 4. When a histamine solution was repeatedly injected into the mucobuccal folds of animals, a remarkable increase of histamine and mast cells in the injected gingivae were recognized with inflammatory changes. An increase of gingival histamine could be hardly recognized by means of a simple mechanical stimulation or local anaphylaxis alone. However, in the combination of two, the increase of histamine was seen and relatively remarkable inflammatory changes suggestive of A. P. were macroscopically and microscopically noticed. 5. Topical applications of the ointment mixed with sinomenine, histamine-liberating substance, and benadryl, antihistamine substance, repeated every other day in the gingival pockets, showed favorable effects in slight or early cases of A. P. 6. These observations suggest the existence of both possible role of histamine in the development of local pathologic condition of A. P. and allergic processes in etiologic factors of the disease.

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RELATIONSHIP OF CHRONIC MARGINAL PERIODONTITIS (ALVEOLAR PYORRHEA) TO HISTAMINE

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The nature and etiology of alveolar pyorrhea (A. P.), chronic marginal periodontitis, are in the state groping in the dark at present. Most of the studies on the disease has been made in detail from the pathological and morphological viewpoints, while few have been made from the cytochemical viewpoint and, especially, only few on its relationship to the inflammation-producing substance. However, inflammatory change, vascular functional disturbance and metabolic disorder among various changes in the affected tissues of A. P. can be regarded as a joint pathological phenomenon occurring in causal relation with each other. In this respect, histamine which exists widely and constantly in living body and can be easily liberated by various physicochemical and biological (including antigen-antibody reaction) stimulations, has a strong action producing such a phenomenon in its extremely small quantity. This is the reason why a great importance is attached to the role of this substance in inflammation¹⁻³ and allergic reaction⁴⁻⁷. This idea is supported by the fact⁷⁻⁹ that much of this substance exists in the focus of chronic inflammation.

The purpose of this study is to investigate to what extent histamine in the local tissues is related to the development of the pathological state of A. P. In this study the quantity of histamine and the quantitative and qualitative changes of the mast cell, which is an important place to stock histamine, were observed in the gingivae of the disease, and, moreover, some experiments were made in dogs and cats in order to produce these changes found in case of human A. P. Furthermore, the effect of topical application of chemical substances liberating histamine and antihistamine preparations were examined in some cases of the disease.

CLINICAL AND EXPERIMENTAL OBSERVATIONS

1. *A. P. and quantity of gingival histamine.* As the first subject for the purpose of investigating the relationship of A. P. to histamine,

the quantity of histamine in each gingiva removed surgically in 51 cases of A. P. and 20 control cases was determined by means of biological method using ileum pieces of guinea pigs, in order to investigate the change of histamine in the periodontal tissues of A. P. At the same time, histological investigation was made by means of the hematoxylin-eosin staining, too.

The quantity of gingival histamine showed a marked increase in A. P., as compared with that in normal healthy cases (Table 1). The

Table 1. Quantity of gingival histamine in A. P. and control cases

	Type	Grade	No. of cases	Minimum ($\mu\text{g./g.}$)	Maximum ($\mu\text{g./g.}$)	Average ($\mu\text{g./g.}$)
A. P.	Inflam-matory	Slight	30	9.2	46	22
		Moderate	9	21	57	32
		Severe	2	43	58	51
	Mixed	Slight	4	11	21	15
		Moderate	6	12	20	15
	Total		51	9.2	58	24
Control cases			20	2.3	9.2	7.8

$$\text{Standard error} = \sqrt{\frac{\sum d^2}{n(n-1)}} \quad \begin{cases} \text{A. P.} & 1.65 \\ \text{Control} & 0.4 \end{cases}$$

$$\text{Standard deviation} = \sqrt{\frac{\sum d^2}{n-1}} \quad \begin{cases} \text{A. P.} & 11.2 \\ \text{Control} & 2.2 \end{cases}$$

$$t = \frac{\frac{m_A}{n_A} - \frac{m_B}{n_B}}{\sqrt{\frac{\sum d^2_A + \sum d^2_B}{n_A + n_B - 2} \cdot \frac{n_A + n_B}{n_A \cdot n_B}}} = 6.1$$

