CURRENT KEY DEVELOPMENTS

Oral rehydration therapy:
applied physiology

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A 2007 poll hailed oral rehydration therapy (ORT) as one of the 15 most important medical milestones of our time.¹ Oral rehydration therapy is 'the administration of fluid by mouth to prevent and correct the dehydration that is a consequence of diarrhoea'.² As John Walker-Smith states, its development is a 'remarkable example of theoretical scientific knowledge being directly applied to a clinical problem'.³ Ironically, clinical use of ORT preceded understanding of the physiology that underpins its efficacy.

For centuries, folk remedies, including cereal broths, were used to treat diarrhoea. Over 3,000 years ago the Indian physician Sushruta recommended 'tepid water with rock salt and molasses' for dehydration.⁴ In the 1940s, on the basis of fluid balance studies in children with diarrhoea, Darrow developed an oral rehydration solution (ORS) containing glucose, a base and electrolytes, sodium and potassium.⁵ Similar solutions were introduced into children's hospitals in the USA and UK where a high glucose, low sodium, high osmolality solution was recommended by the Medical Research Council from 1952.⁶ Sugar was added for nutritional value and to improve palatability. In 1953, Chatterjee first used an oral glucose-electrolyte solution for treating cholera and Phillips subsequently documented that ORT decreased stool output in cholera, a finding confirmed by Hirschhorn and Pierce.⁷⁻¹⁰

It was not until 1971, during a large cholera outbreak in Bangladeshi refugees, that the opportunity arose to test the utility, feasibility and efficacy of ORT in the community.¹¹ Huge numbers of cholera victims, few medical staff, and a paucity of intravenous (iv) fluids, resulted in a 30% mortality at the start of the epidemic.^{1,11} After the introduction of ORT, administered by family and untrained helpers, mortality fell to <4% in those who received ORT and was up to 16 times lower than in patients receiving iv fluids.^{1,11} Subsequently, ORT was proven effective in all age groups with diarrhoea of many aetiologies and in 1976 the World Health Organization launched a global program for prevention and treatment of acute diarrhoea with emphasis on ORT.

In parallel to the use of ORT in clinical settings, understanding of intestinal absorption of glucose, water, sodium and amino acids expanded.^{12,13} During the 1950s and 1960s the interrelationships between the absorption of glucose, sodium and water in the normal human jejunum were elucidated using intestinal perfusion models.¹⁴⁻¹⁶ Because of its implications for understanding the physiological basis for ORT, the *Lancet* declared:

*The discovery that sodium transport and glucose transport are coupled in the small intestine, so that glucose accelerates the absorption of solute and water was potentially the most important medical advance this century.*¹⁷

Other solutes such as amino acids also enhance active transport of sodium across the small intestine.

Diarrhoea results in net losses of water, sodium and chloride from the intestine via a range of mechanisms in response to many triggers. The major implication of active co-transport of solute (eg glucose) and sodium is that, unlike other mechanisms of sodium absorption, this is preserved in cholera and other infectious diarrhoeas. Cholera toxin for example works by activating adenylate cyclase in small intestinal crypt cells, increasing intracellular concentrations of cyclic adenosine monophosphate (cAMP) for the life of the cell.¹² Cyclic adenosine monophosphate is a potent trigger for active chloride secretion from crypt cells and also inhibits sodium and chloride absorption. However, cAMP does not affect the active co-transport of solutes and sodium in the jejunum and ileum. The driving force for this process is extrusion of sodium ions across the basolateral membrane of intestinal cells by the Na-K adenosinetriphosphatase pump. The resultant decreased intracellular sodium concentration allows sodium to enter the cell 'downhill' on its electrochemical gradient and energises the 'uphill' flow of solute into the cell by 'secondary active transport'. Sodium is subsequently pumped out of the cell and the solute leaves by diffusion. Intestinal absorptive and secretory process occur via specific transporters (eg the sodium-glucose transporter (SGLT1) and the sodium amino acid transporter), processes controlled by a complex set of neurohumoral regulators, which interact via signalling pathways.^{18,12}

