

Fifty years of oral rehydration therapy: forgotten contributions from the Indian subcontinent

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Oral rehydration therapy (ORT) is a simple and powerful remedy that saves millions of children from diarrhoeal deaths every year. Improvising a simple oral remedy for diarrhoea was a Third World priority because the West, with good sanitation and ready access to intravenous (IV) fluids, rarely encountered diarrhoeal deaths. The scientific evidence in support of ORT began with researchers demonstrating the 'co-transport phenomenon', in which glucose was shown to enhance sodium absorption by specific transporter proteins. The ensuing clinical trials with ORT solutions of varying concentrations of sugar and salt, produced inconsistent and sometimes dangerous results. Early success came with the crucial 1968 Chittagong trials, when cholera patients in shock were treated intra-gastrically with ORT solutions. Subsequent field trials confirmed that ORT saves lives, even without IV fluids. Yet, translating ORT to the community remained problematic, until the Bangladesh liberation war (1971–72) when Dilip Mahalanabis (Infectious Diseases Hospital, Kolkata) conducted the game-changing field trial in squalid refugee camps under extreme conditions. With neither doctors nor nursing support, family members administered ORT to dying patients. This pragmatic and frugal remedy went on to become the flagship public health programme under UNICEF and WHO. Though under-implemented to this day, ORT remains the greatest contribution from the Indian subcontinent towards achieving Sustainable Development Goals. ORT teaches many lessons: the delays in translating research to therapy, lure of gadgetry smothering frugal innovation, need for institutional endorsement from the West, in addition to the general indifference towards public health priorities.

Oral rehydration therapy has been heralded as one of the most important medical advances of the 20th century.

– UNICEF and WHO

Oral rehydration therapy: triumphs and tribulations

In the 1970s, the world used to witness about 500 million cases of diarrhoea per year in children under five years, with an annual death toll of about five million¹. In the developing world, one in ten children under five died of diarrhoea every year. Today, oral rehydration therapy (ORT) has brought down the mortality to less than 1%, saving a few million poor children every year. ORT is both the simplest and the single greatest contribution from the Indian subcontinent in restricting under-five mortality, a major Sustainable Development Goal. In this context, it is rather surprising that 2018, the golden jubilee year of ORT, went mostly unnoticed in India. The website of the National Health Portal², Government of India, proclaiming the World Oral Rehydration Solution (ORS) day on 29 July, does not appear to have been updated since August 2017. To think that

many of those who formulated ORT and performed decisive field trials are alive, adds a touch of irony to the nation-wide amnesia.

The irony is greater when you realize that these innovations were conceived and developed in the Indian subcontinent. Although the core team of ORT researchers consisted of doctors and scientists trained in the West, we can still call it a home-grown remedy because home-grown it had to be. The poverty of the Indian subcontinent was the necessity (the mother) behind ORT, the invention. In the sixties, when physicians unanimously chose intravenous fluids to treat dehydrated cholera patients, it was hardship that spearheaded the search for frugal innovation. That is also why, unlike most other allopathic remedies, ORT had to be developed in the bosom of poverty, driven by a dire local need. And yet, for many years after ORT was accepted as the standard option by UNICEF and WHO, the developed world remained sceptical about the 'low technology' intrinsic to it. Although prominent British and American researchers were behind the discovery, USA was among the last to concede the legitimacy of ORT, let alone hail its practical value.

A comprehensive, unbiased and chronologically robust account by Ruxin³ expressly declares the difficulties in tracing the developmental history of ORT from scientific literature alone. Therefore, we have frequently quoted from Ruxin's study, which has incorporated insight from multiple anecdotes, personal interviews, and correspondence with major contributors and stakeholders.

The early beginnings

It is difficult to fix a date for the beginning of ORT. The scientific enquiry into the mechanism of diarrhoea started some time in 1940, when Daniel Darrow (Yale University, USA) studied electrolytes expelled by diarrhoea⁴. He identified what was lost through diarrhoea and highlighted the need to replenish with solutions containing potassium, sodium chloride and glucose. But he continued to use IV the same fluids because they were freely available in USA. Although Darrow initiated the prototypical ORT, he was unaware of the scientific logic behind it. In the context of many episodes of imprecisely formulated ORT worsening diarrhoea, doctors preferred to continue with IV fluids, the safest bet.