$$P < 0.001$$

n : Number of cases, m : Quantity on an average,

d : Deviation of each observation from m , A : A. P., B : Control

cases of inflammatory type indicated particularly a remarkable increase of histamine in comparison with those of the so-called mixed type, which is lower than the former in the inflammatory grade of the disease. In the inflammatory type this increase was in proportion to the degree of inflammation. The mixed type showed a little less than twofold increase on the average, the inflammatory type from three to sixfold, and the total average about threefold. These increases had remarkable significance statistically. Moreover, the degree of these increases had a tendency to

become higher in proportion to the degree of inflammatory pathological changes observed in their histopathological state.

2. *Relationship of A. P. to mast cells in the gingiva.* Recently many scholars have recognized that mast cells are closely related with histamine¹⁰⁻¹². Therefore the author intended to investigate what kind of changes of mast cells in the gingiva could be seen quantitatively and morphologically in A. P., and to endorse, according to the changes, the fact of the above-mentioned increase in histamine. Thus the microscopic observation of mast cells in the resected gingivae of A. P. and control cases was tried by means of the staining with one percent solution of toluidine blue after fixation with 95 per cent solution of alcohol simultaneously with the determination of histamine.

It could be known that these cells generally increased in the gingiva of A. P. in comparison with the normal gingivae, that these increases were proved not only around the small vessels in the subepithelial connective tissues where they were usually present in the healthy state, but also markedly even in the deep connective tissue, and that, moreover, various morphological changes of the cells, such as their abnormal outlines, widening of inter-granular space and irregularity of granular arrangement in many cases and disintegration of the cells in some cases, were observed (Figs. 1 and 2). Furthermore, it could be noted that an



Fig. 1. Mast cell in the gingiva of control case. 200 $\times$.



Fig. 2. Mast cells in the gingiva of A. P. 200 $\times$.

increase of histamine in the same tissues was positively correlated with these findings in such cases as showed a remarkable increase and morphologic changes of the cells (Tables 2 and 3).

Table 2. Changes of mast cells and the quantity of histamine in the gingiva (cases of A.P.)

No.	Sex	Age	Removed area	Clinical type and grade	Quantity of histamine ($\mu\text{g./g.}$)	Mast cell count*	Morph. changes of mast cells †
1	♀	20	5 5	Inflam., Slight	12	±	±
2	♀	19	5 5	" "	13	±	+
3	♀	20	6 6	" "	14	+	+
4	♂	51	5 5	" "	15	±	+
5	♀	19	6 6	" "	16	+	+
6	♂	17	5 5	" "	18	+	++
7	♀	23	3 3	" "	19	±	±
8	♀	23	5 5	" "	20	±	+
9	♀	20	5 5	" "	20	+	++
10	♀	22	5 5	" "	21	±	+
11	♀	18	7 7	" "	22	+	++
12	♀	23	2 2	" "	22	+	+
13	♀	20	3 3	" "	23	+	+
14	♀	18	5 5	" "	24	++	++
15	♀	18	5 5	" "	24	++	++
16	♂	18	3 3	" "	26	+	+
17	♀	20	3 4	" "	27	++	++
18	♀	30	3 4	" "	35	++	++
19	♂	18	5 5	" "	41	+++	+++
20	♀	16	3 3	" "	46	++	++
21	♀	20	5 5	" Moderate	21	++	++
22	♀	23	3 3	" "	30	+	++
23	♀	28	5 5	" "	32	++	++
24	♀	22	5 5	" "	36	+++	+++
25	♂	43	5 5	" Severe	43	++	++
26	♀	48	3 3	" "	58	+++	+++
27	♀	21	5 5	Mixed, Slight	13	+	++
28	♀	21	3 3	" "	14	++	++
29	♀	21	5 5	" Moderate	12	±	+
30	♀	21	5 5	" "	13	+	+

* ±, +, ++, and +++ showing average count of 0 - 1, 2 - 5, 6 - 10, and more than 11 respectively in each one field of vision (200×).

