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Mast Cells in the Islets of Langerhans

A Study of Their Behaviour in Connection with Diabetes and with Insular Amyloidosis

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Summary. The number of mast cells in the islets of Langerhans in 60 cases was determined in an autopsy study. The 60 patients were divided into 4 groups, distinguishing between those with diabetes, insular amyloidosis, those with both these pathological conditions and those with neither diabetes nor insular amyloidosis. As compared with the control group, it was discovered that there was a sharp increase in mast cells in the group with insular amyloidosis and in the group with diabetes; the number of mast cells tended to increase even more in the presence of both pathological conditions. With these data in hand, it is assumed that the increase in mast cells in the islets of Langerhans is not only due to the presence of amyloidosis, but that it is also brought about as a direct consequence of diabetes.

Key words: Aging — Amyloidosis — Diabetes Mellitus — Islets of Langerhans — Mast Cells.

Zusammenfassung. In einer Autopsieuntersuchung wurde die Anzahl von Mastzellen in den Pankreasinseln von 60 in 4 Gruppen aufgeteilten Personen (Diabetikern, Amyloidosis-kranken, beide bzw. keine der genannten Krankheitsformen darlegenden Patienten) bestimmt.

Bei Vorliegen von Amyloidosis sowie Diabetes war eine deutliche Erhöhung der Anzahl der MZ gegenüber der Kontrollgruppe zu beobachten, welche bei den von beiden Krankheitsformen befallenen Patienten noch größer erschien.

Auf der Grundlage der obigen Daten wird die Hypothese aufgestellt, daß eine zahlenmäßige Erhöhung der MZ in den Langerhansinseln nicht nur mit der Amyloidbildung in Zusammenhang steht, sondern auch als eine unmittelbare Folge des Diabetes angesehen werden kann.

Introduction

Despite its discovery at the beginning of this century (Opie, 1901), amyloidosis of the islets of Langerhans has neither been described in detail in connection with the etiopathogenetic processes which are at the root of it, nor is its relationship with diabetes very clear. This is mainly due to the fact that the two "degenerative" processes in the islets of Langerhans i.e. hyalinization and amyloidosis, were continuously being confused with one another. However, first attempts to distinguish between the two processes date back to Mallory (1914); later on specific information on this subject was provided by Gellerstedt (1938), Ahronheim (1943), Gomori (1943), Arey (1943), Warren and Le Compte (1952), Ganter (1961). Ehrlich and Ratner (1961) discovered that the substance called "hyaline", present in the islets of Langerhans, had staining reactions especially with Congo red and when observed under a polarizing microscope, it showed to be birefringent and to have a yellow-green dichroism, which is typical for amyloid (Beneke *et al.*,

