Mast Cells in the Circulatory System of Man

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This report is based upon a study of multiple segments of the cardiovascular system of 200 deceased persons and selected surgical specimens. Mast cells are present in the adventitia of all blood vessels. Only the largest vessels have mast cells in the intima and subintima as well. In this location the number of mast cells is highest in grossly normal but microscopically edematous areas. Mast cells are rarely present in early and are never present in advanced atheromatous lesions. The theory is advanced that mast cells are attracted by plasma insulin to release heparin for degradation of lipoproteins. Thus, mast cells might play a role in atherogenesis.

Much has been written about mast cells, but our knowledge is still fragmentary and controversial. References to the presence of mast cells in blood vessels of animals are available but there is none regarding their occurrence in vessels of man. A single paper deals with mast cells in the human heart. Lack of information about mast cells in human blood vessels prompted this study.

Materials and Methods

Two hundred patients were studied: 100 white and 30 Negro male subjects, and 42 white and 28 Negro female subjects. The youngest was an infant born dead in the seventh month of fetal life and a pair of full-term twins who lived 4 hours. The oldest person was 90 years of age. Distribution of subjects over the 9 decades of life was 32, 10, 22, 20, 18, 32, 28, and 6, respectively. The average age was 44 years.

The length of hospitalization prior to death varied widely. Some persons were dead on arrival, some had died a violent death, and others succumbed to various acute or chronic diseases. Causes of death corresponded to general mortality statistics.

Patients' charts and necropsy protocols were studied. All details were recorded for correlation with mast cell studies. Attention was paid to such details as body build and weight, mode and hour of death, interval between last meal and death, alcohol consumption and medication, and time between death and necropsy.

Transverse strips about 2.5 to 3 cm. long and about 0.4 cm. wide were cut from the ascending, thoracic and abdominal aorta. Grossly normal tissue was studied in all cases. Where alterations were visible, strips also were obtained from lesions of varied character. Similar strips were obtained from the main pulmonary artery, the inferior, and superior vena cava.

In each case, rings instead of strips were cut from the right pulmonary artery, left common carotid artery, right renal artery, left common iliac artery, and the portal vein. Normal and altered vessels were collected. Rings, instead of strips, were also cut from the aortas of children.

Selected surgical specimens were studied: 6 varicose veins, 4 femoral and tribial arteries, and others, vessels from a patient with Buerger's disease.

Sections were taken from the heart muscle and coronary arteries of all subjects. Normal and altered heart muscle was sampled.

Tissues were placed into a 4 per cent watery solution of basic lead acetate for 48 hours. They were rinsed twice in 10 per cent formalin solution and then placed for 48 hours in formalin. After fixation, tissues were processed in the usual manner. Paraffin sections, 6 μ thick, were stained with hematoxylin and eosin, with Pollak's trichrome stain, with the Giemsa stain, and in a 1 per cent solution of toluidine blue in methanol. The last 2 methods were found equally satisfactory for demonstration of cells with basophilic granules spoken of as mast cells.

Sections were stained under the high-power lens of the microscope. Mast cells were localized and their appearance was noted. Mast cells were enumerated in the aortic intima (the endothelium) and subintima (subendothelial layer). No attempt was made to count mast cells in the aortic adventitia. No counts were made in any of the other blood vessels. In each aortic strip, at least 100 fields were scanned to obtain the number of intimal-subintimal mast cells per 100 high-power fields. Cells were counted by moving the slide so that the endothelium was close to the edge of the visual field.

Observations

Aorta. Cells with basophilic granules were found in the intima, the subintima, and the adventitia. But for a single slide in which 2 mast cells were seen in a widened space between myofibrils close to the adventitia, the muscularis was always void of mast cells. Adventitial
mast cells were in close proximity to vasa vasorum and were found in all slides, regardless of findings in the inner wall of the aorta.

Most of the mast cells were in the endothelium proper and in the upper layers of the subintima. Except for the basophilic granules they resembled endothelial cells. Fewer mast cells were present in the lower half of the subintima. In this location they were more round and their granules were less dense, as compared to cells located closer to the vascular lumen. The size of granules and their staining ability were the same in all mast cells, but some had a single large vacuole.

Grossly Normal Aorta. The number of intimal-subintimal mast cells varied from person to person, from one aortic sector to the other, and from one visual field to the next. In slides from 36 subjects, 14 of whom were less than 20 years old, no mast cells were found. (Possibly, these results, as other findings, might undergo revision if one were to scan serial sections.) Differences for the 3 aortic sectors studied being disregarded, from 1 to 10 mast cells were counted in 100 fields in 84 persons, 11 to 20 cells in 56 persons, and between 21 and 90 cells in 24 persons. All subjects with more than 11 mast cells per 100 fields were over 20 years old.

