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LABORATORY PROCEDURE
ΕΡΓΑΣΤΗΡΙΑΚΗ ΜΕΘΟΔΟΣ

The role of the microscope in renal disease as described in Giulio Bizzozero's handbook of clinical microscopy

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2020, 37(Συμπλ 2):108–113

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Giulio Bizzozero (20 March 1846–8 April 1901) was an eminent Italian pathologist, the first microscopist to describe the role of platelets as the third morphological element of the blood. He also made innovative discoveries about the haematopoietic function of the bone marrow, the histological structure of the epidermis, phagocytosis and many other original intuitions. Since the beginning, his career was extremely productive: for his valuable research work, at the age of 26 he was appointed full Professor of General Pathology at the University of Turin, Italy. Here he emphasised the use of microscopy against the outdated vision of old academics and promulgated experimental methods in opposition to the vitalistic philosophy of the time. Bizzozero's revolutionary vision of medicine aimed to allow every scientist to reach new discoveries in their field, which were previously the privilege of an elite, making him a model both as a doctor and as a humanist. The advancement of his studies and the development of the art of microscopy led to the publishing of his masterpiece "Manuale di Microscopia Clinica" (Handbook of Clinical Microscopy) in 1879. In that, he underlined how the microscopic examination of the urine gave physicians of the time indicative criteria of kidney alterations, often essential for diagnosis. The author makes a detailed analysis of the methods of his time, laying the foundations for modern microscopy and the diagnosis of renal diseases. During his career, he was elected president of many medical societies and was an active member of several public health commissions. The contribution of this esteemed scientist was significant both in expanding knowledge within the scientific community and in promoting the public understanding of the benefits of medicine.

Ο ρόλος του μικροσκοπίου στις νεφρικές παθήσεις, όπως περιγράφεται στο εγχειρίδιο κλινικής μικροσκοπίας του Giulio Bizzozero

Περίληψη στο τέλος του άρθρου

Key words

Giulio Bizzozero
Manuale di Microscopia Clinica
Platelets as the third morphological elements
University of Turin
Bizzozero's Biography

1. BIZZOZERO'S BIOGRAPHY

Giulio Bizzozero is considered the father of Italian histology. He was born in Varese, Italy, on 20 March 1846, to a middle-class family. He studied in Milan and Pavia, where, at the age of 16, he enrolled at the Medical Faculty. He graduated at the age of 20, and received the "Mateucci Prize", awarded to students who achieving the highest grade in all courses. He began to carry out histological and histopathological research under the direction of Paolo Mantegazza who, in 1861, founded the Laboratory of Experimental Pathology and was Bizzozero's most influential teacher.[1]

In this period, he engaged in research by conventional microscopy and published his first papers (at the age of 16), and visited scientific institutes abroad, Zurich (Heinrich Frey), Würzburg (Rudolf Albert von Kölliker), Wien (Ernst Wilhelm Brücke) and Berlin (Rudolf Virchow).[2]

In the period immediately after his graduation, Italy was at war with the Austro-Hungarian Empire, and Bizzozero volunteered as an army medical officer.[3] Shortly after, in 1868, he was appointed Supplementary Professor of Histology at the University of Pavia and continued to teach there until the end of 1872, when he was appointed Chair of General Pathology at the University of Turin.[4]

In 1873, he began his teaching and scientific activity at the Laboratory of Anatomy, in some rooms granted by the Dean Joseph Timmermans. With the death of the Dean, the concession was revised and Bizzozero had to set up a Laboratory in his home, on Nice Street, Turin.

In 1876, he obtained some rooms in the former Convent of St. Francis da Paola, where he developed great histopathological experience, making use of the microscope.

In 1878, he became a full Professor of Histology, a

position he kept until his death. Many of Italy's younger pathologists have been his pupils: among them Professor B. Golgi (Pavia), Tizzoni (Bologna), Canalis (Genoa), Foà (Turin), Salvioli (Padua), and Morpurgo (Siena).

