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Erythropoietin, a first intuition of renal secretion by Giustiniano Nicolucci

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Ερυθροποιητίνη, μια πρώτη διαίσθηση της νεφρικής απέκκρισης από τον Giustiniano Nicolucci

Περίληψη στο τέλος του άρθρου

In 1846, the medical journal *"Filatre Sebezio"* featured the paper "Sull'Intima struttura dei reni con alcune considerazioni sulla loro funzioni e malattie" by Giustiniano Nicolucci, a young doctor who had graduated just the previous year from the University of Naples. Nicolucci had already taken part as a major speaker at the "VII Congress of Italian Scientists", held in Naples in 1845. On that occasion as well in previous essays, he showcased his skills by using a microscope, at a time when Neapolitan physicians tended to combine medical observation with notions derived from comparative anatomy and physiology. On page 82 of this publication, Nicolucci refers to comparative anatomy, and in particular to Jacobson's 1821 research "De sistemate venoso peculiari in permultis animalibus observato", which showed that in fish, as well in birds and reptiles, there is a type of renal portal, which helps the lungs oxygenate the blood. On this basis, Nicolucci argued for a respiratory function of the kidneys, but, as he was not able to find Jacobson's renal vein in humans, he assumed that this respiratory function of the kidneys could be accomplished through the formation and multiplication of red blood cells, as was recently observed in the liver of a human embryo by Kölliker. According to Nicolucci, further research was needed to seek respiratory principles in urine. The intuition of the Neapolitan physician, unfortunately, did not receive due attention in subsequent studies: it was only in 1977 that Takaji Miyake was able to extract the erythropoietin molecule from the urine of a patient with aplastic anaemia.

Key words

Giustiniano Nicolucci
Kölliker A.
Renal secretion of erythropoietin

1. INTRODUCTION

In 1846, the Neapolitan medical journal *"Filatre Sebezio"* featured the paper "Sull'Intima struttura dei reni con alcune considerazioni sulle loro funzioni e malattie", by Giustiniano Nicolucci.[1] Nicolucci, who had graduated the previous year from the University of Naples, had already taken part as a major speaker at the "VII Congress of Italian Scientists", held in Naples in 1845. On that occasion, he effectively compared his observations with a microscope with that of the other present scientists. At that time, it was common among Neapolitan doctors to combine medical observation with notions taken from comparative anatomy and physiology.[8] His studies were supported by his thorough knowledge of the history of Greek and Latin medicine. He had an in-depth knowledge of Galen's works and he had extensively studied the "Tabulae Anatomicae" (1552) and "De renum structura, officio atque administratione" (1564) by Bartolomeo Eustachio, two studies in which blood circulation of urinary organs was clearly displayed for the first time, as well as the research by Morgagni and Malpighi. The individuality of his work lay in his ability to use the microscope; in fact, he could compare the results of his research with those of the most important English, French and German scientists.

On page 82 of the aforementioned publication, he writes:

"In the three inferior classes of vertebrates another task is performed by the kidneys, which are crossed by a particular venous system making the blood they transport lose its venosity, making it acquire the venous character which reaches fully the respiratory organs. Jacobson, discoverer of this venous system together with other physiologists, found that actually the kidneys in those animals assisted the lungs in their respiratory function. We do not have a complete analysis of the urine of birds, reptiles and fish to confirm that respiratory principles exist in this liquid; that is, if the respiratory function of the kidneys is involved in the formation and multiplication of the blood globules, as observed recently by Kölliker, like the liver in embryonic life. Further research is necessary in this regard and we will soon study it further".

2. MATERIAL AND METHOD

The research carried out previously by Jacobson and Kölliker's observations on an embryo liver will be analysed, starting from Nicolucci's considerations.

About Jacobson's identification of a renal portal vein:

"... But the veins of the stomach, spleen, pancreas, intestines, some small accentuated branches, usually form the "portal vein system".[2]

"According to Jacobson's 1821 "De sistemate venoso peculiari in permultis animalibus observato" in fish, as well as in birds and reptiles, there is a kind of renal portal system, formed by several branches, collecting the blood from a portion of the trunk muscles, which converge in a large vein that runs through the vertebral canal above the medulla, and distributes trunks transversely to the kidneys; but since the portion of this vein situated beyond the abdomen communicates through lateral branches with the vena cava, which flows under the spine, one can well believe that it therefore falls within the class of ordinary veins".[3]

"According to my knowledge, the blood bodies of a human embryo have been studied only by E.H. Weber (thesis at the University of Leipzig) and in a 12-week embryo described as flat globulets with a nucleus of 0.0042 microns in size; it is clear that this indication, although perfectly correct, does not fulfil all the conditions that intervene in the life of the embryo. In fact, when I dealt with investigating the blood bodies of mammals randomly stored in a human embryo for three months, I found such remarkable results that I could not help making them known, although I did not have any other opportunities to further study them.

The blood bodies of the above embryo are divided into three groups:

- Coloured and core-provided
- Coloured and without nucleus
- Not coloured.

The coloured bodies with a core can be seen in the portal vein, reaching approximately ¼ of the coloured bodies. In the remaining blood there are between 1/6 and 1/8 and most of them measure 0.004 microns. Only in the blood of the liver they are slightly larger –up to 0.006 microns– and in some smaller amounts up to 0.003 and even below 0.0025 microns. Most of the bodies are flat; a few are deep in the form of globules, a minor part, only in the blood of the liver, round and elliptical. In the same blood, the bodies are also distinguished by their colour, which goes from pale yellow to reddish-yellow and in the darker ones the phenomenon is really evident so that it is not possible to recognise the nucleus without reagents. In the rest of the blood, almost all the bodies with a nucleus behaved like the darker blood bodies of the liver.

