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Browicz or Kupffer cells? **

THE PROBLEM OF EPONYMOUS medical names of anatomical organs, histological structures, disease symptoms, or nosological units, usually is a ground for discussion if patron's name has been chosen correctly and if reasons of this choice have been thoroughly justified. The question marks appear specially in the cases when two or more names appear in an eponym. Quite often one of these names is used by the local circles only (usually restricted to one country) to emphasize the priority or significance of contribution to the solution of a problem made by the researcher whose name has been added to an eponym. There are known examples of Polish doctors or biologists whose names appear in contexts of a very obviously eponymous nature, although their association with some medical facts is restricted to our own medical environment. Among numerous examples of this type, an uppermost position holds the problem of the name of the cells present in liver sinusoid, known in the European medical literature as Kupffer cells, and in Poland almost always called by the name of Browicz and Kupffer cells. An attempt to determine who has priority in this respect — a professor of anatomy at the university, first, in Königsberg and then in München — Carl Kupffer, or an eminent Polish scientist, professor of pathologic anatomy at the Jagellonian University — Tadeusz Browicz has led to very surprising conclusions.

To make the discussion easier, we should first outline the structure of the liver sinusoid which is found between the cords of hepatocytes. The sinusoid is composed of four different cell types; each type has its own morphology, topography, and function. The sinuses are lined with a discontinuous layer of endothelial cells which are provided with numerous fenestrae. They separate the perisinusoidal Disse's space with protruding microvilli of the hepatocytes. Through the fenestrae and intervillous lacunae, are passing various macromolecules and blood cells. The liver macrophages (the derivatives of blood monocytes), known in the world literature as Kupffer cells, are resting in the lumen of the liver sinusoid, fastened to endothelium. Through intervillous lacunae their protoplasmic processes may penetrate into Disse's space. The main function of Kupffer cells is to remove harmful molecules, microorganisms, the aged and damaged erythrocytes, and the circulating neoplastic cells. Excited by inflammatory factors, these macrophages secrete some specific mediators (eicosanoids, nitrogen oxide, TNF-alpha, gamma interferon and cytokines of various types). They are very important at the early stage of hepatitis, contributing in its initial period to a delayed immune response. These mediators are released specially in the presence of accumulated endotoxins of bacteria (mainly lipopolysaccharides). During hepatocellular damage of the liver or in the state of chronic inflammation, the macrophages release enzymes and cytokines which may damage hepatocytes but which also take an active part in the recovery of extracellular matrix.

Cells of the third type present in the sinusoid are the, so called, perisinusoidal (stellate) cells of the liver present in Disse's space, which in the studies done at the close of the 19th century and at the turn of the 19th and 20th century were described by Kupffer. They have long cytoplasmic processes entwining the sinuses. The cells, nowadays designated as Ito cells or "hepatic stellate cells", play an important role in the metabolism, assist the storage of vitamin A, are involved in production of the intercellular matrix and in the liver regeneration process; they can also undergo transformation into miofibroblasts producing collagen.

