

Israel Medical Association Journal Celebrates 20 Years

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Twenty years ago (1999) the *Israel Journal of Medical Sciences* (existing since 1965) was replaced by the *Israel Medical Association Journal (IMAJ)*. This step was initiated by then president of the Israel Medical Association, Prof. Y. Blachar, who invited Prof. Yehuda Shoenfeld to accept the challenging role of Editor-in-Chief of this newborn journal. Like a small olive tree, *IMAJ* was from the start promising and fast growing, and today, 20 years later, it is sturdy and well established. Covering a wide spectrum of scientific and medical topics, with papers by leading Israeli and foreign scientists, it is a mirror of Israeli medicine to the world. Being the home journal of Israeli physicians, many of the country's young scientists published their first English paper in *IMAJ*. As a monthly journal, *IMAJ* has around 3000 readers and recently received the impact factor of almost 1.1. These achievements would not have been possible without the contribution of co-editors Professors Gad Keren and Joshua Shemer. When Prof. Y. Shoenfeld was asked to give a brief summary of the most noteworthy articles that appeared in *IMAJ* during these two decades, he smiled, declaring that each publication was a joy in itself that energized him to keep aiming for further achievements. Nonetheless, I will try here to make short stops at some of the stations on this journey.

- *The first year of IMAJ:* The first issue was published in September 1999. Prof. Y. Blachar's vision was that *IMAJ* would become a forum for physicians to share experiences and research and would serve as a vehicle to enhance medical education. In welcoming the birth of *IMAJ* Prof. Shoenfeld commented that publishing the first issue in September, the same month of the Jewish New Year, "is surely auspicious" and expressed the wish that *IMAJ* would contribute to raising the level of medicine in Israel. The first issues included articles on relevant local medical topics, for example, "Balneotherapy at the Dead Sea area for knee osteoarthritis," "Financial impact of the introduction of erythropoietin for the treatment of anemia of premature infants in Israel," and "Medics in the Israel Defense Forces and their experience in trauma care during peacetime." The problem of market withdrawals of prescription drug products was one of the early topics presented in *IMAJ* [1]. It was not clear whether drug withdrawals are related to pre-marketing safety issues or to post-marketing changes in drug doses. Many relevant topics in world medicine were also covered, such as "Interventional cardiology – promises and challenges" by leading cardiologists such as Prof. Rafael Beyar. "Thrombolytic therapy in acute myocardial infarction" and its beneficial outcome was also discussed [2]. The newly discovered antiphospholipid syndrome was reviewed by Prof. Graham Hughes, indicating the acute awareness by *IMAJ* of the most relevant medical subjects at the time [3]. One of the notable articles was that of Noel Rose, known as the father of experimental autoimmunity, "The changing face of autoimmune diseases from JAMA to IMAJ."
- *Immune-mediated inflammation and atherosclerosis:* The involvement of immune-mediated inflammation in the development of atherosclerosis was one of the early subjects covered by the young journal. Cellular and humoral immune responses to heat shock protein 60/65 (HSP65) were reported to influence the progression of atherosclerosis. Transfer of HSP65 and beta-glycoprotein I-reactive lymphocytes to syngeneic mice led to the enhancement of fatty streak formation. Immunization with homologous oxidized low-density lipoprotein (oxLDL) in apolipoprotein-E Ko mice led to attenuation of lesion progression concomitant with the production of anti-oxLDL antibodies [4,5]. Immune-mediated inflammatory aspects continued to be assessed in many subsequent issues of *IMAJ*. In one of these, Th1 and T regulatory cells were shown to play a role in the pathogenesis of atherosclerosis, namely, the ability of T regulatory cells to shift T cell responses from Th1 to Th2, and were shown to be reduced in atherosclerosis. Interleukin-33 signaling was also found to promote Th2 response, attenuating atherosclerotic plaque progression [6]. In a recent study the complexity of atherosclerosis and the many risk factors contributing to its development in young adults was widely covered [7].
- *Intravenous and subcutaneous Ig treatment:* The wide spectrum of primary immunodeficiency syndromes in Israel and the beneficial outcome following intravenous immunoglobulin (IVIg) replacement therapy in patients suffering from hypo-gammaglobulinemia featured in many early issues of *IMAJ*. This included both their safety and efficacy.

The practical aspects of subcutaneous immunoglobulin treatment were also covered [8,9]. Later, the effectivity of high doses of IVIG to treat autoimmune diseases was also one of the subjects reported in the journal's early years. In this respect the benefit of IVIG therapy was continuously assessed in systemic lupus erythematosus (SLE), antiphospholipid syndrome with related pregnancy failures, and systemic vasculitis [10-12]. In a very recent issue of *IMAJ*, the efficacy of IVIG in Guillain-Barré syndrome followed by a significant and rapid improvement were reported. In addition, the potential role of IVIG in changing the course of cancer spread was summarized [13,14].