More mast cells were seen in the ascending aorta than in other sectors. Sometimes the thoracic and abdominal aorta had about equal mast cell counts. Usually the count was lowest in the abdominal aorta. Typical examples of the number of mast cells per 100 fields of ascending, thoracic, and abdominal aorta were 33, 24, 13; 53, 25, 10; 99, 40, 18; 146, 54, 32; and 90, 37, 40. Thus, a different average could be arrived at for each sector in every subject, with the highest one for the ascending aorta (fig. 1).

Commonly fields with mast cells alternated with fields without mast cells. The highest total number of fields with mast cells was 50 out of 100. The highest number of consecutive fields with mast cells was 15. Maximum count of mast cells per single high-power field was 8.

The highest concentration of mast cells was seen in areas that, though grossly normal, appeared edematous on microscopic study. This was reflected in mast cell counts per field, per aortic sector, and per subject. In some instances fine basophilic granules were scattered

Fig. 1. A visual field of the inner coat of an ascending aorta. Left, X 200; middle, X 420; right, X 1100, Giemsa stain. Note the location of mast cells in the edematous intima-subintima, the round shape of one of the subintimal mast cells and the oval shape of the other mast cells, the lesser density of granules in subintimal mast cells compared to intimal mast cells, and the vacuolization of one intimal mast cell.
through edematous, metachromatic subintimal ground substance.

Grossly Abnormal Aorta. As a rule atheromatous plaques were without mast cells. This held true for all organized plaques, whether fibrosed or calcified, without or with parietal thrombi. In most instances early plaques were also without mast cells. A few were found at the edges of an intimal “cushion” in some slides. Lipophages seemed to replace mast cells of the intima-subintima. Between plaques the number of mast cells was the same as in strips obtained from grossly normal areas of the particular aortic sector. Adventitial mast cells were present regardless of intimal alterations.

Intimal-subintimal mast cells from a syphilitic aneurysm of the ascending aorta numbered 33 per 100 high-power fields. In 4 patients with ruptured aneurysm of the descending aorta, mast cell counts were 3, 12, 22, and 40, respectively. Sections from the thoracic aorta perforated by a shot had only 5 mast cells in the inner aortic wall. There were 16 mast cells per 100 fields in sections from the thoracic aorta with a transverse tear sustained in an automobile accident. The number of adventitial mast cells was about the same in damaged parts and unharmed parts of the aorta in all patients.

Other Arteries. In the main pulmonary artery the number of intimal-subintimal mast cells was about the same as in the thoracic aorta of each subject. None of the arteries of smaller caliber had mast cells in the inner coat. In the adventitia of all these arteries mast cells were abundant. Findings were the same in grossly normal and abnormal sectors, with the exception of coronary arteries, where adventitial cells were more numerous around atheromatous vessels than around normal ones. The outer muscularis of altered coronary arteries was usually besieged by mast cells (fig. 2).

Femoral and tibial arteries, intact, with atheromatosis, free, or thrombosed were surrounded by mast cells. Arteries and veins from a patient with advanced obliterating thromboangiitis had no mast cells in the inner coat but quite a few in the adventitia.

Veins. The inferior and superior venae cavae had mast cells in the inner layers but saphenous veins had none. All veins had many adventitial mast cells. In the large veins mast cells were located mainly in the deeper layers of the subintima and numbered at least as many as in the ascending aorta from the same person. Often there were almost twice as many mast cells in the large veins as in the aorta. Mast cells were more plentiful in the inferior vein than in the superior vein. The portal vein was
always surrounded by mast cells but none was found in the intima.

Heart. In normal portions of the heart mast cells were seen in the interstitial tissue and the epicardium, often in proximity to small blood vessels. In recently infarcted areas (18 patients) the number of mast cells was the same as in adjacent normal areas. Organized infarctions were without mast cells (16 patients) save for isolated cells at the periphery of scar tissue. In the heart of a patient who died of rupture of a recently infarcted left ventricle, mast cells were as numerous in the lacerated as in intact tissue. Average mast cell counts in the aortas of patients without, with recent, or with old myocardial infarction were about equal.

Discussion

It is debatable which of the following should be considered the normal for aortic intima-subintima: absence of mast cells, presence of a few mast cells, or presence of numerous mast cells. In small animals (frog, rat, guinea pig, rabbit) mast cells were found in the adventitia only, while these cells were seen in the aortic intima of large animals (cow, calf, horse, dog, pig). We observed that children had no, or but few, aortic intimal mast cells; also that only large blood vessels had mast cells in the inner coat. A physiologic relationship between intimal mast cells and the caliber of blood vessels seems likely.