† ±, +, ++, and +++ showing normal or very little, slight, moderate, and marked changes respectively.

Table 3. Changes of mast cells and the quantity of histamine in the gingiva (control cases)

No.	Sex	Age	Diagnosis	Area	Quantity of histamine ($\mu\text{g./g.}$)	Mast cell count*	Morph. changes of mast cells †
1	♀	20	Difficult dent.	8	4.5	±	±
2	♂	22	Impaction	8	5.5	±	±
3	♂	26	Pericoronitis	8	6.7	±	±
4	♂	22	Pericoronitis	8	7.8	±	±
5	♀	22	Impaction	3	8.3	±	±
6	♀	22	Pericoronitis	8	8.4	±	±
7	♂	25	Fracture	3	8.5	±	±
8	♀	30	Residual stump	67	8.6	±	+
9	♀	19	Malposition	3	8.7	±	±
10	♀	24	Prognathism	3+3	8.8	±	±
11	♂	25	Impaction	8	8.9	+	+
12	♂	27	Difficult dent.	8	8.9	±	±
13	♀	23	Pericoronitis	8	8.9	±	+
14	♂	30	Residual stump	8	9.0	±	±
15	♂	17	Follicular cyst	567	9.1	±	+

For *, † see footnote in Table 2.

3. *Changes of gingival histamine and local gingiva due to topical injection of histamine and anaphylaxis.* The conditions necessary to form such a state artificially were investigated, according to the previous researches that a quantitative increase of histamine and a numerical increase of mast cells could be noticed in the gingivae of A. P.

First, as a result of repeated injections of histamine solution in the mucobuccal folds of 7 dogs and 8 cats, a remarkable increase of histamine—threefold in dogs and 2.3-fold in cats on an average in comparison with their normal gingivae—and mast cells and local obvious inflammatory changes could be recognized in the gingiva of the injected side, and, moreover, an increase of histamine was observed slightly spreading in the opposite gingiva. The more frequently repeated the injection was, the more remarkable became such changes.

Next, an increase of gingival histamine could be hardly recognized as the result of subsequent physical stimulations given to 23 dogs for 20 to 70 days: detachment of the gingiva, heat application of 60°C to the gingiva, phosphate cement application and suturing at the tooth-necks and percussion of the teeth. In the cases of injection of antigen into the gingivae of 4 sensitized dogs, or of its application to the gingiva-detached

tooth-necks of 4 similar dogs for 12 hours, a remarkable increase of gingival histamine was not recognized on 10th to 14th days after these procedures. However, its increase became particularly remarkable when the above-mentioned physical stimulations continuously given for a long period were combined following these procedures in cases of 9 dogs (Table 4). In these cases of dog experiments relatively marked changes, suggestive of A. P., were recognized macroscopically and microscopically (Figs. 3 and 4).

Table 4. Quantity of gingival histamine ($\mu\text{g./g.}$) in dogs when physical stimulations following procedures inducing local anaphylaxis were made

No.	Physical * stimulations	Times of stimulation	Upper		Lower	
			Left †	Right	Left	Right
1	Ph	3	1.6	1.5	1.3	1.5
2	Ph	5	1.6	1.5	1.3	1.4
3	D	3	2.1	2.0	1.8	1.7
4	D	5	2.1	2.0	1.7	1.6
5	D & P	5	2.8	2.1	2.0	1.8
6	D & H	5	2.5	1.7	1.5	1.7
7	D & S	5	2.7	2.3	2.1	1.9
8	{D, P, H} & S }	3	2.8	1.7	1.5	1.5
9		5	3.2	2.1	1.6	1.5
Average		3—5	2.4	1.9	1.6	1.6
Standard deviation			0.18	0.29	0.29	0.17

* Physical stimulations are as follows: Phosphate cement application (Ph) to the tooth-necks, detachment (D) of the gingiva, suturing the tooth-necks (S), percussion (P) of the teeth, and heat application (H) of the gingiva.

† Procedures inducing local anaphylaxis were made.

