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Oral Rehydration Therapy (ORT) and the Inventive Measures in Bangladesh, 1968-1990

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Abstract: The development of Oral Rehydration Therapy (ORT) is deeply rooted in the advancement of technology, understanding of how things work, and the changing needs of people. While early trials of ORT showed that glucose, sodium, and electrolytes could help treat fluid loss in diseases like cholera and diarrhea, it was just the beginning of a prolonged journey. Progress in this field has been driven by adapting to new technologies, discovering better ways to help patients, and ensuring widespread awareness and adoption, particularly in Bangladesh. It has been three-fold: scientific discoveries and precise measurement techniques, the integration of medical professionals with these innovations, and the dissemination of knowledge to empower individuals in preparing and administering ORS. These efforts were carried out through laboratory testing and operational research at the field level. The successful trial of oral rehydration solution (ORS) led to the publication of an article titled "Oral Maintenance Therapy for Cholera in Adults" in *The Lancet* in August 1968. This publication underscored the rationale behind ORT's emergence, initially driven by the scarcity of intravenous saline and its technical complexities. Today, ORS stands as the mainstream solution for rehydrating dehydrated patients. This lengthy journey was fraught with challenges and the continuous search for new approaches to achieve the ultimate goal. At every turn, individuals and organizations in Bangladesh assumed the responsibility of upholding this mission, establishing the country as a pioneer in the field.

Keywords: ORT, ORS, Invention, Cholera, Diarrhea, PSCRL, Bangladesh, ICDDR,B, BRAC.

Introduction

The Bengal Delta is considered the home of cholera in the world. Due to the convenient weather, throughout the year, cholera germs (*vibrio cholerae*) survive and attack the human body.[1] The US experts established the SEATO Cholera Research Laboratory (CRL) in the Matlab area (presently an upazila of Chandpur district), located in the Delta, in 1960 to study cholera and diarrheal diseases. A Cholera Hospital was

set up in Matlab, and the research laboratory was established in the Mohakhali area in the capital city of Dhaka. It is argued that the US army, stationed in the Southeast Asian region, was frequently attacked by the cholera germ, and they needed a handy solution against the disease. Intravenous therapy was most common in the 1960s to treat dehydrated patients in developed countries, but it required hospitalization or extra care for the patient. Additionally, administering intravenous saline therapy necessitated the expertise of professionals such as nurses or doctors. To address this issue, the CRL was established to invent a handy medicine for cholera and diarrhea. Initially, the US government fully funded the CRL.[2]

In 1968, researchers at the CRL pioneered the development of an Oral Rehydration Solution (ORS) and validated its effectiveness through successful trials conducted at both the Mohakhali Cholera Hospital and the Matlab Cholera Hospital. Following the triumph of these trials, the prestigious British medical journal, *The Lancet*, published an article in August 1968 titled 'Oral Maintenance Therapy on Cholera in Adults.'[3] Principal contributors to the advancement of oral maintenance therapy in East Pakistan (now Bangladesh) included David Nalin, Richard Cash, Rafiqul Islam, and Majid Molla. The invention of oral therapy was spurred by the scarcity of IV saline and its technical complexities, ultimately leading to the rise of ORS as the mainstream therapy for rehydrating cholera patients. The popularity of this treatment has grown to the point where even village grocery shops in Bangladesh keep packets of ORS on hand for mass selling. Despite its success, the journey from invention to popular therapy was fraught with challenges, and it was the pioneering field of Bangladesh that paved the way for all major experiments. The ICDDR,B (International Centre for Diarrheal Disease Research, Bangladesh) made significant contributions that helped make ORT a success story in Bangladesh and beyond.

