

20 Years Anniversary for *IMAJ*: Looking Back into the Future

Eitan Israeli PhD

Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel

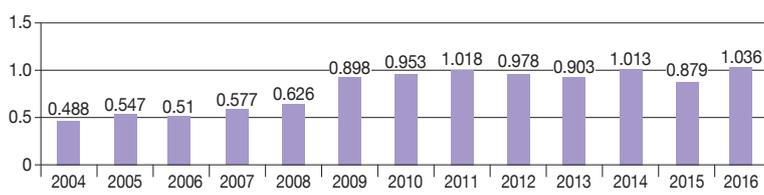
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The *Israel Medical Association Journal (IMAJ)* is the successor of the *Israel Journal of Medical Sciences* that was founded in 1965 by Prof. Moshe Prywes. As *IMAJ* approaches the end of its 20th year of publication, its impact on the scientific and medical communities in Israel and abroad is well established. *IMAJ* publishes articles from Israel as well as from countries all over the world, but the foremost purpose of this journal is opening a window for Israeli medical and scientific research to the world.

The effect of *IMAJ* is reflected in the rising impact factor attributed to the journal, climbing from 0.488 in 2004 and reaching 1.036 in 2016 [Figure 1]. The articles published in *IMAJ* are on diverse subjects, ranging from internal medicine, including heart and lung diseases, to cancer, infectious diseases, vaccinology, autoimmunity and more. In 2018, 58% of the articles were original studies, 25% were case reports, and 8% were reviews [Figure 2]. Every year *IMAJ* receives more than 300 papers to consider for publication, of which around 40% are rejected.

IMAJ also publishes special editions focusing on a specific subject, or summing up an interesting meeting; for example, an international conference on Medical Cannabis in September 2016, the Israel-Italy Meeting on Advances in Rheumatology and Autoimmunity in July 2017, the Israel-Greece Meeting on the same subject in September 2016, and on Radiology in November 2017. The journal serves as a stage for research involving the special demography of Israel, with its diverse minorities and different genetic origins.

Figure 1. *IMAJ* impact factor 2004–2016



Over the last 20 years, *IMAJ* has published a vast range of clinical topics. For example, in the field of infectious diseases, it covered among others, brucellosis and leishmaniasis which are representatives of endemic diseases, while Clostridia, methicillin-resistant *Staphylococcus aureus* (MRSA), papilloma or rotaviruses are omnipresent. In the field of vaccines. *IMAJ* publishes many research papers every year, with emphasis on the influenza vaccines, new and old, and its effect on healthcare workers and the population at large. Infectious diseases and vaccines are involved with autoimmunity, and the journal sets the stage for research dealing with these aspects as well.

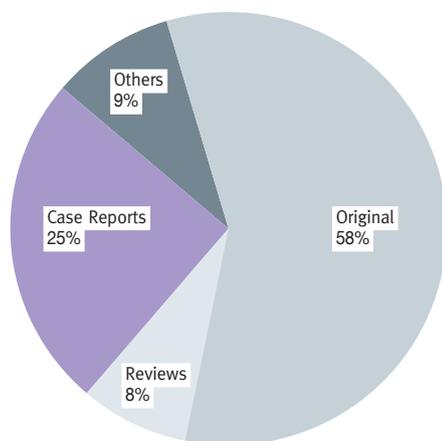
In the present article some papers are highlighted, representing the character and trends of clinical research in Israel, aiming to look back into the future, as depicted in *IMAJ*.

Some articles get special attention from readers, receiving from 600 to more than 700 reads online [Figure 3]. The highest score was 747 reads for the article by Naftali et al. from August 2011: “Treatment of Crohn’s disease with cannabis: an observational study.”

Figure 2. Most read articles in *IMAJ* from 2011 to 2015

1	Treatment of Crohn’s disease with cannabis: an observational study T. Naftali, L. Bar Lev, D. Yablekovitz, E. Half and F.M. Konikoff <i>IMAJ</i> August 2011 Number of reads: 747
2	Hepatitis C virus in children: deferring treatment in expectation of direct-acting antiviral agents E. Granot and E.M. Sokal <i>IMAJ</i> November 2015 Number of reads: 727
3	Non-radiographic axial spondyloarthritis G. Slobodin and I. Eshed <i>IMAJ</i> December 2015 Number of reads: 723
4	Acute viral myocarditis: current concepts in diagnosis and treatment Shauer, I. Gotsman, A. Keren, D.R. Zwas, Y. Hellman, R. Durst and D. Admon <i>IMAJ</i> March 2012 Number of reads: 634
5	Parenteral nutrition in very low birth weight preterm infants Riskin, C. Hartman and R. Shamir <i>IMAJ</i> May 2015 Number of reads: 613

Figure 3. IMAJ articles classification 2018



For 20 years, IMAJ has filled the empty spaces at the end of articles with “Capsules,” which are summaries from recent scientific and medical journals. These help the reader pick relevant articles in their field of expertise.

