

## In Remembrance

Roberto Romero\*

# A tribute to Professor Moshe Mazor, M.D.

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Professor Moshe Mazor served as Chair of the Division of Obstetrics and Gynecology at the Soroka Medical Center and Ben Gurion University in Be'er-Sheva, Israel, for more than a decade. He held the Deichmann-Lerner Endowed Chair in Obstetrics and Gynecology at the University. Moreover, he was an extraordinary figure of medicine in Israel and around the world. His career as a clinician, researcher, teacher, and mentor was a source of inspiration to those who knew and worked with him. He labored tirelessly to elevate Soroka Medical Center into a thriving hospital that met the needs of the region's growing population. Professor Mazor trained a great number of physicians who now hold positions of leadership throughout Israel. He passed away on February 2, 2015. Herein, we celebrate his enormous contributions to the field of Obstetrics and Gynecology, to the Perinatology Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development in Detroit, Michigan, and to Ben Gurion University and the Soroka Medical Center.

## Early life in Romania, Israel, and Italy

Moshe was born in Romania in 1948 and moved with his family to Israel 10 years later. After his military service (1966–1969), he began medical school at the University of Bologna, Italy. In his third year, he returned to Israel to complete his medical education at the Faculty of Medicine, Technion, Haifa. Moshe did his internship and residency in Obstetrics and Gynecology at the Soroka Medical Center and subsequently joined Ben Gurion University as a faculty member. He began a productive academic career with his



Professor Moshe Mazor, M.D.

colleagues who included Professors Joseph Ruben Leiberman [1, 2], Zion Hagay [3], and Vaclav Insler [4]. Moshe's research focused on clinical issues that emerged during the course of his obstetrical practice: the clinical significance of changes in fetal heart rate tracings [3–6], ethical dilemmas posed by the diagnosis of congenital anomalies [1, 2], complications of twin gestation [7, 8], and medical complications of pregnancy [9, 10].

## A sabbatical at Yale University

As soon as Moshe became eligible for a sabbatical year, he came to Yale University to pursue a fellowship in

\*Corresponding author: Roberto Romero, MD, DMedSci, Pregnancy Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, United States Department of Health and Human Services, Bethesda, Maryland, USA; Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA; and Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA,  
E-mail: romeror@mail.nih.gov

Maternal-Fetal Medicine. His wife, Dafna, and their three children, Efrat, Shai, and Merav, joined him in Connecticut. At that time, the major focus of the Perinatal Unit at Yale was the prenatal diagnosis of congenital anomalies with ultrasound. Moshe and I began another line of investigation—the relationship between intra-amniotic infection and preterm labor. For 18 months, we laid the groundwork for the coming 40 years of advances in this field. Although our resources were slim in those days (our office space was situated under a parking garage), we creatively explored many ideas about the importance of infection, inflammation, and the role of cytokines in labor at term as well as in preterm labor [11–15]. Perhaps one of the most valuable assets Moshe brought to our team was his focus. He insisted we pursue a single line of investigation, encouraging our team to resist the temptation to chase multiple inquiries simultaneously, as it was all too easy to become distracted and inefficient by the daily happenings of a busy and challenging obstetrical high-risk service.

We began by summarizing evidence reported in the literature that hinted at a link between infection and the onset of preterm labor. Our review article, published in 1988, became a Citation Classic [11] (Supplementary Figure S1) and served to identify the gaps in knowledge at the time. We drew figures to explain the pathway and the stages of ascending intra-amniotic infection [11] (Supplementary Figure S2), which have been presented and reproduced by many investigators worldwide. We also outlined how cytokines could link microbial products, macrophages, and prostaglandins to the onset of labor. The effort was shared

with Dr. Enrique Oyarzun, a Professor from the Pontificia Universidad Católica de Chile and a Kellogg Scholar. Little did we know that this work would ignite an intellectual partnership that would last for decades.

## Diagnosis of intra-amniotic infection in patients with preterm labor and premature rupture of the membranes

The High-Risk Obstetrical Service at Yale University had begun to offer amniocentesis to diagnose intra-amniotic infection in patients who presented with preterm labor and intact membranes and with preterm premature rupture of the membranes (PPROM). The impetus for this change in practice was the death of one preterm newborn. At that time, the standard protocol for the management of PPROM was to induce patients after 18 h of latency if the gestational age was more than 33 weeks. We thought infection was a greater risk than prematurity in these patients. Yet, of them, one patient underwent serial induction and eventually delivered a baby, weighing nearly 2,200 g, who developed severe respiratory distress syndrome and a massive intracranial hemorrhage and died without evidence of infection. This difficult experience led us to two important conclusions: that the management of patients diagnosed with PPROM needed to be individualized and that further



**Figure 1:** A gathering of academic physician-researchers and fellows at the Perinatology Research Branch, NICHD/NIH/DHHS, in Detroit, Michigan, circa 2006. L-R (back row): Gian Carlo Mari, Jimmy Espinoza, Eleazar Soto, and Joaquin Santolaya. L-R (front row): Mi Ran Kim, Gi Jin Kim, Jyh Kae Nien, Moshe Mazor, Yeon Mee Kim, Karina Richani, Luis Goncalves, and Joon-Seok Hong. Photo courtesy of Roberto Romero.

investigation into the microbial status of the amniotic cavity and lung maturity was essential to balance the relative risk of infection and prematurity.