Use of intestinal perfusion models at St Bartholomew's Hospital London allowed study of the physiology of ORT. This led to modifications in the composition and osmolality of ORS in order to maximise water and electrolyte absorption and subsequent clinical trials.¹⁹⁻²⁶ In children without shock, ORT given by oral or nasogastric routes is now known to be as safe and effective as iv fluids.²⁷ Hyposmolar solutions are now recommended worldwide.²⁸⁻³⁰ Cereal (including rice)-based oral electrolyte solutions, while superior to glucose-electrolyte solutions for reducing stool output in children with cholera, have no advantage in non-cholera diarrhoea.³¹ Future developments may include the inclusion in ORT of resistant starch, a substrate for short chain fatty acids, which stimulate colonic water absorption and reduce volume and duration of diarrhoea in cholera.¹² The value of adding probiotics and/or new anti-secretory agents to ORT requires clarification.³²

Undoubtedly the application of physiology to the development and refinement of ORT has had a major global impact:

*Rarely has science so swiftly transmuted an arcane biophysical observation into a practical, low-cost treatment that continues to save millions of lives each year without the need for hospitals, trained staff, or advanced technologies.*³³

Oral rehydration therapy is safe and effective, cheap to produce, readily available and has saved approximately 50 million lives in

the last 25 years.¹ Nevertheless, at least 1.8 million preventable deaths occur each year in young children with gastroenteritis in developing communities where ORT is not available.¹

Despite proven efficacy, ORT is under-utilised in developing and developed communities.^{34,35} Possible reasons for this include the pressure to prescribe medications; the perception that ORT is not a 'drug' and iv fluids are superior; and that ORT does not stop diarrhoea. Above all, is lack of understanding of the physiology underpinning diarrhoea and the rationale for ORT. In the USA, direct health costs resulting from failure to use ORT are over \$1 billion per year.³⁵ The challenge is to persuade carers and clinicians of the benefits and safety of ORT and ensure this remarkable therapy is available to all children.

