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WHO DISCOVERED THE WATER CHANNELS (AQUAPORINS) ?

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INTRODUCTION

Recently the Nobel Lecture of Peter Agre was published and it deserves some comments. Peter Agre (Johns Hopkins University, Baltimore, USA) was awarded half of the 2003 Nobel Prize for Chemistry "for the discovery of water channels" (1), actually for the discovery of the first water channel protein from the human red blood cell (RBC) membrane, known today as aquaporin 1 (AQP1) (the other half went to Roderick MacKinnon for structural and mechanistic stuudies of ion channels).

"No one had seen this protein before" said Agre (2). However, this protein was first seen in 1985 by Gheorghe Benga and his coworkers (working at The "Iuliu Hatieganu" University of Medicine and Pharmacy in Cluj-Napoca, Romania), who reported their results in publications in 1986 (refs. 8, 9) and reviewed them in subsequent years (3 - 6). The seminal contributions from 1986 of Benga's group were overlooked by Peter Agre and by the Nobel Prize Committee.

After a decade of systematic studies on water channels in human RBC Benga discovered the presence and location of the water channel protein among the polypeptides migrating in the region of 35-60 kDa on the electrophoretogram of RBC membrane proteins (8). This was achieved by a very selective radiolabelling of RBC membrane proteins with the water transport inhibitor ^{203}Hg-*p*-chloromercuribenzene sulfonate (PCMBS), under conditions of specific inhibition. The inhibitor was bound to the membrane proteins migrating in the band 3 and band 4.5 on the electrophoretogram. This binding pattern suggested that either or both band 3 and band 4.5 proteins could be associated with water channels. However, Benga et al. (8) pointed out that polypeptides migrating in these regions had already been identified in other transport functions, notably anion exchange (band 3 protein) and the transport of glucose and nucleosides (band 4.5 protein). Since there was no evidence that a specific inhibitor of one of these processes would inhibit water transport, Benga correctly concluded: "It remains possible that a minor membrane protein that binds PCMBS is involved in water transport." The way in which the specific protein could be further characterized was also indicated: by purification and reconstitution in liposomes. The work was extended (9) and reviewed in several articles (3-6).

In 1988, Agre and coworkers while working on the rhesus blood group antigen at Johns Hopkins University in Baltimore, USA, serependitously isolated a new protein from the RBC membrane (10), nicknamed CHIP28 (channel-forming integral membrane protein of 28 kDa). However, in addition to the 28 kDa component, this protein had a 35-60 kDa glycosylated component, the one detected by the Benga's group. Agre and coworkers suggested that CHIP28 "may play a role in the linkage of the membrane skeleton to the lipid bilayer" (12). Only in 1992 Agre's group suggested that "it is likely that CHIP28 is a functional unit of membrane water channels" (11); in this paper they cited a paper of Benga and coworkers from 1983 proving that "water channels are impervious to proteolytic digestion" (7), without mentioning their landmark 1986 papers (8,9) or any of the reviews (3-6). In 1993 CHIP28 was renamed aquaporin 1 (AQP1). Although in his Nobel Lecture (2) Agre mentioned twice Benga

Abbreviations: **AQP**: aquaporin; **CHIP28**: channel-forming integral membrane protein of 28 kDa; **PCMBS**:^{203}Hg-*p*-chloromercuribenzene sulfonate; RBC: red blood cell.

among "pioneers in water transport field" Benga's publications were not listed among the references.

An invited review on the history of the discovery of water channel proteins was published by Benga in September 2003, one month before the Nobel Prize was announced (6). As pointed out in this review, looking in retrospect and asking the crucial question: "when was the first water channel protein, aquaporin 1, discovered?", a fair and clear cut answer would be: the first water channel protein, now called aquaporin 1, was identified or "seen" in situ in the human RBC membrane by Benga and coworkers in 1985. It was again "seen" when it was by chance purified by Agre and coworkers in 1988 and was again identified when its main feature, the water transport property, was found by Agre and coworkers in 1992.

If a comparison with the discovery of the New World of America is made (6), the first man who has "seen" a part, very small indeed, of the New World was Columbus; later others, including Amerigo Vespucci (whose name was assigned to the new continent) have "seen" a larger part of the new Continent and in the subsequent years many explorers discovered the complexity of the Americas!

Benga's claim is presented on the web site of the Ad Astra Association (www.ad-astra.ro/benga). As can be seen on this site, the recognition of Gheorghe Benga as a discoverer of the first water channel protein from the human RBC membrane is growing. Thousands of science-related professionals from hundreds of academic and research units, as well as participants in several international scientific events, have signed as supporters of Benga; his priority is also mentioned in several comments about the 2003 Nobel Prize, as presented on the site.

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