The enquiry into the pathophysiological mechanism behind ORT progressed substantially when in 1953, Fisher and Parsons⁵ (University of Oxford, UK), found that the absorption of glucose required specialized cells in the rat intestinal walls. Schultz *et al.*⁶ (Harvard University, USA) later demonstrated that sugar and sodium are absorbed together (co-transport) from the small intestine. Researchers focusing on 'co-transport' subsequently identified specific proteins that help sugar and sodium to be absorbed together. The final picture emerged in 1960, when Robert Crane delineated the precise mechanism for the active co-transport of glucose and sodium by the sodium-glucose linked transporter (SGLT)⁷. The proof of concept for ORT is widely attributed to the contributions from Crane, who is also maximally cited in the literature³.

Still unaware of the advances in the physiology of co-transport, Robert A. Phillips, a US physician and researcher, during the 1962 cholera epidemic in the Philippines, added glucose to oral electrolyte solutions. Diarrhoea improved dramatically in two patients, showing that glucose in the oral rehydration solution could enhance sodium absorption. Emboldened by the unprecedented success, Phillips planned a clinical trial in September 1962. He was so sure that he even held a press conference to announce the 'landmark trial'. Unfortunately, the trial was unsuccessful, in which five out of 30 patients died. It had unwittingly employed hypertonic ORT solutions. Devastated by the fiasco, Phillips even deferred the publication of trial results. The take-home lesson was that ORT is dangerous without adequate validation by 'balance studies'³. Clinicians concluded that there is no one-size-fits-all ORT for all patients. The failure of the trial set the clock back by some years.

American initiatives in the Indian subcontinent

The definitive success of ORT can be traced to American initiatives in the Indian subcontinent. Beginning in the early sixties, USA had established two cholera research laboratories in the Indian subcontinent; the South East Asia Treaty Organisation (SEATO) Cholera Research Lab in Dacca (then East Pakistan) under the US governmental agencies, and the

Johns Hopkins Center for Medical Research and Training in Calcutta (now Kolkata). Together, the two laboratories cooperated as well as competed with one another in improvising a simple solution to fight death from cholera³.

Ruxin³ has chronicled at length, and in great detail, the chain of events that culminated in ORT. It is a must read for anybody interested in medical history. In 1960, Greenough, a cholera physiologist, who came to work at the Cholera Lab in Dacca, was forced to try his luck with ORT because IV fluids were unaffordable. He monitored fluid intake/output and tested different ORT solutions with varying compositions. He brought down mortality rates considerably. It was then that Phillips arrived in Dacca. The failed Philippines trial of 1962 had sort of implied that cholera infections poisoned the sodium pump, aggravating electrolyte loss. Cholera endotoxin was widely believed to be the culprit behind the poisoned sodium pump. Such a possibility had to be dismissed before attempting oral fluid replacement therapy. Meanwhile, electrophysiological experiments by core researchers had shown that sugar increases the negative potential of the normal gut lumen. Thus, the 'poisoned sodium pump' hypothesis would indicate that glucose would fail to raise the negative potential in the cholera gut lumen. Sachar, a basic researcher who joined the Dacca Lab, went to Copenhagen and learnt laboratory techniques to quantify electric potentials in the gut lumen. Upon his return to Dacca, David B. Sachar showed that the sodium pump was unaffected in cholera. His experiments showed that glucose actually augmented the negative potential in the cholera-infected gut. Sachar's role was critical in providing scientific evidence to support ORT, galvanizing the clinical community to attempt future trials that made history.