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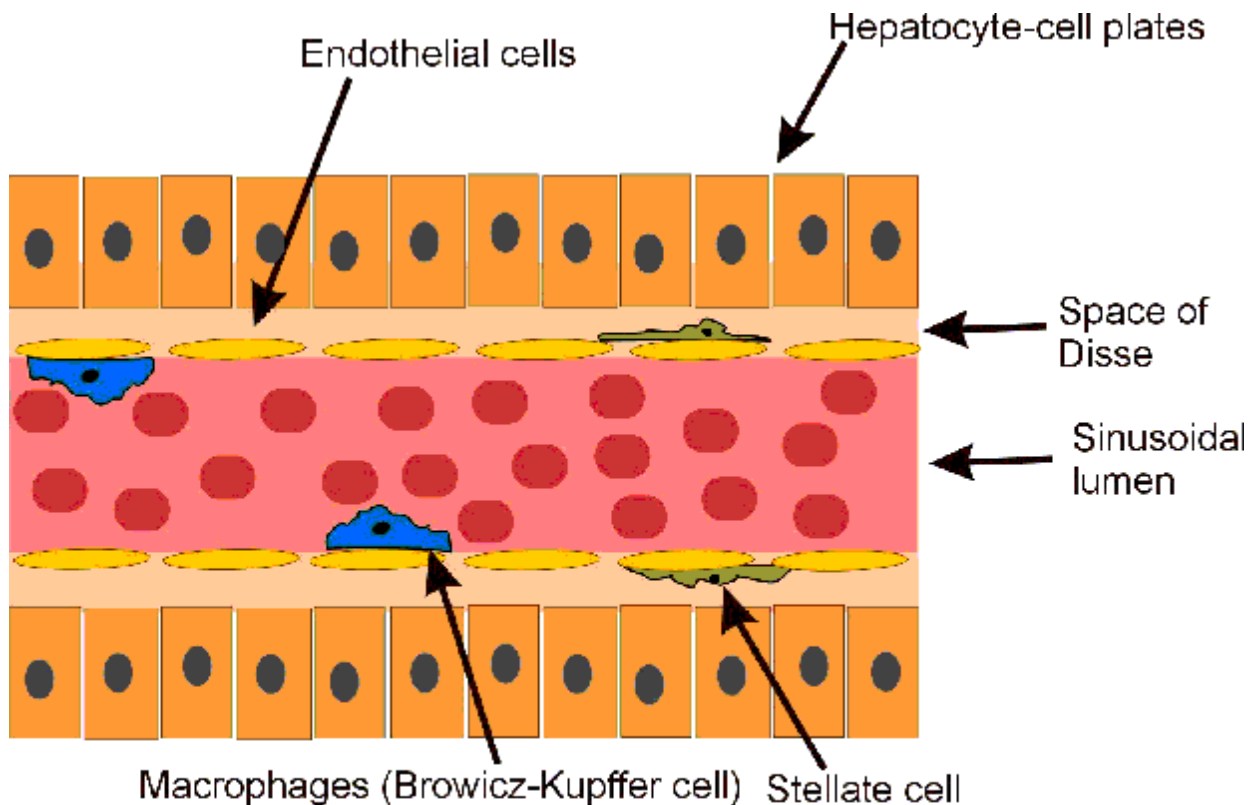


Fig. 1. The hepatic sinusoid and the sinusoidal cells

The fourth type of the sinusoidal cells, disregarded in further discussions, are the, so called, „liver-associated lymphocytes”.

Basing on the available source materials it can be assumed that the, characterized by a specific star-like shape, cells were for the first time examined by a German researcher Carl Kupffer in year 1876. He also gave them the name of *Sternzelle*, that is, ‘stellate cells’.¹ Kupffer noted their presence during his studies on nerve fibres in the liver, an arrangement of which he tried to disclose by application, according to Gerlach technique, of gold chloride solution. The, stained in black, ‘stellate cells’ were distinctly visible in hepatic lobule. Then, the German researcher suggested that cells of this type belong to the family of perivascular cells of the connective tissues or to the adventitial cells (pericytes).²

The subject of ‘stellate cells’ was taken up again in early 80ties of the 19th century. At that time, Kupffer’s disciple and assistant, Paul Rothe, repeated his master’s experiment using gold chloride. Rothe confirmed *in extenso* the presence of these cells not only in liver tissues of the mammals but also in the chicken livers.³

Kupffer himself resumed the subject of the cells he had discovered not earlier than in year 1898 during the 12th Congress of Anatomy held in Cologne. The revised and completed text of Kupffer’s

¹ von Kupffer C (1876), “Ueber Sternzellen der Leber. Briefliche Mitteilung an Prof. Waldyer”, *Archiv für Mikroskopische Anatomie* 12, p. 353–358; Wake K., “Karl Wilhelm Kupffer and his Contributions to modern Hepatology” (text in manuscript), p. 1–10.

² Browicz T. (1899), “Ueber intravasuläre Zellen in den Blutcapillaren der Leberacini”. Separat aus dem *Anzeiger der Akademie der Wissenschaften in Krakau*, p. 6–8.

³ Wake K., “Karl Wilhelm Kupffer and his Contributions to modern Hepatology” (text in manuscript), p. 1–10.

paper was printed one year later. It is certainly a most comprehensive and exact description of the studies and conclusions offered by this German researcher in which he revises his earlier approach to the nature of the 'stellate cells'. As a result of detailed comparative studies, Kupffer arrived at a conclusion that the 'stellate cells' form an integral constituent of the vascular walls and correspond to the specific cells of endothelium, capable of phagocytising alien materials.⁴

