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PROBLEM OF THE SO-CALLED MYOCYTES

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Peculiar cells were in 1901 found by OPPEL [9] while studying the granulation tissue developing after cardiac injury to replace the destroyed parts of the myocardium. He thought that they originated from degenerating muscle fibres, called them myoblasts and supposed that they had a role in the development of the granulation tissue. ANITSCHKOW [2] (1913), in his work entitled "Formation of Granulation Tissue in Heart Muscle" was the first to deal in detail with these cells and the first to use the term "myocyte".

The histological appearance of the myocytes is as follows. Most characteristic is the special arrangement of the nuclear chromatin (Fig. 1). The chromatin accumulates in the nuclear axis and is serrated. Fine fibrils of chromatin radiate from the serrated ends extending towards the nuclear membrane. These fibrils seem to fix the central chromatin to the nuclear membrane. The nucleus mostly assumes an oval shape. Beside this arrangement, some myocytes exist that show the chromatin in the nuclear axis to take a wavy form (Fig. 2). In cross sections the chromatin is found in the central axis of the nucleus. It is clearly visible that the chromatin fibrils originating from it extend through a clear area to reach the inner surface of the nuclear membrane. As these cells resemble an owl's eye, they have been called owl-eye cells.

Azocarmine and neutral red staining reveals the chromatin condensed into the nuclear axis to be built up of minute granules. With eosin-azur the protoplasm stains a pale red, with Heidenhain's iron-haematoxylin a pale greyish brown and shows a fine, foaming vacuolar structure. In most cases this is so faint that its detection is difficult, but Giemsa and azocarmin staining make its detailed examination possible. The cells are generally polymorphous, oval or round and some of them have long processes. The processes have a rounded tip, not a pointed one as the fibroblasts. They greatly vary in size and are between that of a leukocyte up to 25—30 micron in diameter. Those lying directly beside the muscle fibres or on degenerating fibres are especially large. The myocytes do not produce fibres. Collagen fibrils are never found in the peripheral parts of the cytoplasm.

As regards the origin and location of myocytes, the different authors hold different views.

SALTYKOW [10] (1905) considered them myogenous.

GÖBEL (1910) repeated the experiments of OPPEL. He denied that muscular elements had a part in the development of granulation tissue and considered the scar tissue to derive exclusively from connective tissues.

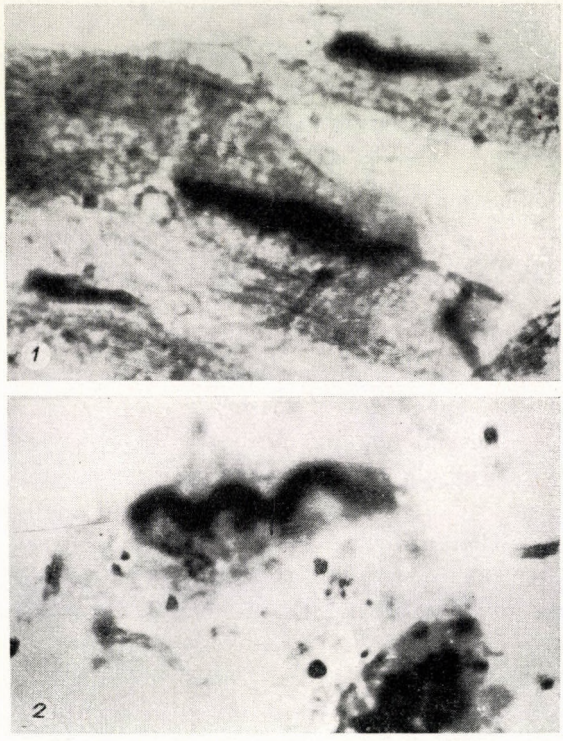


Fig. 1. Giant myocyte. The chromatin has condensed into the nuclear axis; serrated parts radiate from it. Oil immersion, Heidenhain's iron haematoxylin stain

Fig. 2. Myocyte, the nuclear axis of which fails to show a chromatin bar but there is a wavy formation of chromatin. Oil immersion, Heidenhain's iron haematoxylin stain

ANITSCHKOW suggested that the myocytes originated partly from muscle and partly from connective tissue.

KARSNER and DWYER [7] (1916) found myocytes 24 hours after experimentally induced infarction of the heart. They observed similar specific nuclear changes in the myocardium, in the macrophages and in the connective tissue cells.

J. W. WATJEN [13] (1921) was the first to describe in a case of pancarditis subepicardial rheumatic nodules at the border of which some myocytes were found, and also the first to find myocytes outside the myocardium.