- *Autoimmunity and rheumatology:* Autoimmune diseases are associated with high morbidity and mortality, representing a significant health problem. Despite the development of advanced serologic diagnoses, we are still far from identifying all pathogenic pathways and from curing these diseases. During the last two decades, *IMAJ* has published several studies focusing on how to better understand autoimmune responses and markers. One of the first studies was on immune responses to DNA. DNA is immunologically diverse and, depending upon sequence and backbone structure, can stimulate or suppress immune responses. In mice genetically predisposed to autoimmunity, bacterial DNA was found to elicit anti-DNA autoantibodies. In contrast, mammalian DNA has suppressive properties preventing macrophages from producing cytokines. The failure of self-tolerance and the induction of anti-DNA in SLE reflect a failure of this suppression [15]. Early studies alluded to the finding that dead cells serve as a repertoire for autoantigens that can stimulate an autoimmune response in susceptible individuals. During the process of apoptosis, several events occur, including migration of intracellular components to the cell membrane and the attempt of macrophages to remove components. At this point evidence has accumulated that autoimmune responses can be induced as a result of increased apoptosis and defects in the removal of apoptotic materials [16]. The role of impaired apoptosis in pancreatic beta-cell function in type 2 diabetes was described in a recent issue of *IMAJ*, reinforcing the relevance of this process in immune-mediated inflammation [17]. The question of viruses being inducers of pathogenic autoantibodies and autoimmune disorders such as mixed cryoglobulinemia and its association with hepatitis C virus was reported in the late 1990s. Since then, this disease has been widely studied, as seen in the journal's early publications. Among the topics in rheumatology appearing in numerous *IMAJ* publications is the importance of genetic factors and their contribution to the development of the 'mosaic of autoimmune diseases' [18]. Today, the most widely used method is genome-wide association studies (GWAS), a method based on screening large panels of patients and controls with thousands of single nucleotide polymorphisms (SNPs) using microarray-based technology [19,20]. Natural autoantibodies such as the polyreactive natural immunoglobulin M and their role in pathogen elimination, B-cell survival and homeostasis, as well as their role in preventing autoimmunity and maintaining self-tolerance were also reviewed in *IMAJ*, as was the question of T and B regulatory cells and their role in autoimmunity, allergy and infectious diseases. The identification of new markers for the classification of T and B regulatory cells and the attempt to target these markers was a successful step in the search for effective and focused treatments in autoimmunity [21-23].
- *Infections, vaccines and other environment triggers of autoimmunity:* Infections, both bacterial and viral, are known to induce and exacerbate autoimmune diseases, mainly by the mechanism of molecular mimicry. This mechanism is also responsible for the reported autoimmune disorders (though rare) following some vaccines [24]. Immune thrombocytopenic purpura was reported after measles/mumps/rubella vaccine, and myopericarditis after smallpox vaccination. Reports on multiple sclerosis following hepatitis B vaccine or immune mediated disorders following influenza vaccines have yet to be confirmed. Larger epidemiological studies are needed to obtain more reliable data on the frequency of adverse reactions following many routine vaccines. One of the still relevant topics under discussion is the prolonged immune response against various adjuvants rather than against viral particles alone [25]. Several mechanisms whereby adjuvants induce inflammation have been proposed. Some of them trigger inflammasome, or bind DNA and lipid moieties in cells acting as lipophilic or hydrophobic substances. This sustained inflammation increases the risk of genetic predisposition where polyclonal activation is shifted by monoclonality. The evidence linking many immune mediated diseases – such as systemic sclerosis, sarcoidosis and malignancies such as lymphoma – with environmental triggers such as metals is increasing. Environmental factors such as pollution, smoking, diet and silicone implants were reported to affect the immune system, particularly in genetically predisposed individuals [26-28].
- *Malignancy – incidence and diagnosis:* The incidence of cancer is increasing worldwide. In a report by the Israel National Cancer Registry (INCR) database, almost 600,000 invasive cancer cases were diagnosed during the years 1960–2000. In this period, the incidence of new patients with cancer increased fivefold. The growing number of cancer patients in Israel presents a challenge to the national health and social services due to the long-term health outcomes and accompanying costly treatments [29]. Another study assessed the incidence of gastrointestinal malignancies in both Israeli

Jewish and Arab ethnic groups in order to better understand the risks prevalent in those groups. Based on the INCR database, colon, rectal and gastric cancers were examined. The period between 1980 and 2012 saw a decline in the incidence of gastric cancer in the Jewish population but a significant increase among Arab women. The incidence of colon and rectal cancers declined in the Jewish population but increased among Arabs. This difference in incidence of gastrointestinal cancers between Jewish and Arabs should be evaluated, taking into consideration relevant risk factors [30]. When breast carcinoma is suspected, based on mammography or ultrasound, stereotactic core needle biopsy (CNB) or excisional biopsy is usually required. A recent study compared these two methods in 894 patients. CNB was found to be an accurate method to establish a pathological diagnosis of breast lesion. Excisional biopsies are required for lesions with sampling errors or when CNB findings do not concur with clinical or mammographic findings [31]. When biopsy of pathologically enlarged lymph nodes (ELN) is indicated, one should decide whether percutaneous needle biopsy (NB) is sufficient or if surgical excisional biopsy is required. Biopsies of ELN were performed in 118 patients between the years 2004 and 2013. Both NB and surgical biopsies were of sufficient sensitivity and specificity, but the investigative time period until the final diagnosis was twice as long in patients who had NB [32]. The Israeli experience using robotic thymectomy in patients with suspected thymic neoplasm was shown in another very recent study to be safe and technically effective [33].