From the beginning of the twentieth century, intravenous saline was accepted as the treatment of diarrheal diseases to replace the fluid loss in the human body. Routinely, after drinking water, the body absorbs a portion of it while access water gets expelled from the body through urination. Saline water (glucose and salt) also goes out by urination, but glucose has a way of absorption that was unknown before the 1960s. Scientists discovered that glucose is necessary to catch the saline water to the stomach wall and in the bloodstream. They also found the absorption time and the degree of transmission through the stomach walls into the bloodstream. Finally, the successful trial of ORS (in 1968) in the SEATO Cholera Research Laboratory for rehydrating diarrhea patients opened up a new era in the history of medicine.[4]

This article delves into the contributions made by the scientists at ICDDR,B, and the fundamental role of this pioneering institution. Additionally, it explores the innovative measures undertaken by various individuals and organizations to ensure the effectiveness of ORT. It is a qualitative study based on both primary and secondary data sources. In-depth interviews of the experts and the inventors of the ORS, analysis of contemporary writings and reports, and secondary data analysis are the major methods of the research.

Establishment of the CRL in Dhaka

Medical advisers of the Southeast Asia Treaty Organization (SEATO) proposed that SEATO, beyond its military programs, needs to build laboratories for medical research in different countries of Southeast Asia. In 1960, they sent a group of infectious disease experts to visit Thailand and Pakistan to make recommendations to set up a cholera research laboratory. Cholera and diarrheal diseases were major concerns of both Thailand and Pakistan, especially East Pakistan. So, the experts visited different parts of both countries and recommended setting up a Cholera Research

Laboratory (CRL) in East Pakistan.[5] Richard Cash provided insight into the rationale behind the creation of the SEATO Cholera Research Laboratory in Dhaka. The SEATO was a military alliance led by the USA in opposition to the Soviet Union, and Pakistan was a member of the alliance. East Pakistan was the home of cholera, so the CRL was established in Dhaka.[6]

According to Majid Molla, one of the inventors of ORS, a significant number of American troops lost their lives to cholera during the Vietnam War. In response, US authorities launched an investigation and pinpointed East Pakistan as the region most susceptible to the disease. Consequently, a research institution was established in the area to further study cholera. In 1960, the CRL was founded in East Pakistan, thus marking a crucial milestone in the battle against cholera.[7] M. A. Wahed, a retired scientist of ICDDR,B, mentioned two reasons behind the establishment of the CRL in Dhaka. Firstly, after the Second World War, the US army was deployed in Taiwan, the Philippines, Japan, and they were suffering from cholera; and some soldiers unfortunately died from the disease. At that time, SEATO's headquarters was in Bangkok, and they were searching for a solution to treat cholera patients and identify areas with a high prevalence of diarrhea. In the 1960s, a team came to East Pakistan and found that Borguna was the most cholera-prone area in the country. However, setting up a station in Borguna was difficult, so they decided to establish an office in Dhaka and a health center in Matlab. This was done under the Pakistan SEATO pact, and the SEATO Cholera Research Laboratory was born. Secondly, intravenous fluid therapy was expensive and related to technical issues, so there was an urge for innovation of new medicine that would be handy and cheap; the CRL was established to fulfill that urge.[8]

Emeritus Scientist of ICDDR,B, formerly CRL, Dr. Mohammad Yunus,[9] and Dr. Sirajul Islam[10] talked about similar reasons behind the establishment of the CRL in Dhaka. Thus, the

experts at CRL detailed four key factors that led to its establishment in East Pakistan: the military need to support US soldiers, the US Government's pledge to SEATO member nations under the SEATO Pact, the prevalence of cholera in East Pakistan, and the pressing need for an effective vaccine or affordable treatment for cholera patients.