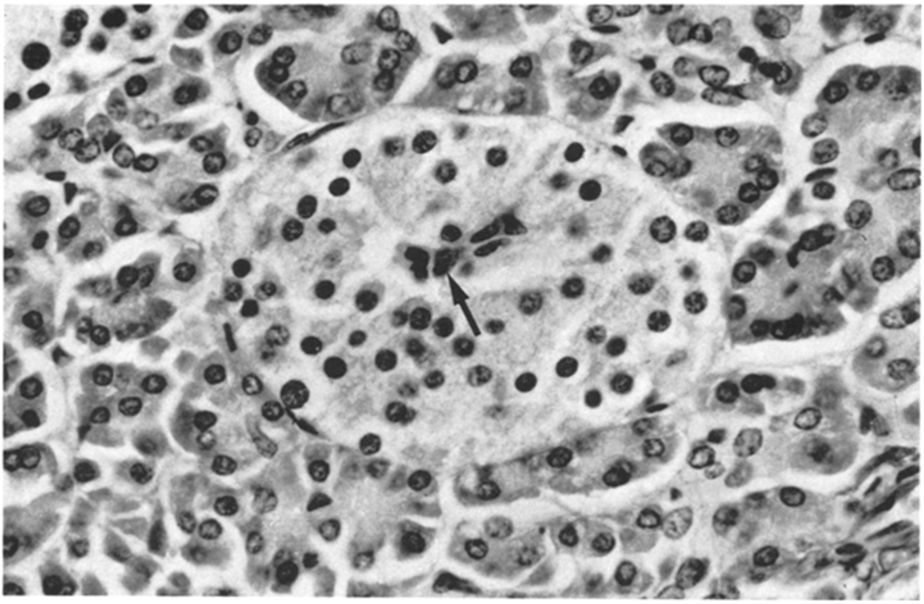

Fig. 1. Aldehyde Fuchsin 160 × ; M. Z. in Langerhans' islet of a diabetic person

1970). Schwartz (1965), using special fluorochroms, noticed that amyloid is present in the islets of Langerhans of diabetics and non diabetics. Recently, Westermark (1971), in a study of 23 patients, of whom 11 were diabetics and 12 non diabetics, pointed out that there was an increase in mast cells in the islets with amyloidosis.

Moreover, a change in the number of mast cells in association with amyloidosis had already been discovered in other vital organs and in different pathological conditions by Christensen (1968), Steiner (1969), Brini and Porte (1970).

In this study we wish to specify the variations in the number of mast cells in connection with two parameters: (a) diabetes, (b) amyloidosis of the islets.

Material and Methods

The study was carried out on autopsy material. We examined the pancreas of 60 patients divided into 4 groups as follows: 15 patients without diabetes or amyloidosis of the islets of Langerhans; 15 patients with diabetes; 15 patients with amyloidosis of the islets of Langerhans; 15 patients with diabetes and with amyloidosis of the islets. The patients in each group were chosen in such a way as to have 8 females cases and 7 male cases; the average age of the patients in the 4 groups were: 72 years for the group of non diabetics without amyloidosis of the islets; 69.40 for the diabetic group; 77.50 for the group with amyloidosis of the islets; 71.50 for the diabetics with amyloidosis of the islets.

We used clinical records to certify the presence of diabetes; cases in which the presence of diabetes was doubtful or little convincing were not included in the study. In addition to the clinical diagnosis, we also used all histological data (kydney and eye injuries) of a generally accepted diabetic nature.

As soon as it was possible, small pieces from the tail of the pancreas were removed after death and were quickly placed in a fixative solution of neutral formalin, 10%.

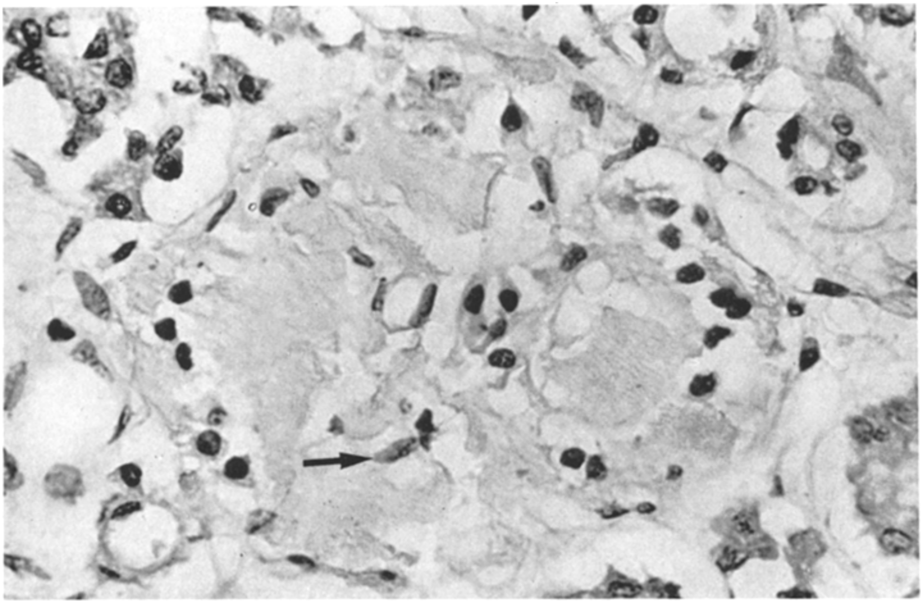

Fig. 2. Aldehyde Fuchsin 160×: M. Z. in amyloidotic Langerhans' islet of a diabetic person