FOCUS ON ARTICLES RECENTLY PUBLISHED IN IMAJ

Physical activity is now regarded as a principal and integral intervention in the primary and secondary prevention of chronic diseases. Using physical exercise as part of a medical regimen is not a new concept, but the acceptance of this integration and concept, surprisingly, did not occur until the last decade. The impact of exercise spans from prevention to treatment. Epidemiological studies and interventional longitudinal research support its role in the primary prevention of chronic diseases. Physical inactivity is a pivotal factor in the development and progression of various chronic diseases. Tayer-Shifman et al. [1] conducted a retrospective screening of patient records from the Medical Fitness Facility at Meir Medical Center, Israel. Intake of subjects was done by a multidisciplinary team. For each individual, personalized diet and exercise plans were developed and patients attended the facility twice a week. Each participant was evaluated at enrolment and after 4 months for well-being, metabolic parameters, exercise capacity, and laboratory blood tests. The study group comprised 838 individuals whose mean age was 57 years. Only 40.5% of participants adhered to the regimen, with advanced age being the best predictor for adherence. At the follow-up visit, body mass index was lower (31.2 vs. 30.2 kg/m², $P < 0.0001$), exercise capacity increased (measured as maximal MET, 7.1 vs. 8.1, $P < 0.0001$), and well-being improved (measured by the Short Form Survey [SF-36], 69.3 vs. 76.0, $P < 0.0001$). The authors showed that a fitness program for patients with multiple chronic diseases is feasible and effective in improving prognostic parameters, albeit significantly challenged by adherence limitations.

This article was accompanied by an insightful editorial by Sharif and Amital [2].

Tick-borne relapsing fever (TBRF) is an arthropod-borne infection caused by a bacterial spirochete species, *Borrelia*. The case presented by Koton and Bisharat [3] is rather typical of TBRF. The authors’ aim was to increase the awareness of physicians to the possible outcomes of treatment and to consider Jariczc-Herxheimer reaction (JHR) when administering antimicrobial agents to patients with TBRF. JHR is defined as an acute exacerbation of the patient’s symptoms possibly occurring upon initial treatment with an effective antimicrobial for relapsing fever. The pathophysiology of JHR has been best studied in louse-borne relapsing fever (LBRF). During this reaction, the spirochetes disappear rapidly from the circulation with massive cytokine release. Symptoms often include hypotension, tachycardia, chills, rigors, diaphoresis, and marked elevation of body temperature. The reaction typically begins within 1 to 4 hours of the first dose of antimicrobial therapy.

Afifi et al. [4] attempted to evaluate the impact of dialogue between surgeons and pathologists in lymph node (LN) evaluation. LN retrieval and assessment is essential for accurate staging and treatment planning in colorectal cancer. According to U.S. National Cancer Institute recommendations, the minimal number of LNs needed for accurate staging of node-negative colorectal cancer is 12. Awareness and implementation of the guidelines have been shown to improve after assigning an opinion leader who has a special interest in colorectal cancer. Consecutively treated patients in the Department of Surgery B at Rambam Medical Center from 1 January 2000 through 30 July 2005 were identified from hospital discharge files. Demographic, surgical, and pathological data were extracted. Patients were divided into two groups. Group I patients underwent surgery before the initiation of a structured surgical oncology service (1 January 2000 to 30 October 2004). Group II patients underwent surgery after the initiation of the service (1 November 2004 to 30 July 2005). The study comprised 212 patients (170 in Group I and 42 in Group II). The median number of LNs examined was 9 in Group I and 14 in Group II ($P = 0.003$). Only 35% of patients in Group I received adequate LN evaluation compared to 79% in Group II ($P = 0.0001$). Patients with left-sided or rectal cancer were less likely to receive adequate LN evaluation than patients with right-sided cancers.

Returning to the topic of physical activity, although exercise has been shown to improve mood and well-being, the precise mechanism remains unknown. Neurosteroids are important neuroactive molecules with demonstrated involvement in several neurophysiological and disease processes. Previous research noted neurosteroid changes in dehydroepiandrosterone (DHEA) levels following exercise. Sonnenblick et al. [5] tried to determine whether changes in DHEA levels are associated with mood improvement after exercise, and whether

there are any differences in the effects on younger and older individuals. The individuals recruited for study participation were ≤ 50 years of age or > 65 years of age. Before and after 30 minutes of a standardized cycling regimen, each patient provided a blood sample and completed a questionnaire on mood and well-being. The findings confirmed a significant increase in DHEA levels post-exercise. A decrease in negative factors (fatigue, tension, depression, anger) and an increase in positive mood factors were noted. No difference in change of measures was observed between younger and older subjects. A positive correlation was noted between mood change and DHEA blood level changes in older subjects. Among older males, DHEA appeared to be associated with mood change after exercise.