The CRL was jointly run by the Pakistan Government and the SEATO. In 1960, the Laboratory was set up in Dhaka, but the hospital facilities started in Matlab.[11] Within two years, a hospital facility was established in Dhaka also (1962), and from 1966, the Health and Demographic Surveillance program operated in Matlab.[12] Its reputation spread all over the world with the invention of ORS in 1968. During the Liberation War of Bangladesh in 1971, the CRL passed a severe hurdle in running its activities and was forced to cut some of its programs. Moreover, CRL and its experts worked to save the people from the epidemic of cholera in Bangladesh and the refugee camps in India.[13]

Initially, cholera patients in the Matlab area received treatment from doctors in various locations, including open fields and abandoned areas. The doctors from the CRL provided treatment without a fixed establishment until 1963, when they acquired an abandoned barge to use as a temporary field station. The barge had previously been used by the police, with a prison inside, but they later withdrew their activities and fully allotted the space to the SEATO Laboratory. The barge was repaired and converted into a hospital and laboratory, with the first floor used for living quarters and the ground floor for patient treatment. This continued until 1966 when a permanent building was constructed nearby; in the same year (1966), the Health and Demographic Surveillance of Matlab, with a population of 43 thousand, was started.[14] Now, the Matlab population represents the most extensive population in the world, where, from birth to death, they are under continuous surveillance.[15]

Figure 1: Picture of the Abandoned Barge in Matlab.[16]

The Liberation War of Bangladesh and the CRL

David Nalin, a CRL scientist, and his colleagues played an active role in supporting Bangladesh during the 1971 liberation war. Despite US government support for Pakistan, they protested arms shipments to Pakistan and organized a rally in front of the White House.[17] During the war, oral therapy was used in refugee camps in India. Immediately after the war, Nalin visited the camps and was the first American to return to independent Bangladesh. He received a letter from MR Siddiqui allowing him to enter the newborn country and help re-establish the cholera laboratory. Nalin also served as a senior consultant to the International Rescue Committee, securing continued funding for the CRL despite Islamabad's cuts.[18] Richard A Cash, another CRL scientist and ORS inventor, left Dhaka in 1970 but returned after the war to continue important research and training programs on ORT. Immediately after the Liberation War, America did not recognize Bangladesh, so they stopped the money flow, and the CRL authority set up some training programs in the CRL to train people about the use of ORT.[19]

Under the name of PL-480, the US government provided financial assistance to the CRL, which then received a shipment of wheat as a donation for Pakistan. Proceeds from the sale of the wheat were directed towards the CRL's operations, which were primarily funded by USAID at that time. During the Liberation War, the CRL was limited to operating a hospital due to political unrest and financial constraints. The hospital treated three groups: Pakistan Army, Freedom Fighters, and Rajakars.[20] Due to a scarcity of IV saline, both packet and loose forms of ORS were used at CRL and other hospitals. Since it was difficult to transport IV saline to Matlab, ORS was mainly used. Doctors would administer only ORS if there was no vomiting.[21]

Mass Trial of ORS in the Refugee Camps of India

During the Liberation War of Bangladesh, Dr. Dilip Mahalanabis, a pediatrician and scientist at CRL, provided care to cholera patients in the refugee camps of India. Due to the unsanitary conditions, cholera spread rapidly among the refugees, creating a crisis with no medicine or knowledge available to prevent the disease. Dr. Mahalanabis recognized that ORT had been discovered prior to the war and decided to test it by mixing salt and sugar with water in the proper ratio and distributing it to those affected by the disease.[22] Experts estimated that without ORT, the mortality rate would have been over 40%. Fortunately, as a result of the use of ORT, the mortality rate caused by cholera and diarrhea was less than 5% in the camps. It was a miracle; where 90% of people were suffering from diarrhea, only 5% died in the most unhygienic environment, where children were in the highest number.[23]

In February 2009, the World Health Organization (WHO) published an interview with Dilip Mahalanabis in their bulletin (Volume 87, Number 2, pp. 81-160). In the interview, Mahalanabis discusses an empirical study of a mass trial that took place in the Bangaon refugee camp in India.