M. Hesse and E. Hesse [6] (1924) studying human hearts after injury, suggested that myocytes were transformed muscular nuclei the contractile substance of which had degenerated.

K. Semsroth and E. Pool [11] assumed an endothelial origin.

Intravital staining was applied by Wenezianowa-Grusdkowa [14] (1929) to study the origin and function of the myocytes. She is of the opinion that myocytes are histiocytes of the common type and of non-myogenous origin, and that they belong to the various elements of the mesenchymal tissue.

Ehrlich and Lapan [4] (1939) pointed out that the myocytes were normal constituents of the verebrate heart. In the embryonal and postembryional phases of development they are parts of the supporting tissue of the heart and belong to the fixed elements of the reticuloendothelial system. Extracardially, though a large number of organs and tissues had been subjected to examination, myocytes were not found in human tissues. Ehrlich and Lapan suggest rather the term cardiac reticulocyte instead of the term myocyte.

Clawson [3] (1941), in agreement with Ehrlich and Lapan stated that the myocytes were present in cardiac muscle and the valves also under normal conditions. As he could not find them extracardially, he suggested them to be specific of the heart. He termed them histiocytes and stated that they derived from cardiac interstitial tissues.

Hamilton and Syverton [5] (1950) observed Anitschkow type nuclei in a great number of typical metachromatic histiocytes. Part of the so-called Anitschkow cells was identified with tissue histiocytes, (basophilic tissue cell, "mucinoblast", "heparinoblast").

Mainwaring and Ayres [8] (1952) found typical Anitschkow-type myocytes in primary fibrosarcoma of the heart. These myocytes did not occur in the pulmonary metastases and this was the first time that a cardiac tumour containing myocytes was reported.

According to Albertini [1] (1953), postembryonally and also in adults, the moycytes appear only as pathological cell forms, they derive from the connective tissue.

Led by the contradictory and divergent facts of the literature, I have carefully examined an extensive material by different staining methods, searching after a uniform, acceptable point of view concerning the problem of myocytes. In course of these studies 31 cases of rheumatic carditis, 5 of pericarditis, 9 of coronary sclerosis and thrombosis, 8 of infarction, 17 of acute and chronic endo- and myocarditis, further a stabbed heart, the heart of 3 dogs with previous heart operation, the heart of 3 human embryos, that of 6 guinea-pig embryos were examined. The heart of patients dead of various other diseases served as control, e. g. 12 cases dead of influenza, pneumonia, or after different operations, 12 cases of chronic and acute pleuritis and, further, 4 uteri, either pregnant or inflamed, and inflamed cross-striated muscles in 2 cases. The following staining

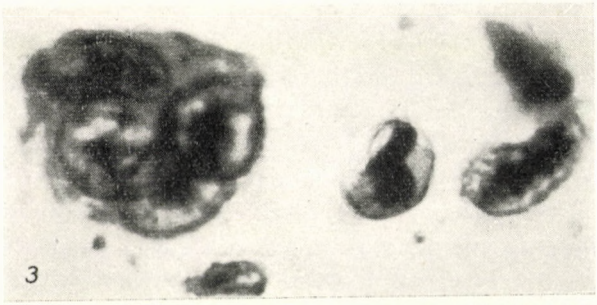
methods were used : 1. haematoxylin-eosin, 2. van Gieson's, 3. Heidenhain's iron-haematoxylin, 4. Heidenhain's azan, 5. neutral red, 6. methyl green-pyronin, and 7. Giemsa's.

Rheumatic nodules are most suited for studying in the first and second stage. Different parts of the heart were examined ; the frontal and posterior wall of the left ventricle, the posterior papillary muscle of the bicuspid valve, the interventricular septum, a part of the apex and parts of the right ventricular and left auricular wall. Myocytes occured with similar frequency in the different parts ; most of them, however, in the left ventricle, displaying the gravest lesion.

Muscle fasciculi built up of myocardial fibres lie closely beside each other under normal conditions and connective tissue cells can be found in a considerable amount in the wider interfascicular and perivascular areas where the major veins distribute into capillaries. At best, one or two fibrocytes with compact nucleus and one or two mono-nuclear cells of the lymphoid type may be found between the muscle fibres. Owing to the inflammatory stimulus, the muscular fibres are pushed aside by the oedema and the dilated capillaries. The capillaries, invisible until this moment, strongly dilate and become filled with erythrocytes. Large fibroblasts with an enlarged nucleus appear in the interfascicular areas. The endothelial and advetitial cells of the capillaries are also enlarged. First only fibroblasts, some reticular cells and polyblasts are to be observed. At a later period some cells appear among the enlarged fibroblasts in the nuclei of which the chromatin has concentrated into the nuclear axis. Some cells with the typical chromatin arrangement characteristic of myocytes are found near them. Occasionally, especially in perivascular areas and in larger septa, cellular groups can be detected in which myocytes dominate. The courtesy of Dr. ÁRVAY of the Institute of Forensic Medicine has enabled me to study the heart of dogs which had undergone a heart operation. In the heart of a dog that lived 40 days following the operation I could find in the scar tissue fibrocytes the chromatin of which had condensed into the nuclear axis. These cells completely agree in their form with the fibrocytes and may be considered myocytes only because of the characteristic arrangement of chromatin in their nucleus. My observations, consequently, correspond to the findings of Anitschkow, according to whom during the later phase of inflammation the myocytes cannot any more be differentiated from fibrocytes.