Giulio Bizzozero was a member of the most influential Italian and foreign societies of his time. He was one of the most active members of the Superior Council of Public Instruction and the Superior Council of Public Health. For his great service to science and education, he was named a Senator of the Kingdom of Italy by King Humbert I.[5]

He remained active at the University of Turin until his death on 8 April 1901, aged 55 years, caused by pneumonia. On the occasion of his death, Virchow, who enjoyed ties of great mutual respect with Bizzozero, wrote to his family: "la perte de l'homme le plus célèbre dans notre science" ("the loss of the most famous man in our science").

2. GIULIO BIZZOZERO'S MAIN CONTRIBUTIONS TO MEDICINE

Over his lifetime, Bizzozero published nearly 80 papers, on various topics. In 1868, he discovered that red blood cells originate in the bone marrow from nucleated precursor cells and wrote "Sulla funzione ematopoetica del midollo delle ossa. Comunicazione preventiva"[6] (On the haematopoetic function of bone marrow. Prior communication). In his work, he also underlined the importance of haemotransfusion[7] in anaemic patients.

Bizzozero's name is linked with the discovery of platelets but actually he was not the first to identify these elements; instead, he coined the term and was the first to clearly demonstrate their role in promoting thrombosis *in vivo* and blood coagulation *in vitro*.[8] "The existence of a constant blood particle differing from red and white blood cells has been suspected by several authors", states Bizzozero in his introductory historical review of his masterpiece paper.[9] "It is astonishing" –he continues– "that none of the previous investigators made use of the observation of circulating blood in living animals". By his investigations, he reached "the surprising conclusion that indeed morphological elements of a third kind are circulating within the vessels, besides red and white blood corpuscles. The former corresponds to extremely thin platelets".[10]

He also commented that "An investigator who is not prepared in advance to look for other than the known elements will be attracted only by the red and white corpuscles".[11]

Another remarkable discovery attributed to Bizzozero are the desmosomes, intercellular junctions of epithelia and cardiac muscle that can resist mechanical stress due the adoption of a strongly adhesive state.[12] They are also called "connecting bodies", and they have also been named after him as Nodes of Bizzozero.[13]

Bizzozero also provided a detailed description of the phagocytosis process, in the anterior chamber of the eye, in two papers, published in 1871 and 1872 in the Italian medical journal *Gazzetta Medica Italiana – Lombardia*.[14,15]

In 1893, Giulio Bizzozero was also the first to observe and describe spiral organisms in the stomach of animal models,[16] depicting *Helicobacter pylori*.

He gave special attention to the process of cellular differentiation, classifying the tissues concerning their capacity to self-renew during the adult life in labile, stable and permanent tissues.[17]

3. THE "HANDBOOK OF CLINICAL MICROSCOPY"

The advancement of his studies and the development of the art of microscopy led to the publishing of his masterpiece "Manuale di Microscopia Clinica" (Handbook of Clinical Microscopy) in 1879. In that, he underlined how the microscopic examination of the urine gave physicians of the time indicative criteria of kidney alterations, often essential for diagnosis. The author makes a detailed analysis of the methods of his time, laying the foundations for modern microscopy and the diagnosis of renal diseases.

The first chapter of the book is dedicated to the description and use of the microscope.

Bizzozero details the techniques for using the microscope through an accurate list of existing types of machines, making a meticulous analysis of their main characteristics. An interesting detail is the reference to the name and address of the manufacturer, the cost of the microscope depending on the price of gold established during the sale, on the financial conditions of the owner. The following chapters are dedicated to the examination of blood, exudates, pus, skin, mouth contents, vomit, faeces, spit, nasal mucus, eye and annexed parts, secretions of the male and female genitals, breast secretions, pathogenic schizomycetes and urine. Interesting to note that Bizzozero personally designed most of the elements of the urinary sediment (fig. 1).