Sachar's findings goaded his Dacca colleague Norbert Hirschhorn to venture into more clinical trials³. Once bitten twice shy from his Philippines experience, Phillips resisted, but Hirschhorn prevailed. Mechanistic considerations were employed in the preparation of isotonic ORT solutions. Patients were monitored with advanced equipment. In the crucial 1967 Dacca experiment, eight cholera cases in shock were given electrolyte solutions intra-gastrically. Combination of glucose and salt decreased stool output, whereas salt without glucose increased

stool output. The possibility of an oral therapy was self-evident, but Hirschhorn remained sceptical about its feasibility in the community setting. Everything had happened under expert supervision, employing nasogastric and multiluminal tubes to administer the solutions.

Fate took a turn in 1967, when two American youngsters, David Nalin and Richard Cash, without the prejudicial burden of experience, arrived in Dacca. Nalin had not even completed his internship. Cash had only just completed. The First Chittagong protocol led by Nalin and Cash, in September 1967, failed because all patients were administered a fixed volume of ORT, regardless of output. Nobody died, but many were either dehydrated or overhydrated. The Second Chittagong Protocol paid attention to balancing input and output. It was not only a resounding success, but also showed that ORT can save critically ill patients in a state of shock. Nalin was the driving force behind experimenting with exclusive oral therapy; cutting down IV fluids by 80%. Publication of the results of the Second Protocol in *Lancet* in 1968, marked the beginning of a new era in modern medicine. Encouraged, Calcutta followed suit and confirmed the Dacca experience independently. Nalin and Cash followed up with a full-fledged field trial at Matlab Bazaar, Bangladesh, which confirmed that ORT alone (without IV fluids) can save severely afflicted children too. The Matlab trial expanded the repertory of ORT and cemented its foundation.

Breakthrough in refugee camps

In retrospect, ORT was neither fluke nor serendipity. Decades of persistent toil preceded the many conceptual discoveries that led to the present-day ORT. Theoretical foundations were laid down by 1960 but clinical evidence came in tentative bursts, with many a slip between the cup and the lip. Unfortunately, the 'low tech' ORT looked inferior to the IV route. The breakthroughs from benchwork did not reach clinical practice quickly enough. The world had to wait until 1968 for clinical trials to be backed by hard scientific evidence. Physicians' doubts still lingered because trials were often going wrong on account of the inappropriate tonicity of the oral rehydration solution. Moreover, even after tasting

success in 1968, translating the remedy to the community level was problematic, because all trials had happened in controlled conditions under expert medical supervision. Even the protagonists were not sure of success without medical supervision, especially in the uneducated community setting.

Then came the opportunity in the form of a calamity. During the Bangladesh liberation war in 1971–72, hundreds of thousands of Bangladesh refugees thronged the many relief camps. Cholera began to spread in the cramped unhygienic shelters, with fatality as high as 30%. It was an Indian team led by Dilip Mahalanabis, working for the Infectious Diseases Hospital at Kolkata, who conducted the pivotal field trial in squalid refugee camps of Bangaon, under extremely perilous, unspeakable conditions. IV fluids, trained personnel, hospital beds were simply non-existent. Under immense pressure, Mahalanabis's team improvised a pragmatic, ready-to-use ORT sachet consisting of inexpensive ingredients available in a local grocery store. The low-cost formula was nothing but a mixture of table salt (four level teaspoons), baking soda (three-level teaspoons) and commercial glucose (20 level teaspoons). Not even weighing machines were required to prepare these ORT packets. Thousands of these packets were distributed among refugees of the Bangaon camp. The ingredients of the packet, when dissolved in 4 l of water, yielded the ORT solution, which patients were persuaded to drink as much as they could⁸. Mahalanabis recruited the patients' family members to administer ORT. He could offer nothing more in that state of emergency. The results were overwhelmingly reassuring. The mortality at Bangaon plummeted to less than 4%, similar to what was generally expected in standard hospital settings. Even when administered by inexperienced, untrained bystanders, ORT, *ad libitum*, not only controlled mortality, but also averted the lingering hazard of possible overhydration. The resounding success of the superbly frugal field trial, even without medical supervision or nursing support, was instrumental in winning global recognition for ORT as the fool-proof remedy for diarrhoea⁸. Impressed by the simplicity and practical wisdom intrinsic to it, WHO and UNICEF implemented ORT as a policy directive. The rest is history.