In all of my rheumatic cases I could find the myocytes in the Aschoff nodes of the heart. Some nodes showed a myocyte predomination in the cellular forms. A remarkable case might help to elucidate their relation to basophilic giant cells. Searching for normal, healthy controls in the material of the Institute of Forensic Medicine I examined a 17 year-old girl whose forehead had been hit by a javelin and thus she died on the sports-field. She had been healthy and her organs appeared to be absolutely intact. Histological examination, however,

revealed an increase of the fine loose connective tissue in the myocardium and fibrinoid degeneration. There were numerous typical myocytes among the fibres of connective tissue. Also minute Aschoff nodes in which the giant cells were just about to develop could be detected in other parts of the left ventricle. In thin sections the nuclear structure characteristic of the myocytes could well be recognized in the nuclei of giant cells which had a cytoplasm light in colour (Fig. 3). In some giant cells there was a typical "owl-eye" formation. The nuclear



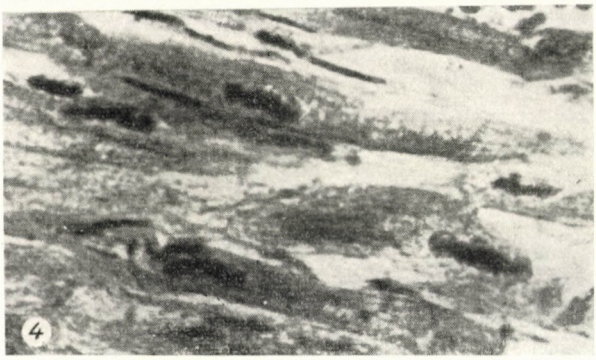


Fig. 3. Part of an Aschoff-node. 2 dissected "owl-eyes" and 3 vertical myocyte nuclei are visible in a giant cell with 4 nuclei. 2 free myocytes are seen beside the giant cell. Oil immersion, haematoxylin-eosin stain

Fig. 4. Necrobiotic fragment of cardiac muscle from a case of rheumatic carditis, with a great number of myocytes. Left from the centre 3 myocytes close to each other are attached to the muscle fibre. Above, one of them takes place at the axis of the muscle fibre as if it were a myocardial nucleus. Oil immersion, Heidenhain's iron haematoxylin stain

structure characteristic of myocytes could be discovered in most of the giant cells and when they had disappeared, myocytes were found at their place. Myocytes of the Aschoff nodes are derived from the adventitial cells and take part in the formation of giant cells. After the giant cell phase they probably retransform into histiocytes with a nuclear structure of the myocytes. It may be supposed that they transform into fibroblasts and fibrocytes in the third phase of the node. Some of them still retain their characteristic nuclear structure.

Myocardial fibres are severely lesioned by rheumatic fever. The cells of the myocardium lose their cross striation, undergo cloudy swelling as well as vacuolar and fatty degeneration in the cytoplasm. Myocytes can be found especially in and near those parts of the myocardium where necrobiotic changes have developed. At some places as many as 3 or 4 myocytes can be discovered on a single muscle fibre or immediately adjacent to it (Fig. 4). Doubtlessly, there are some places where the nuclei of the myocardial fibres are in a transitional form, their nuclei, however, can be differentiated from those of the myocytes. They become enlarged in course of their degeneration but their ends remain round. The chromatin is condensed into one or two axes in the centre of the nucleus. In some of them the chromatin structure is arranged as in the myocytes : the cap-like lipofuscin granulation may be discovered at the two ends of the nuclei. Cross-sectioned muscle fibres showed nuclei, the chromatin of which had condensed into the nuclear axis and the chromatin fibrils had extended toward the nuclear membrane. The muscle fibres were absolutely intact. The major part of the myocytes next to the muscle fibres or on them is not myogenous ; the nuclear structure of myocytes may be discovered also in the nuclei of the myocardial cells, owing to the inflammatory stimulus. Elsewhere the nuclear membrane of cells transformed in the manner of myocytes and disappeared, and part of the nucleus disintegrated. It seemed that the nucleus of the muscle cell degenerated in the myocardial fibres after the nuclear structure of myocytes had developed and had no part in the formation of granulation tissue.

