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This Week's Citation Classic®

Clarke C A, Edwards J W, Haddock D R W, Howel-Evans A W, McConnell R B & Sheppard P M. ABO blood groups and secretor character in duodenal ulcer: population and sibship studies. *Brit. Med. J.* 2:725-31, 1956.
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The relationship of ABO blood groups to duodenal ulcer was studied. A significantly higher proportion of duodenal ulcer patients as compared with controls were unable to secrete ABO blood-group antigens in the body fluids. [The *SCI*® indicates that this paper has been cited in over 160 publications since 1956.]

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My interest in blood groups stemmed from breeding Swallowtail butterflies because the method of inheritance of their wing patterns is similar to the single-gene differences of the ABO blood groups. Thirty years ago, when the relationship of blood groups to disease was beginning to be investigated, E.B. Ford emphasised that the blood groups formed polymorphic systems and that diseases might help to keep the various morphs in balance. Blood group A and cancer of the stomach[1] were the first to be studied, followed by peptic ulcer and blood group O.[2] My colleagues and I in Liverpool joined the fray by studying duodenal ulcer and found a marked association with group O.

In general, the association was regarded as bona fide throughout the world, but Lionel Penrose, the well-known geneticist in charge of the Galton Laboratory, would not accept it, for he thought the controls being used—students, nurses, blood donors, and sometimes patients with other diseases—were not good enough. Specifically, he thought that there might be a population high in group O (e.g., the Scots) who were also prone, for other reasons, to duodenal ulcer. Penrose said he would only believe the association if it showed up when unaffected sibs were used as controls to rule out racial stratification.

The method of calculation is described in the paper and our results shown in Table 1, where it will be seen that the increase of group O is clearly wildly nonsignificant. Penrose was right.

TABLE 1: DUODENAL ULCER
CHANCE OF THE PROPOSITUS BEING GROUP O

Sibship no. (3 examples)	Sibs who are group O	Sibs who are not group O	Group O propositi Observed	Expected
62	2	2	1	0.5
68	1	2	0	0.33
69	1	3	1	0.25
..	..	..	..	..
112 segregating sibships			59	54.9
			$p > 0.4$	

Part 2 of the paper studied duodenal ulcer and the ability to secrete the ABO blood group antigens in the body fluids. In 514 unrelated duodenal ulcer patients from the general population, we found a significantly higher proportion (35 percent) of nonsecretors compared with 491 controls (24.2 percent). In sibs, although the numbers were small, there was a nonsignificant increase in nonsecretors.

To my mind, the interest of the paper lies first in the selection of proper controls. If one were looking at the fertility of patients with Huntington's chorea, "unaffected" sibs would be highly inappropriate. Second, we were all general physicians, knowing little or no genetics. We were greatly helped by Philip Sheppard, a butterfly geneticist, and we picked up advice from many other sources. My memory is of what fun it all was.

Thirty years later, the medical world has lost interest in the ABO blood groups and duodenal ulcer, for the findings have not proved to be of any practical importance and the disease has become rarer. HLA typing now holds sway but again there are problems—for example, both males and females have locus BW27, but typical ankylosing spondylitis remains much commoner in men.

The butterfly work later became more complicated and led to a study of mimicry. This aroused our interest in the rhesus problem, where the blood group system has many genetic parallels with butterflies. In the 1960s we (now also with Ronald Finn) found a highly successful way of preventing rhesus babies.[3-5]

1. **Aird I, Bentall H H & Roberts J A F.** A relationship between cancer of stomach and the ABO blood groups. *Brit. Med. J.* 1:799-801, 1953. (Cited 300 times since 1955.)
2. **Aird I, Bentall H H, Mehigan J A & Roberts J A F.** The blood groups in relation to peptic ulceration and carcinoma of colon, rectum, breast, and bronchus. *Brit. Med. J.* 2:315-21, 1954. (Cited 260 times since 1955.)
3. Prevention of Rh-haemolytic disease: results of the clinical trial. A combined study from centres in England and Baltimore. *Brit. Med. J.* 2:907-14, 1966.
4. **Clarke C A.** *Rhesus haemolytic disease: selected papers and abstracts with commentaries.* Lancaster: Medical and Technical Publishing Company, 1975. 313 p.
5. **Clarke C A, Mollison P L & Whitfield A G W.** Deaths from rhesus haemolytic disease in England and Wales in 1982 and 1983. *Brit. Med. J.* 291:17-19, 1985.

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