4. *Treatment of A. P. with histamine-antidote.* As it is reasonable to consider that there exists an important relationship between the development of the pathologic condition and an increase of histamine in the gingiva in the case of A. P. from the above-mentioned results, so it would not be fruitless to attempt to investigate what kind influences may be exerted upon the disease and to see whether it is possible to relieve symptoms of the disease, when a procedure to reduce histamine in the focus tissue is to be taken.

Following this idea, topical application of the ointment mixed with sinomenine^{3,13-20}, histamine-liberating substance, and benadryl²¹⁻²⁴, anti-histamine substance, had been made repeatedly in 32 cases of A. P. every other day in gingival pockets, and, subsequently, favorable results were



Fig. 3. Exposed gingiva when a physical stimulation was made continuously for a long time following a procedure inducing local anaphylaxis (dog).



Fig. 4. Gingiva on the opposite side of Fig. 3. The same stimulation without application of antigen was made.

obtained in the cases of local itchy feeling, swelling, redness, and bleeding (Figs. 5 and 6). It was effective to a certain extent for the cases with discharge of pus, loosening of the teeth and deepening of the gingival pockets, while ineffective for the cases with advanced symptoms. In slight cases regeneration of the bone was observed by roentgenogram (Table 5). And histologic findings were suggestive of antiphlogistic effects of the antidote.



Fig. 5. A case of A. P. before topical treatment with a histamine antidote is made.

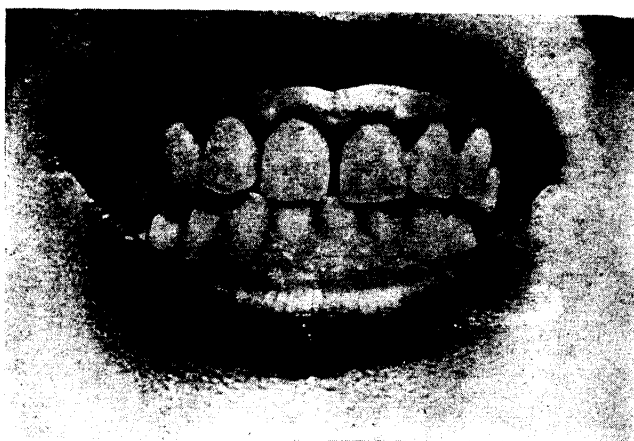


Fig. 6. The same case of Fig. 5. after treatment, 20 applications of antidote every other day.

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Table 5. Effect of sinomenine-benadryl ointment in case of A. P.