> When the cholera epidemic began in 1971, we had to leave our research and go out into the field to work with the refugees. The government was unprepared

> for the large numbers. There were many deaths from cholera and many horror stories. When I arrived, I was really taken aback. There were two rooms in the hospital in Bangaon that were filled with severely ill cholera patients lying on the floor. In order to treat these people with IV saline, you literally had to kneel down in their faces and their vomit. Within 48 hours of arriving there, I realized we were losing the battle because there was not enough IV and only two members of my team were trained to give IV fluids. I didn't have the privilege of consulting knowledgeable people at that time. I had to decide on my own what to do. I had no choice but to go ahead and use ORS to the maximum, hoping for the best. I was confident that it could work, but not necessarily in these circumstances. I also feared that if it didn't work, we would have no more options. It was a huge relief when we saw that it really did work. Within two or three weeks, we realized that it was working and that it seemed to be all right in the hands of untrained people. However, people did need some supervision and persuasion that it really would work. People knew that IV saline was the treatment for cholera because cholera is endemic in the region. At that time, we coined the term 'oral saline'. We told them that this was also saline, but that it was given by the mouth. At the time, we didn't know that it would become so well-known and that people would take it up everywhere. We were just happy that it worked there and that we could help these people. We prepared pamphlets describing how to mix salt and glucose and distributed them along the border. The information was also broadcast on a clandestine Bangladeshi radio station. The cholera outbreak was not just among refugees, but also in Bangladesh itself.[24]

Prior to the mass trial led by Mahalanabis, controlled community trials were implemented. Mahalanabis and his colleagues arranged this experiment and demonstrated a significant reduction in mortality rates. Following the success

of Mahalanabis's mass trial, numerous trials were conducted in various locations and scenarios across the globe, all yielding favorable results. That is why it is recognized as the most significant innovation of the century. In a true sense, it is simple, and its solution is also simple.[25]

ICDDR,B and the Use of ORS in Bangladesh

After the independence of Bangladesh, the name of CRL was changed to ICDDR,B. The ICDDR,B ordinance was signed on 6th December 1978 for twenty-five years, and then in 1998, it was extended up to fifty years. Despite the successful invention of the ORS, only two hospitals under the CRL were administering it to dehydrated patients, while others were not. To address this, ICDDR,B initiated a training course for national and international doctors and nurses aimed at disseminating knowledge on cholera and the ORS. This training course began in 1972, but took shape in 1974, with a regular course starting in 1978. Dr. Dhiman Barua, a senior professor, taught the trainees about cholera and ORS, including the technicalities regarding the proportion of the ORS. The Social Marketing Company (SMC) took responsibility for the production and distribution of ORS packets to the market. Prior to this, the government of Bangladesh had implemented the National Oral Rehydration Program (NORP), which involved the production and distribution of ORS packets throughout the country, while ICDDR,B promoted the government's efforts. In addition to NORP, BRAC was involved in dehydration programs in the 1970s and 1980s, utilizing *Labon Gur* (salt and molasses) rather than ORS packets. Notably, Dr. Mohammad Yunus, a scientist from ICDDR,B, conducted a study on the efficacy of home-based oral therapy for diarrhea, which is available on PubMed under the title "Home-based oral therapy for diarrhea, a laboratory study of safety and efficacy."[26]

The concern of the home-administered *Labon Gur* Solution (LGS) was related to the safety of medication. BRAC prescribed one pinch of *labon* and one scoop of *gur*, and they tested the

samples in the laboratory of ICDDR,B, and the result was satisfactory. After the solution was tested in the laboratory, one important thing emerged: the availability of potassium in *gur* that is more effective for dehydrated patients. However, there was another concern about its measurement process. In response, the ICDDR,B developed a spoon for both sodium and glucose; one smaller side was for salt, and another bigger side was for molasses. To make the LGS popular among the people of Bangladesh, BRAC worked on the application and operation aspects, while ICDDR,B concentrated on research endeavors. The overarching objective aimed at democratizing access to the therapeutic regimen across the national landscape. Notably, while the foundational composition of the LGS remained consistent, disparities arose in the sourcing methodology of requisite ingredients; BRAC personnel sourced *labon* and *gur* directly from households; in contrast, the ICDDR,B provided *labon* and *gur* from the institution. So, the formula was the same, but the way of collecting the ingredients was different.[27]

