This paper reviews the limited knowledge available in 1966 concerning the serology, genetics, and biochemistry of the blood-group ABH and Lewis blood-group systems and delineates the proposed biosynthetic pathways for the formation of the antigens. The SCi® indicates that this paper has been cited in over 445 publications.

**Carbohydrate Antigens, Glycosyltransferases, and Blood-Group Genes**

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After obtaining my PhD with Arthur Wommel in the Biochemistry Department at St. Bartholomew's Hospital Medical School, London, in 1958, I joined Walter Morgan's laboratory at the Lister Institute of Preventive Medicine, London. Work on human ABO blood-group antigens had begun in this laboratory in the early 1940s and, as attempts by others to extract blood-group active materials from red blood membranes had met with little success, attention was focussed on the water-soluble glycoproteins in secretions that carry the same specific structures. By 1959 the overall compositions of A, B, H, and Lewis active glycoproteins had been established, but their similarity made it apparent that chemical analysis alone would not reveal the basis of blood-group specificity. This realization led us to try a series of indirect methods to obtain clues to the nature of the determinants.

In 1952, employing the Landsteiner principle that simple substances with structures related to the immunological determinant groups of an antigen can act as competitive inhibitors of antigen-antibody reactions, we treated the constituent sugars of the blood-group active glycoproteins for inhibition of agglutination with an array of human and animal anti-A, anti-B, and anti-H sera. A positive answer was obtained with only one reagent; a naturally occurring anti-H in the serum of the eel Anguilla anguilla was inhibited by A-bloodserum. Soon thereafter, a new specificity as a different specificity with remarkable precision and to deduce that a difucosylated tetrasaccharide structure was involved in H specificity. Parallel studies on the sequential action of exoglycosidases on the blood-group active glycoproteins led to the revelation that loss of one immunological specificity following the removal of a single sugar from an oligosaccharide chain was accompanied by the development of a new specificity as a different specificity was exposed. By 1959 sufficient information on the chemistry, genetics, and serology of the ABH and Lewis antigens was available to warrant speculation on their genetic interrelationships and pathways of biosynthesis. Therefore, when this review article was written in 1966, the genetic regulation of blood-group antigenic expression was rapidly becoming an exciting and coherent story. In the next decade it was shown by Bloch's group in the US and by Koscielak in Poland that, although the carrier molecules differed, the blood-group determinant structures on the red-cell membrane were identical to those established for the secreted glycoproteins.

The predicted enzymic basis of the blood-group specificity was confirmed in our laboratory and by Glimburg in the US, and the discovery of these glycosyltransferases provided new genetic markers for forensic studies and for investigation of rare blood-group phenotypes. With the advent of molecular genetic techniques, identification of the DNA encoding the enzymes has become the next exciting chapter to be explored in the blood-group antigen saga.