In 1853 he was appointed Professor of Natural History in Queen's College, Cork; in 1854 he became Professor of Mineralogy and Geology in Queen's College, Belfast, and afterwards, in 1860, Professor of Natural Science in the same college; in 1868 he held the additional post of Professor of Botany in the Royal College of Science, Dublin.

He was associated with Dr. W. B. Carpenter, C.B., F.R.S., and Dr. J. Gwyn Jeffreys, F.R.S., in the deep-sea explorations in the North Atlantic, conducted by H.M.SS. "Porcupine" and "Lightning" in 1868 and 1869.

In 1870 he was appointed Professor of Natural History in the University of Edinburgh.

In 1872 he obtained leave of absence from the Senatus Academicus of Edinburgh University, on his appointment by the Lords Commissioners of the Admiralty, as Director of the Civilian Scientific Staff on board H.M.S. Challenger.

On the return of the Challenger to England in 1876, he received the honour of knighthood, and was appointed by the Lords Commissioners of Her Majesty's Treasury, Director of the "Challenger Expedition Commission." In the same year he was awarded a Royal medal by the Royal Society for his successful direction of the scientific investigations carried on by H.M.S. Challenger.

In 1877 he was one of the deputation from Edinburgh University to Sweden, on the occasion of the quatercentenary of the foundation of the University of Upsala, and on that occasion was created, by King Oscar, a knight of the Order of the Polar Star.

In 1877 he delivered the Rede Lecture at Cambridge, and in 1878 he was President of the Geographical Section of the British Association at Dublin.

Sir Wyville had a severe illness in the summer of 1879; he continued after that date in failing health, and was not again able to deliver his lectures in the University of Edinburgh. He died at his residence, Bonsyde, near Linlithgow, on the 10th of March 1882.