Simply providing technology is not sufficient; it is crucial for people to understand how to effectively utilize it. Recognizing this, ICDDR,B recommended households to maintain two separate pots: one for salt and another for molasses. Their objective was to ensure prompt treatment initiation at the onset of diarrhea. To disseminate this approach widely, ICDDR,B initiated training sessions for mothers, emphasizing the role of a designated "Bari Mother" (House Mother) in Bangladesh. This strategy capitalized on the observation that in rural Bangladesh, multiple families often reside within a single compound. By entrusting the LGS ingredients to a trained mother within each household, affected individuals could readily access treatment guidance. Moreover, ICDDR,B addressed logistical challenges by implementing a 'Depo System' in Teknaf, Cox's Bazar, whereby village leaders facilitated the distribution of ORS. Thus, ICDDR,B's initial interventions comprised the establishment of 'Bari Mothers' and the 'Depo System', tailored to local infrastructure constraints.[28]

ICDDR,B, BRAC, and SMC made extensive efforts in research, training, teaching, and social marketing in the country. As a result, within one decade (the 1980s), 12 million mothers were taught how to prepare ORT at home.[29] Subsequently, there was a robust campaign and dissemination of packaged ORS by multiple entities, including the government.[30] The pharmaceutical industries started to produce the ORS, which was a more effective advancement for production and distribution because every pharmaceutical company has a production and supply chain in the country. Over time, the importance of *Labon Gur* decreased among people as ORS packets became easily available at their doorstep, as well as in tea stalls and grocery shops in the countryside. Initially, ORS was mixed with one liter of water but was later reduced to half a liter to prevent wastage. This was due to several observations, including that cholera patients, who are primarily children, cannot consume one liter of ORS within 12 hours, and sometimes mothers are not willing to leave the remaining mixed ORS after 12 hours. Additionally, half a liter is a more practical amount for home use.

Usually, diarrhea does not exist for more than five days, and mothers are not willing to give the medicines after the diarrhea is over. Doctors frequently recommend solely using ORS to rehydrate children, which can become tedious for mothers who desire more than just saline water. Children in Bangladesh commonly suffer from zinc deficiencies, making the combination of zinc and ORS particularly effective in treating dehydration. Initial research on zinc tablets was conducted by S K Roy, followed by continued exploration by Dr. Mohammad Yunus and Abdullah Baki. A subsequent study revealed that supplementing with zinc for ten days significantly reduced the severity and duration of diarrhea, as well as lowering the need for antibiotics. Mohammad Yunus then conducted a comparative study on five and ten days of zinc supplementation, demonstrating that both durations produced similar results. Furthermore, there is no harm in overdose for patients with

sufficient zinc levels, and it serves as an additional supplement for their overall health.[31]

The Invention of Rice ORS

In 1982, Dr. Majid Molla and his colleagues successfully experimented with rice ORS in ICDDR,B and demonstrated that the rice powder-based ORS was as effective as the simple ORS.[32] The study was conducted on 124 older children and adults with acute diarrhea owing to *Vibrio cholerae* or *Escherichia coli*. The patients were divided into two groups. Half of the patients were treated with sucrose electrolyte solution (ORS), and half were treated with cereal-based electrolyte solution (rice ORS) per liter containing 30-gram rice power and electrolyte based on the recommendation of WHO. There was no difference in the success rate of patients compared to the treatment through ORS and rice ORS. This study suggested that rice ORS is sufficient to treat cholera patients like the ORS.[33] Thenceforth, in the same year in West Bengal, a randomized control trial with a higher quantity of rice powder (50 grams per liter) was conducted by Patra and his colleagues. It significantly reduced the duration (by 30 percent) and volume (by 49 percent) of diarrhea.[34]