At that time, the gold standard for the diagnosis of infection was a positive culture for microorganisms. However, cultivation took several days to grow microorganisms from amniotic fluid, and a clinical decision to utilize tocolysis in preterm labor or to induce labor in the setting of PPROM needed more rapid results. To address this issue, we conducted studies to assess the value of rapid testing, e.g., a Gram stain, to detect bacteria in amniotic fluid that could be performed in the labor and delivery unit. Indeed, a positive Gram stain proved helpful because its true positive rate was 99 %. Nevertheless, we quickly realized that many patients had a positive amniotic fluid culture for microorganisms and a negative Gram stain [16], and many of them had genital mycoplasmas that are not visible by Gram stain because they are too small. This set of findings led us to a search for additional tests that could rapidly diagnose intra-amniotic infection/inflammation, which included a Limulus test to detect endotoxins [17], an amniotic fluid white blood cell count [18–20], an amniotic fluid glucose concentration [19–21], interleukin (IL)-6 [19, 20, 22], leukocyte esterase [23], and gas liquid chromatography to detect organic acids [23], as well as a combination of the tests [19, 20]. This collaboration with Moshe catalyzed the development of another rapid test to detect intra-amniotic inflammation, i.e., matrix metalloproteinase-8 (MMP-8) [24]. This test was developed in collaboration with Dr. Bo Hyun Yoon, a Professor at the Seoul National University in the Republic of Korea who had been with us at Yale University during his sabbatical.

## Prostaglandins in premature labor and PPROM

Once we established the link between intra-amniotic infection and the onset of preterm labor, we initiated studies to investigate the mechanisms of parturition. Given that prostaglandins were considered the universal mediators of the onset of labor, we examined amniotic fluid concentrations of prostaglandin E2 (PGE2) and PGF2-alpha and those of their stable metabolites [25]. Prostaglandins, known to stimulate uterine contractility, are also involved in the process of cervical ripening. Among patients with preterm labor, we found that concentrations of amniotic fluid prostaglandins were elevated only in those diagnosed with intra-amniotic infection/inflammation [26, 27]. These observations suggested that premature labor is a heterogeneous condition,

i.e., a syndrome, which was the prelude to the discovery that cytokines play a role in the onset of labor in the context of infection and in physiologic spontaneous parturition at term.

## The discovery of cytokines as mediators in premature labor

Interleukin-1 was the first cytokine to be implicated in the onset of labor. The story of this discovery began with our team's efforts to link bacterial infection, prostaglandins, and labor [28–31]. The first set of experiments to see whether bacterial endotoxin would stimulate prostaglandin production yielded negative results (and we tried this experiment many times with explants of chorioamniotic membranes). This finding was unexpected because endotoxin administered to pregnant animals induces labor. We reasoned there must be an intermediary, such as IL-1 (also known as endogenous pyrogen), a cytokine produced by macrophages in response to endotoxin that can stimulate prostaglandin production. Hence, we proposed that bacteria induce labor through the production of IL-1. Once this hypothesis was formulated, we gathered the evidence systematically. We showed that the human decidua produces IL-1 in response to endotoxin, that IL-1 stimulates prostaglandin production by amnion cells (in primary culture), and that there is a high concentration of IL-1 in patients with premature labor and infection [32]. Key evidence was derived from experiments conducted in Israel at the Weizmann Institute with Moshe and Professor Boris Tartakovsky. We administered IL-1alpha and IL-1beta systemically to pregnant mice and all went into premature labor [30]. This effect was prevented by pretreatment with the IL-1 receptor antagonist [33]. Collectively, these observations made a compelling case for the role of IL-1 in the onset of labor. We also demonstrated that the administration of IL-1 intravenously to human uteri in extracorporeal circulation would lead to the onset of regular uterine contractions and that this could be blocked by treatment with indomethacin [34].

## Return to Soroka Medical Center and Ben Gurion University

After his initial sabbatical in the United States, Moshe returned to Israel and was appointed Director of the High-Risk Obstetrical Service at Soroka Medical Center. He was then called to a leadership role, first named as Acting Chair

in the Division of Obstetrics and Gynecology in 1996, and then appointed as Permanent Chair later that year, a position he held until 2003 at Ben Gurion University. During his tenure, Moshe had a transformational effect on clinical care, education, and research. He promoted and fostered a culture of excellence, leading by example with optimism and a sense of humor. He had aplomb, elegance, and wisdom. Many of his colleagues say that meeting and working with him marked a turning point in their lives.