The most common complication after tonsillectomy is bleeding. Mendel et al. [6] investigated whether performing the procedure during summer or winter affects the bleeding rate. The authors wished to determine whether there is an association between meteorological conditions and the occurrence of post-tonsillectomy hemorrhage (PTH) in the southern Negev region. The study group consisted of all patients who underwent tonsillectomy from 2001 to 2013 at the Soroka Medical Center in Beer Sheva. The authors collected patients' demographic data and indications for surgery. Meteorological data were obtained from a weather station operated by the Israel Ministry of Environmental Protection. Of 4438 patients who underwent tonsillectomy, with or without adenoidectomy, 432 (9.73%) experienced hemorrhage. Patients who suffered from PTH were significantly older (median age 9.61 vs. 4.7 years, $P < 0.0001$). When comparing patients without PTH to those who bled within 0–3 days after surgery, there was a higher risk for bleeding during the warmer seasons: relative risk (RR) 1.38, 95% confidence interval ([95%CI] 1.07–1.77), 1.45 (95%CI 1.17–1.80), and 1.62 (95%CI 1.27–2.06) comparing the winter to spring, summer, and fall, respectively. A statistically significant positive association was also found with the average temperature on the day of surgery. Bleeding more than 3 days after surgery was less likely in summer: RR 0.82, 95%CI 0.69–0.97. The authors found no association with temperature on the day of surgery and PTH after postoperative day 3.

Williams syndrome (WS) is a neurogenetic syndrome characterized by a variety of medical conditions and cognitive deficits along with distinct psychiatric and behavioral characteristics. To the best of our knowledge, no studies to date have comprehensively reported the prevalence of medical complaints, cognitive deficits, and psychiatric disorders in one cohort of people with WS. Dror and co-workers [7] investigated the prevalence of the various clinical features of WS in a large nationwide Israeli cohort. To examine potential risk factors for attention deficit hyperactivity disorder (ADHD) in WS, the authors examined the effects of cardiovascular anomalies, intellectual quotient (IQ), and phonophobia (fear of sounds) on the likelihood of ADHD. The study included 80 participants

with WS (mean age 7.76 years). Relevant medical information from medical records was obtained retrospectively. In addition, IQ testing and psychiatric assessments using structured tools were conducted. The association between ADHD and cardiovascular anomalies, IQ, and phonophobia was analyzed using a logistic regression. Supravalvular aortic stenosis and supravalvular pulmonary stenosis are the prevalent cardiovascular anomaly in WS. Phonophobia and ADHD are the most prevalent psychiatric diagnoses in people with WS. Phonophobia was significantly associated with the risk for ADHD in WS participants. These findings regarding the type and prevalence of medical, cognitive, and psychiatric characteristics in WS correspond to results in previous publications. The authors also showed a potential link between phonophobia and ADHD that merits further research.

These and other cited articles [8-30] reflect the activity in all fields of medical research in Israel, as well as outside. Scientists and physicians in Israel should take advantage of the opportunity to publish their research results in *IMAJ*, thus promoting the contribution of the country and the journal to the world scientific community.

Correspondence

Dr. E. Israeli

Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer 52621, Israel

Phone: (972-3) 530-8070

Fax: (972-3) 530-3673

email: eitanister@gmail.com

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Capsule

B1 or B2? The BCR decides

Immunological B cells are generally divided into two major subsets. B2 cells generate specific antibodies against foreign antigens in secondary lymphoid organs. B1 cells, found predominantly in the peritoneal and pleural cavities, instead produce “natural” antibodies as part of the innate immune system. Two models to explain this split exist: the “lineage model,” wherein both subsets have distinct progenitors, and the “selection model,” in which fates are directed by different

B cell antigen receptors (BCRs). Graf et al. provide support for the selection model using a transgenic system in which BCR specificities can be changed. Mature B2 cells differentiated into functional B1 cells when a self-reactive B1 BCR was swapped in, in the absence of B1 lineage precommitment.

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Eitan Israeli

Capsule

SERPINB1-mediated checkpoint of inflammatory caspase activation

Inflammatory caspases [caspase-1, caspase-4, caspase-5 and caspase-11 (caspase-1/-4/-5/-11)] mediate host defense against microbial infections, processing pro-inflammatory cytokines and triggering pyroptosis. However, precise checkpoints are required to prevent their unsolicited activation. Choi et al. report that serpin family B member 1 (SERPINB1) limited the activity of those caspases by suppressing their caspase-recruitment domain (CARD) oligomerization and enzymatic activation. While the reactive center loop of SERPINB1 inhibits neutrophil serine proteases, its carboxy-terminal CARD-binding motif restrained the activation of pro-caspase-1/-4/-5/-11.

Consequently, knockdown or deletion of SERPINB1 prompted spontaneous activation of caspase-1/-4/-5/-11, release of the cytokine IL-1 β and pyroptosis, inducing elevated inflammation after non-hygienic co-housing with pet-store mice and enhanced sensitivity to lipopolysaccharide- or *Acinetobacter baumannii*-induced endotoxemia. These results reveal that SERPINB1 acts as a vital gatekeeper of inflammation by restraining neutrophil serine proteases and inflammatory caspases in a genetically and functionally separable manner.

Nature Immunol 2019; 20: 276
Eitan Israeli

“Freedom of speech is a principal pillar of a free government; when this support is taken away, the constitution of a free society is dissolved, and tyranny is erected on its ruins”

Benjamin Franklin (1706–1790), American statesmen, author, printer, and satirist