Dr. Molla and his colleagues did another randomized trial between December 1982 to March 1983 at ICDDR,B with an increased quantity of rice powder (per liter 80 grams). The study showed that even with severe cholera, the ORS could be replaced by the rice-based ORS with better absorption. It resulted in a reduction of 28% in diarrheal stools and less consumption of ORS by 27%. As rice is the staple food in Bangladesh, it is an available ingredient compared to glucose and sucrose, which are manufactured products. Moreover, it provides more nutrition in the acute stage of dehydration.[35] Patra and his colleagues did another study containing rice powder (50 grams per liter) and glycine (8 grams per liter), but it did not improve the absorption efficiency.[36]

Dr. Molla shared the inspiration behind Rice ORS in an interview with the researcher. When one of his relatives fell ill with cholera, he began treatment with standard ORS. However, the patient was vomiting, and Dr. Molla's mother suggested feeding them liquid rice powder, which she had used to treat her own children when they were young. Dr. Molla recognized the scientific merit of this idea as the stomach wall can absorb rice more easily than other substances. He tested this theory with some patients without informing the authority of ICDDR,B, and was astonished to see the immediate results of the rice-based ORS. After further discussion with experts at ICDDR,B, they agreed to conduct a trial of ORS vs Rice ORS under their supervision, following Dr. Molla's formula. The first trial had 5:5 patients with the same conditions and some other factors, and they achieved outstanding results.[37]

Conclusion

The study explored the continuing efforts behind the inventions of ORT and its adoption led by the ICDDR'B. It also examined the innovative measures undertaken to develop and promote ORS as a vital tool in combating diarrheal diseases. The establishment of the SEATO Cholera Research Laboratory (CRL) in 1960 in the Matlab area within the Bengal Delta was a response to the prevalence of cholera in the region and the necessity for a practical solution against the disease. The pioneering development of Oral Rehydration Solution (ORS) by researchers at the CRL in 1968 marked a significant breakthrough in cholera treatment. The invention of ORS addressed the challenges associated with intravenous therapy, particularly its scarcity and technical complexities, making ORS the mainstream therapy for rehydrating cholera patients. The ICDDR,B continued efforts to improve the efficacy of ORT through rice-based ORS and other supplementary medicines. Research conducted at ICDDR,B demonstrated the efficacy of rice-based ORS as an alternative to traditional ORS solutions.

Studies showed that rice ORS was as effective as sucrose-based ORS in treating cholera patients, leading to its adoption as a viable treatment option.

The widespread adoption of ORT in Bangladesh was facilitated by collaborative efforts between the government and institutions like ICDDR,B, BRAC, and SMC. Through research, training, and social marketing initiatives, millions of mothers were educated on how to prepare ORT at home, leading to a significant reduction in diarrheal disease mortality rates. The production and distribution of packaged ORS by pharmaceutical industries further enhanced accessibility to ORT in Bangladesh. The availability of ORS packets in tea stalls and grocery shops across the country reduced reliance on traditional home remedies like *Labon Gur* Solution.

Although it was handy technology and miraculous in result, it was mainly limited within medical professionals before the beginning of the Oral Therapy Extension Program of BRAC in 1979.[38] The first ten years of the invention of ORS concentrated on the improvement of the formula of ORS and higher studies to validate early studies. Oral Rehydration Solution (ORS), Oral Rehydration Therapy (ORT), Labon Gur Solution (LGS), and Rice Saline are all inventions of the ICDDR,B based on scientific expansion and social needs. By this time, ICDDR,B worked with 'Bari Mother' and 'Depo System' to disseminate the knowledge of ORS among the people, but that intervention was in selected areas, not at the mass level. The Oral Therapy Extension Program of BRAC was administered to disseminate the knowledge of ORS to the mass people of Bangladesh. Both ICDDR,B and BRAC played pioneering roles in this regard. Overall, these findings highlight the critical role of scientific research, innovative interventions, and collaborative efforts in combating diarrheal diseases and improving public health outcomes in Bangladesh and beyond from 1968 to 1990.

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