Moshe led the studies in premature labor in Israel. He characterized the microbiology of intra-amniotic infection in patients in preterm labor and PPROM and reported that patients with intrauterine contraceptive devices often developed an intra-amniotic infection with *Candida albicans* [35, 36]. He also established a productive and successful collaboration with Dr. Shulamith Horowitz by studying genital mycoplasmas in premature labor. Moshe and his team explored many aspects of premature labor and multiple gestation, including the role of tocolysis, antibiotics, and endocrinology. Importantly, he demonstrated the successful eradication of intra-amniotic infection in patients with preterm labor and PPROM [37–42] (Supplementary Figures S3 and S4).

## Obstetrical ultrasound at the Soroka Medical Center

Another example of Moshe's transformational leadership was rooted in his position on obstetrical ultrasound. He thought of ultrasound as an important diagnostic tool that should be used by all obstetricians. In the early days of ultrasound, transducers and machines were locked up at the end of the working day in many centers around the world, including Soroka Medical Center. Moshe insisted on 24/7 usage of the ultrasound machines so that residents and fellows could master this technique (Supplementary Figure S5). He supported the appointment of Professor Reli Hershkovitz as Director of the Ultrasound Unit. Reli is now Chair of the Department of Obstetrics and Gynecology and a model of contemporary leadership.

Moshe possessed a strong moral compass; he was comfortable with challenging the status quo whether it be in patient care, medical training, research, or obstetric practices. Professor Offer Erez says that he first met Moshe when requesting a rotation at the Soroka Medical Center. Moshe agreed and informed Offer that he would be registered into an open competition for a residency position the following month. Moshe and Offer worked side-by-side while Offer was a resident, junior and senior faculty member, and

Director of the Maternal-Fetal Medicine Unit. Moshe had a formative influence and mentored other faculty members, besides Offer and Reli, including those who would become Professors such as Drs. Eyal Sheiner and Ashar Bashiri.

## Moshe at the Perinatology Research Branch, NICHD/NIH/DHHS

Moshe spent two sabbaticals with the Perinatology Research Branch, NICHD/NIH/DHHS, in Detroit, Michigan. The members and trainees of the Branch remember his insight, sense of humor, and ability to find a solution to any problem. He left an indelible mark on the Branch's research agenda and training program (Figure 1; Supplementary Figures S6–S9). Over the years, Moshe welcomed fellows who had trained at the Branch to visit and take advanced training in his department in Israel—Dr. Fabio Ghezzi, among others. The reverse is also true: Moshe recommended a number of colleagues in Israel for training experiences in the United States, including Drs. Zion Hagay, Arnon Wiznitzer, and Eitan Lunenfeld, all of whom became Chairs of departments.

## Moshe and Dafna

Moshe met his wife Dafna on their first day of high school when they were 14 years old. Dafna tells the story of when the teacher introduced Moshe to the class, recalling that she sensed he was special, and it was love at first sight (Figure 2). Dafna says, too, that Moshe was determined to become a physician even at that young age. "Moshe was a wonderful and loving father with a big heart and always full of wise counsel," she said.



**Figure 2:** Dafna and Moshe Mazor at a celebratory reception. Photo courtesy of Roberto Romero.



**Figure 3:** Moshe and Dafna Mazor with their children and grandchild during a visit to Canada. Photo courtesy of Roberto Romero.

While Moshe maintained his intense professional drive, ultimately authoring more than 475 papers, Dafna describes his last decade as a time when he came to enjoy spending more and more time with his family, especially with his seven grandchildren (Figure 3). Moshe took his entire family—Dafna, the children, and grandchildren—on a trip to the town of his youth in Romania. He showed his children and grandchildren his primary school where he had first met Dafna and dreamed of becoming a physician (Supplementary Figure S10).

## A life in academic medicine

During our academic journey, Moshe and I had opportunities to establish collaborations and travel as part of our scientific endeavors. We were in Europe, South America, Asia, Australia, and many places in the United States. Moshe visited our Branch generally once a year, usually in preparation for scientific meetings in which his team and ours would create presentations. Those yearly events were stimulating and are remembered with fondness (Supplementary Figures S11–S14).

We were last together at the 2013 annual meeting of the Yale Obstetrics and Gynecology Society. New Haven was the place where Moshe, Enrique Oyarzun, and I first met and worked with such passion 25 years earlier (Supplementary Figure S15). Upon their arrival in the United States, Moshe and Enrique literally bumped into each other at the baggage carousel as each had landed in New York and shared transportation to New Haven. In retrospect, I know that Enrique was happy to have spent those extra hours with Moshe to reflect on all that had been accomplished since they

were first fellows together at Yale University. It is fortunate when one can find a friend who deepens the level of inquiry and rigor in science and who also makes doing the work a more enjoyable and richer experience. Moshe was such a person (Supplementary Figure S16).

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