Examination of the rheumatic cases and of dogs previously subjected to heart surgery revealed the nuclei of both the endothelial and the adventitial cells to be able to transform into typical myocytes. Adventitial cells significantly increase in number owing to the inflammatory stimulus and among them there are typical myocytes as well as cellular formations resembling them. The nuclear structure of myocytes may be discovered in both the capillary endothelial and in the adventitial cells. In the smooth muscle of small blood vessels of a heart with rheumatic pancarditis there were numerous smooth muscle nuclei showing the structure of myocytes, suggesting that the nuclear structure of myocytes may develop in nuclei of smooth muscles in blood vessels as well.

Material obtained from the Institute of Forensic Medicine [12] made it possible to control the findings of WENEZIANOWA-GRUSDKOWA. In a heart pierced by a needle with suicidal purposes microscopic examination revealed subacute inflammation in the injured part, in the middle of the wound a bean-sized softening the centre of which contained much fibrin with an abundant infiltration of erythrocytes, lymphocytes and leukocytes. At the peripheral part of the softening there was an increase in connective tissue and many freshly developed capillaries. Other parts of the myocardium showed cloudy swelling and fatty degeneration. The protoplasm of the klasmatocytes around the softened area was full of minute brown granules. A great number of myocytes was found among

the klasmatocytes, fibroblasts, lymphoid elements and leukocytes. Changes in the chromatin arrangement as in myocytes were observed in the nuclei of muscle fibres as well. It was striking that there were transitional forms among the fibroblasts, fibrocytes and myocytes. Myocytes derived from fibroblasts had a form similar to a longish, thin oat grain with pointed tips. On the other hand, those derived from muscle or endothelial and adventitial cells were more swollen, larger and their ends were rounded. This also shows that few myocytes are phagocytizing. A difference must be made between myocytes derived from the reticulo-endothelial elements having phagocytic ability and between those derived from the connective tissue and less inclined to phagocytizing.

A small haemangioma was found in the heart of a 5 year-old girl who had died of rheumatic pancarditis. The major part of the haemangioma was located in the pericardium and part of it among the muscle fibres. In the connective tissue stroma of the tumour there were myocytes and in the protoplasma of them fine yellow granules were present.

Further examinations disclosed typical myocytes also in inflamed pericardium. They were found in endocardial granulation tissue and in cases with subacute bacterial endocarditis also in the valves and in accretions adhering to them. Consequently, myocytes are doubtlessly present both in the endocardium and in the pericardium as well as in endocardial adhesions. In addition to the rheumatic cases they occur in considerable numbers in the myocardium of patients with subacute bacterial endocarditis.

As to the interesting problem of the division of myocytes, the characteristic nuclear structure disappears when mitotic division takes place. Their nuclear form being closely similar to that of the fibroblasts, it is difficult to determine whether the dividing cell is a fibrocyte or a myocyte. Myocytes in amitosis were more common. We may observe the protoplasm and the nucleus to begin to divide, in other cells myocytes just after division, connected by a thin bridge occur. The findings, as well as data in the literature prove the myocytes to multiply mostly by amitosis.

In one of the rheumatic cases there was a typical histiocyte in the perivascular area, in the nucleus of which the chromatin formed a characteristic bar. According to this finding, the characteristic chromatin arrangement may develop also in histiocytes.

Control examinations disclosed some myocytes in the interfascicular area of intact hearts as well. They are most frequent in the very young, from 1—2 days up to one year of age being present in the heart of the 6 week-old embryo as well as in the heart of the 95 year-old patient. Their number was the highest at the age of 5 months. All these point to the fact that myocytes may be found during both the embryonal and the postembryonal stages of development, but in a significantly lower number than in injured hearts. By comparing different cases their number seemed to be increased mostly in rheumatic carditis and

subacute bacterial endocarditis. They are also frequent in cardiac muscle scarred in consequence of coronary sclerosis.

It is an old problem whether myocytes may be met with extracardially. Examination of a 6 week-old embryo revealed extracardially in the mesenchymal tissue nuclei the chromatin of which had condensed into the nuclear axis. Nuclear formations characteristic of myocytes could, however, not be detected. Thickened pleura in acute or chronic pleuritis, further, pregnant or inflamed uteri were also examined. Neither contained typical myocytes. In a case of subacute inflammation of the thigh muscles, though a large of histiocytes, reticular cells and fibroblasts were present among the inflammatory elements, myocytes were not found, only some chromatin condensation. All these suggest that myocytes occur only in the heart and never extracardially.