Bizzozero proposed a classification for pathological urine: (a) Sediment consisting of normal or altered cells (epithelial cells, red blood cells, leukocytes) or made by products collected in the kidneys or in their excretory ducts, (b) sediment consisting of chemical elements precipitated

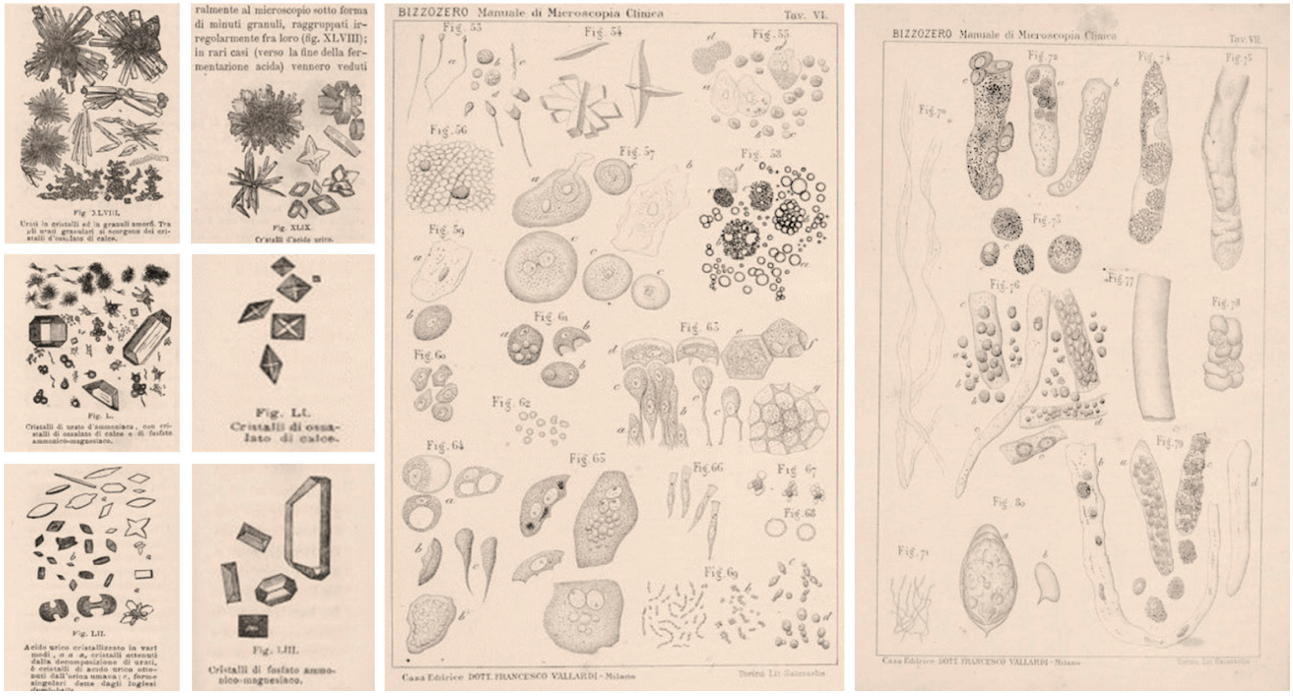

Figure 1. Tables representing different kind of urinary calculi and elements of urinary sediment, 1879 "Handbook of Clinical Microscopy", G. Bizzozero.

in the urine, (c) sediment formed by vegetable or urinary cylinders.

The presence of red blood cells represented a great diagnostic sign in urinary sediment. Bizzozero emphasises that red blood cells *"come from the kidneys when, by means of fibrin or exudation materials, they come together in cylinders that reproduce the shape and diameter of the renal canaliculi".*[18]

Red blood cells, on the other hand, did not have strictly renal origin but could be traced back to the urinary tract when:

- There is a significant presence of epithelia of the lower urinary tract
- The blood in the urine is well represented
- Urine at the beginning of excretion comes out lighter than urine at the end of urination
- Urine takes on a light red colour
- There is presence of clots.

In his treatise, Bizzozero also described the different types of cylinders visible with the microscope.

Urinary cylinders were identified for the first time in 1837 by Dottor Valentin and Dottor Vigla in urine.

The author, following Dottor Carlo Rovida's classification, divides urinary cylinders into three classes: (a) Cylinder hyaline or colourless; (b) cylindroid; (c) yellow or waxy cylinders.

