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This Week's Citation Classic®

Bullen J J, Rogers H J & Leigh L. Iron-binding proteins in milk and resistance to Escherichia coli infection in infants. *Brit. Med. J.* 1:69-75, 1972.
[National Institute for Medical Research, Mill Hill, London, England and Rowett Research Institute, Bucksburn, Aberdeen, Scotland]

Human milk inhibits *Escherichia coli,* and the iron-binding protein lactoferrin is essential for this. Bacteriostasis is abolished by adding iron. In suckled guinea pigs, *E. coli* is inhibited in the small intestine, and unsaturated iron-binding proteins are essential for this protective effect. [The *SCI*® indicates that this paper has been cited in over 380 publications.]

Iron Is Important in Infection

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In 1968 I arrived at the National Institute for Medical Research to take charge of the Animal Division. The director, Sir Peter Medawar, had arranged for Henry J. Rogers, who was the chemist in our "team," to come as well. Sir Peter asked me to explain our research interests. After listening for a bit, he said, "I think you ought to give a colloquium." I said I would prefer to do so with Rogers, who could explain the intricacies of the binding of iron to transferrin, which was central to our work. To this he said, "In that case, you had better give a duet!" So a duet it was. This was the start of an investigation of the role of iron in infection that has gone on ever since.

Our investigation into the bacteriostatic properties of human milk was our first venture into the clinical field, and it led eventually to fundamental studies of the way in which antibodies, and sometimes complement, cooperate with iron-binding proteins to inhibit bacterial growth. Eventually we were joined by Elwyn Griffiths, who was the first to show that iron-binding proteins, together with specific antibody and complement, could interfere directly with the metabolism of the bacterial cell: the depression of net RNA synthesis being the first sign of interference with bacterial growth.[1]

In our paper in the *British Medical Journal* we showed that milk not only inhibited *E. coli,* and that iron-binding proteins[2] were essential for this, but also that it had a direct antibacterial effect in the small intestine. Guinea-pig milk contains large amounts of unsaturated lactoferrin and transferrin. When suckled guinea pigs were given *E. coli,* the bacterial counts declined rapidly in the small intestine, but when the animals were dosed with hematin, which contains iron available to *E. coli,* the counts increased 10,000-fold. Thus, the iron-binding proteins in the milk could only function properly in the small intestine when they had a large unsaturated iron-binding capacity.

Young guinea pigs and babies resemble each other to the extent that both receive maternal antibodies prenatally via the placenta and are, therefore, likely to be protected from septicemia by circulating IgG. Septicemia is the invariable fate of calves, pigs, and lambs deprived of colostrum. Babies deprived of breast milk may, therefore, have some resistance to septicemia yet be unusually susceptible to diarrhea caused by bacterial growth in the small intestine. This suggestion is supported by clinical evidence. Breast-fed infants are more resistant to infectious gastroenteritis caused by *E. coli.*[2,3] In addition, breast feeding encourages a lactobacillary type of flora in the large intestine, which may also make a significant contribution to resistance.[3]

1. **Griffiths E.** Mechanism of action of specific antiserum on *Pasteurella septica*: selective inhibition of net macromolecular synthesis and its reversal by iron compounds. *Eur. J. Biochem.* 23:69-76, 1971. (Cited 35 times.)
2. **Davidson L A & Lönnerdal B.** Persistence of human milk proteins in the breast-fed infant. *Acta Paediat. Scand.* 76:733-40, 1987. (Cited 15 times.)
3. **Bullen C L & Willis A T.** Resistance of the breast-fed infant to gastroenteritis. *Brit. Med. J.* 3:338-43, 1971. (Cited 110 times.)

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