The origin of tissue mast cells is a matter of dispute. Identity of tissue mast cells with circulating basophils is suggested by location of mast cells in and around blood vessels. Origin of tissue mast cells from connective tissue cells has been widely accepted. The suggestion of epithelial origin of mast cells might deserve more attention. The position of mast cells between intimal endothelium cells and their structural resemblance to these cells is intriguing.

Correlation of counts of aortic mast cells with clinical and necropsy data was unsuccessful. Attention is focused on the observation that high mast cell counts were obtained from fields with edematous tissues. Focal intimal-subintimal edema is often seen in grossly intact blood vessels of persons who died in shock.16 In our series, all subjects in whom mast cell counts were high had experienced shock, but not all persons who had been in shock had high aortic mast cell counts. Some persons may have died too quickly, before an increase of mast cells could take place. Other persons recovered from shock; mast cells could have appeared and disappeared, degranulated, or disintegrated. Such speculation finds support in the observation of extracellular basophilic matter in edematous ground substance.

Multiple reports concern a reduction of basophils during stress1 and in experimental shock.17 Disintegration of tissue mast cells following stress,1 adrenocorticotropic hormone injection,18 cortisone medication,19-22 or adrenalectomy2 was observed. Cortisone effect was, however, denied by some authors.7, 23, 24 A link between mast cells and shock has been established, but the nature of the relationship is not clear.

Shedding of granules of tissue mast cells in response to a variety of stresses has been reported25 and various functions have been ascribed to these cells. Apparently mast cells have multiple functions: uptake, transport, and release of macromolecular matter, such as histamine,26 heparin-histamine,27 or hyaluronic acid.28 Parallel increase in these substances and in mast cell counts need not be interpreted as evidence that mast cells are the source of these substances.

Highest counts of aortic mast cells were obtained in patients whose blood plasma was milky at autopsy. A man weighing close to 300 lb, who died in shock following an accident had 150 mast cells per 100 high-power fields in the intima-subintima of the ascending aorta. Possibly mast cells are attracted by lipoproteins carried into the vessel wall by blood plasma insudate. This thought finds support in the results of experiments. Intraperitoneal injection of fat to rats caused an increase in mast cells and severe degranulation.29 Upon intracorneal injection of serum lipoprotein fractions to dogs mast cells appeared in edematous tissues where normally none was found.30 Heparin carried and released by tissue mast cells might serve to break down lipoproteins into soluble protein and insoluble lipids. The presence of mast cells in edematous tissues and their absence in
atheromatous plaques possibly implicate these cells as participants in atherogenesis.

**Summary**

Mast cells were studied in grossly normal and grossly altered segments of the heart, aorta, pulmonary artery, the venae cavae, and multiple smaller blood vessels of 200 deceased persons. Vessels were also studied in 11 surgical specimens. They were counted in the inner layer of the ascending, thoracic, and abdominal aorta. The number was expressed per 100 high-power fields in each sector. Observations on the absence, presence, and quantitative differences of intimal-subintimal mast cells in various parts of the cardiovascular system are reported. Interpretation is attempted of the observation of the presence of mast cells in the inner coat of large vessels, their absence from small vessels, and their frequency in edematous areas of the intima-subintima and absence or rarity in atheromatous lesions.

A theory concerning the quantitative increase and function of mast cells is advanced.

**Summario in Interlingua**

Mastzellen esseva studiate in macroscopicamentemente normal e macroscopicamente alterate segmentos del corde, del aorta, del arteria pulmonar, del venas cave, e de varie vasos minor de 200 personas decedite. Esseva etiam studiate le vasos de 11 specimens chirurgic. Le mastzellen esseva contate in le strato interior del aorta ascendent, descendent, e abdominal. Lor numeros esseva exprimite in tantos pro 100 campos a alte potentia in omne sector. Es reportate observationes in re le absorbita, presentia, e le differentias intimal-subintimal de mastzellen in varie partes del sistema cardiovascular. Es tenta un interpretation del observation del presentia de mastzellen in le tunica intime del grande vasos, de lor absorbita in vasos minor, e de lor frequentia in areas edematose intima-subintimal e absentia o raritate in lesiones atheromatose.

Es formulate un theoria in re le augmento quantitative e le function de mastzellen.

**References**

7. —: The relationship of the tissue mast cells to the blood vessels in the rat. J. Path. & Bact. 65: 461, 1953.
A thing is important if any one think it important. The process of history consists in certain folks becoming possessed of the mania that certain special things are important infinitely, whilst other folks cannot agree in the belief. The Shah of Persia refused to be taken to the Derby Day, saying, “It is already known to me that one horse can run faster than another.” He made the question “which horse?” immaterial. Any question can be made immaterial by subsuming all its answers under a common head.—WILLIAM JAMES, Principles of Psychology, 1842–1910.
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