After deparaffinization of 4 μ thick sections, these were stained with a solution of alkalin-alcoholic Congo red (Puchtler *et al.*, 1962) and afterwards, with the use of a polarizing microscope, the birefringence and the yellow-green dichroism, which are typical for amyloid, were examined (Romhanyi, 1949).

We then proceeded to the count of the mast cells. They could be seen clearly because they had been stained with aldehyde fuchsin, according to Gomori (Gomori, 1941) (Figs. 1, 2 and 3). With this method, the mast cells could be seen without any difficulty due to the dark reddish-purple colouring of their granulation; only mast cells with a nucleus were included in the count.

Mast cells lying at the borderline between the endocrine and exocrine tissue were counted as belonging to the islets only if they lay inside the basement membrane. We standardized our research by deciding to count the number of mast cells in 130 islets of Langerhans in each pancreatic section.

Results

Tables 1, 2, 3 and 4 show the final data obtained after having counted the percentage of mast cells (mast cells/100 islets), of the 4 groups of patients under examination. In addition, Tables 3 and 4 show the percentages of the islets with an amyloid deposit (in comparison with the islets without amyloidisis) which were found in the sections under study.

In the diabetic group there is a strong correlation between the number of mast cells and the presence of diabetes ($r = 0.63$; $P < 0.001$) in patients with insular amyloidosis. The correlation is also strong between the number of mast cells and the presence of amyloid in the islets ($r = 0.70$; $P < 0.001$) in the group of patients with diabetes, amyloidotic and non-amyloidotic, considered collectively.

Table 5 shows the indexes of correlation obtained from the overall analysis of the cases examined. These indexes show the existence of an extremely positive

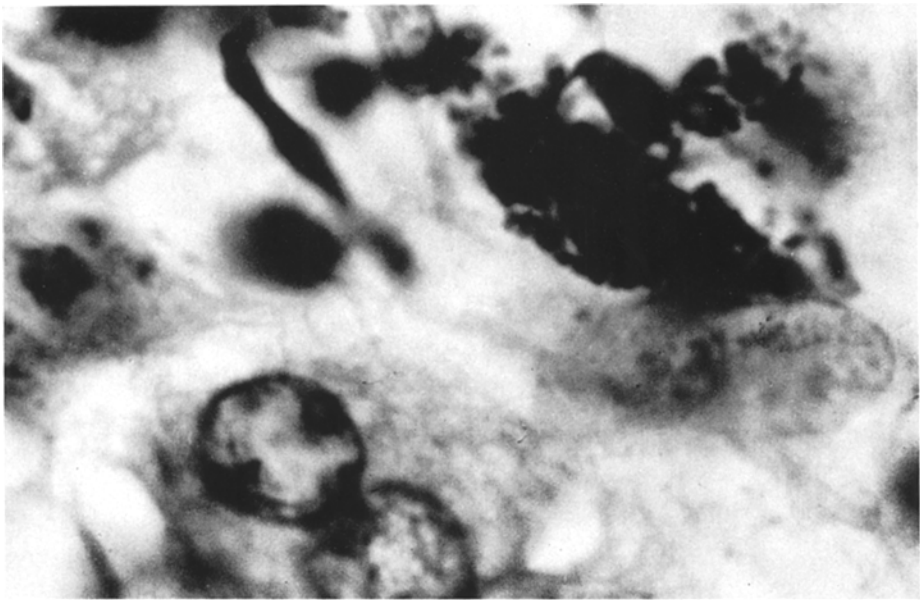

Fig. 3. Aldehyde Fuchsin 630× : M. Z. in the same islet of the previous figure

and significant correlation between the number of mast cells per hundred islets and, the presence of diabetes ($t = 4.75$; $P < 0.001$), and the presence of amyloid ($t = 7.14$; $P < 0.001$) respectively.