Forgotten attempts by unknown innovators

It is not that oral therapy was never contemplated before the sixties. Sushruta, dating back to 800 BC, prescribed something akin to ORT (containing rock salt and molasses) for diarrhoea³. And much later, in November 1953, *Lancet* carried an interesting article by Hemendra Nath Chatterjee⁹ (Chittaranjan Hospital, Calcutta). He suggested 'avomine' (a combination of 14 mg promethazine and 11 mg 8-chlorotheophylline) to control vomiting. And for the first time, Chatterjee suggested oral fluid replacement with a solution containing sodium chloride (0.04%) and glucose (2.5%); long before cotransport was recognized. But he was ahead of his time. Moreover, the logical rigour in Chatterjee's paper was blunted by a lack of robust mechanistic evidence. His treatment protocol, apart from omitting controls, also mentioned an Indian herb for the control of diarrhoea, denting his credibility even further. Despite the global sway of *Lancet*, Chatterjee went unnoticed. Cholera continued to kill millions for another 15 years. According to Ruxin³, Chatterjee was not the only one. In the Baghdad cholera epidemic of 1966, Al-Awqati, already familiar with Crane's work, saved many lives with ORT of an undefined concentration. But his work was published only in 1969 after he landed in USA¹⁰. Neither Chatterjee nor Al-Awqati get credit for their pioneering efforts. Significantly, the scourge of cholera was partly overcome in the West by improved sanitation and IV fluids.

The simplicity of ORT also served to subvert its popular appeal. Physicians believed that ORT was merely an escape route for those who cannot afford IV drips. Nobody believed that something simpler and cheaper could also be better. Many public health campaigns to promote ORT, even in the nineties, encountered stiff resistance from Indian doctors. IV therapy was not only easier to control, but also seemed the natural choice when vomiting was severe. Hospitals, up until the nineties, continued to employ IV whenever feasible. It took decades for WHO and UNICEF to convince the world of the need for ORT, not only in cholera, but diarrhoea from many other causes. In fact, in 1994, when Dhaka celebrated the 25th anniversary of ORT, top officials from the United Nations, in-

fluent politicians, researchers and international health advocates expressed anguish at how ORT remained underutilized for 25 years³.

Vicissitudes of therapeutic revolutions: lessons from history

Atul Gawande¹¹ recently highlighted the paradox of how some innovations become popular quickly, while others languish for decades before becoming standard practice. For instance, a simple procedure like handwashing was ignored for many years, killing thousands. Quite by contrast, the practice of anaesthesia crossed the Atlantic in a matter of months after it was first demonstrated in October 1846, at the Massachusetts General Hospital, USA. Quite inappropriately though, sophistication and gadgetry gave credibility to IV drips in the sixties. Ruxin³ asserts much the same thing by quoting Nalin: '... people ... got kudos for the extent to which [their] work was not practical... As soon as it became practical it was discarded like a soiled towel – it was too common, too hands-on... prestige went to people who measured trans-intestinal fluxes or electrical currents.'³

The developmental history of ORT offers many lessons: the gaps between core science and its application in therapy, the bewitching lure of inappropriate technology smothering frugal innovation, the questionable merit of clinical experience in shaping breakthrough innovations, the obligatory need for institutional endorsement from the West, in addition to the socio-political indifference towards public health priorities in India. Last but not least: our inability to spot, recognize and nurture talent. Ironically, Mahalanabis has won more recognition and awards from abroad than within India; for instance The Prince Mahidol Award (Thailand) and the Pollin Prize (USA). The former awardees include Nobel laureates.

Despite having reduced the global burden of infectious diseases substantially, ORT remains under-implemented (Bangladesh is far ahead of India), but supremely relevant after 50 years. In the WHO mortality data for 2016, diarrhoea ranks second in low-income countries and sixth in lower-middle income countries¹². Even without the charisma of Nobel recognition, ORT remains the greatest contribution from the Indian

subcontinent towards the achievement of Sustainable Development Goals.

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