- *Hyaline or colourless cylinder could be: straight, curved, variously folded, with regular margins.*
  The diameter is up to 12 micrometers, reaching up to 40–50. They have been mostly associated with acute nephritis.
- *Cylindroids: they are very thin (5–20) micrometers, often several cylindroids are grouped in a ball-shaped string. They are frequently found in normal urine sediments, although the author finds them abundantly associated with cystitis cases. They have the form of filaments or form of ribbons. They have an irregular outline, a very wavy or tortuous course.*
- *Yellow or waxy cylinders are formed by a slightly yellowish coloured substance, more refracting and with more distinct contours, more massive, harder and less elastic (reason why they get crushed under the coverslip sometimes). They are characterized by regular, smooth, wavy contours. Waxy cylinders are larger than hyaline cylinders, they have a length that varies from a few micromillimeters to two tenths of a millimeter.*

They were often associated with chronic processes and refer to more severe morbid processes. Of particular interest

is Bizzozero's classification concerning the examination of urine in the main kidney and urinary tract diseases:

- *Venous congestion*
- *Acute diffuse inflammation*
- *Chronic diffuse inflammation*
- *Interstitial chronic nephritis*
- *Kidney amyloid degeneration*

Venous congestion presents these urine characteristics: scarce amount, strongly coloured, high specific weight, little albuminous content, few hyaline cylinders, red blood cells, white blood cells.

Acute diffuse inflammation presents poor presence or total absence of urine, intensely coloured, turbid, due to precipitates of urates and red blood cells, high specific weight, white blood cells generally numerous, renal epithelia well preserved or browned by the colouring substance of the blood, cylinders often in large quantities.

Chronic diffuse inflammation presents a small amount of yellowish, turbid urine, a high specific weight, mostly above 1020, acidic with a lot of albumin, white blood cells in large quantities, red blood cells of low quantity, renal epithelia in fair quantities often in fatty degeneration, cylinders usually in large quantities, both hyaline and yellowish cylinders.

Interstitial Chronic Nephritis: more abundant urine than normal due to hypertrophy of the heart (could be less represented due to a decrease in the strength of the heart), light in colour, clear, low specific weight, acidic, little or no albumin. Urinary sediment is usually scarce with generally thin hyaline cylinders.

Kidney Amyloid Degeneration: associated with various forms of chronic nephritis and systemic diseases. The diagnosis in this case is contradictory and a confirmation with systemic symptoms is needed to identify the disease. The presence or absence of cardiac hypertrophy or amyloid degeneration in other organs must be assessed.

This masterpiece of medicine literature (his "scientific testament" according to Matoni[19]) saw, besides five Italian editions (from 1880 to 1901), also translations in German, French, Danish, Spanish, English and even in Russian and Japanese.[20]

Interestingly, probably influenced by the Manual of Frey,[21] it stands out for the autonomy of content development and a strongly clinical and completely original approach for those times.[22,23]

Bizzozero's masterpiece definitely represents a milestone in scientific literature, a witness of the radical evolution of modern medicine and experimental research.

4. CONCLUSIONS

During his career, Bizzozero emphasised the use of microscopy against the obsolete vision of old academics and promulgated experimental methods in opposition to the vitalistic philosophy of the time. Bizzozero underlined the idea of "teamwork" and his strong connection with his close collaborators, saying that in a laboratory "*a mind should give the idea and the direction of work while other minds join together dealing with particular executions*".[24]

Bizzozero's revolutionary vision of medicine aimed to allow every scientist to reach new discoveries in their field, which were previously the privilege of an elite, making him a model both as a doctor as a humanist.[25] In one of his memorable speeches he declared: *"We need to undress science of the cloak of mystery and authority: the professor in the school must not offer a series of dogmas supported by the prestige of his name, he must instead expose science in the real state in which it is found, with its doubts and its unresolved mysteries".*

Benedetto Morpurgo, Bizzozero's successor to the Turin Chair, said about him: *"He entered the difficult environment of a university aged and closed in dogmatic teachings, fearful of any innovation. The admirable instrument of Bizzozero's discoveries, the microscope, appeared to be an infernal weapon, destined to bring down the consecrated dogmas of the cathedratics.*

Bizzozero and the microscope were considered as one entity, as were Galileo and his glasses, dangerous threats to the solemn quiet of classical university teaching".