Case	No.	Age	Sex	Times of appl.	Local findings before and after appl.					Effect	
					Swelling & redness*	Bleeding †	Pus-discharge†	Gingival pocket depth ‡	Tooth-mobility ‡	Local findings §	X-ray findings
Slight (12)	1	18	♀	3	+ → -	+ → -	± → -	- → -	- → -	++	+
	2	22	♀	3	+ → -	+ → -	± → -	- → -	- → -	++	+
	3	19	♀	3	+ → -	+ → -	± → -	- → -	- → -	++	+
	4	31	♀	4	+ → -	+ → -	± → -	- → -	- → -	++	+
	5	25	♀	4	+ → -	+ → -	± → -	- → -	± → -	++	+
	6	20	♂	5	+ → -	+ → -	± → -	- → -	± → -	++	+
	7	21	♀	5	+ → -	+ → -	± → -	- → -	± → -	++	++
	8	29	♂	6	+ → -	+ → -	+ → -	- → -	± → -	++	+
	9	33	♀	7	+ → -	+ → -	+ → -	± → -	± → -	++	+
	10	18	♀	9	+ → ±	+ → -	+ → ±	± → -	± → -	+	+
	11	20	♂	8	++ → -	+ → -	+ → -	± → -	± → -	++	++
	12	21	♀	8	++ → ±	+ → -	+ → ±	± → -	± → -	+	+
Mid- dle (14)	13	18	♀	13	+ → -	++ → -	++ → -	+ ← -	± → -	++	+
	14	21	♀	20	+ → -	++ → -	++ → ±	+ → -	± → -	++	±
	15	20	♂	19	+ → -	++ → -	++ → -	+ ← -	± → -	++	+
	16	19	♀	21	++ → -	++ → ±	+ → -	+ → -	± → -	++	+
	17	24	♀	17	++ → ±	+ → -	+ → ±	+ → ±	+ → +	+	±
	18	32	♀	25	++ → -	+ → -	+ → -	+ → ±	+ → +	+	±
	19	25	♂	19	++ → ±	+ → -	+ → -	+ → ±	+ → ±	++	±
	20	20	♀	16	++ → ±	++ → ±	+ → -	+ → ±	+ → +	+	-
	21	18	♀	20	++ → -	++ → -	+ → -	+ → ±	+ → +	+	-
	22	19	♀	18	+ → -	± → -	++ → +	++ → +	+ → +	+	-
	23	24	♂	15	++ → -	++ → ±	+ → ±	+ → -	+ → +	+	±
	24	31	♀	22	++ → -	++ → -	+ → ±	+ → -	+ → ±	+	±
	25	29	♀	23	++ → ±	++ → -	+ → ±	+ → ±	+ → +	+	-
	26	20	♀	17	++ → ±	++ → ±	+ ← ±	+ → ±	+ → +	+	-
Se- vere (6)	27	23	♀	21	++ → +	++ → +	+ → +	+ → +	+ → +	±	-
	28	21	♀	33	++ → +	++ → +	± → ±	± → ±	+ → +	±	-
	29	29	♀	30	++ → +	++ → +	+ → +	+ → +	++ → ++	±	-
	30	30	♂	15	++ → +	++ → +	+ → +	+ → +	++ → ++	±	-
	31	25	♀	12	++ → ++	++ → ++	++ → ++	++ → ++	++ → ++	-	-
	32	24	♀	17	++ → ++	++ → ++	++ → ++	++ → ++	++ → ++	-	-

* ++, +, ±, and - showing generalized marked swelling and redness on the gingiva, localized medium swelling and redness mainly on the gingival papilla, localized slight redness without swelling on the gingival margin, and no pathology respectively.

† ++, +, ±, and - showing distinct, moderate indistinct, and no pathology respectively.

- ‡ ++, +, ±, and — showing more than 4 mm., 3—4 mm., 2—3 mm., and less than 2 mm. respectively.
- § ++, +, ±, and — showing distinct, moderate indistinct, and no effect respectively.
- || ++, +, ± and — showing distinct, slight, indistinct and no regeneration of the alveolar bone respectively.

DISCUSSION

It seems that various kinds of knowledge obtained from many recent studies on A. P. make it more and more complicated to grasp the real state of the nature and etiology of the disease. These studies will give us many suggestions that A. P. may be caused not only by a local factor or factors but also by a constitutional factor or factors for the present. Thus the studies in these respects should be made on the basis of sufficient comprehension of local pathologic changes characteristic of A. P.

Histamine, which exists constantly in the tissue and produces inflammatory reaction by means of its easy liberation out of the cell, likewise plays an important role in allergic reactions⁴⁻⁷. In this sense the factors in its liberating process may also have an important relation with constitutional factors. From this standpoint it was the first object of the author's studies to attempt to catch histamine in the periodontal tissue in case of the disease and to investigate its role at the onset of the disease by making clear a relationship of this substance to a morphological pathological figure of the disease. Admitting that the author's object has not been sufficiently fulfilled, it appears considerable relationship exists between pathological figures of the disease and histamine.

At first a fact that the quantity of histamine in the affected gingiva of A. P. showed about threefold increase on an average as compared with that in the normal healthy gingiva could be recognized in the author's study. And it could be known by means of parallel investigations between macroscopic and microscopic observations that the case of inflammatory type indicated particularly a remarkable increase in histamine and, moreover, its increase became more marked in proportion to the progress of inflammation. These observations will suggest that this increase of histamine has an intimate relationship with inflammation itself in the disease.