- *Cardiology*: Cardiology featured in many IMAJ publications, reflecting the growing interest in this field among Israeli researchers. Papers included the presence of anemia in patients with heart failure and the possible association with increased mortality. As part of the Heart Failure Survey in Israel in 2003, anemia was found in 55% of 4102 heart failure patients and was found to correlate with worse baseline heart failure. Mortality was higher in anemic patients and was reported to be 14.9%, 23.7%, and 26.3% at 6 months for patients with no anemia, mild anemia, and severe anemia respectively. The study found that anemia was common in Israeli patients with acute heart failure and was associated with increased mortality [34]. The use of beta-blockers for the prevention of myocardial infarction was reviewed and shown to reduce one-year mortality by 25%. In that review data on long-term beta-blocker therapy for myocardial infarction survivors was reported to still be relevant even in the era of primary percutaneous coronary intervention [35]. The differentiation between hypertrophic cardiomyopathy (HCM) and physiological left ventricular hypertrophy (athlete's heart) is challenging. HCM is the main cause of exercise-induced sudden cardiac death, mainly in young athletes who have overlapping features of HCM and athlete's heart.

Both echocardiography assessments and genetic studies are required for this differentiation. In this respect, the incidence and magnitude of athlete's heart in a group of Israeli cyclists was assessed. Among 56 cyclists, there were significant differences in left ventricular end-diastolic diameter (LVEDD) when compared to the control group. In 5% of the cyclists LVEDD exceeded the upper normal limit. Sport activity in well-trained Israeli sportsmen is associated with a modest increment in LV dimensions. These results indicate that abnormal echocardiography dimensions in Israeli athletes must be followed carefully and not assumed to be simply the result of sport activity [36]. A recent study suggested that T wave inversion in electrocardiographs of an athletic population is of additional value to the routinely used echocardiography, improving the diagnostic sensitivity and specificity in athlete's heart [37]. The therapeutic approach to patients suffering from heart failure differs in various countries. A study comparing Israeli heart failure patients (n=467) with patients (n=11,973) from other European countries evaluated the one-year outcome. Israeli chronic heart failure patients were older, had a higher co-morbidity incidence and higher mortality rates, and were more frequently hospitalized compared to similar patients from other countries [38]. Aiming to determine the risk score profile of patients presenting with a first acute coronary event and to evaluate its association with long-term mortality, a study comprising 1338 patients was designed based on a retrospective cohort from the 2010–2013 Acute Coronary Syndrome Israeli Surveys (ACSIS). No risk scores were independently associated with 5-year survival after an acute coronary event [39,40].

- *Orthopedics*: Being a platform for all Israeli physicians IMAJ has published studies on various surgery problems, including orthopedic. In one review, a meta-analysis of nine studies was performed to determine whether routine histological examination during total joint replacement is informative. All the studies concluded that routine histological examination is not required and should be reserved for cases with controversial and unexpected findings [41]. Cardiovascular complications should be assessed in ankylosing spondylitis (AS) as one of the frequent co-morbidities of this disease. The early recognition of these complications was considered of high importance [42]. In this respect, the renin-angiotensin-aldosterone axis (being involved in the pathogenesis of cardiovascular events) was investigated in patients with rheumatoid arthritis and AS. The post-hoc tests demonstrated that both AS and RA patients had lower renin values than controls, suggesting the involvement of this system in the development of cardiovascular complications in AS [43]. When AS is suspected, magnetic resonance imaging should be undertaken to both establish a definite diagnosis and define the extent of joint inflammation at sites such as the craniocervical junction [44].

A recent study assessed hip fracture outcomes in order to define the relationship of hip fractures with ethnicity, mortality and other complications [45].

- *International meetings and updates:* International meetings, collaborations and updates on advances in rheumatology and autoimmunity are routinely covered by *IMAJ*. The first Israel-Italy meeting took place in Haifa, Israel, in October 2012. Since then, seven bilateral meetings were held in which therapeutic innovations and new scientific findings were first presented. In addition, the content of two bilateral Israel-Greece meetings were also reported, emphasizing the success of these collaborations and the birth of multicenter research projects [46,47].

In conclusion, the achievements of *IMAJ* since its inception two decades ago are indeed admirable. May it continue to go from strength to strength.

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