This, extremely important, paper Kupffer delivered in Kiel on the 18th of April 1898. Meanwhile, exactly one week later, on the 25th of April, in Krakow, during a session held at the Faculty of Mathematics and Natural Sciences of the Academy of Learning in Krakow, Tadeusz Browicz, professor of pathologic anatomy at the Jagellonian University, delivered a lecture entitled: *On the intravascular cells in capillary blood vessels of the hepatic lobule*. The same year, the text of the lecture was published in the German language,⁵ and one year later it was published in Polish.⁶ Browicz describes in a rather exact manner the appearance of the cells and their position in respect of the vessels. He observes that to the inner wall of a capillary vessel are adhering large oblong cells; sometimes they are fastened to the wall of a vessel by a „tail” which confers to them a pear-like shape. Similar cells but free he also noted to be present in the lumen of the vessel, surrounded by blood cells. He also described their nuclei (oblong, alveolar, or corrugated) and a granular cytoplasm with processes, often comprising leucocytes, erythrocytes, vacuoles, and deposits of pigment. Finally, he concludes that the origin and place where these cells are formed is to him quite unknown.⁷

Quite interesting in our considerations remains the fact that in the above mentioned text Browicz did not make even a single reference to the 'stellate cells' which had been known since 1876; Kupffer's name was not mentioned even once, either. It is difficult to find a straight answer why it was so. Firstly, it is very probable that an object of his studies were not the cells of a star-like shape, and therefore this name was not mentioned in his study. Secondly and simply, at that time Browicz did not know either Kupffer's publication which appeared in 1876, nor Rothe's work. And so it must have been indeed, because publishing in 1900 in "Archiv für Mikroskopische Anatomie" the next work under the same title — *Ueber intravasculäre Zellen in den Blutcapillaren der Leberacini*, Browicz broadly discusses the results of Kupffer's work and makes reference to his presentation in Kiel in April 1898. The researcher from Krakow stresses very explicitly the differences between his own findings and an approach of his German colleague.

The most important is probably Browicz's announcement in which he contradicts Kupffer's statement as if the examined cells formed an integral structure. According to Browicz, they are resting on the cell boundaries of capillary vessels but never form a part of them. These divergences Browicz explained as due to different methods of fixation and staining of the histological material used in his own studies and in the studies done by Kupffer.⁸

In 1914 Kiyono, applying special technique of staining, observed in the liver two types of cells characterized by similar features (intravital uptake of the stain): histiocytes and cells of endothelium; according to his opinion, the cells of both types have one common origin. Ten years later, an eminent German pathologist Ludwig Aschoff proposed to include these cells into a separate system which he called a reticulo-endothelial system. Still during Browicz's lifetime, in 1928, Zimmermann distinguished three types of sinusoidal liver cells: endothelial cells, pericytes, and endocytes. The definition of the former ones leaves no doubts; pericytes are the cells today designated as stellate cells, and hence endocytes would be these cells which were described for the first time by Browicz in 1898.

⁴ von Kupffer C. (1899), "Ueber die sogenannten Sternzellen der Säugethierleber." *Archiv für Mikroskopische Anatomie* 54, p. 254–288.

⁵ Browicz T (1899), "Ueber intravasuläre Zellen in den Blutcapillaren der Leberacini." Separat aus dem *Anzeiger der Akademie der Wissenschaften in Krakau*, p. 6–8

⁶ Browicz T. (1899), "O śródnacyniowych komórkach we włoskowatych, krwionośnych naczyniach zrazików wątroby. Zbiór prac T. Browicza". Akademia Umiejętności w Krakowie, p. 6–8.

⁷ *Ibid.*

⁸ Browicz T. (1899), "Ueber intravasuläre Zellen in den Blutcapillaren der Leberacini." Separat aus dem *Anzeiger der Akademie der Wissenschaften in Krakau*: 6-8, Szymańska R, Schmidt-Pospuła M, (1979), "Z historii badań Tadeusza Browicza (1847-1928) i Karola Kupfera (1829-1902) nad komórkami siateczkowo-śródbłonkowymi wątroby", *Archiwum Historii Medycyny* 42 (3), p. 331–336.

However, only further studies conducted by means of various methods have proved quite explicitly that the original Kupffer stellate cells (described in 1876) were neither the sinusoidal endothelial cells, nor the Kupffer cells at present called phagocytising cells, but the perisinusoidal cells storing vitamin A (Ito cells). On the other hand, to the, so called, phagocytising sinusoidal endothelial cells (1898) he also ascribed numerous features characteristic of the perisinusoidal cells, which in the years to follow caused a lot of misapprehension in the relevant nomenclature.

So, it follows that in an eponymous name of the intrasinusoidal hepatic macrophages a credit should be given to the Krakow researcher since he was the first one who in a very precise (as for those times) manner described those cells.