Then comparison between affected and normal gingivae on the distribution and the shape of tissue mast cells was made, as these cells have been considered as the main depots where histamine exists¹⁰⁻¹². As the result it has been noticed that the former obviously shows an increase of the cells and their extensive distribution and has relatively greater ten-

dency of disintegration in their form than the latter. Furthermore, such a numerical increase and morphological changes could be recognized to become remarkable in proportion to an increase of gingival histamine, in other words, according to the progress of inflammation. However, considering the previous studies²⁵⁻²⁸ on the cells, it might be regarded that such findings of the cell is not specific changes in the pathologic condition of the disease, but is a factor following or constituting the chronic inflammation²⁷⁻³⁰.

It is considered that the first principal cause of an increase of these cells in such a chronic inflammation is that the liberation of histamine into the tissues occurs in the area affected by inflammation, according to BENSLEY's experience³¹ of a local increase in this cell in the case of repeated injections of histamine or to similar results in the author's third study. It may be possible that mast cells produced in such a way, as shown from their histological figure, will repeat their disintegration one after another and, moreover, discharging the histamine contained in disintegrated cells will lead to a persistent increase of the cells. The fact that the histamine liberated repeatedly by this causal relation in such a mechanism participates in the local changes by means of its characteristic action^{12,32,33}, is supposed to have a very great significance in the formation of chronic inflammatory findings⁷⁻⁹.

Next comes a problem, what cause or causes can give rise to such an increase of histamine. The author tried to cause the development of inflammation and an increase of histamine in the local region by means of various stimulations. Though the appearance of such an inflammatory change was not observed as the result of the repeated applications of various physical stimulations, it could be noticed with an increase of local histamine to a certain degree when an inflammatory condition was maintained by means of a certain mechanical stimulation following the antigen procedure. It might be considered by this result that chronic inflammation, suggestive of A. P., in the animal gingiva where an increase of histamine was observed simultaneously could be induced by the repetition of a definite stimulation suitable to produce such inflammation. Thus the above-mentioned experiment will suggest the importance of local anaphylactic mechanism. Therefore, it will be a fascinating supposition to observe these local changes of the disease with a conception of so-called allergy from the viewpoint of the above-mentioned observation, taking into consideration of constitutional factors in A. P.

Finally the author's fourth study showed that symptoms of the disease were remarkably reduced when topical applications of the ointment mixed

with sinomenine, histamine-liberating substance, and benadryl, antihistamine substance, were repeated every other day in gingival pockets. It is still unknown, however, whether this effect is due to a decrease of local histamine effected by sinomenine^{3,13-17}, to antagonism of an antihistamine^{21,34,35} to histamine, or to anaesthetic action given by two substances^{17,18,21}. Further investigations seem to give us interesting problems from the viewpoint that the symptoms of this disease may be related to histamine.

SUMMARY

1. Considering an imaginable important role of histamine in inflammations or allergic reactions, some clinical and experimental studies were made for the purpose of findings the relationship of the pathological changes of A. P. to local histamine.

2. Gingivae in the case of A. P. showed a remarkable quantitative increase of histamine, compared with those in the case of normal healthy controls. It could be noticed that this increase had an increasing tendency in proportion to the degree of inflammatory pathologic changes in the gingiva.

3. In the gingivae of A. P. an increase of mast cells and their morphologic changes, particularly disintegration, were seen and the grade of changes was almost parallel to an increase of histamine.

4. When a histamine solution was repeatedly injected into the mucobuccal folds of animals, a remarkable increase of histamine and mast cells in the injected gingivae were recognized with inflammatory changes. An increase of gingival histamine could be hardly recognized by means of a simple mechanical stimulation or local anaphylaxis alone. However, in the combination of two, the increase of histamine was seen and relatively remarkable inflammatory changes suggestive of A. P. were macroscopically and microscopically noticed.

5. Topical applications of the ointment mixed with sinomenine, histamine-liberating substance, and benadryl, antihistamine substance, repeated every other day in the gingival pockets, showed favorable effects in slight or early cases of A. P.

6. These observations suggest the existence of both possible role of histamine in the development of local pathologic condition of A. P. and allergic processes in etiologic factors of the disease.

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