References

- Fontaine O, Garner P, Bhan MK. Oral rehydration therapy: the simple solution for saving lives. *BMJ* 2007;334:14.
- World Health Organization, United Nations Children's Fund. *Oral rehydration salts. Planning, establishment and operation of production facilities*. WHO, UNICEF 1985;85:1–136.
- Walker-Smith JA, Elliott E, Heuschkel R, Phillips A. Paediatric gastroenterology 1966–2000. *Clin Med* 2008;8:292–5.
- Cunha-Ferreira RCM, Cash RA. History and development of ORT. *Clin Therap* 1990;12(Suppl A):2–13.
- Darrow DC. The retention of electrolyte during recovery from severe dehydration due to diarrhoea. *J Pediatr* 1946;28:515–40.
- Harrison HE. The treatment of diarrhoea in infancy. *Pediatr Clin N America* 1954;1:335–48.
- Chatterjee HN. Control of vomiting in cholera and oral replacement of fluid. *Lancet* 1953;2:1063.
- Phillips RA. Water and electrolyte losses in cholera. *Fed Proc (Baltimore)* 1964;23:705–9.
- Hirschhorn N, Kinzie JL, Sachar DB *et al*. Decrease in net stool output in cholera during intestinal perfusion with glucose containing solutions. *N Eng J Med* 1968;279:176–81.
- Pierce NF, Sack RB, Mitra RC *et al*. Replacement of water and electrolyte losses in cholera by an oral glucose electrolyte solution. *Ann Intern Med* 1969; 70:1173–81.
- Mahalanabis D, Choudhuri AB, Bagchi NG *et al*. Oral fluid therapy of cholera among Bangladesh refugees. *Johns Hopkins Med J* 1973;132: 197–205.
- Rao MC. Oral rehydration therapy: new explanations for an old remedy. *Annu Rev Physiol* 2004;66:385–417.
- Farthing MJG. Oral rehydration: an evolving solution. *J Pediatr Gastroenterol Nutr* 2002;34:S64–S67.
- Schedl HP, Clifton JA. Solute and water absorption by human small intestine. *Nature* 1963;199:1264–7.
- Schultz SG, Zalusky R. Ion transport in isolated rat ileum. II. The interaction between active sodium and active sugar transport. *J Gen Physiol* 1964;47:1043–59.
- Sladen GE, Dawson AM. Interrelationships between the absorptions of glucose, sodium and water by the normal human jejunum. *Clin Sci* 1969;36:119–32.
- Water with sugar and salt. *Lancet*. 1978;2:300–1.
- Wright EM, Hirayama BA, Loo DDF *et al*. Structure and function of the Na⁺/glucose cotransporter. *Acta Physiol Scand Suppl* 1998;643: 257–64.
- Elliott EJ, Watson AJ, Walker-Smith JA, Farthing MJG. Effect of bicarbonate on efficacy of oral rehydration therapy: studies in an experimental model of secretory diarrhoea. *Gut* 1988;28:1052–7.
- Elliott EJ, Armitstead JA, Farthing MJG, Walker-Smith JA. Bicarbonate in oral rehydration solutions: a double-blind controlled trial in gastroenteritis. *Aliment Pharmacol Therap* 1988;2:253–62.
- Hunt JB, Elliott EJ, Farthing MJG. Efficacy of a standard United Kingdom oral rehydration solution (ORS) and a hypotonic ORS assessed by human intestinal perfusion. *Aliment Pharmacol Ther* 1989;3:565–71.
- Elliott EJ, Hunt JB, Cameron D, Walker-Smith JA, Farthing MJG. Clinical experience of an hypotonic oral rehydration solution for treatment of paediatric gastroenteritis in the United Kingdom. *Clin Therap* 1990;12(Suppl A):86–94.
- Elliott EJ, Watson AJM, Walker-Smith JA, Farthing MJG. Search for the ideal oral rehydration solution: studies in a model of secretory diarrhoea. *Gut* 1991;32:1314–24.
- Hunt JB, Elliott EJ, Farthing MJG. Comparison of rat and human intestinal perfusion models for assessing efficacy of oral rehydration solutions. *Aliment Pharmacol Ther* 1991;5:49–59.
- Hunt JB, Elliott EJ, Fairclough PD, Clark ML, Farthing MJG. Water and solute absorption from hypotonic glucose-electrolyte solutions in human jejunum. *Gut* 1992;33:479–83.
- Hunt JB, Thillainayagam AV, Carnaby S *et al*. Absorption of a hypotonic oral rehydration solution in a human model of cholera. *Gut* 1994;35:211–4.
- Hartling L, Bellemare S, Wiebe N *et al*. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. *Cochrane Database Syst Rev* 2006;3:CD004390.
- World Health Organization, United Nations Children's Fund. *Joint statement – oral rehydration salts (ORS) – a new reduced osmolarity formulation*. Accessed September 2006. www.who.int/medicines/publications/pharmacopoeia/OralRehySalts.pdf
- Hahn S, Kim Y, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhea in children: systematic review. *BMJ* 2001;323:81–5.
- Murphy C, Hahn S, Volmink J. Reduced osmolarity oral rehydration solution for treating cholera. *Cochrane Database Syst Rev* 2006;3.
- Fontaine O, Gore S, Pierce NF. Rice-based oral rehydration solution for treating diarrhoea. *Cochrane Database Syst Rev* 2004;1.
- Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for treating infectious diarrhoea. *Cochrane Database Syst Rev* 2006;3.
- Greenhough WB. The human, societal, and scientific legacy of cholera. *J Clin Invest* 2004;113:334–9.
- Vashantha VM. Letters. Doctors in India still seem not to be convinced. *BMJ* 2001;323:1068.
- Kelly DG, Nadeau J. Oral rehydration solution: a 'low-tech' oft neglected therapy. *Pract Gastroenterol* 2004;51–62.

Inflammatory bowel disease in children

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The incidence of inflammatory bowel disease (IBD), particularly Crohn's disease (CD), in children appears to be increasing. About 20% of patients with IBD present before the age of 19, and thus a significant burden of this illness falls on adolescents and young adults.

Paediatricians and adult gastroenterologists must be increasingly aware of the management priorities of these young people with potentially disabling chronic intestinal disease. Children with such complex chronic disorders should have easy access to a multidisciplinary team that includes paediatric dietitian,