Water and acetic acid have similar effects on these bodies as in those of adults, that is, they deprive them of colour more or less rapidly, make them swell to such an extent that the membrane rarely explodes and lets the core out, and even after a rather long application, they do not melt. The cores, with no exception, maintain the membrane and in the case of the flat ones, are found more on the margins.[6]

3. DISCUSSION

Nicolucci does not find in the human kidney the anatomical formation of the so-called "portal vein", found in fish, birds and reptiles: in fact, the circulating blood does not change in appearance and does not acquire the characteristics of oxygenated blood. Surely, however, Comparative Anatomy had affirmed the existence of a respiratory function in this organ. The evolution of the species to mammals suggested that this function had been preserved, no longer as an anatomical apparatus, but through another –perhaps humoral– mechanism, at the base of the formation and multiplication of red blood cells.

Therefore, Nicolucci refers to Weber's research, confirmed by Kölliker, that is, to the evidence of erythropoiesis in the human embryonic liver. The progenitor cells from which the "globules" derive would also be at the base of "neoangiogenesis".

Therefore, the anatomical and perhaps humoral research would only be a different aspect of the same function: in fact Nicolucci states that the analysis of urine carried out on birds, reptiles and fish had not yet highlighted the existence of substances with a respiratory function. In other words, the respiratory function should also have occurred through humoral action, which could not be limited to the multiplication and growth of red blood cells, but should also have affected the formation of new vessels.

4. CONCLUSIONS

Only about 50 years after the hypothesis made by Nicolucci, it was noticed that the bone marrow was capable of producing a greater quantity of red blood cells in subjects who lived in environments lacking oxygen (for example at higher altitudes).

The existence of a hormone able to regulate the production of erythrocytes by the bone marrow was hypothesised in 1906 by Paul Carnot, professor of the Hôtel-Dieu of Paris,

and his assistant Camille Deflandre. The substance was called haemopoietin.

In the 1940s, Finnish researchers,[4,5] Bonsdorff and Jalavisto, continuing their studies on red blood cells, named this substance erythropoietin. A few years later, Kurt Reismann showed that the kidney was the main production site of this substance, but only in 1977 was Takaji Miyake able to extract the molecule from the urine of a patient with aplastic anaemia.[7]

The young Neapolitan doctor could not continue his studies on this interesting theme because of his liberal ideas: the Bourbon police became hostile to him, and exiled him to his homeland. There, he started studies of Anthropology, becoming the first anthropologist in Italy.

ΠΕΡΙΛΗΨΗ

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Το 1846, το ιατρικό περιοδικό *"Filatre Sebezio"* παρουσίασε το άρθρο "Sull'Intima struttura dei reni con alcune considerazioni sulla loro funzioni e malattie" του Giustiniano Nicolucci, ενός νεαρού γιατρού που είχε αποφοιτήσει μόλις το προηγούμενο έτος από το Πανεπιστήμιο της Νάπολης. Ο Nicolucci είχε ήδη συμμετάσχει ως κύριος ομιλητής στο «7ο Συνέδριο Ιταλών Επιστημόνων», που πραγματοποιήθηκε στη Νάπολη το 1845. Με την ευκαιρία αυτή καθώς και σε προηγούμενα δοκίμια, παρουσίασε τις δεξιότητές του χρησιμοποιώντας ένα μικροσκόπιο, σε μια εποχή που οι Ναπολιτάνοι ιατροί τείνουν να συνδυάζουν ιατρική παρατήρηση με έννοιες που προέρχονται από συγκριτική ανατομία και φυσιολογία. Στη σελίδα 82 αυτής της δημοσίευσης, ο Nicolucci αναφέρεται στη συγκριτική ανατομία και ειδικότερα στην έρευνα του Jacobson του 1821 "De sistemate venoso peculiari in permultis animalibus observato", η οποία έδειξε ότι σε ψάρια, καθώς και σε πτηνά και ερπετά, υπάρχει ένας τύπος νεφρικής πύλης, η οποία βοηθά τους πνεύμονες να οξυγονώνουν το αίμα. Σε αυτή τη βάση, ο Nicolucci υποστήριξε την αναπνευστική λειτουργία των νεφρών, αλλά επειδή δεν κατάφερε να βρει την νεφρική φλέβα του Jacobson στους ανθρώπους, υπέθεσε ότι αυτή η αναπνευστική λειτουργία των νεφρών θα μπορούσε να επιτευχθεί μέσω του σχηματισμού και του πολλαπλασιασμού των ερυθρών αιμοσφαιρίων, όπως παρατηρήθηκε πρόσφατα στο ήπαρ ενός ανθρώπινου εμβρύου από τον Kölliker. Σύμφωνα με τον Nicolucci, χρειάζονται περαιτέρω έρευνες για την αναζήτηση αναπνευστικών αρχών στα ούρα. Η διαίσθηση του Ναπολιτάνου ιατρού, δυστυχώς, δεν έλαβε τη δέουσα προσοχή στις μετέπειτα μελέτες: μόλις το 1977 το Takaji Miyake κατάφερε να απομακρύνει το μόριο της ερυθροποιητίνης από τα ούρα ενός ασθενούς με απλαστική αναιμία.

Λέξεις ευρετηρίου: Giustiniano Nicolucci, Kölliker A., Νεφρική απέκκριση ερυθροποιητίνης

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