Serendipity: a necessity for the progress of dialysis therapy

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The word ‘Serendipity’ was coined by Horace Walpole (1717–1797), 4th Earl of Orford. In a letter he wrote in 1757, he talked about a ‘silly fairy tale’ that he had once read, from which he derived the word ‘serendipity’ for describing the ability to make accidental discoveries. ‘As their Highnesses travelled, they were always making discoveries, by accident and sagacity, of things they were not in quest of’ says the fairy tale.

Accidental discoveries have, for sure, been the most important ones in the development of science. According to Freeman Dyson’s opinion [1]: ‘every important discovery in science is, by definition, unpredictable. If it were predictable, it would not be an important discovery. The purpose of science is to create opportunities for unpredictable things to happen.’

One of the most famous examples of serendipity is that of Arno Penzias and Robert Wilson. They were working at Bell Laboratories, and were in charge of building a very sensitive antenna intended for communicating with satellites such as Telstar. On building the device, they encountered radio noise, the cause of which they could not explain. Since the signal was isotropic, they assumed that the antenna was subject to terrestrial interference. After having rejected all possible sources of interference, they published a paper describing their finding, which was later identified as the cosmic microwave background radiation (CMBR) and is regarded, together with the cosmological redshift, as the best available evidence for the Big Bang theory. CMBR, predicted in 1948 by George Gamow and Ralph Anders, was thus discovered by accident in 1965, thanks to the finding of Penzias and Wilson, who were in fact not ‘in quest of’ it.

Serendipity is commonly encountered in the field of nephrology too, as highlighted by two recent examples: AN69 was the first biocompatible and highly permeable membrane to be launched in the market, about 35 years ago. It was, however, at great risk of disappearing from the market, when hypersensitivity reactions (HSR) were observed at a high frequency in the late 80’s. It was thus a question of ‘survival’ of the membrane, which prompted research to understand what factors might be responsible for these reactions and how the problem could be resolved. Renaux et al. [2], demonstrated the role of the electronegativity (or more precisely, the greatness of the zeta potential) of the membrane in the activation of the kallikrein-kinin system, which was already known as a trigger of HSRs. They also demonstrated the role of the pH of the blood diluted by the rinsing solution. This led, on one hand, to propose the use of bicarbonate priming [3], and on the other, to hide the negative charges on the membrane. Hiding of the negative charges was achieved by layering the AN69 membrane with a polycationic biopolymer, polyethyleneimine (PEI); the PEI-treated membrane was then renamed AN69 ST.

The second example may be even more striking: Pierre Merville et al. (Nephrology and Transplantation, University Hospital, Bordeaux, France) were studying the sCD40 protein in dialysed patients who came for renal transplantation. They found that the sCD40 levels in the uraemic patients were 3–5-fold greater than those observed in healthy subjects, and that the sCD40 levels returned to normal within a few days of restoration of the renal functions by renal transplantation. They also made the interesting observation that patients who responded to hepatitis B vaccination had significantly lower levels of sCD40 than those who did not respond.

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that the patients with normal sCD40 levels were dialysed using the same type of membrane, PMMA BK-F. Moreover, after shifting three patients from their usual membrane to PMMA BK-F, they observed that the sCD40 levels returned to normal within two months.

This has opened up a wide field of investigation, with dialysis membranes no longer being viewed as simple diffusive devices, but as protein-modifying tools (especially those membranes that exhibit marked adsorption capacity).

In this issue, Björn Wikström’s article stresses the clinical importance of one of the most common complications of end-stage renal disease: uraemic pruritus. Something serendipitous has emerged from the paper of Aucella et al.: the relief (discovered initially by accident) of uraemic pruritus by the use of the PMMA membrane. Aoike and Galli argue strongly in support of the role of proteomic analysis in determining the pathophysiology of the uraemic syndrome. Proteomic analysis appears to be a powerful tool for identifying and classifying the protein bound uraemic toxins, and for facilitating a better understanding of their roles in the clinical manifestations of the uraemic syndrome. It should not be considered, however, as a means for simply testing some medical and scientific hypotheses (neither heparin binding to PEI-coated AN69, nor sCD40 normalization under PMMA membrane treatment had been previously hypothesized).

We may expect much more: proteomic analysis might be one more tool with which we can travel around in the field of uraemia, and could then make, by accident or sagacity, discoveries ‘of things we are not in quest of’.

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References