The correlation between the number of mast cells per hundred islets and the patients' age is negative ($t = 0.848$; $P < 0.2$).

Table 1. Non-diabetic and non-amyloidotic persons

Case No.	Sex	Age of death (years)	Islet mast cells/ 100 islets
1	M	83	5.00
2	M	69	8.82
3	F	74	7.27
4	M	61	7.00
5	M	72	0.80
6	M	74	2.40
7	M	74	3.20
8	F	63	5.26
9	M	66	3.20
10	F	57	2.34
11	F	73	3.13
12	F	97	8.59
13	F	83	1.56
14	F	76	0.00
15	F	58	0.00

Table 2. Diabetic persons

Case No.	Sex	Age of death (years)	Islet mast cells/ 100 islets
1	F	92	9.66
2	F	83	10.40
3	M	68	5.00
4	F	70	14.06
5	F	75	26.92
6	F	75	5.34
7	F	60	12.10
8	M	62	23.93
9	M	63	17.60
10	F	68	18.75
11	F	74	10.67
12	M	68	13.93
13	M	81	10.16
14	M	58	8.00
15	M	44	13.00

Table 3. Amyloidotic persons

Case No.	Sex	Age of death (years)	Islet mast cell/ 100 islets	% islets with amyloid
1	F	92	9.66	42
2	F	81	16.67	44
3	F	89	10.40	30
4	M	81	8.33	5
5	M	64	17.39	74
6	F	67	21.50	29
7	M	82	15.57	30
8	M	69	21.88	10
9	M	61	28.13	27
10	M	85	31.25	9
11	M	83	7.81	3
12	F	83	15.63	5
13	F	69	10.94	22
14	F	73	24.60	7
15	F	84	8.00	8

Table 4. Diabetic and amyloidotic persons

Case No.	Sex	Age of death (years)	Islet mast cells/ 100 islets	% islets with amyloid
1	M	71	50.98	28
2	F	72	62.50	63
3	M	48	20.80	23
4	F	75	37.01	20
5	F	77	44.09	61
6	M	83	14.40	10
7	F	77	34.67	10
8	M	79	40.80	29
9	M	64	34.62	82
10	F	70	43.38	45
11	F	68	33.71	20
12	M	65	22.31	22
13	M	59	61.42	19
14	F	85	57.79	34
15	F	84	18.58	24

Table 5. Coefficients of correlation in the simple correlation analysis

	Presence of diabetes	Presence of amyloid	Age
Islet mast cells/100 islets	0.48	0.60	−0.11
t-value	4.75	7.14	0.848
Significance	$P < 0.001$	$P < 0.001$	$P < 0.2$

Table 6. Coefficients of partial correlation in the multiple regression analysis

	Presence of diabetes	Presence of amyloid	Age
Islet mast cells/100 islets	14.04	17.25	−0.14
t-value	4.20	5.66	0.87
Significance	$P < 0.001$	$P < 0.001$	$0.4 < P < 0.5$

Highly significant are the regression coefficients (Table 6) showing the correlation between the number of mast cells per hundred islets, both in the presence of diabetes ($t = 4.20$; $P < 0.001$), and of amyloid ($t = 5.66$; $P < 0.001$).

The regression coefficient is also significant when examining the number of mast cells per hundred islets and the patients' age ($t = 0.87$; $0.4 < P < 0.5$).

Table 7 shows the mean value of mast cells present in one hundred islets $\pm$S.E., whereas in Table 8 we have analysed the statistical significance of the difference between the mean value of mast cells per hundred islets in patients without

Table 7. The islet mast cell frequencies per cent islets ± S.E.