As in the heart, in patients dead of eclampsia of pregnancy, the nuclei of liver cells occasionally show the chromatin to arrange into the centre of the nucleus, but no fine chromatin fibres extending from the central chromatin mass toward the surface of the nuclear membrane were discovered.

Thus myocytes are present in the heart during the embryonal stage of development, as well as in postembryonal life. They may, however, considerably increase in number owing to different damaging effects. As a result of injury, various cells, such as those of the cardiac connective tissue, the endothelial and perithelial cells, the nuclei of histiocytes and the nuclei of the giant cells of rheumatic nodules may show the nuclear structure characteristic of myocytes. As they do not occur extracardially, we may suppose the local and functional conditions of the heart to have a decisive role in their development. Chromatin condensation into the nuclear axis in liver cells of patients with eclampsia is probably a phenomenon caused by water uptake. This factor, beside a number of others, may occur also in the heart muscle when the formation of nuclear structure of myocytes takes place. Their numerical increase caused by the different kinds of injury supports the view that their appearance is a degenerative phenomenon.

Owing to various damaging factors, especially to rheumatism, the characteristic arrangement of nuclear chromatin may appear in the cells of all the elements of the heart. This may be in relation with the common mesenchymal origin.

According to the examinations reported, the classification of myocytes on a genetical basis is not fortunate. Consequently, the terms myoblast given by OPPEL, myocyte by ANITSCHKOW, cardiac histiocyte by CLAWSON, cardiac reticulocyte by EHRICH and LAPAN, are not exact. Considering, however, that these cells are best known in the literature under the term "Anitschkow myocyte" it seems correct to retain this name.

Summary

A histological study has been made of 135 human and 3 dog hearts to determine the cellular type, histogenesis and place of occurrence of the myocytes. Rheumatic carditis was represented by 31 cases and 3 human, 6 guinea-pig and 8 mouse embryo hearts have also been examined. Myocytes were present in hearts both during embryonal development and in postembryonal life. They, however, showed a considerable increase in number as a response to different damaging factors. The nuclear structure of myocytes may occur in the cells of cardiac connective tissue, in endothelial and perithelial cells of the blood vessels, in myocardial cells, in histiocytes and in the giant cells of rheumatic nodules.

Myocytes were not found extracardially. Probably local, functional and degenerative factors have a role in their development.

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ГРОБЛЕМА ТАК НАЗ. МИОЦИТОВ

Ф. ТОТ

В целях выяснения мест встречаемости, типа клеток и гистогенеза миоцитов автор проводил гистологические исследования над сердцами 135 людей и 3 собак. 31 случай оказался ревматическим. Для эмбриологического исследования применялись эмбриональные сердца 3 людей, 6 морских свинок и 8 мышей. Автор установил, что миоциты можно обнаружить как в эмбриональной стадии развития сердца, так и в постэмбриональных сердцах. Однако, на действие различных вредных факторов они в большой степени размножаются. Миоцитовая ядерная структура может проявляться в сердце также и в клетках соединительной ткани, в эндотелиальных и перителиальных клетках сосудов, в клетках сердечной мышцы, в тучных клетках, и в гигантских клетках ревматических узлов. Внесердечно нельзя было обнаружить миоцитов.

В возникновении миоцитов могут играть роль функциональные и дегенеративные факторы.

DAS PROBLEM DER SOG. MYOCYTEN

F. TÓTH

Zur Klärung des Zellentyps und der Histogenese der Myocyten, sowie der Stellen ihres Vorkommens wurden histologische Untersuchungen an insgesamt 3 Hunde- und 135 Menschenherzen (darunter 31 rheumatischen) durchgeführt. Es wurden ferner die Herzen von 3 Menschen-, 6 Meerschweinchen- und 8 Mäuseembryonen untersucht. Es wurde festgestellt, dass Myocyten sowohl im embryonalen, als auch in den postembryonalen intakten Herzen vorhanden sind. Auf Wirkung von verschiedenen Schädigungen können sie sich jedoch bedeutend vermehren. Myocytenkernstruktur kann im Herzen auch in den Bindegewebezellen der Gefässe, den Herzmuskelzellen, den Mastzellen, sowie in den Riesenzellen der rheumatischen Knoten in Erscheinung treten. Extrakardial konnten keine Myocyten nachgewiesen werden.

In der Entstehung der Myocyten können örtliche funktionale und degenerative Faktoren eine Rolle spielen.

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