For the author, the microscope was an instrument of pivotal importance, to the point where it could definitely be claimed that no other scientific instrument of the time could offer such a broad range of characterisation techniques and strategic functions for the progress of medicine. The innovation brought by the use of the microscope represented a real revolution in the methods and approach to science, in which Bizzozero was a real guide and pioneer.

ΠΕΡΙΛΗΨΗ

Ο ρόλος του μικροσκοπίου στις νεφρικές παθήσεις, όπως περιγράφεται στο εγχειρίδιο κλινικής μικροσκοπίας του Giulio Bizzozero

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Ο Giulio Bizzozero (20 Μαρτίου 1846–8 Απριλίου 1901) ήταν ένας διάσημος Ιταλός παθολόγος, ο πρώτος μικροβιολόγος που περιέγραψε το ρόλο των αιμοπεταλίων ως το τρίτο μορφολογικό στοιχείο του αίματος. Έκανε επίσης καινοτόμες ανακαλύψεις σχετικά με την αιματοποιητική λειτουργία του μυελού των οστών, την ιστολογική δομή της επιδερμίδας, τη φαγοκυττάρωση και πολλές άλλες πρωτότυπες διαισθήσεις. Από την αρχή, η καριέρα του ήταν εξαιρετικά παραγωγική: χάρη στο πολύτιμο ερευνητικό του έργο, στην ηλικία των 26 ετών διορίστηκε τακτικός Καθηγητής Γενικής Παθολογίας στο Πανεπιστήμιο του Τορίνο της Ιταλίας. Εκεί, υποστήριξε τη χρήση μικροσκοπίας ενάντια στο ξεπερασμένο όραμα των παλαιών ακαδημαϊκών και υιοθέτησε πειραματικές μεθόδους που έρχονταν σε αντίθεση με τη βιταλιστική φιλοσοφία της εποχής. Το επαναστατικό όραμα του Bizzozero για την ιατρική είχε ως στόχο να επιτρέψει σε κάθε επιστήμονα να φτάσει σε νέες ανακαλύψεις στον τομέα του, οι οποίες ήταν προηγουμένως το προνόμιο μιας ελίτ, καθιστώντας τον πρότυπο τόσο ως ιατρό όσο και ως ανθρωπιστή. Η πρόοδος των σπουδών του και η ανάπτυξη της τέχνης της μικροσκοπίας οδήγησε στη δημοσίευση του αριστουργήματός του "Manuale di Microscopia Clinica" (Εγχειρίδιο Κλινικής Μικροσκοπίας) το 1879. Σε αυτό, υπογράμμισε πώς η μικροσκοπική εξέταση των ούρων παρείχε στους ιατρούς της εποχής ενδεικτικά κριτήρια νεφρικών αλλοιώσεων, που ήταν συχνά απαραίτητα για τη διάγνωση. Ο συγγραφέας κάνει μια λεπτομερή ανάλυση των μεθόδων της εποχής του, θέτοντας τα θεμέλια για τη σύγχρονη μικροσκοπία και τη διάγνωση των νεφρικών νόσων. Κατά τη διάρκεια της σταδιοδρομίας του, εξελέγη πρόεδρος πολλών ιατρικών συλλόγων και ήταν ενεργό μέλος πολλών επιτροπών δημόσιας υγείας. Η συνεισφορά αυτού του αξιότιμου επιστήμονα ήταν σημαντική τόσο στην επέκταση της γνώσης μέσα στην επιστημονική κοινότητα όσο και στην προώθηση της κατανόησης του οφέλους της ιατρικής από το κοινό.

Λέξεις ευρετηρίου: Giulio Bizzozero, Manuale di Microscopia Clinica, Πανεπιστήμιο του Τορίνο, Τα αιμοπετάλια ως το τρίτο έμμορφο στοιχείο

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