Non-amyloidotic and non-diabetic persons	3.90 ± 0.76
Diabetic persons	13.30 ± 1.62
Amyloidotic persons	16.52 ± 1.96
Amyloidotic and diabetic persons	35.67 ± 3.98

Table 8. Statistical significance of the differences between the mean value of the frequency of M.Z. per 100 islets of non diabetic and non amyloidotic persons and, respectively, the mean values of each of the 3 remaining classes of persons

	Non-amyloidotic and non-diabetic persons	
	t-value	Significance
Diabetic persons	3.80	$P < 0.001$
Amyloidotic persons	4.09	$P < 0.001$
Amyloidotic and diabetic persons	4.47	$P < 0.001$

diabetes and without amyloidosis, and the mean value of each of the other 3 groups of patients respectively.

In this way we have seen that this difference is always highly significant ($P < 0.001$).

Discussion

From the present study, the results show that there is a clear per cent increase in mast cells in the islets of Langerhans in diabetics and non diabetics but with amyloidosis of the islets; this increase is higher if the two pathological conditions, here studied, are combined.

The per cent increase in insular mast cells in patients with amyloidosis, pointed out by Westermark (1971), is also confirmed by our results. In our opinion, it is worth noticing that this increase is also present in diabetics (without insular amyloidosis). Therefore we could assume that the cause of the increase in question is twofold: amyloidosis and diabetes; when the two causes are combined, the increase is greater (see Fig. 4).

We believe that this seems to fall into line with the generally accepted hypothesis according to which the cause of insular amyloidosis is diabetes (Warren *et al.*, 1966) on the one hand, and the general process of growing old (Bell, 1959; Ehrlich and Ratner, 1961; Schwartz, 1965; Ludwig and Heitner, 1967), on the other hand. Moreover such beliefs do not contradict each other and a twofold cause is freely or implicitly accepted by many (Westermark and Grimelius, 1973).

As far as the insular mast cells are concerned, their increase in patients with diabetes and without amyloidosis is apparently caused by the dismetabolic disease itself, which seems to be the causal agent of insular amyloidosis and, at the same time, of mast cellular increase in the islets. As for the amyloid deposit, as

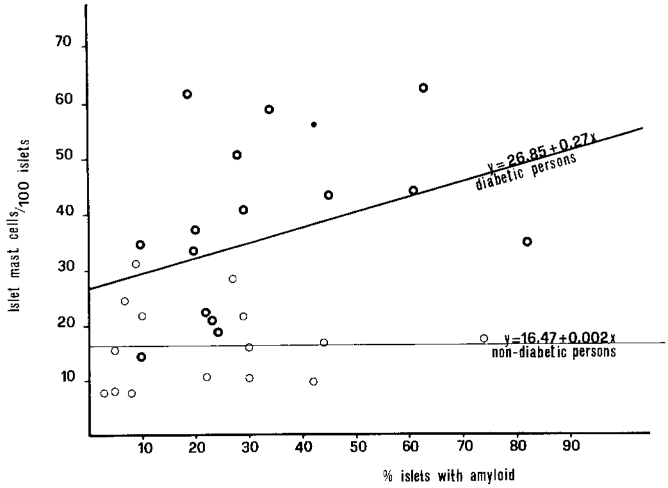

Fig. 4. Correlation between the frequency of islets with amyloidosis and the number of intra-insular mast cells in diabetic (o) and non-diabetic (○) persons

shown by cases where its presence is not associated with diabetes, it could conceivably cause (or be the effect of) an increase in mast cells (Westermark, 1971). If the two causes combine, the increase per cent is greater.

In conclusion we could formulate the following hypothesis; the presence of amyloidosis in the islets of old people implies an increase in mast cells (be it the cause or effect of amyloidosis itself); in addition, it seems conceivable that diabetes causes amyloidosis in the islets of Langerhans and at the same time increases the mast cells, even if the two phenomena do not occur in the same pancreas.

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